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Enantioselective synthesis of [1,2]-oxazinone scaffolds and [1,2]-oxazine core structures of FR900482

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This paper is dedicated to Professor Csaba Szantay on the occasion of his 80th birthday

Abstract—Several chiral unsaturated [1,2]-oxazinone heterocycles have been synthesized by iridium-catalyzed allylic substitution and ring-closing metathesis (RCM) reaction in high yields with excellent enantiomeric excesses. In addition, the synthesis of [1,2]-oxazine core structures of FR900482 was achieved via iridium-catalyzed allylic substitution, followed by RCM and Heck reactions, respectively.

1. Introduction

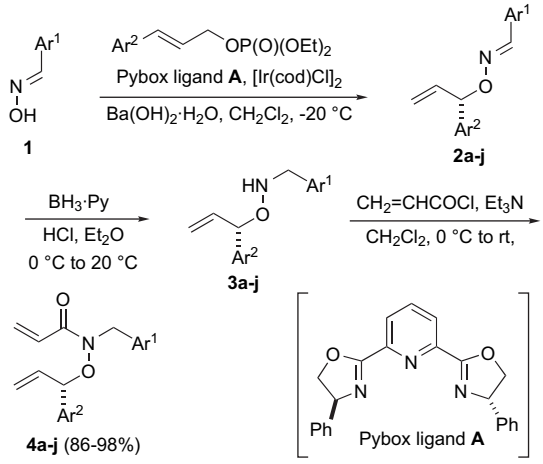
The potent biological activities of many pharmaceutical drugs containing heterocyclic ring structures have already been proved.[1] The concept of privileged structures was recently introduced as molecular frameworks capable of binding to several diverse biological receptors.[2] In rational drug discovery process,[3] the design of libraries may involve novel heterocyclic scaffolds to which diverse side chains are attached, the trajectories of which seek to explore three-dimensional space.[4] Herein we describe the synthesis of [1,2]-oxazinones, which are able to introduce multiple hydrophobic residues, as new chiral drug scaffolds and further application to obtain core structures of FR900482 and its derivatives.

[1,2]-Oxazines are relatively uncommon heterocycles, which can be generally obtained by [4+2] cycloaddition of nitroso derivatives with conjugated dienes.[5] Recently, Kerr reported the synthesis of tetrahydro[1,2]-oxazines by [3+2] cycloaddition of nitrones with cyclopropane.[6] Since [1,2]-oxazine and [1,2]-oxazinone skeletons have recently been found to be the central features in several antitumor and antibiotic compounds,[1a,7] synthetic methods of these skeletons have been attracting considerable attention.[8] As a part of our program directed toward the synthesis of achiral [1,2]-oxazines,[9] we newly investigated synthetic routes to obtain chiral [1,2]-oxazinones based on asymmetric iridium-catalyzed allylic substitution and RCM reactions.[10,11]

2. Results and discussion

2.1. Synthesis of chiral [1,2]-oxazinones

The RCM precursors **4a–j** were prepared as shown in Scheme 1. Chiral oxime ethers **2a–j** and further reduced derivatives **3a–j** were prepared via enantioselective iridium-catalyzed allylic substitution and reduction using $BH_3 \cdot Py$ complex according to our previous report.[10] Reaction of **3a–j** with acryloyl chloride afforded the RCM precursors **4a–j** in 86–98% yields.



Scheme 1. Preparation of RCM precursors **4a–j**.

The RCM precursors **4a–j** were treated with Grubbs' catalyst to obtain the desired six-membered [1,2]-oxazinones

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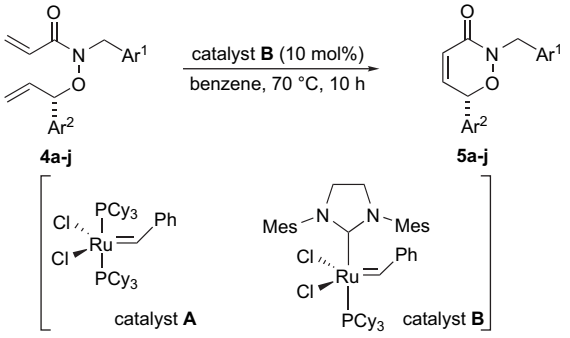
5a–j (Scheme 2). Initial attempts with Grubbs' first generation catalyst **A** did not give the desired compound though the reactions were conducted in different solvents like dichloromethane or benzene at reflux and the amount of catalyst was increased to 10 mol %. However, when second generation Grubbs' catalyst **B** was used (5 mol %) in dichloromethane (10 h, 40 °C), 30% conversion of **4a** to **5a** was observed along with 50% recovery of the starting material. To our surprise, by simply switching the solvent from dichloromethane to benzene (10 h, 70 °C), the conversion rose to 60% and was further increased to 95% using a higher catalyst loading (10 mol %). Under the latter conditions, compound **5a** was isolated in 92% yield (Table 1, entry 1). Using these optimum reaction conditions, the other substrates **4b–j** were also treated with catalyst **B** and cyclization proceeded smoothly. Although RCM reaction has been widely employed to construct cyclic compounds,[11] the cyclization of acrylic amide substrates is less common, and in some cases did not give the desired cyclic ring.[12] Therefore, it is worthy to stress that RCM precursors **4a–j** bearing acrylic amide moiety worked well. Several points are noteworthy to discuss. Entries 2, 4, and 10 of Table 1 indicate that almost quantitative conversion was achieved and the corresponding desired compounds **5b**, **5d**, and **5j** are obtained in excellent isolated yields. In iridium-catalyzed allylic substitution, compound **4i** was obtained with lower enantioselectivity (60% ee), it is due to the unstable phosphate (Ar^2= 4-MeO–C_6H_4) which was used in its crude form without further purification (Scheme 1). Attempts to purify this phosphate by flash column chromatography were unsuccessful and found to be less stable comparing with other phosphates. The sterically hindered 2-naphthyl group (entry 8) also produced the desired compound **5h** in high yield (83%) with an excellent enantioselectivity. Furthermore, after one time recrystallization (in hexane), products (entries 1, 2, 5–7) have given ≥97% ee.



Scheme 2. RCM of precursors **4a–j**.

