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Studies on palladium-catalyzed enantioselective cyclization of 3,4-allenylic hydrazines with organic halides

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ABSTRACT

A convenient route to optically active pyrazolidine derivatives from Pd(0)/(*R*,*R*)-Bn-BOX-catalyzed enantioselective cyclization of 3,4-allenylic hydrazines in the presence of organic halides has been developed, the ee value is 75–84%. The absolute configuration of the products was determined by the conversion of one of the products to a known product prepared in this group. The reaction may proceed via the oxidative addition, intermolecular carbometallation of the allene moiety forming a π-allylic palladium intermediate, and the intramolecular enantioselective allylation.

1. Introduction

Pyrazolidine, an important heterocyclic unit existed in many natural and bioactive products,[1] has attracted more and more attention of both bio- and synthetic chemists. Although the pyrazolidine structural unit is usually available from [3+2] cycloaddition[2,3] and hetero-Diels–Alder cycloaddition of 1,3-cyclopentadiene with diethyl azodicarboxylate,[4] these existing methods often suffer from the complexity of starting materials. Since enantiomers often exhibit significant variance in biological activities,[5] the development of asymmetric synthetic methodologies has been of prime importance to organic chemists. However, the catalytic asymmetric synthesis of pyrazolidine derivatives has been much less explored.[6]

Transition metal-catalyzed coupling–cyclization reactions involving functionalized allenes have been demonstrated to be one of the most powerful protocols to construct carbo- and heterocycles.[7] We and others have developed transition metal-catalyzed coupling–cyclization reactions of functionalized allenes with organic halides.[8] Meanwhile, the palladium-catalyzed asymmetric allylic substitution reaction has been shown to be a useful means for forming new carbon–carbon,[9] carbon–nitrogen,[10] carbon–oxygen,[11] and carbon–sulfur[12] bonds in an enantioselective manner. Most work in this area has been focused on the development of improved chiral ligands for intermolecular nucleophilic substitution of the allylic systems.[13] In contrast, relatively little work has been done with more complicated intramolecular systems.[14] Larock et al. reported a palladium-catalyzed asymmetric hetero- and carboannulation of allenes using aryl and vinylic iodides bearing a nucleophilic functionality to construct various cyclic products in moderate to good ee.[15] In 2004, our group reported an efficient method for the synthesis of pyrazolidine derivatives through Cu- and Pd-catalyzed asymmetric one-pot tandem addition–cyclization reaction of 2-(2′,3′-alkadienyl)-3-ketoesters and dibenzyl azodicarboxylate in the presence of organic halides in high ee (up to 99%) but moderate diastereoselectivity (cis/trans=33:77 to 45:55).[16] Recently, a highly diastereoselective palladium-catalyzed cyclization of optically active 3,4-allenylic hydrazines with organic halides was also realized in our group by using $Pd(OAc)_2$ and (*R*,*R*)-Bn-BOX as the ligand.[17] However, the high enantiopurities of the products in the above mentioned two methods came partially from the preintroduced chiral information in the substrates. Herein, we wish to report a catalytic enantioselective synthesis of pyrazolidine derivatives by cyclization of 3,4-allenylic hydrazines in the presence of organic halides.

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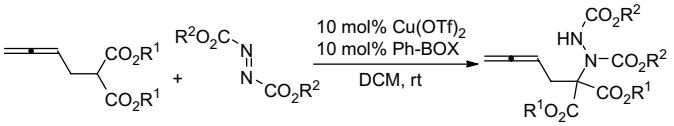
2. Results and discussion

2.1. Synthesis of starting 3,4-allenylic hydrazines

The starting 3,4-allenylic hydrazines were synthesized via Cu-catalyzed Michael addition of 2-(2′,3′-butadienyl)malonate with azodicarboxylate (Scheme 1).



1a: R^1 = Me, R^2 = Bn, 88%
1b: R^1 = Bn, R^2 = Bn, 77%
1c: R^1 = Et, R^2 = Et, 85%
1d: R^1 = Et, R^2 = Bn, 54%

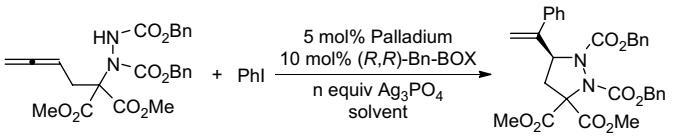
Scheme 1. Synthesis of 3,4-allenylic hydrazines **1a**–**1d**.

2.2. Pd(0)-catalyzed enantioselective cyclization of 3,4-allenylic hydrazines with organic halides

Our initial efforts were focused on the cyclization of 3,4-allenylic hydrazine **1a** with iodobenzene. The effect of solvents and the amount of silver salt were screened with Ag_3PO_4 being used as the base (Table 1). THF was found to be the best solvent in terms of the enantioselectivity (compare entries 1–5, Table 1). No remarkable change of ee of the product was observed by increasing the amount of Ag_3PO_4 from 0.4 to 0.5 equiv, although the use of 0.45 equiv of Ag_3PO_4 afforded the product **3aa** in the highest yield (entries 5–7, Table 1). Lowering the reaction temperature to 70 °C further improved the yield and the enantioselectivity (compare entries 7 and 8, Table 1).

However, because it is quite difficult to prepare pure **1a**, allenylic hydrazine with dibenzyl malonate moiety **1b** was used instead to screen the ligands for the reaction (Table 2). As shown in Table 2, the reaction in THF at 70 °C with 0.45 equiv of Ag_3PO_4 as the base afforded the desired product **3ba** in good enantiomeric excess (83%) when bisoxazoline (*R*,*R*)-**L1** and $Pd(dba)_2$ were used as the catalysts (entry 1, Table 2). Notably, the trioxazoline ligands **L4** and

Table 1
The effect of solvent and base on the Pd-catalyzed enantioselective coupling–cyclization of **1a** with PhI[a]

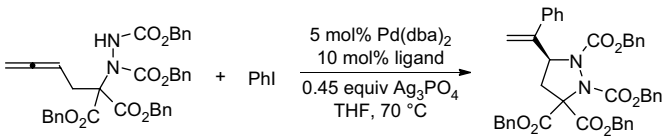


1a **3aa**

Entry	Solvent	*n* equiv Ag_3PO_4	Temperature (°C)	Yield of **3aa**[b] (%)	ee[c] (%)
1	DMF	0.4	80	72	63
2	1,4-Dioxane	0.4	80	69	71
3	Toluene	0.4	80	68	62
4	THF/DMF[d]	0.4	80	57	77
5	THF	0.4	80	54	81
6	THF	0.45	80	67	82
7	THF	0.5	80	61	82
8[e]	THF	0.45	70	75	84

[a] The reaction was carried out using 0.2 mmol of **1a**, 0.24 mmol of PhI, 0.2×*n* mmol of Ag_3PO_4, 5 mol % of $Pd(OAc)_2$, and 10 mol % of (*R*,*R*)-Bn-BOX in 2 mL of solvent in a Schlenk tube with a screw cap unless otherwise stated.
[b] Isolated yields.
[c] The ee values were determined by chiral HPLC analysis.
[d] THF/DMF=1:1.
[e] $Pd(dba)_2$ (5 mol %) and (*R*,*R*)-Bn-BOX (10 mol %) were used.

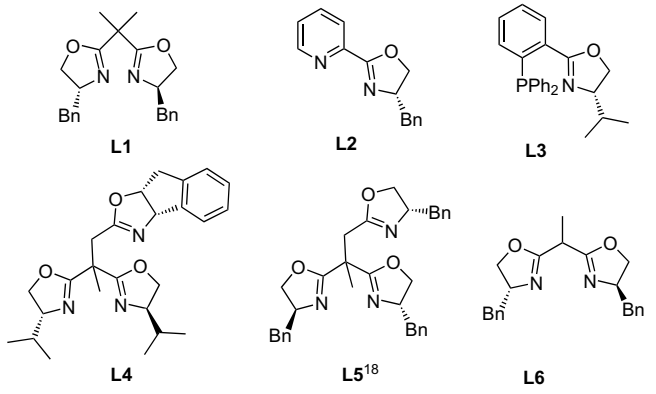
Table 2
Ligand effect on the Pd-catalyzed enantioselective coupling–cyclization of **1b** with PhI[a]



1b **2a** **3ba**

Entry	Ligand	Yield of **3aa** (%)[b]	ee[c] (%)
1	**L1**	75	83
2	**L2**	Complex	—
3	**L3**	NR[d]	—
4	**L4**	75	80
5	**L5**	69	83
6	**L6**	NR[d]	—

[a] The reaction was carried out using 0.1 mmol of **1b**, 0.12 mmol of PhI, 0.045 mmol of Ag_3PO_4, 5 mol % of $Pd(dba)_2$, and 10 mol % of ligand in 2 mL of THF at 70 °C in a Schlenk tube with a screw cap.
[b] Isolated yields.
[c] The ee values were determined by chiral HPLC analysis.
[d] NR=No reaction.

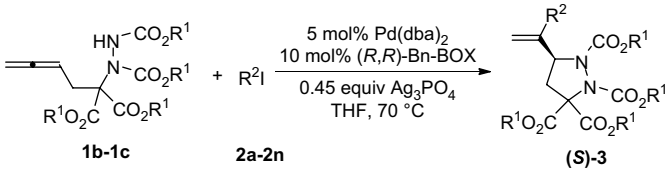


L5[18] also catalyzed the reaction to afford the product in 80% ee and 83% ee, respectively (entries 4 and 5, Table 2). However, ligands **L2**, **L3**, and **L6** were ineffective (entries 2, 3, and 6, Table 2). On the basis of these results, we defined 1.0 equiv of **1b**, 1.2 equiv of **2a**, 0.45 equiv of Ag_3PO_4, 5 mol % of $Pd(dba)_2$, and 10 mol % of (*R*,*R*)-Bn-BOX(**L1**) in THF at 70 °C as the standard reaction conditions.

With the optimized reaction conditions in hand, we studied the scope of this catalytic stereoselective cyclization reaction with respect to organic halides and allenylic hydrazines (Table 3). As shown in Table 3, pyrazolidines were obtained in good yields with good enantiopurity (>80%) in most cases. Not only aryl halides with electron-donating and -withdrawing groups could be used in this reaction (entries 2–9, Table 3), heteroaryl and 1-alkenyl iodides are also suitable substrates (entries 10–13, Table 3). Moreover, (*S*,*S*)-Bn-BOX can also catalyze the reaction to form the opposite enantiomer in comparable yield and ee value (entry 14, Table 3).

Since all the pyrazolidines obtained above are viscous oils, we tried to vary R^1 and R^2 groups on the substrate, intending to prepare a solid product to elucidate the absolute configuration of the products (entries 15 and 16, Table 3), but all efforts proved to be fruitless. Thus, tentative assignment on the configuration in the products was made based on the previous results in our group.[16,17] By using (*R*,*R*)-Bn-BOX as the ligand, the reaction of (*R*), (*S*), or racemic 2-(*N*,*N*-bis-(benzyloxycarbonyl)hydrazino)-2-(2′,3′-butadienyl)-3-oxobutyric acid ethyl ester with phenyl iodide all afforded the 5*S*-isomers as the major products. In consideration of the similarity of these two systems, the absolute configuration of

Table 3
Pd-catalyzed enantioselective coupling–cyclization reaction of **1** with different organic halides[a]



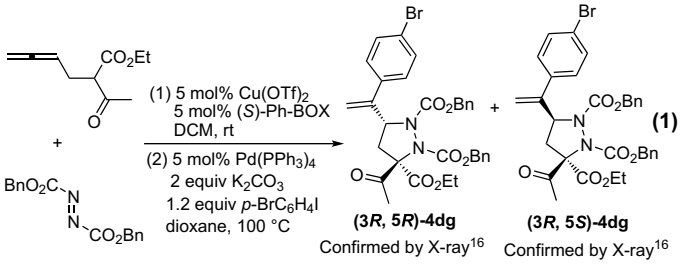
Entry	R^1	R^2I	Yield of **3**[b] (%)	ee[c] (%)
1	Bn (**1b**)	C_6H_5I (**2a**)	74 (**3ba**)	83
2	Bn (**1b**)	4-MeC_6H_4I (**2b**)	72 (**3bb**)	82
3	Bn (**1b**)	3-MeC_6H_4I (**2c**)	68 (**3bc**)	83
4	Bn (**1b**)	4-$MeOC_6H_4I$ (**2d**)	77 (**3bd**)	84
5	Bn (**1b**)	4-$MeO_2CC_6H_4I$ (**2e**)	71 (**3be**)	81
6	Bn (**1b**)	4-$MeOCC_6H_4I$ (**2f**)	63 (**3bf**)	81
7	Bn (**1b**)	4-BrC_6H_4I (**2g**)	75 (**3bg**)	80
8	Bn (**1b**)	4-NCC_6H_4I (**2h**)	69 (**3bh**)	81
9	Bn (**1b**)	4-PhC_6H_4I (**2i**)	74 (**3bi**)	81
10	Bn (**1b**)	(*E*)-*n*-$C_4H_9C_2H_2I$ (**2j**)	51 (**3bj**)	80
11	Bn (**1b**)	(*E*)-PhC_2H_2I (**2k**)	71 (**3bk**)	75
12	Bn (**1b**)	3-Oxocyclohexenyl iodide (**2l**)	73 (**3bl**)	77
13	Bn (**1b**)	2-Iodothiophene (**2m**)	70 (**3bm**)	82
14[d]	Bn (**1b**)	4-BrC_6H_4I (**2g**)	75 (*R*-**3bg**)	81
15	Bn (**1b**)	4-(4′-BrC_6H_4)C_6H_4I (**2n**)	70 (**3bn**)	84
16	Et (**1c**)	4-BrC_6H_4I (**2g**)	70 (**3cg**)	79

[a] The reaction was carried out using 0.1–0.15 mmol of **1**, 1.2 equiv of R^2I, 0.45 equiv of Ag_3PO_4, 5 mol% of $Pd(dba)_2$, and 10 mol% of (*R*,*R*)-Bn-BOX in 2 mL of THF in a Schlenk tube with a screw cap.
[b] Isolated yields.
[c] The ee values were determined by chiral HPLC analysis.
[d] $Pd(dba)_2$ (5 mol%) and (*S*,*S*)-Bn-BOX (10 mol%) were used.

products **3** from reactions catalyzed by $Pd(dba)_2$ and (*R*,*R*)-Bn-BOX was tentatively assigned to be *S*.

In order to further confirm the absolute configuration of the products, the tentatively assigned product (*S*)-**3dg** (81% ee), which was prepared from the reaction of **1d** and 4-bromophenyl iodide **2g** under the standard reaction conditions, was treated with MeMgBr in Et_2O, during which one of the ethoxycarbonyl group was reacted with MeMgBr to form the acyl group to afford a new product **4dg**.

As compared with the spectra, HPLC analysis, and specific rotation measurement of the authentic sample (3*R*,5*R*)-**4dg** prepared from our previous study (Eq. 1, see pages S81–S89 of Supplementary data



for the details of these data), we concluded that the absolute configuration of the product **4dg** prepared according to Scheme 2 is (3*S*,5*S*). Based on this, the absolute configuration of the product **3dg** prepared with (*R*,*R*)-Bn-Box as the ligand has been confirmed to be *S*.