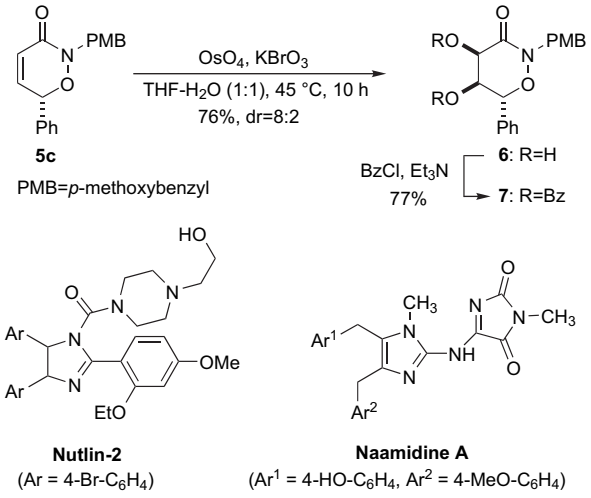
To evaluate the chiral [1,2]-oxazinones **5a–j** as drug scaffolds, the compound **5c** having 4-MeO substituent on *N*-phenyl ring is further transformed to **6** and **7** via osmium-catalyzed cis-dihydroxylation and benzoylation (Scheme 3). The dihydroxylation of **5c** produced an 80/20 mixture of diastereomers that were separated by flash chromatography on silica gel. Relative configuration of the major and minor diastereomers was determined by several NOE experiments. The major isomer **6** was then treated with benzoyl chloride in the presence of triethylamine base to give **7** in 77% yield with 93% ee. The final compound **7** has some structural

Table 1. RCM reaction of **4a–j** using catalyst **B**[a]

Entry	Precursor	Ar^1	Ar^2	Yield (%)	ee[b] (%)
1	**4a**	Ph	Ph	92	95 (99)[c]
2	**4b**	4-CF_3–C_6H_4	Ph	95	92 (99)[c]
3	**4c**	4-MeO–C_6H_4	Ph	82	93
4	**4d**	2-NO_2–C_6H_4	Ph	95	92
5	**4e**	Ph	4-F–C_6H_4	92	90 (97)[c]
6	**4f**	Ph	4-Cl–C_6H_4	91	89 (98)[c]
7	**4g**	Ph	4-Me–C_6H_4	88	90 (99)[c]
8	**4h**	Ph	2-Naph	83	89
9	**4i**	Ph	4-MeO–C_6H_4	88	60
10	**4j**	2-I–C_6H_4	4-Me–C_6H_4	94	85

[a] All reactions run in the presence of second generation catalyst **B** (10 mol %) in benzene under an atmosphere of argon.
[b] ee was determined by HPLC analysis using chiral AD-H column.
[c] ee after one time recrystallization.

similarities with antitumor agents, for example, Nutlin-2 (where the ether side chain on phenyl ring is an optimized functionality for potency of Nutlins (*cis*-imidazoline analogs) to inhibit p53-MDM2 binding)[13] and Naamidine A.[13] Additionally, the N–O linkage could be reductively cleaved to generate chiral amino alcohol functionalities, which are synthetically valuable.[14]



Scheme 3. Transformation of **5c** to **6** and **7**.

2.2. Synthesis of core structures of FR900482

[1,2]-Oxazine structures can be efficiently modified to create compounds for which utility has already been demonstrated, such as the natural antitumor antibiotics FR900482 and FR66979 and their synthetic derivatives FK973 and FK317, etc.[1a,7,15] FR900482 and its derivatives hold significant promise for replacing the structurally related and widely used antitumor drug Mitomycin C.[16] Modification of these cyclic rings in obtaining the tetracyclic core of Nakadomarin A has also been proved.[6] To prepare the analogous core structures of FR900482 as drug scaffolds, the synthetic strategy is demonstrated in Figure 1.

Controlling the regioselectivities has been of great importance in allylic substitution. Our synthetic approach includes the regioselective allylic substitution of allylated hydroxylamine **8** as a key reaction. Recently, highly regioselective allylic substitution with allylic alcohol derivatives was

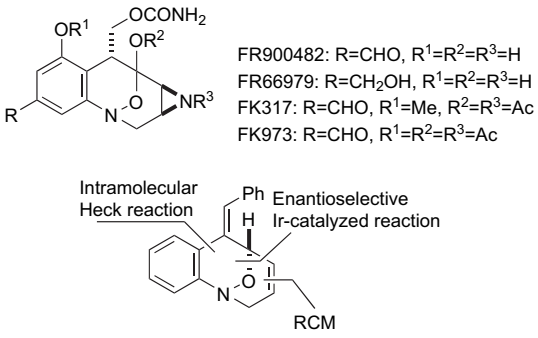
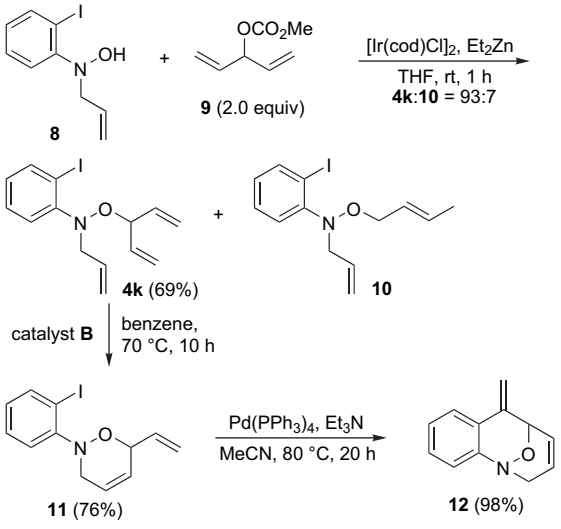


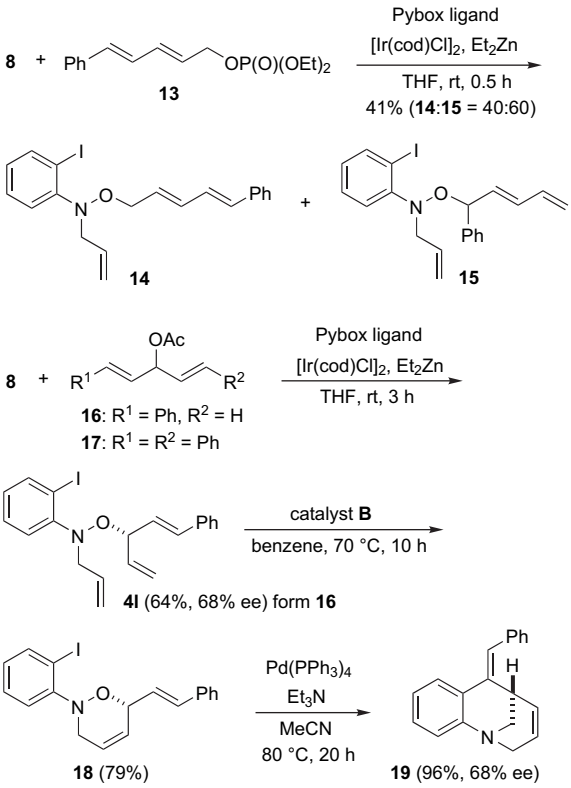
Figure 1. [1,2]-Oxazine core structures of FR900482.