3. Conclusion

We have demonstrated an enantioselective route to synthesize optically active pyrazolidines from easily available 3,4-allenylic hydrazines in the presence of organic halides. Further study in this area is being pursued in our laboratory.

4. Experimental section

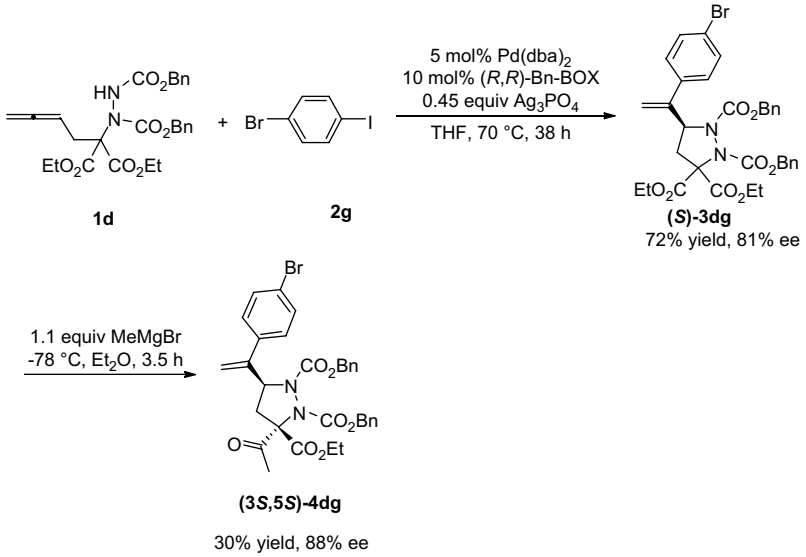
4.1. General

All reactions were carried out in a flame-dried Schlenk tube with a screw cap under argon atmosphere unless otherwise stated. THF and diethyl ether were dried over sodium wire with benzophenone as the indicator and distilled freshly before use. DCM and 1,4-dioxane were dried over CaH_2 and distilled freshly before use.

4.2. Preparation of starting materials

*4.2.1. Synthesis of dimethyl 2-(1′,2′-bis(benzyloxycarbonyl) hydrazinyl)-2-(2″,3″-butadienyl)malonate (**1a**)*[17]

Under an argon atmosphere, $Cu(OTf)_2$ (36 mg, 0.099 mmol), (*R*,*R*)-Ph-BOX (47 mg, 0.14 mmol), and 5 mL of dichloromethane were sequentially added into a flame-dried three-necked flask. After stirring at rt for 1 h, dimethyl 2-(2′,3′-butadienyl)malonate



Scheme 2. Synthesis of (3*S*,5*S*)-**4dg**.

(184 mg, 1.00 mmol), dibenzyl azodicarboxylate (600 mg, 1.21 mmol), and 5 mL of dichloromethane were added sequentially, and then the resulting solution was stirred at rt. When the reaction was finished as monitored by TLC, the solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=30:1 to 10:1 to 5:1) to afford **1a** (425 mg, 88%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.23 (m, 10H), 6.88–6.63 (m, 1H), 5.27–5.04 (m, 5H), 4.65–4.61 (m, 2H), 3.78–3.58 (m, 6H), 2.98–2.79 (m, 2H). It is very difficult to purify this compound, thus, it was used in the enantioselective cyclization directly without further characterization.

4.2.2. Synthesis of dibenzyl 2-(1′,2′-bis(benzyloxycarbonyl) hydrazinyl)-2-(2″,3″-butadienyl)malonate (**1b**)

The reaction of $Cu(OTf)_2$ (90 mg, 0.25 mmol), (*R*,*R*)-Ph-BOX (90 mg, 0.27 mmol), dibenzyl 2-(2′,3′-butadienyl)malonate (520 mg, 1.42 mmol), and dibenzyl azodicarboxylate (610 mg, 1.84 mmol) in CH_2Cl_2 (20 mL) afforded **1b** (693 mg, 77%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.18 (m, 20H), 6.82–6.61 (m, 1H), 5.38–4.97 (m, 9H), 4.58–4.46 (m, 2H), 3.15–2.90 (m, 2H); MS (ESI): *m*/*z* 657 ($M+Na^+$), 635 (M^++1); IR (neat): 3318, 1956, 1740, 1608, 1587, 1498, 1455, 1394, 1306; HRMS: calcd for $C_{37}H_{34}N_2O_8$ [$M+Na^+$]: 657.2207; found: 657.2205.

4.2.3. Synthesis of diethyl 2-(1′,2′-bis(ethoxycarbonyl)hydrazinyl)-2-(2″,3″-butadienyl)malonate (**1c**)

The reaction of $Cu(OTf)_2$ (40 mg, 0.11 mmol), (*R*,*R*)-Ph-BOX (36 mg, 0.10 mmol), diethyl 2-(2′,3′-butadienyl)malonate (212 mg, 1.0 mmol), and diethyl azodicarboxylate (250 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) afforded **1c** (328 mg, 85%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52–6.26 (m, 1H), 5.37–5.26 (m, 1H), 4.68–4.60 (m, 2H), 4.32–4.10 (m, 8H), 3.01–2.80 (m, 2H), 1.34–1.19 (m, 12H); MS (ESI): *m*/*z* 409 ($M+Na^+$), 387 (M^++1); IR (neat): 3313, 1957, 1740, 1468, 1445, 1375, 1304, 1228, 1096, 1068; HRMS: calcd for $C_{17}H_{26}N_2O_8$ [$M+Na^+$]: 409.1581; found: 409.1599.

4.2.4. Synthesis of diethyl 2-(1′,2′-bis(benzyloxycarbonyl) hydrazinyl)-2-(2″,3″-butadienyl)malonate (**1d**)

The reaction of $Cu(OTf)_2$ (7 mg, 0.019 mmol), (*R*,*R*)-Ph-BOX (7 mg, 0.021 mmol), diethyl 2-(2′,3′-butadienyl)malonate (44 mg, 0.21 mmol), and dibenzyl azodicarboxylate (79 mg, 0.24 mmol) afforded **1d** (57 mg, 54%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.22 (m, 10H), 6.78–6.49 (m, 1H), 5.38–5.10 (m, 5H), 4.65–4.60 (m, 2H), 4.22–4.03 (m, 4H), 3.02–2.84 (m, 2H), 1.22–1.03 (m, 6H); MS (ESI): *m*/*z* 533 ($M+Na^+$), 511 (M^++1); IR (neat): 3308, 1957, 1740, 1499, 1456, 1392, 1304, 1218, 1159, 1069; HRMS: calcd for $C_{27}H_{30}N_2O_8$ [$M+Na^+$]: 533.1894; found: 533.1911.

Due to the presence of four different conformations and severe rotameric broadening of many of signals, the NMR spectra for these compounds are in general complicated.[19] ^{13}C NMR spectra are just attached in Supplementary data.

4.3. Palladium-catalyzed enantioselective cyclization of 3,4-allenylic hydrazines with organic halides

4.3.1. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-phenylethenyl)-pyrazolidine (*S*-**3ba**)

Typical procedure. To a Schlenk tube with a screw cap were added $Pd(dba)_2$ (4 mg, 0.0071 mmol), Ag_3PO_4 (27 mg, 0.064 mmol), (*R*,*R*)-Bn-BOX (6 mg, 0.016 mmol), and 1 mL of THF. The resulting mixture was stirred for 1 h at rt, which was followed by sequential introduction of **1b** (97 mg, 0.15 mmol), 1 mL of THF, and phenyl iodide **2a** (37 mg, 0.18 mmol) at rt. The resulting solution was stirred at 70 °C. When the reaction was completed as monitored by TLC, the mixture was extracted by ether, and the organic layer was washed by water and brine, then dried over sodium sulfate. Filtration and chromatography on silica gel (eluent: petroleum ether/ethyl acetate=10:1 to 5:1) afforded 81 mg of (*S*)-**3ba** (74%) as a viscous oil; 83% ee (determined by HPLC analysis (Chiralcel AD, 20% *i*-PrOH in hexane, 0.7 mL/min, 214 nm), t_R 52.4 (minor), 58.3 (major)); $[\alpha]_D^{20}$ +3.6 (*c* 1.35, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.18 (m, 21H), 7.18–7.07 (m, 4H), 5.66 (s, 1H), 5.53 (m, 1H), 5.23–4.86 (m, 9H), 3.11 (dd, *J*=13.5, 8.7 Hz, 1H), 2.58 (dd, *J*=13.5, 2.7 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.7, 166.0, 157.0, 153.3, 143.6, 138.4, 135.5, 135.3, 134.8, 134.4, 128.39, 128.38, 128.35, 128.2, 128.15, 128.11, 128.07, 127.9, 127.8, 127.6, 126.6, 113.7, 72.2, 68.4, 68.3, 68.2, 68.0, 61.2, 41.3; MS (ESI): *m*/*z* 749 ($M+K^+$), 733 ($M+Na^+$), 728 ($M+NH_4^+$), 711 (M^++1); IR (neat): 1740, 1498, 1455, 1398, 1340, 1277, 1190, 1069; HRMS: calcd for $C_{43}H_{38}N_2O_8$ [$M+Na^+$]: 733.2520; found: 733.2500.

4.3.2. 1,2-Bis(benzyloxycarbonyl)-3,3-bis(methoxycarbonyl)-5-(1′-phenylethenyl)pyrazolidine (*S*-**3aa**)

The reaction of 5 mol % $Pd(OAc)_2$, 10 mol % (*R*,*R*)-Bn-BOX, Ag_3PO_4 (34 mg, 0.081 mmol), **1a** (97 mg, 0.20 mmol), and **2a** (50 mg, 0.25 mmol) in THF (2 mL) afforded 60 mg of (*S*)-**3aa** (54%) as a viscous oil; 81% ee (determined by HPLC analysis (Chiralcel OD, 25% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 13.0 (minor), 16.3 (major)); $[\alpha]_D^{20}$ +12.0 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.27 (m, 15H), 5.64 (s, 1H), 5.49 (m, 1H), 5.31–5.10 (m, 5H), 3.59 (s, 6H), 3.07 (dd, *J*=13.8, 8.7 Hz, 1H), 2.56 (dd, *J*=13.8, 3.3 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 168.5, 166.5, 157.0, 153.4, 144.2, 138.7, 135.5, 135.4, 128.5, 128.4, 128.1, 127.9, 127.7, 126.6, 113.5, 72.0, 68.5, 68.3, 61.4, 53.3, 53.1, 41.5; MS (MALDI): *m*/*z* 597 ($M+K^+$), 581 ($M+Na^+$); IR (neat): 1743, 1498, 1455, 1399, 1344, 1263, 1214, 1072; HRMS: calcd for $C_{31}H_{30}N_2O_8$ [$M+Na^+$]: 581.1894; found: 581.1896.

4.3.3. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(4″-methyl phenyl)ethenyl)pyrazolidine (*S*-**3bb**)

The reaction of $Pd(dba)_2$ (4 mg, 0.0071 mmol), (*R*,*R*)-Bn-BOX (5 mg, 0.014 mmol), Ag_3PO_4 (28 mg, 0.067 mmol), **1b** (93 mg, 0.15 mmol), and **2b** (41 mg, 0.19 mmol) in THF (2 mL) afforded 76 mg of (*S*)-**3bb** (72%) as a viscous oil; 83% ee (determined by HPLC analysis (Chiralcel OD, 40% *i*-PrOH in hexane, 0.5 mL/min, 214 nm), t_R 8.2 (minor), 10.2 (major)); $[\alpha]_D^{20}$ +9.6 (*c* 1.10, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.19 (m, 18H), 7.16–7.02 (m, 6H), 5.64 (s, 1H), 5.54 (m, 1H), 5.26–4.88 (m, 9H), 3.12 (dd, *J*=13.5, 8.7 Hz, 1H), 2.52 (dd, *J*=13.5, 3.0 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.7, 166.0, 157.0, 153.3, 143.3, 137.5, 135.5, 135.4, 135.3, 134.8, 134.4, 129.0, 128.4, 128.34, 128.30, 128.13, 128.10, 128.06, 128.0, 127.9, 127.6, 126.4, 112.9, 72.1, 68.4, 68.2, 68.1, 68.0, 61.2, 41.3, 21.0; MS (ESI): *m*/*z* 763 ($M+K^+$), 747 ($M+Na^+$); IR (neat): 1739, 1498, 1455, 1398, 1339, 1276, 1191, 1069; HRMS: calcd for $C_{44}H_{40}N_2O_8$ [$M+Na^+$]: 747.2677; found: 747.2655.

4.3.4. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(3″-methyl phenyl)ethenyl)pyrazolidine (*S*-**3bc**)

The reaction of $Pd(dba)_2$ (4 mg, 0.0071 mmol), (*R*,*R*)-Bn-BOX (6 mg, 0.016 mmol), Ag_3PO_4 (28 mg, 0.067 mmol), **1b** (96 mg, 0.15 mmol), and **2c** (39 mg, 0.18 mmol) in THF (2 mL) afforded 74 mg of (*S*)-**3bc** (68%) as a viscous oil; 83% ee (determined by HPLC analysis (Chiralcel OD, 40% *i*-PrOH in hexane, 0.5 mL/min, 214 nm), t_R 8.0 (minor), 9.7 (major)); $[\alpha]_D^{20}$ +3.3 (*c* 0.85, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.05 (m, 22H), 6.99–6.90 (m, 2H), 5.64 (s, 1H), 5.52 (m, 1H), 5.24–4.84 (m, 9H), 3.11 (dd, *J*=13.2, 8.4 Hz, 1H), 2.59 (dd, *J*=13.2, 2.4 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.8, 166.0, 157.0, 153.3, 143.7, 138.4, 138.0, 135.6, 135.4, 134.9, 134.4, 128.6, 128.42, 128.38, 128.35, 128.3, 128.2, 128.15, 128.12, 128.07, 128.0, 127.6, 127.2, 123.6, 113.4, 72.2, 68.4, 68.3, 68.2, 68.0, 61.3, 41.4, 21.4; MS (ESI): *m*/*z* 763 ($M+K^+$), 747 ($M+Na^+$); IR (neat): 1738, 1498, 1455, 1397, 1339, 1276, 1188, 1069; HRMS: calcd for $C_{44}H_{40}N_2O_8$ [$M+Na^+$]: 747.2677; found: 747.2653.