achieved by using iridium catalyst.[17–19] Therefore, the iridium-catalyzed reaction with diallylic alcohol derivatives such as **9**, **13**, **16**, and **17** has been a subject of current interest. We initially investigated the regioselectivity on allylic substitution of allylated hydroxylamine **8** with carbonate **9** to access achiral [1,2]-oxazine core structures of FR900482 (Scheme 4). The allylated hydroxylamine **8** was easily prepared from 2-iodonitrobenzene via reduction of nitro group followed by selective N-allylation of resulting hydroxylamine. Based on our recent studies on allylic substitution of allylated hydroxylamine,[9,10] Et_2Zn (1.0 M solution in hexane) was employed as a base.[20] Using 5 mol % of iridium catalyst and carbonate **9** (2.0 equiv) as an electrophile gave the desired *O*-allylic derivative **4k**, after being stirred at 20 °C for 1 h. Better results have been obtained using 1.0 equiv of Et_2Zn. As expected, excellent regioselectivity was observed and ^1H NMR analysis of crude compound **4k** showed only the trace formation of linear isomer **10**. The compound **4k** was found to be unstable and immediately converted to the stable form **11** by ring-closing metathesis reaction. Finally, intramolecular Heck coupling of **11** gave the desired core structure **12** in an excellent yield, 98%. The Heck reaction has been used as a key step in the construction of the core of molecules of the FR900482 family.[15]



Scheme 4. Synthesis of achiral [1,2]-oxazine structures.

To approach the chiral core structure, we next investigated iridium-catalyzed reaction of **8** with diallylic alcohol derivatives **13**, **16**, and **17** (Scheme 5), because these electrophiles have three electrophilic centers, therefore, controlling the regioselectivity is a challenging and promising task for the successful preparation. Initial studies using linear phosphate **13** gave the undesirable regioisomers **14** and **15** without formation of the desired isomer **4l**. In our previous studies,[9,10,19] the regioselectivity and enantioselectivity were dramatically influenced by the structure of electrophiles. As an observed trend, the branched electrophiles gave the branched products with excellent regioselectivities. It is also assumed that a stable conjugated diene unit of phosphate **13** influenced the regioselectivity. Thus, we next investigated the reaction of **8** with the branched acetate **16** in the presence of 1.0 equiv of Et_2Zn as a base. As expected, the selective formation of the branched compound **4l** was observed. Therefore, the desired compound **4l** was obtained in 64% yield with 68% ee using chiral pybox ligand. However, several attempts, like changing the reaction temperature (20 to 40 °C), solvent (CH_2Cl_2), or molar ratio of chiral ligand (8–12 mol %) did not improve the enantioselectivity. In particular, lower temperatures (0 to −20 °C) led to produce racemic compound with lower product conversions. By applying the reaction conditions shown in Scheme 5, core structure **19** was obtained with 68% ee. It is noteworthy to state that RCM reaction of compound **4l** exclusively occurred at unsubstituted olefinic bonds and gave single isomer of product **18**. The *Z*-configuration of external olefinic bond of compound **19** was confirmed by NOE analysis and the absolute configuration is assumed to be *S* because the applied reaction conditions are consistent with other compounds **5a–j**, whose absolute configuration is known.[10] To confirm the effect of the branched electrophile on regioselectivity, the reaction of **8** with diphenyl acetate **17** was studied. As expected, the



Scheme 5. Synthesis of chiral [1,2]-oxazine structures.

reaction proceeded at center carbon of acetate **17** with high regioselectivity. Additionally, the RCM reaction of this product gave a 68% yield of product **18** as racemic form.

In summary, we have demonstrated a synthetic approach to obtain chiral [1,2]-oxazinone heterocycles in high yields and with excellent enantioselectivities. In addition, the utility of this reaction was illustrated in the preparation of FR900482 core structures.

3. Experimental

3.1. General

Infrared (IR) spectra were recorded on an FTIR spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-LA500 MHz spectrometer. ^{13}C NMR spectra were recorded on a JEOL JNM-LA500 MHz (at 126 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane as the internal standard. Enantiomeric ratios were determined by high-performance liquid chromatography (HPLC) on Shimadzu chromatograph. Optical rotations were measured using a JASCO DIP-360 digital polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on Yanagimoto micro melting point apparatus and are uncorrected.

3.2. Representative procedure for the acrylation

To a solution of compound **3a** (50 mg, 0.21 mmol) in CH_2Cl_2 (1.0 mL) was added acryloyl chloride (0.020 mL, 0.25 mmol) at 0 °C followed by triethylamine (0.089 mL, 0.63 mmol). Then, the solution was stirred at room temperature for 2 h, diluted with saturated $NaHCO_3$ solution, and extracted with chloroform. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude compound was purified by preparative TLC (hexane/EtOAc=5/1) to give compound **4a** (60 mg, 98%). When the reaction was scaled up, the crude product was purified by flash column chromatography on silica gel.

3.2.1. *N*-((*S*)-1-Phenylallyloxy)-*N*-benzylacrylamide (4a). A colorless oil; IR ($CHCl_3$) 3009, 1650, 1617, 1414, 1231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.59 (1H, d, J=15.5 Hz), 4.88 (1H, d, J=15.5 Hz), 5.16 (1H, d, J=7.6 Hz), 5.25–5.33 (2H, m), 5.71 (1H, dd, J=10.3, 1.9 Hz), 6.03–6.10 (1H, m), 6.44 (1H, dd, J=17.1, 1.9 Hz), 6.73 (1H, dd, J=17.1, 10.3 Hz), 7.26–7.38 (10H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 51.5, 88.5, 120.3, 126.9, 127.8, 128.0, 128.7, 128.9, 129.1, 129.5, 135.6, 136.6, 138.0, 167.8, one peak of ^{13}C NMR is missing due to overlapping; MS (FAB$^+$) m/z (%): 294 (M+H$^+$, 92), 117 (100); $[\alpha]_D^{26}$ −33.9 (c 1.1, $CHCl_3$).

3.2.2. *N*-((*S*)-1-Phenylallyloxy)-*N*-(4-(trifluoromethyl)-benzyl)acrylamide (4b). A colorless oil; IR ($CHCl_3$) 3019, 1652, 1618, 1419, 1214 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.57 (1H, d, J=15.9 Hz), 4.92 (1H, d, J=15.9 Hz), 5.17 (1H, d, J=7.4 Hz), 5.28–5.35 (2H, m), 5.75 (1H, dd, J=10.3, 1.9 Hz), 6.04–6.11 (1H, m), 6.46 (1H, dd, J=17.1, 1.9 Hz), 6.74 (1H, dd, J=17.1, 10.3 Hz), 7.26–7.37 (7H, m), 7.54 (2H, d, J=8.3 Hz); MS (EI$^+$) m/z (%): 361 (M$^+$, 25), 115 (100); $[\alpha]_D^{21}$ −48.1 (c 0.15, $CHCl_3$).