*4.3.5. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(4″-methoxyl phenyl)ethenyl)pyrazolidine (S-**3bd**)*

The reaction of $Pd(dba)_2$ (4 mg, 0.0071 mmol), (*R*,*R*)-Bn-BOX (6 mg, 0.016 mmol), Ag_3PO_4 (28 mg, 0.067 mmol), **1b** (99 mg, 0.16 mmol), and **2d** (42 mg, 0.18 mmol) in THF (2 mL) afforded 89 mg of (*S*)-**3bd** (77%) as a viscous oil; 84% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.5 mL/min, 230 nm), t_R 31.6 (minor), 38.3 (major)); $[\alpha]_D^{20}$ +12.0 (*c* 0.95, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.18 (m, 18H), 7.13–7.01 (m, 4H), 6.79 (d, *J*=8.4 Hz, 2H), 5.58 (s, 1H), 5.48 (m, 1H), 5.24–4.85 (m, 9H), 3.79 (s, 3H), 3.10 (dd, *J*=13.5, 9.0 Hz, 1H), 2.60 (dd, *J*=13.5, 2.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.8, 166.0, 159.2, 157.0, 153.3, 142.9, 135.6, 135.4, 134.9, 134.4, 130.8, 128.43, 128.39, 128.36, 128.17, 128.12, 128.08, 128.0, 127.7, 127.6, 113.7, 112.3, 72.2, 68.4, 68.3, 68.2, 68.0, 61.3, 55.2, 41.3; MS (ESI): *m*/*z* 764 ($M+Na^+$), 758 ($M+NH_4^+$), 741 (M^++1); IR (neat): 1739, 1608, 1513, 1455, 1398, 1339, 1271, 1249, 1188, 1069; HRMS: calcd for $C_{44}H_{40}N_2O_9$ [$M+Na^+$]: 763.2626; found: 763.2608.

*4.3.6. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(4″-methoxyl carbonylphenyl)ethenyl)pyrazolidine (S-**3be**)*

The reaction of $Pd(dba)_2$ (4 mg, 0.0071 mmol), (*R*,*R*)-Bn-BOX (6 mg, 0.016 mmol), Ag_3PO_4 (28 mg, 0.067 mmol), **1b** (93 mg, 0.15 mmol), and **2e** (49 mg, 0.19 mmol) in THF (2 mL) afforded 80 mg of (*S*)-**3be** (71%) as a viscous oil; 81% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.5 mL/min, 214 nm), t_R 48.9 (minor), 65.8 (major)); $[\alpha]_D^{20}$ +12.5 (*c* 1.05, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J*=8.1 Hz, 2H), 7.35–7.05 (m, 22H), 5.73 (s, 1H), 5.52 (m, 1H), 5.26 (s, 1H), 5.22–4.84 (m, 8H), 3.92 (s, 3H), 3.13 (dd, *J*=13.8, 8.7 Hz, 1H), 2.51 (dd, *J*=13.8, 2.7 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.6, 166.6, 165.9, 156.9, 153.2, 143.0, 142.9, 135.4, 135.2, 134.8, 134.3, 129.6, 129.3, 128.5, 128.40, 128.36, 128.2, 128.1, 127.9, 127.6, 126.5, 115.5, 72.1, 68.5, 68.3, 68.2, 68.0, 61.0, 52.1, 41.2; MS (ESI): *m*/*z* 807 ($M+K^+$), 791 ($M+Na^+$), 769 (M^++1); IR (neat): 1720, 1608, 1498, 1455, 1402, 1279, 1189, 1069; HRMS: calcd for $C_{45}H_{40}N_2O_{10}$ [$M+Na^+$]: 791.2575; found: 791.2561.

*4.3.7. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(4″-acetyl phenyl)ethenyl)pyrazolidine (S-**3bf**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*R*,*R*)-Bn-BOX (4 mg, 0.011 mmol), Ag_3PO_4 (20 mg, 0.048 mmol), **1b** (69 mg, 0.11 mmol), and **2f** (37 mg, 0.15 mmol) in THF (2 mL) afforded 51 mg of (*S*)-**3bf** (63%) as a viscous oil; 81% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.7 mL/min, 214 nm), t_R 19.5 (minor), 31.6 (major)); $[\alpha]_D^{20}$ +15.3 (*c* 1.35, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J*=8.7 Hz, 2H), 7.38–7.14 (m, 20H), 7.10–7.05 (m, 2H), 5.72 (s, 1H), 5.52 (m, 1H), 5.26 (s, 1H), 5.21–4.82 (m, 8H), 3.11 (dd, *J*=13.2, 8.4 Hz, 1H), 2.57 (s, 3H), 2.54 (dd, *J*=13.2, 2.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 197.4, 167.6, 165.9, 157.0, 153.2, 143.1, 142.9, 136.2, 135.4, 135.2, 134.8, 134.3, 128.44, 128.38, 128.22, 128.18, 128.1, 128.0, 127.6, 126.7, 115.7, 72.1, 68.6, 68.3, 68.2, 68.1, 61.0, 41.2, 26.5; MS (ESI): *m*/*z* 791 ($M+K^+$), 775 ($M+Na^+$); IR (neat): 1736, 1683, 1604, 1498, 1455, 1401, 1341, 1267, 1189, 1068; HRMS: calcd for $C_{45}H_{40}N_2O_9$ [$M+Na^+$]: 775.2626; found: 775.2597.

*4.3.8. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(4″-bromo phenyl)ethenyl)pyrazolidine (S-**3bg**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*R*,*R*)-Bn-BOX (4 mg, 0.011 mmol), Ag_3PO_4 (19 mg, 0.045 mmol), **1b** (64 mg, 0.10 mmol), and **2g** (37 mg, 0.15 mmol) in THF (2 mL) afforded 60 mg of (*S*)-**3bg** (75%) as a viscous oil; 80% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 11.7 (minor), 18.4 (major)); $[\alpha]_D^{20}$ +7.8 (*c* 0.95, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.18 (m, 20H), 7.12–7.06 (m, 2H), 6.94 (d, *J*=8.4 Hz, 2H), 5.65 (s, 1H), 5.44 (m, 1H), 5.21–4.83 (m, 9H), 3.09 (dd, *J*=13.5, 9.0 Hz, 1H), 2.52 (dd, *J*=13.5, 2.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.7, 165.9, 157.0, 153.2, 142.7, 137.4, 135.5, 135.3, 134.8, 134.4, 131.5, 128.5, 128.44, 128.41, 128.23, 128.22, 128.1, 128.0, 127.7, 121.8, 114.5, 72.2, 68.6, 68.3, 68.2, 68.1, 61.1, 41.2; MS (ESI): *m*/*z* 829 ($M(^{81}Br)+K^+$), 827 ($M(^{79}Br)+K^+$), 813 ($M(^{81}Br)+Na^+$), 811 ($M(^{79}Br)+Na^+$); IR (neat): 1736, 1587, 1498, 1490, 1455, 1394, 1341, 1274, 1190, 1071; HRMS: calcd for $C_{43}H_{37}N_2O_8Br$ [$M(^{79}Br)+Na^+$]: 811.1626; found: 811.1611.

*4.3.9. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(4″-cyanophenyl)ethenyl)pyrazolidine (S-**3bh**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*R*,*R*)-Bn-BOX (4 mg, 0.011 mmol), Ag_3PO_4 (19 mg, 0.045 mmol), **1b** (63 mg, 0.099 mmol), and **2h** (30 mg, 0.13 mmol) in THF (2 mL) afforded 50 mg of (*S*)-**3bh** (68%) as a viscous oil; 81% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.7 mL/min, 214 nm), t_R 20.6 (minor), 36.7 (major)); $[\alpha]_D^{20}$ +8.9 (*c* 0.95, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J*=8.7 Hz, 2H), 7.39–7.17 (m, 18H), 7.16–7.04 (m, 4H), 5.72 (s, 1H), 5.45 (m, 1H), 5.23–4.83 (m, 9H), 3.11 (dd, *J*=13.5, 8.7 Hz, 1H), 2.47 (dd, *J*=13.5, 2.7 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.5, 165.9, 156.9, 153.2, 143.1, 142.7, 135.3, 135.2, 134.7, 134.3, 132.1, 128.6, 128.4, 128.3, 128.24, 128.20, 128.0, 127.7, 127.3, 118.5, 116.7, 111.3, 72.1, 68.6, 68.4, 68.3, 68.1, 60.9, 41.1; MS (ESI): *m*/*z* 774 ($M+K^+$), 758 ($M+Na^+$); IR (neat): 2227, 1736, 1606, 1587, 1498, 1455, 1400, 1341, 1277, 1191, 1069; HRMS: calcd for $C_{44}H_{37}N_3O_8$ [$M+Na^+$]: 758.2473; found: 758.2481.