3.2.3. *N*-((*S*)-1-Phenylallyloxy)-*N*-(4-methoxybenzyl)-acrylamide (4c). A colorless oil; IR ($CHCl_3$) 3011, 1649, 1614, 1512, 1439, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.79 (3H, s), 4.55 (1H, d, J=15.3 Hz), 4.82 (1H, d, J=15.3 Hz), 5.16 (1H, d, J=7.7 Hz), 5.28–5.33 (2H, m), 5.67 (1H, dd, J=10.4, 2.2 Hz), 6.08–6.09 (1H, m), 6.40 (1H, dd, J=17.1, 2.2 Hz), 6.71 (1H, dd, J=17.1, 10.4 Hz), 6.82 (2H, d, J=8.5 Hz), 7.20 (2H, d, J=8.5 Hz), 7.28–7.38 (5H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 50.9, 55.4, 88.5, 114.1, 120.3, 127.1, 128.0, 128.9 (2C), 129.1, 129.3, 130.2, 135.7, 138.2, 159.3, 167.8; MS (FAB$^+$) m/z (%): 324 (M+H$^+$, 65), 121 (100); $[\alpha]_D^{28}$ −17.7 (c 1.2, $CHCl_3$).

3.2.4. *N*-((*S*)-1-Phenylallyloxy)-*N*-(2-nitrobenzyl)acrylamide (4d). A colorless oil; IR ($CHCl_3$) 3012, 1654, 1618, 1527, 1421, 1354, 1243 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.12 (1H, d, J=17.7 Hz), 5.05 (1H, d, J=17.7 Hz), 5.21 (1H, d, J=7.7 Hz), 5.27–5.36 (2H, m), 5.79 (1H, dd, J=10.4, 1.9 Hz), 6.05–6.12 (1H, m), 6.47 (1H, dd, J=17.1, 1.9 Hz), 6.79 (1H, dd, J=17.1, 10.4 Hz), 7.26–8.00 (9H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 48.5, 88.7, 120.2, 124.7, 125.8, 127.3, 127.9, 128.5, 128.8, 129.5, 129.9, 131.6, 133.3, 134.8, 137.1, 148.5, 167.6; MS (FAB$^+$) m/z (%): 339 (M+H$^+$, 68), 117 (100); $[\alpha]_D^{18}$ −42.3 (c 0.7, $CHCl_3$).

3.2.5. *N*-((*S*)-1-(4-Fluorophenyl)allyloxy)-*N*-benzylacrylamide (4e). A colorless oil; IR ($CHCl_3$) 3019, 1649, 1618, 1510, 1423, 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.63 (1H, d, J=15.6 Hz), 4.91 (1H, d, J=15.6 Hz), 5.15 (1H, d, J=7.4 Hz), 5.24–5.34 (2H, m), 5.71 (1H, dd, J=10.4, 1.9 Hz), 6.01–6.07 (1H, m), 6.43 (1H, dd, J=17.1, 1.9 Hz), 6.69 (1H, dd, J=17.1, 10.4 Hz), 7.02–7.32 (9H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 51.7, 87.6, 116.0 (d, J=22 Hz), 120.4, 126.8, 127.9, 128.7, 128.8, 129.6, 129.9 (d, J=8 Hz), 134.0, 135.5, 136.6, 164.2 (d, J=248 Hz), 167.9; MS (EI$^+$) m/z (%): 311 (M$^+$, 25), 91 (100); $[\alpha]_D^{25}$ −34.4 (c 1.0, $CHCl_3$).

3.2.6. *N*-((*S*)-1-(4-Chlorophenyl)allyloxy)-*N*-benzylacrylamide (4f). A colorless oil; IR ($CHCl_3$) 3011, 1652, 1618, 1492, 1412, 1232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.66 (1H, d, J=15.6 Hz), 4.88 (1H, d, J=15.6 Hz), 5.14 (1H, d, J=7.4 Hz), 5.24–5.34 (2H, m), 5.72 (1H, dd, J=10.3, 1.9 Hz), 5.97–6.04 (1H, m), 6.44 (1H, dd, J=16.9, 1.9 Hz), 6.69 (1H, dd, J=16.9, 10.3 Hz), 7.19–7.32 (9H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 51.3, 87.2, 120.2, 126.3, 127.4, 128.2, 128.3, 128.6, 128.8, 129.2, 134.5, 134.8, 136.1 (2C), 167.4; MS (EI$^+$) m/z (%): 327 (M$^+$, 5), 55 (100); $[\alpha]_D^{21}$ −87.0 (c 0.7, $CHCl_3$).

3.2.7. *N*-((*S*)-1-(4-Methylphenyl)allyloxy)-*N*-benzylacrylamide (4g). A colorless oil; IR ($CHCl_3$) 3012, 1649, 1617, 1436, 1414, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.35 (3H, s), 4.60 (1H, d, J=15.3 Hz), 4.88 (1H, d, J=15.3 Hz), 5.14 (1H, d, J=7.4 Hz), 5.23–5.31 (2H, m), 5.70 (1H, dd, J=10.3, 1.9 Hz), 6.03–6.11 (1H, m), 6.42 (1H, dd, J=16.9, 1.9 Hz), 6.73 (1H, dd, J=16.9, 10.3 Hz), 7.15–7.31 (9H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 20.9, 51.5, 88.0, 119.5, 126.5, 127.3, 127.5, 128.2, 128.9, 129.1,

134.6, 135.3, 136.2, 138.5, 167.4, one peak of ^{13}C NMR is missing due to overlapping; MS (FAB$^+$) *m/z* (%): 308 (M+H$^+$, 65), 131 (100); $[\alpha]_D^{26}$ −33.5 (*c* 0.7, $CHCl_3$).

3.2.8. *N*-((*S*)-1-(Naphthalen-2-yl)allyloxy)-*N*-benzylacrylamide (4h). A colorless oil; IR ($CHCl_3$) 3011, 1650, 1618, 1496, 1413, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.62 (1H, d, *J*=15.6 Hz), 4.89 (1H, d, *J*=15.6 Hz), 5.30–5.33 (2H, m), 5.71 (1H, dd, *J*=10.4, 1.9 Hz), 5.82 (1H, d, *J*=7.1 Hz), 6.21–6.28 (1H, m), 6.44 (1H, dd, *J*=17.4, 1.9 Hz), 6.79 (1H, dd, *J*=17.4, 10.4 Hz), 7.14–7.94 (12H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 51.4, 87.4, 120.2, 125.5, 126.2, 126.4, 126.5, 127.7, 128.6, 128.7, 129.1, 129.2, 129.7, 129.8, 130.4, 134.3, 134.4, 136.7, 167.4, two peaks of ^{13}C NMR are missing due to overlapping; MS (FAB$^+$) *m/z* (%): 344 (M+H$^+$, 75), 167 (100); $[\alpha]_D^{28}$ −47.0 (*c* 0.7, $CHCl_3$).