*4.3.10. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(4″-phenylphenyl)ethenyl)pyrazolidine (S-**3bi**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*R*,*R*)-Bn-BOX (4 mg, 0.011 mmol), Ag_3PO_4 (20 mg, 0.048 mmol), **1b** (63 mg, 0.099 mmol), and **2i** (35 mg, 0.12 mmol) in THF (2 mL) afforded 58 mg of (*S*)-**3bi** (74%) as a viscous oil; 81% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 13.7 (minor), 22.4 (major)); $[\alpha]_D^{20}$ +14.7 (*c* 1.10, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.56 (m, 2H), 7.53–7.42 (m, 4H), 7.40–7.17 (m, 21H), 7.11–7.06 (m, 2H), 5.69 (s, 1H), 5.57 (m, 1H), 5.29–4.85 (m, 9H), 3.15 (dd, *J*=13.5, 9.0 Hz, 1H), 2.64 (dd, *J*=13.5, 2.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.8, 166.0, 157.0, 153.3, 143.1, 140.6, 140.4, 137.3, 135.6, 135.4, 134.9, 134.4, 128.8, 128.44, 128.43, 128.40, 128.38, 128.2, 128.15, 128.11, 128.0, 127.7, 127.4, 127.1, 126.9, 72.2, 68.5, 68.3, 68.2, 68.0, 61.2, 41.4; MS (ESI): *m*/*z* 825 ($M+K^+$), 809 ($M+Na^+$); IR (neat): 1738, 1498, 1488, 1455, 1399, 1340, 1274, 1189, 1069; HRMS: calcd for $C_{49}H_{42}N_2O_8$ [$M+Na^+$]: 809.2833; found: 809.2801.

*4.3.11. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-methylene-2′(E)-heptenyl)pyrazolidine (S-**3bj**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*R*,*R*)-Bn-BOX (4 mg, 0.011 mmol), Ag_3PO_4 (19 mg, 0.045 mmol), **1b** (63 mg, 0.099 mmol), and **2j** (29 mg, 0.14 mmol) in THF (2 mL) afforded 37 mg of (*S*)-**3bj** (51%) as a viscous oil; 78% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 8.5 (minor), 10.0 (major)); $[\alpha]_D^{20}$ −11.1 (*c* 1.15, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.13 (m, 20H), 5.92 (d, *J*=16.8 Hz, 1H), 5.44 (dt, *J*=16.8, 6.9 Hz, 1H), 5.38 (s, 1H), 5.20–4.83 (m, 10H), 3.20 (dd, *J*=13.2, 8.7 Hz, 1H), 2.73 (dd, *J*=13.2, 3.3 Hz, 1H), 2.07–2.00 (m, 2H), 1.38–1.22 (m, 4H), 0.89 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.9, 165.9, 156.8, 153.2, 141.5, 135.6, 135.3, 134.9, 134.5, 131.3, 129.1, 128.4, 128.3, 128.2, 128.10, 128.06, 127.99, 127.96, 127.6, 113.7, 72.2, 68.3, 68.2, 68.0, 59.6, 42.0, 32.7, 31.2, 22.2, 13.9; MS (ESI): *m*/*z* 755 ($M+K^+$), 739 ($M+Na^+$), 717 (M^++1); IR (neat): 1736, 1498, 1456, 1398, 1341, 1270, 1190, 1071; HRMS: calcd for $C_{43}H_{44}N_2O_8$ [$M+Na^+$]: 739.2990; found: 739.3000.

*4.3.12. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-methylene-3′-phenyl-2′(E)-propenyl)pyrazolidine (S-**3bk**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*R*,*R*)-Bn-BOX (4 mg, 0.011 mmol), Ag_3PO_4 (19 mg, 0.045 mmol), **1b** (63 mg, 0.099 mmol), and **2k** (29 mg, 0.13 mmol) in THF (2 mL) afforded 52 mg of (*S*)-**3bk** (71%) as a viscous oil; 75% ee (determined by HPLC analysis (Chiralcel OD, 40% *i*-PrOH in hexane, 0.5 mL/min, 214 nm), t_R 12.4 (minor), 15.3 (major)); $[\alpha]_D^{20}$ +3.0 (*c* 1.05, EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.18 (m, 23H), 7.17–7.10 (m, 2H), 6.66 (d, *J*=16.8 Hz, 1H), 6.34 (d, *J*=16.8 Hz, 1H), 5.59 (s, 1H), 5.29 (m, 1H), 5.21–4.90 (m, 9H), 3.33 (dd, *J*=13.5, 9.0 Hz, 1H), 2.83 (dd, *J*=13.5, 3.3 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.8, 165.9, 156.8, 153.2, 141.5, 136.6, 135.5, 135.3, 134.9, 134.4, 128.9, 128.6, 128.4, 128.3, 128.23, 128.17, 128.13, 128.08, 128.0, 127.8, 127.6, 126.4, 116.7, 72.2, 68.5, 68.3, 68.14, 68.10, 59.6, 42.1; MS (ESI): *m*/*z* 775 ($M+K^+$), 759 ($M+Na^+$); IR (neat): 1736, 1607, 1497, 1455, 1398, 1341, 1271, 1190, 1070; HRMS: calcd for $C_{45}H_{40}N_2O_8$ [$M+Na^+$]: 759.2677; found: 759.2665.

*4.3.13. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(3″-oxocyclohexenyl)ethenylpyrazolidine (S-**3bl**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*R*,*R*)-Bn-BOX (5 mg, 0.014 mmol), Ag_3PO_4 (19 mg, 0.045 mmol), **1b** (68 mg, 0.11 mmol), and **2l** (35 mg, 0.16 mmol) in THF (2 mL) afforded 57 mg of (*S*)-**3bl** (73%) as a viscous oil; 77% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.7 mL/min, 214 nm), t_R 21.5 (minor), 24.6 (major)); $[\alpha]_D^{20}$ +1.4 (*c* 1.15, EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.17 (m, 18H), 7.12–7.08 (m, 2H), 5.86 (s, 1H), 5.79 (s, 1H), 5.39 (s, 1H), 5.24–4.85 (m, 9H), 3.25 (dd, *J*=13.5, 8.7 Hz, 1H), 2.60 (dd, *J*=13.5, 2.7 Hz, 1H), 2.47–2.31 (m, 3H), 2.09 (dt, *J*=18.0, 5.4 Hz, 1H), 2.01–1.80 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 199.6, 167.4, 166.0, 156.6, 155.8, 153.0, 142.7, 135.3, 135.1, 134.7, 134.3, 128.5, 128.43, 128.38, 128.34, 128.30, 128.24, 128.17, 128.1, 127.7, 125.1, 118.6, 72.1, 68.6, 68.4, 68.23, 68.20, 59.5, 42.4, 37.2, 26.6, 22.2; MS (ESI): *m*/*z* 767 ($M+K^+$), 751 ($M+Na^+$), 729 (M^++1); IR (neat): 1736, 1668, 1585, 1498, 1455, 1399, 1328, 1276, 1191, 1069; HRMS: calcd for $C_{43}H_{40}N_2O_9$ [$M+Na^+$]: 751.2626; found: 751.2622.