3.2.9. *N*-((*S*)-1-(4-Methoxyphenyl)allyloxy)-*N*-benzylacrylamide (4i). A colorless oil; IR ($CHCl_3$) 3012, 1649, 1614, 1512, 1438, 1414, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.81 (3H, s), 4.60 (1H, d, *J*=15.3 Hz), 4.88 (1H, d, *J*=15.3 Hz), 5.13 (1H, d, *J*=7.4 Hz), 5.23–5.31 (2H, m), 5.69 (1H, dd, *J*=10.4, 2.2 Hz), 6.03–6.11 (1H, m), 6.41 (1H, dd, *J*=17.1, 2.2 Hz), 6.71 (1H, dd, *J*=17.1, 10.4 Hz), 6.86–6.89 (2H, m), 7.21–7.31 (7H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 51.5, 55.5, 88.1, 114.3, 119.8, 127.0, 127.8, 128.7, 129.3, 129.5, 130.1, 135.7, 136.7, 160.4, 167.8, one peak of ^{13}C NMR is missing due to overlapping; MS (FAB$^+$) *m/z* (%): 324 (M+H$^+$, 65), 121 (100); $[\alpha]_D^{28}$ −17.7 (*c* 1.2, $CHCl_3$).

3.2.10. *N*-((*S*)-1-(4-Methylphenyl)allyloxy)-*N*-(2-iodobenzyl)acrylamide (4j). A colorless oil; IR ($CHCl_3$) 3011, 1650, 1617, 1428, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.33 (3H, s), 4.78 (1H, d, *J*=16.4 Hz), 4.94 (1H, d, *J*=16.4 Hz), 5.16 (1H, d, *J*=7.6 Hz), 5.25–5.32 (2H, m), 5.69 (1H, dd, *J*=10.4, 1.9 Hz), 6.04–6.12 (1H, m), 6.44 (1H, dd, *J*=17.1, 1.9 Hz), 6.78 (1H, dd, *J*=17.1, 10.4 Hz), 6.93–7.81 (9H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.4, 56.0, 88.5, 98.4, 120.5, 126.8, 128.0, 128.7, 129.2, 129.3, 129.7, 129.8, 134.8, 135.6, 138.5, 139.1, 139.6, 167.4; MS (FAB$^+$) *m/z* (%): 434 (M+H$^+$, 75), 131 (100); $[\alpha]_D^{29}$ −15.5 (*c* 0.4, $CHCl_3$).

3.3. Representative procedure for the ring-closing metathesis (RCM) reaction

A solution of compound **4a** (100 mg, 0.34 mmol) and Grubbs' second generation catalyst **B** (28 mg, 0.034 mmol) in benzene (2.0 mL) was stirred at 70 °C for 10 h under an atmosphere of argon. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (hexane/EtOAc=5/1) to give compound **5a** (83 mg, 92%).

3.3.1. 2-Benzyl-6-(*S*)-phenyl-2*H*-1,2-oxazin-3(6*H*)-one (5a). A colorless crystal; mp 100–102 °C (*n*-hexane); IR ($CHCl_3$) 3019, 1673, 1638, 1426, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.52 (1H, d, *J*=15.5 Hz), 4.88 (1H, d, *J*=15.5 Hz), 5.51 (1H, br d, *J*=3.1 Hz), 6.21 (1H, d, *J*=10.1 Hz), 6.74 (1H, dd, *J*=10.1, 3.1 Hz), 7.21–7.38 (10H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 50.7, 78.9, 123.3, 127.7, 128.5, 128.6, 129.0, 129.6, 135.5, 136.2, 141.3, 163.9, one peak of ^{13}C NMR is missing due to overlapping; MS (EI$^+$) *m/z* (%): 265 (M$^+$, 12), 144 (100). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28, found: C, 76.70; H, 5.70; N, 5.25; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 254 nm) t_R (*S*)=19.7 min, t_R (*R*)=23.8 min. A sample of 99% ee (*S*) by HPLC analysis gave $[\alpha]_D^{26}$ −7.7 (*c* 1.0, $CHCl_3$).

3.3.2. 2-((4-Trifluoromethyl)benzyl)-6-(*S*)-phenyl-2*H*-1,2-oxazin-3(6*H*)-one (5b). A colorless crystal; mp 112–115 °C (*n*-hexane); IR ($CHCl_3$) 3019, 1671, 1613, 1325, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.68 (1H, d, *J*=15.3 Hz), 4.74 (1H, d, *J*=15.3 Hz), 5.49 (1H, d, *J*=1.9 Hz), 6.24 (1H, d, *J*=10.1 Hz), 6.76 (1H, dd, *J*=10.1, 1.9 Hz), 7.22–7.30 (5H, m), 7.33 (2H, d, *J*=10.0 Hz), 7.42 (2H, d, *J*=10.0 Hz); MS (EI$^+$) *m/z* (%): 333 (M$^+$, 27), 145 (100). Anal. Calcd for $C_{18}H_{14}F_3NO_2$: C, 64.86; H, 4.23; N, 4.20, found: C, 64.76; H, 4.41; N, 4.16; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 254 nm) t_R (*S*)=17.6 min, t_R (*R*)=25.8 min. A sample of 99% ee (*S*) by HPLC analysis gave $[\alpha]_D^{26}$ −70.6 (*c* 0.5, $CHCl_3$).

3.3.3. 2-(4-Methoxybenzyl)-6-(*S*)-phenyl-2*H*-1,2-oxazin-3(6*H*)-one (5c). A colorless oil; IR ($CHCl_3$) 3019, 1668, 1610, 1513, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (3H, s), 4.46 (1H, d, *J*=15.2 Hz), 4.78 (1H, d, *J*=15.2 Hz), 5.47 (1H, d, *J*=2.1 Hz), 6.19 (1H, d, *J*=10.1 Hz), 6.71 (1H, dd, *J*=10.0, 2.1 Hz), 6.77 (2H, d, *J*=8.5 Hz), 7.13 (2H, d, *J*=8.5 Hz), 7.26–7.35 (5H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 49.5, 54.9, 78.3, 113.5, 122.8, 127.8, 128.0, 128.4, 129.0, 129.5, 135.0, 140.6, 158.8, 163.1; MS (EI$^+$) *m/z* (%): 295 (M$^+$, 4), 144 (100); HRMS calcd for $C_{18}H_{17}NO_3$ (M$^+$): 295.1208, found: 295.1205; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 254 nm) t_R (*S*)=29.1 min, t_R (*R*)=33.9 min. A sample of 93% ee (*S*) by HPLC analysis gave $[\alpha]_D^{26}$ −102 (*c* 0.6, $CHCl_3$).