*4.3.14. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(2″-thienyl) ethenyl)pyrazolidine (S-**3bm**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*R*,*R*)-Bn-BOX (5 mg, 0.014 mmol), Ag_3PO_4 (19 mg, 0.045 mmol), **1b** (49 mg, 0.077 mmol), and **2m** (25 mg, 0.12 mmol) in THF (2 mL) afforded 39 mg of (*S*)-**3bm** (70%) as a viscous oil; 82% ee (determined by HPLC analysis (Chiralcel OD, 40% *i*-PrOH in hexane, 0.5 mL/min, 214 nm), t_R 10.5 (minor), 15.0 (major)); $[\alpha]_D^{20}$ +3.0 (*c* 1.05, EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.18 (m, 19H), 7.11–7.05 (m, 2H), 6.94 (dd, *J*=4.8, 3.6 Hz, 1H), 6.82 (d, *J*=3.6 Hz, 1H), 5.55 (s, 1H), 5.38 (m, 1H), 5.33 (s, 1H), 5.20–4.84 (m, 8H), 3.25 (dd, *J*=13.5, 9.3 Hz, 1H), 2.78 (dd, *J*=13.5, 3.0 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.7, 165.9, 156.8, 153.2, 141.6, 137.4, 135.5, 135.2, 134.8, 134.4, 128.42, 128.40, 128.35, 128.3, 128.2, 128.14, 128.09, 128.0, 127.6, 127.3, 124.6, 123.7, 112.4, 72.3, 68.5, 68.3, 68.2, 68.1, 61.0, 42.0; MS (ESI): *m*/*z* 755 ($M+K^+$), 739 ($M+Na^+$); IR (neat): 1736, 1498, 1455, 1398, 1342, 1276, 1190, 1070; HRMS: calcd for $C_{41}H_{36}N_2O_8S$ [$M+Na^+$]: 739.2085; found: 739.2078.

*4.3.15. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(4″-bromo phenyl)ethenyl)pyrazolidine (R-**3bg**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*S*,*S*)-Bn-BOX (5 mg, 0.014 mmol), Ag_3PO_4 (19 mg, 0.045 mmol), **1b** (60 mg, 0.094 mmol), and **2g** (37 mg, 0.15 mmol) in THF (2 mL) afforded 56 mg of (*R*)-**3bg** (75%) as a viscous oil; 82% ee (determined by HPLC analysis (Chiralcel AD, 25% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 17.3 (major), 29.4 (minor)); $[\alpha]_D^{20}$ −6.8 (*c* 1.05, EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.08 (m, 20H), 7.10–7.07 (m, 2H), 6.94 (d, *J*=8.4 Hz, 2H), 5.65 (s, 1H), 5.44 (m, 1H), 5.22–4.85 (m, 9H), 3.09 (dd, *J*=13.8, 9.0 Hz, 1H), 2.52 (dd, *J*=13.8, 2.7 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.6, 165.9, 157.0, 153.2, 142.7, 137.4, 135.4, 135.3, 134.8, 134.3, 131.5, 128.5, 128.42, 128.40, 128.2, 128.1, 128.0, 127.7, 121.8, 114.5, 72.1, 68.5, 68.3, 68.2, 68.1, 61.1, 41.2; MS (MALDI): *m*/*z* 829 ($M(^{81}Br)+K^+$), 827 ($M(^{79}Br)+K^+$), 813 ($M(^{81}Br)+Na^+$), 811 ($M(^{79}Br)+Na^+$); IR (neat): 1738, 1587, 1498, 1455, 1394, 1345, 1273, 1189, 1071; HRMS: calcd for $C_{43}H_{37}N_2O_8Br$ [$M(^{79}Br)+Na^+$]: 811.1626; found: 811.1617.

*4.3.16. 1,2,3,3-Tetrakis(benzyloxycarbonyl)-5-(1′-(4″-(4‴-bromo phenyl)phenyl)ethnyl)pyrazolidine (S-**3bn**)*

The reaction of $Pd(dba)_2$ (4 mg, 0.0071 mmol), (*R*,*R*)-Bn-BOX (5 mg, 0.014 mmol), Ag_3PO_4 (20 mg, 0.048 mmol), **1b** (65 mg, 0.10 mmol), and **2n** (46 mg, 0.13 mmol) in THF (2 mL) afforded 62 mg of (*S*)-**3bn** (70%) as a viscous oil; 84% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 20.8 (minor), 33.0 (major)); $[\alpha]_D^{20}$ +13.7 (*c* 1.05, EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J*=8.4 Hz, 2H), 7.45–7.41 (m, 4H), 7.37–7.17 (m, 20H), 7.10–7.07 (m, 2H), 5.69 (s, 1H), 5.55 (m, 1H), 5.27 (s, 1H), 5.23–4.87 (m, 8H), 3.13 (dd, *J*=13.5, 8.7 Hz, 1H), 2.62 (dd, *J*=13.5, 3.0 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.7, 166.0, 153.3, 143.0, 139.26, 139.21, 137.7, 135.5, 135.3, 134.8, 134.4, 131.8, 128.44, 128.41, 128.36, 128.3, 128.2, 128.1, 127.9, 127.6, 127.0, 126.8, 121.6, 72.2, 68.5, 68.3, 68.2, 68.0, 61.1, 41.3; MS (ESI): *m*/*z* 889 ($M(^{81}Br)+Na^+$), 887 ($M(^{79}Br)+Na^+$), 867 ($M^+(^{81}Br)+1$), 865 ($M^+(^{79}Br)+1$); IR (neat): 1740, 1587, 1498, 1483, 1455, 1391, 1340, 1275, 1189, 1070; HRMS: calcd for $C_{49}H_{41}N_2O_8Br$ [$M(^{79}Br)+Na^+$]: 887.1938; found: 887.1924.

*4.3.17. 1,2,3,3-Tetrakis(ethoxycarbonyl)-5-(1′-(4″-bromo phenyl)ethenyl)pyrazolidine (S-**3cg**)*

The reaction of $Pd(dba)_2$ (4 mg, 0.0071 mmol), (*R*,*R*)-Bn-BOX (5 mg, 0.014 mmol), Ag_3PO_4 (26 mg, 0.062 mmol), **1c** (54 mg, 0.14 mmol), and **2g** (48 mg, 0.17 mmol) in THF (2 mL) afforded 53 mg of (*S*)-**3cg** (70%) as a viscous oil; 79% ee (determined by HPLC analysis (Chiralcel AD, 40% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 4.5 (minor), 5.2 (major)); $[\alpha]_D^{20}$ +20.7 (*c* 1.05, EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J*=8.1 Hz, 2H), 7.21 (d, *J*=8.1 Hz, 2H), 5.67 (s, 1H), 5.39–5.33 (m, 2H), 4.3–4.10 (m, 8H), 3.02 (dd, *J*=13.8, 9.0 Hz, 1H), 2.49 (dd, *J*=13.8, 3.3 Hz, 1H), 1.32–1.23 (m, 9H), 1.19 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 168.0, 166.1, 157.1, 153.5, 143.5, 137.7, 131.6, 128.3, 121.9, 114.1, 72.1, 63.1, 62.6, 62.5, 60.9, 41.4, 14.4, 13.9, 13.7; MS (ESI): *m*/*z* 597 ($M(^{81}Br)+MeOH+Na^+$), 595 ($M(^{79}Br)+MeOH+Na^+$), 565 ($M(^{81}Br)+Na^+$), 563 ($M(^{79}Br)+Na^+$), 543 ($M^+(^{81}Br)+1$), 541 ($M^+(^{79}Br)+1$); IR (neat): 1747, 1488, 1466, 1404, 1377, 1336, 1303, 1276, 1196, 1073; HRMS: calcd for $C_{23}H_{29}N_2O_8Br$ [$M(^{79}Br)+Na^+$]: 563.1000; found: 563.0996.

*4.3.18. 1,2-Bis(benzyloxycarbonyl)-3,3-bis(ethoxycarbonyl)-5-(1′-(4″-bromophenyl)ethenyl)pyrazolidine (S-**3dg**)*

The reaction of $Pd(dba)_2$ (3 mg, 0.0053 mmol), (*R*,*R*)-Bn-BOX (4 mg, 0.011 mmol), Ag_3PO_4 (19 mg, 0.045 mmol), **1d** (51 mg, 0.10 mmol), and **2g** (34 mg, 0.12 mmol) in THF (2 mL) afforded 48 mg of (*S*)-**3dg** (72%) as a viscous oil; 81% ee (determined by HPLC analysis (Chiralcel OD, 15% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 7.5 (minor), 12.2 (major)); $[\alpha]_D^{20}$ +10.8 (*c* 1.25, EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, *J*=8.4 Hz, 2H), 7.38–7.24 (m, 10H), 7.19 (d, *J*=8.4 Hz, 2H), 5.67 (s, 1H),5.42 (m, 1H), 5.31 (s, 1H), 5.26 (d, *J*=12.3 Hz, 1H), 5.20 (s, 2H), 5.07 (d, *J*=12.3 Hz, 1H), 4.20–3.97 (m, 4H), 3.07 (dd, *J*=13.5, 9.0 Hz, 1H), 2.53 (dd, *J*=13.5, 3.3 Hz, 1H), 1.11 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.9, 166.1, 156.9, 153.3, 143.2, 137.6, 135.5, 135.4, 131.6, 128.44, 128.35, 128.30, 128.2, 128.1, 127.6, 121.9, 114.4, 72.2, 68.6, 68.3, 62.5, 61.1, 41.3, 13.7, 13.6; MS (ESI): *m*/*z* 689 ($M(^{81}Br)+Na^+$), 687 ($M(^{79}Br)+Na^+$), 666 ($M^+(^{81}Br)+1$), 664 ($M^+(^{79}Br)+1$); IR (neat): 1736, 1587, 1489, 1455, 1393, 1341, 1278, 1198, 1072; HRMS: calcd for $C_{33}H_{33}N_2O_8Br$ [$M(^{79}Br)+Na^+$]: 687.1313; found: 687.1296.

4.4. Determination of the absolute configurations of the products 3

*4.4.1. Synthesis of 1,2-dibenzyloxycarbonyl-3-ethoxycarbonyl-3-acetyl-5-(1′-(4″-bromophenyl)ethenyl)pyrazolidine (**4dg**) ((3R,5R)-**4dg** and (3R,5S)-**4dg**) from the reaction of ethyl 2-(2′,3′-butadienyl)-3-oxobutyrate with dibenzyl azodicarboxylate*[16]

A solution of $Cu(OTf)_2$ (4 mg, 0.011 mmol) and (*S*,*S*)-Ph-BOX (4 mg, 0.012 mmol) in 2 mL of CH_2Cl_2 was stirred at rt for 1 h. Then, ethyl 2-(2′,3′-butadienyl)-3-oxobutyrate (18 mg, 0.099 mmol) and dibenzyl azodicarboxylate (36 mg, 0.11 mmol) were added to the solution at 0 °C. The mixture was stirred at this temperature for 3 h as monitored by TLC. Then, potassium carbonate (28 mg, 0.20 mmol), $Pd(PPh_3)_4$ (6 mg, 0.0050 mmol), *p*-bromoiodobenzene (34 mg, 0.12 mmol), and 1,4-dioxane (2 mL) were sequentially added into this mixture. The resulting mixture was heated at 100 °C for 4 h as monitored by TLC. After evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=5:1) to afford 19 mg (29%) of (3*R*,5*R*)-**4dg** and 38 mg (60%) (3*R*,5*S*)-**4dg**.

Compound (3*R*,5*R*)-**4dg**: >99% ee (determined by HPLC analysis (Chiralcel OD, 2% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 21.2 (major), 23.7 (minor)); $[\alpha]_D^{20}$ +44.1 (*c* 0.50, EtOAc); $[\alpha]_D^{20}$ +45.3 (*c* 0.45, $CHCl_3$) (lit.[16] +45.4); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41 (d, *J*=8.4 Hz, 2H), 7.40–7.19 (m, 10H), 7.17 (d, *J*=8.4 Hz, 2H), 5.63 (s, 1H), 5.35 (m, 1H), 5.31–5.05 (m, 5H), 4.13–3.95 (m, 2H), 3.25 (dd, *J*=13.5, 9.3 Hz, 1H), 2.34 (s, 3H), 2.21 (dd, *J*=13.5, 3.0 Hz, 1H), 1.10 (t, *J*=7.5 Hz, 3H).

Compound (3*R*,5*S*)-**4dg**: 97% ee (determined by HPLC analysis (Chiralcel OD, 15% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 9.2 (minor), 11.3 (major)); $[\alpha]_D^{20}$ +13.7 (*c* 1.15, EtOAc); $[\alpha]_D^{20}$ +11.1 (*c* 1.00, $CHCl_3$) (lit.[16] +8.5); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43 (d, *J*=8.4 Hz, 2H), 7.38–7.24 (m, 10H), 7.18 (d, *J*=8.4 Hz, 2H), 5.63 (s, 1H), 5.40–5.07 (m, 6H), 4.21–3.98 (m, 2H), 3.03 (dd, *J*=13.5, 9.0 Hz, 1H), 2.30 (d, *J*=13.5 Hz, 1H), 2.10 (s, 3H), 1.13 (t, *J*=7.2 Hz, 3H).

*4.4.2. Synthesis of 1,2-dibenzyloxycarbony-3-ethoxycarbonyl-3-acetyl-5-(1′-(4″-bromophenyl)ethenyl)pyrazolidine (3S,5S)-**4dg** from the reaction of (S)-**3dg** with MeMgBr*

Under an argon atmosphere, (*S*)-**3dg** (69 mg, 0.10 mmol) and 3 mL of Et_2O were added into a Schlenk tube, then MeMgBr (38 μL, 0.11 mmol, 3.0 M in diethyl ether) was added to the solution at −78 °C. The resulting solution was stirred at this temperature for 3.5 h as monitored by TLC, then it was quenched by 3 M HCl at −78 °C. After warming up to rt, the mixture was extracted with 20 mL of diethyl ether, and the organic layer was washed sequentially with water and brine, and dried over sodium sulfate. Filtration and chromatography on silica gel (eluent: petroleum ether/ethyl acetate=5:1) afforded 20 mg of (3*S*,5*S*)-**4dg** (30%); 88% ee (determined by HPLC analysis (Chiralcel OD, 2% *i*-PrOH in hexane, 0.7 mL/min, 230 nm), t_R 21.6 (minor), 23.3 (major)); $[\alpha]_D^{20}$ −41.2 (*c* 1.0, EtOAc); $[\alpha]_D^{20}$ −41.0 (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, *J*=8.4 Hz, 2H), 7.40–7.20 (m, 10H), 7.17 (d, *J*=8.4 Hz, 2H), 5.63 (s, 1H), 5.36 (m, 1H), 5.31–5.05 (m, 5H), 4.13–3.95 (m, 2H), 3.26 (dd, *J*=13.5, 9.6 Hz, 1H), 2.35 (s, 3H), 2.21 (dd, *J*=13.5, 3.3 Hz, 1H), 1.10 (t, *J*=7.5 Hz, 3H).

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Supplementary data

$^1H/^{13}C$ NMR spectra of all new compounds. This material is available free of charge via the Internet. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.049.

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