3.3.4. 2-(2-Nitrobenzyl)-6-(*S*)-phenyl-2*H*-1,2-oxazin-3(6*H*)-one (5d). A colorless oil; IR ($CHCl_3$) 3013, 1674, 1613, 1529, 1356, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.07 (1H, d, *J*=17.1 Hz), 5.17 (1H, d, *J*=17.1 Hz), 5.58 (1H, d, *J*=1.8 Hz), 6.27 (1H, d, *J*=10.1 Hz), 6.84 (1H, dd, *J*=10.0, 1.8 Hz), 7.26–7.44 (8H, m), 7.95 (1H, d, *J*=7.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 48.5, 78.8, 123.1, 125.1, 128.4, 128.7, 129.1, 129.8, 129.9, 131.6, 133.6, 135.1, 141.8, 148.7, 164.7; MS (FAB$^+$) *m/z* (%): 311 (M+H$^+$, 100); HRMS calcd for $C_{17}H_{15}N_2O_4$ (M+H$^+$): 311.0954, found: 311.1036; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 254 nm) t_R (*S*)=34.3 min, t_R (*R*)=39.5 min. A sample of 92% ee (*S*) by HPLC analysis gave $[\alpha]_D^{26}$ +52.2 (*c* 2.6, $CHCl_3$).

3.3.5. 2-Benzyl-6-(*S*)-(4-fluorophenyl)-2*H*-1,2-oxazin-3(6*H*)-one (5e). A colorless crystal; mp 75–78 °C (*n*-hexane); IR ($CHCl_3$) 3019, 1672, 1606, 1512, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.60 (1H, d, *J*=15.2 Hz), 4.76 (1H, d, *J*=15.2 Hz), 5.46 (1H, br d, *J*=5.0 Hz), 6.22 (1H, d, *J*=10.0 Hz), 6.71 (1H, dd, *J*=10.0, 5.0 Hz), 6.97 (2H, d, *J*=10.0 Hz), 7.16–7.26 (7H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 50.6, 78.0, 116.0 (d, *J*=22 Hz), 123.6, 127.8, 128.6, 128.7, 130.6 (d, *J*=7 Hz), 131.2, 136.0, 140.7,

162.6 (d, J=248 Hz), 163.6; MS (EI$^+$) m/z (%): 283 (M$^+$, 65), 163 (100). Anal. Calcd for $C_{17}H_{14}FNO_2$: C, 72.07; H, 4.98; N, 4.94, found: C, 71.81; H, 5.12; N, 4.88; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 254 nm) t_R (*S*)=22.1 min, t_R (*R*)=26.3 min. A sample of 97% ee (*S*) by HPLC analysis gave $[\alpha]_D^{26}$ −96.8 (*c* 0.5, $CHCl_3$).

3.3.6. 2-Benzyl-6-(*S*)-(4-chlorophenyl)-2*H*-1,2-oxazin-3(6*H*)-one (5f). A colorless crystal; mp 71–74 °C (*n*-hexane); IR ($CHCl_3$) 3012, 1671, 1611, 1492, 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.64 (1H, d, J=15.2 Hz), 4.70 (1H, d, J=15.2 Hz), 5.45 (1H, dd, J=3.4, 1.6 Hz), 6.23 (1H, dd, J=9.8, 1.6 Hz), 6.70 (1H, dd, J=9.8, 3.4 Hz), 7.14–7.26 (9H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 50.3, 77.6, 123.4 (2C), 127.5, 128.5, 128.9, 129.6, 133.6, 135.4, 135.7, 140.2, 163.3; MS (EI$^+$) m/z (%): 299 (M$^+$, 12), 178 (100); HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 254 nm) t_R (*S*)=21.2 min, t_R (*R*)=25.8 min. A sample of 98% ee (*S*) by HPLC analysis gave $[\alpha]_D^{25}$ −120 (*c* 1.9, $CHCl_3$).

3.3.7. 2-Benzyl-6-(*S*)-(4-methylphenyl)-2*H*-1,2-oxazin-3(6*H*)-one (5g). A colorless crystal; mp 80–83 °C (*n*-hexane); IR ($CHCl_3$) 3019, 1668, 1608, 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.35 (3H, s), 4.50 (1H, d, J=15.2 Hz), 4.86 (1H, d, J=15.2 Hz), 5.46 (1H, br dd, J=3.1, 1.9 Hz), 6.20 (1H, dd, J=10.1, 1.9 Hz), 6.72 (1H, dd, J=10.1, 3.1 Hz), 7.11–7.26 (9H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.4, 50.1, 78.3, 122.7, 122.8, 127.1, 128.1 (2C), 129.2, 131.9, 135.8, 139.2, 141.4, 163.3; MS (EI$^+$) m/z (%): 279 (M$^+$, 15), 159 (100); HRMS calcd for $C_{18}H_{17}NO_2$ (M$^+$): 279.1259, found: 279.1262; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 254 nm) t_R (*S*)=19.2 min, t_R (*R*)=23.1 min. A sample of 99% ee (*S*) by HPLC analysis gave $[\alpha]_D^{26}$ −134 (*c* 0.1, $CHCl_3$).

3.3.8. 2-Benzyl-6-(*S*)-(naphthalen-2-yl)-2*H*-1,2-oxazin-3(6*H*)-one (5h). A colorless oil; IR ($CHCl_3$) 3012, 1668, 1608, 1212 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.42 (1H, d, J=15.1 Hz), 4.82 (1H, d, J=15.1 Hz), 6.16 (1H, dd, J=3.4, 1.8 Hz), 6.33 (1H, dd, J=10.1, 1.8 Hz), 6.89 (1H, dd, J=10.1, 3.4 Hz), 7.05–7.83 (12H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 49.9, 75.4, 123.2, 123.5, 124.5, 125.6, 126.4 (2C), 127.1, 127.8, 128.1, 128.5, 130.1 (2C), 131.3, 133.7, 135.5, 140.9, 163.2; MS (EI$^+$) m/z (%): 315 (M$^+$, 5), 194 (100); HRMS calcd for $C_{21}H_{17}NO_2$ (M$^+$): 315.1259, found: 315.1253; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 254 nm) t_R (*S*)=25.8 min, t_R (*R*)=29.1 min. A sample of 89% ee (*S*) by HPLC analysis gave $[\alpha]_D^{29}$ +112 (*c* 3.0, $CHCl_3$).

3.3.9. 2-Benzyl-6-(*S*)-(4-methoxyphenyl)-2*H*-1,2-oxazin-3(6*H*)-one (5i). A colorless oil; IR ($CHCl_3$) 3019, 1673, 1609, 1258 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.80 (3H, s), 4.51 (1H, d, J=15.2 Hz), 4.82 (1H, d, J=15.2 Hz), 5.43 (1H, br dd, J=3.2, 1.9 Hz), 6.21 (1H, dd, J=10.1, 1.9 Hz), 6.71 (1H, dd, J=10.1, 3.2 Hz), 6.82 (1H, dd, J=6.7, 2.1 Hz), 7.17–7.26 (8H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 50.6, 55.5, 78.5, 114.2, 123.3, 127.3, 127.7, 128.6 (2C), 130.2, 136.2, 141.3, 160.8, 163.9; MS (EI$^+$) m/z (%): 295 (M$^+$, 5), 174 (100); HRMS calcd for $C_{21}H_{17}NO_2$ (M$^+$): 295.1208, found: 295.1204; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=90/10, 0.5 mL/min, 254 nm) t_R (*S*)=28.7 min, t_R (*R*)=35.4 min. A sample of 60% ee (*S*) by HPLC analysis gave $[\alpha]_D^{20}$ −9.2 (*c* 0.1, $CHCl_3$).

3.3.10. 2-(2-Iodobenzyl)-6-(*S*)-(4-methylphenyl)-2*H*-1,2-oxazin-3(6*H*)-one (5j). A colorless oil; IR ($CHCl_3$) 3018, 1668, 1611, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.33 (3H, s), 4.65 (1H, d, J=16.2 Hz), 4.84 (1H, d, J=16.2 Hz), 5.51 (1H, br dd, J=3.1, 1.7 Hz), 6.24 (1H, dd, J=10.1, 1.7 Hz), 6.77 (1H, dd, J=10.1, 3.1 Hz), 6.88–7.16 (7H, m), 7.73 (1H, d, J=7.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.4, 55.4, 78.6, 98.8, 123.1, 128.3, 128.6, 129.2, 129.5, 129.6, 132.1, 138.1, 139.6, 141.7, 164.1; MS (FAB$^+$) m/z (%): 406 (M+H$^+$, 70), 296 (100); HRMS calcd for $C_{18}H_{17}INO_2$ (M+H$^+$): 406.0226, found: 406.0316; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=95/5, 0.5 mL/min, 254 nm) t_R (*S*)=30.5 min, t_R (*R*)=33.1 min. A sample of 85% ee (*S*) by HPLC analysis gave $[\alpha]_D^{26}$ −61.5 (*c* 0.4, $CHCl_3$).

3.4. Preparation of (4*R*,5*S*,6*R*)-4,5-dihydroxy-2-(4-methoxybenzyl)-6-phenyl[1,2]oxazin-3-one (6)

To a solution of compound **5c** (70 mg, 0.24 mmol) in THF/H_2O (6.0 mL, 1/1, v/v) were added $KBrO_3$ (100 mg, 0.6 mmol) and catalytic amount of OsO_4 at room temperature. Then the resultant solution was stirred at 45 °C for 10 h. The solvent was removed under reduced pressure, followed by extraction of the residue with chloroform, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resultant crude product was purified by column chromatography on silica gel ($CHCl_3$/MeOH=10/1) to give major isomer **6** (50 mg, 64%) and minor isomer (10 mg, 12%). *Major isomer* ***6***: a colorless oil; IR ($CHCl_3$) 3565, 3013, 1674, 1606, 1513, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.01 (1H, br s), 3.81 (3H, s), 4.05 (1H, br s), 4.55 (1H, d, J=15.3 Hz), 4.58 (1H, dd, J=4.6, 3.7 Hz), 4.59 (1H, d, J=3.7 Hz), 4.63 (1H, d, J=4.6 Hz), 5.04 (1H, d, J=15.3 Hz), 6.88 (2H, d, J=8.9 Hz), 7.23–7.36 (7H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 50.27, 55.48, 68.87, 76.48, 89.67, 114.34, 126.97, 127.72, 129.10, 129.30, 130.52, 136.73, 159.85, 169.75; MS (FAB$^+$) m/z (%): 330 (M+H$^+$, 95), 121 (100); $[\alpha]_D^{21}$ −71.0 (*c* 0.5, $CHCl_3$). *Minor isomer (diastereomer)*: a colorless oil; IR ($CHCl_3$) 3562, 3015, 1674, 1604, 1510, 1225 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.61 (1H, br s), 3.79 (3H, s), 4.01 (1H, br s), 4.54 (1H, d, J=3.4 Hz), 4.56 (1H, dd, J=3.7, 3.4 Hz), 4.59 (1H, d, J=15.3 Hz), 5.05 (1H, d, J=15.3 Hz), 5.20 (1H, d, J=3.7 Hz), 6.84 (2H, d, J=8.5 Hz), 7.26–7.36 (7H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 50.6, 55.0, 68.8, 69.6, 82.1, 113.9, 127.1, 127.2, 128.2, 128.4, 129.7, 134.7, 159.2, 169.3; MS (FAB$^+$) m/z (%): 330 (M+H$^+$, 92), 121 (100); $[\alpha]_D^{21}$ −38.0 (*c* 0.1, $CHCl_3$).

3.5. Preparation of compound 7

The major isomer **6** (40 mg, 0.13 mmol) was dissolved in acetone (1.0 mL) followed by the addition of benzoyl chloride (0.060 mL, 0.52 mmol) and triethylamine (0.50 mL) at −10 °C. The resultant solution was stirred at room temperature for 10 h and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc=5/1) to give compound **7**

(50 mg, 77%) as a colorless oil; IR ($CHCl_3$) 3030, 1726, 1701, 1607, 1512, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.70 (3H, s), 4.41 (1H, d, J=11.9 Hz), 4.73 (1H, d, J=2.1 Hz), 5.29 (1H, d, J=11.9 Hz), 5.99 (1H, dd, J=3.9, 2.1 Hz), 6.22 (1H, d, J=3.9 Hz), 6.71 (2H, d, J=8.5 Hz), 7.25–8.06 (17H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 50.2, 55.4, 69.5, 78.2, 88.2, 114.3, 127.1, 127.4, 128.7, 128.7, 128.9, 129.2, 129.3, 129.8, 130.3, 130.4, 130.6, 133.8, 134.0, 135.2, 159.8, 165.2, 165.8 (2C); MS (FAB^+) m/z (%): 538 ($M+H^+$, 95), 121 (100); HRMS calcd for $C_{32}H_{28}NO_7$ ($M+H^+$): 538.1788, found: 538.1860; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=10/90, 0.5 mL/min, 254 nm) t_R (*S*)=26.4 min, t_R (*R*)=30.2 min. A sample of 93% ee (*S*) by HPLC analysis gave $[\alpha]_D^{26}$ −119 (*c* 2.4, $CHCl_3$).

3.6. Preparation of *N*-allyl-*N*-hydroxy-2-iodobenzenamine (8)

A mixture of 2-iodohydroxylamine[21] (0.30 g, 1.3 mmol), K_2CO_3 (0.35 g, 2.5 mmol), and allyl bromide (0.12 mL, 1.4 mmol) in *N*,*N*-dimethylacetamide (5.0 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with H_2O. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc=5/1) to give compound **8** (0.20 g, 57%) as a pale yellow oil; IR ($CHCl_3$) 3566, 1579, 1461, 1437, 1334, 1018 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.50 (2H, d, J=6.1 Hz), 5.20–5.35 (2H, m), 6.04–6.10 (2H, m), 6.84–7.79 (4H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 63.2, 92.6, 118.7, 121.1, 126.7, 128.8, 133.4, 139.0, 153.2; MS (FAB^+) m/z (%): 276 ($M+H^+$, 100).

3.7. Iridium-catalyzed reaction

3.7.1. Reaction of hydroxylamine 8 with carbonate 9. To a solution of hydroxylamine **8** (140 mg, 0.52 mmol) in THF (2.0 mL) was added Et_2Zn (1.0 M solution in hexane, 0.52 mL, 0.52 mmol) under argon atmosphere at 20 °C. After being stirred at the same temperature for 10–20 min, a solution of carbonate **9**[22] (200 mg, 1.0 mmol) and $[Ir(cod)Cl]_2$ (18 mg, 0.026 mmol) in THF (1.0 mL) was added to the reaction mixture at 20 °C. After being stirred for 1 h, the reaction mixture was diluted with saturated aqueous potassium sodium (+)-tartrate and then extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash short column chromatography on silica gel (hexane/EtOAc=1/1) to give compound **4k** (120 mg, 69%) as a colorless oil, which was immediately subjected to the next RCM.

3.7.2. Reaction of hydroxylamine 8 with acetate 16. To a solution of hydroxylamine **8** (50 mg, 0.19 mmol) in THF (1.0 mL) was added Et_2Zn (1.0 M solution in hexane, 0.19 mL, 0.19 mmol) under argon atmosphere at 20 °C. After being stirred at the same temperature for 10–20 min, a solution of acetate **16**[22] (74 mg, 0.37 mmol) and $[Ir(cod)Cl]_2$ (7.0 mg, 0.0095 mmol) in THF (1.0 mL) was added to the reaction mixture at 20 °C. After being stirred for 3 h, the reaction mixture was diluted with saturated aqueous potassium sodium (+)-tartrate and then extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash short column chromatography on silica gel (hexane/EtOAc=1/1) to give compound **4l** (48 mg, 64%) as a colorless oil, which was immediately subjected to the next RCM.

3.8. Ring-closing metathesis reaction of 4k and 4l

Conversion of **4k** and **4l** to **11** and **18** was performed according to the representative procedure for RCM reaction of **4a**. *Compound **11***: a pale yellow oil; IR ($CHCl_3$) 3010, 1618, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.67–3.71 (2H, m), 5.21–5.26 (2H, m), 5.37 (1H, dd, J=17.4, 1.5 Hz), 5.87–6.01 (3H, m), 6.87–7.84 (4H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 53.1, 79.4, 93.9, 117.8, 120.7, 123.6, 127.1, 128.1, 128.9, 135.5, 139.3, 151.1; MS (EI^+) m/z (%): 313 (M^+, 6), 130 (100). *Compound **18***: pale yellow oil; IR ($CHCl_3$) 3015, 1635, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.62–3.80 (2H, m), 5.36 (1H, m), 5.95 (1H, dd, J=10.1, 1.9 Hz), 6.05–6.06 (1H, m), 6.36 (1H, dd, J=16.2, 7.4 Hz), 6.67 (1H, d, J=16.2 Hz), 6.87–6.92 (1H, m), 7.22–7.85 (9H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 53.6, 79.7, 94.7, 121.0, 121.4, 124.4, 127.0, 127.1, 127.7, 128.2, 128.8, 129.5, 133.6, 136.9, 139.8, 151.6; MS (EI^+) m/z (%): 389 (M^+, 10), 346 (100); $[\alpha]_D^{21}$ −106 (*c* 1.1, $CHCl_3$).

3.9. Representative procedure for the Heck reaction

To a solution of compound **11** (7.0 mg, 0.023 mmol) in CH_3CN (1 mL) were added triethylamine (0.010 mL, 0.069 mmol) and $Pd(PPh_3)_4$ (5.2 mg, 0.0045 mmol). The reaction mixture was refluxed under argon atmosphere for 20 h, after which TLC indicated complete consumption of the starting material. The reaction mixture was cooled to room temperature and directly absorbed onto the preparative TLC plate and eluted using hexane/EtOAc (10/1) as an eluent to give compound **12** (4.5 mg, 98%).

3.9.1. Achiral core structure of FR900482 (12). A pale yellow oil; IR ($CHCl_3$) 3010, 1638, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.50 (1H, dd, J=17.7, 4.9 Hz), 4.48 (1H, dd, J=17.7, 1.9 Hz), 4.80 (1H, d, J=1.9 Hz), 5.04 (1H, s), 5.61 (1H, s), 5.74–5.76 (1H, m), 5.93–5.95 (1H, m), 6.91–7.67 (4H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 54.6, 71.6, 106.0, 120.4, 121.0, 121.4, 123.8, 127.1, 128.6, 137.8, 146.8, one peak of ^{13}C NMR is missing due to overlapping; MS (EI^+) m/z (%): 185 (M^+, 100); HRMS calcd for $C_{12}H_{11}NO$ (M^+): 185.0841, found: 185.0835.

3.9.2. Chiral core structure of FR900482 (19). A pale yellow oil; IR ($CHCl_3$) 3012, 1628, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.54 (1H, dd, J=17.7, 2.1 Hz), 4.48 (1H, dd, J=17.7, 2.1 Hz), 5.23 (1H, s), 5.89–5.92 (1H, m), 6.15–6.17 (1H, m), 7.11–7.42 (7H, m), 7.69 (1H, d, J=7.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 55.5, 66.1, 120.8, 122.3, 123.0, 123.1, 124.2, 124.4, 126.8, 127.9, 128.6, 128.8, 129.1, 132.2, 136.4, 147.4; MS (EI^+) m/z (%): 261 (M^+, 70), 260 (100); HRMS calcd for $C_{18}H_{15}NO$ (M^+): 261.1154, found: 261.1159; HPLC (chiral AD-H column, *n*-hexane/*i*-PrOH=95/5, 0.5 mL/min, 254 nm)

t_R (*S*)=12.4 min, t_R (*R*)=14.4 min. A sample of 68% ee (*S*) by HPLC analysis gave $[\alpha]_D^{26}$ −72.5 (*c* 0.3, $CHCl_3$).

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