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Synthesis of chiral oxime ethers based on regio- and enantioselective allylic substitution catalyzed by iridium–pybox complex

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ABSTRACT

The oxygen atom of oximes acts as a reactive nucleophile in the iridium-catalyzed allylic substitution of unsymmetrical substrates to give the branched oxime ethers. Among several chiral ligands evaluated, the iridium complex of pybox ligand having phenyl group catalyzed the allylic substitution of phosphates with high activity to form the branched oxime ethers with good enantioselectivities.

1. Introduction

The transition metal-catalyzed allylic substitutions have been developed as a fundamentally important reaction.[1] The allylic substitutions of 1,3-symmetrical substrates have been widely studied including enantioselective versions. In contrast, the allylic substitutions of unsymmetrical substrates are challenging, since both regio- and enantioselectivities should be controlled to give the desired chiral products. Although highly regio- and enantioselective reactions with carbon nucleophiles have been achieved,[1] little success was achieved with heteroatom nucleophiles. Palladium complexes are general and versatile catalysts. However, the palladium-catalyzed allylic substitutions of unsymmetrical substrates with heteroatom nucleophiles generally give the linear products.[1,2] Recent studies show that rhodium,[3] iridium,[4] ruthenium,[5a–d] iron,[5e] and nickel[5f–i] complexes serve as catalysts for allylic amination. The regioselectivities in the reaction using these catalysts are quite different from those of palladium-catalyzed reaction. Among them, the allylic amination and etherification using chiral iridium complex have been a subject of current interest.[6] The control of regio- and enantioselectivities in iridium-catalyzed reaction with heteroatom nucleophiles was mainly studied by Hartwig[7] and Helmchen,[8] respectively.[9–13] Recently, we also reported that the iridium complex of pybox catalyzed the allylic substitution to form the branched products with good enantioselectivity.[14,15]

In comparison with allylic amination, the allylic etherification has received much less attention due to the poor nucleophilic property of the oxygen atom nucleophiles.[16] Therefore, *O*-allylic substitution had been largely limited to carboxylate and phenol nucleophiles,[17,18] except for the intramolecular reactions. We have recently reported the utility of oximes as a soft oxygen nucleophile in transition metal-catalyzed allylic substitution[19,20] and the application into iridium-catalyzed asymmetric reaction.[14a] In this paper, we describe full details of the regio- and enantioselective *O*-allylic substitution with oximes by using an iridium–pybox complex.

2. Results and discussion

2.1. Regio- and enantioselectivities in allylic substitution of oximes

Oximes are attractive nucleophiles for allylic substitution, since they have oxygen and nitrogen atoms as nucleophilic sites. Recently, we have shown the viability of oximes as a nucleophile in allylic substitutions and the selective synthesis of oxime ethers and nitrones by changing the palladium catalysts.[19] Additionally, the selective formation of the branched oxime ethers **3** from

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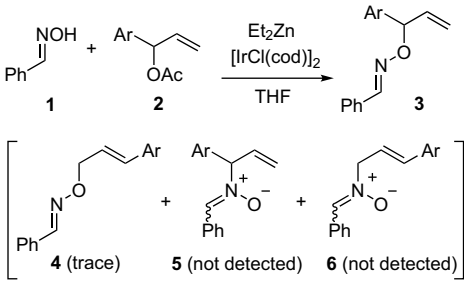


Scheme 1. Selective formation of the branched oxime ethers **3**.

unsymmetrical substrates **2** was achieved by using $[IrCl(cod)]_2$ as a catalyst and 0.5 equiv of Et_2Zn as a base (Scheme 1).[21]

Based on these results, we initially investigated the enantioselective iridium-catalyzed *O*-allylic substitution with oxime **1** under basic conditions (Scheme 2). As a preliminary experiment, the phosphate **8a** was employed to prove the efficiency of chiral ligands, since it has shown excellent reactivity toward carbon nucleophile in our previous iridium-catalyzed allylic alkylation.[15] At first, the reactions of **8a** with oxime **1** were evaluated in CH_2Cl_2 in the presence of Et_2Zn.[22] We have found that the iridium complex of pybox ligands catalyzed the allylic substitution of phosphate **8a** with good catalytic activity. In general, the utility of C_2-symmetric pybox ligand in transition metal-catalyzed allylic substitution has not wildly investigated compared with that of phosphorus ligands.[23] Table 1 outlines the optimization of the pybox ligands **7A**–**J**.[24] In the absence of the pybox ligands, the reaction of phosphate **8a** with **1** did not proceed effectively;[25] thus, it is noteworthy that the pybox ligands enhance the catalytic activity of iridium.

To a solution of oxime **1** in CH_2Cl_2 was added a 1.0 M solution of Et_2Zn in hexane (0.5 equiv) at 20 °C. After being stirred at 20 °C for 10 min, a solution of the phosphate **8a**, $[IrCl(cod)]_2$ (4 mol %) and chiral ligand (8 mol %) in CH_2Cl_2, was added to the reaction mixture at the temperature indicated in Table 1. The iridium complex of pybox **7A** having benzyl group catalyzed the reaction to form the branched oxime ether **3a** with 43% ee and the linear product **4a** in 67:33 ratio, after being stirred at 20 °C for 2 h (entry 1). Although the branched oxime ether **3a** was obtained with 63% ee by using pybox **7B** having isopropyl group (entry 2), the bulky ligand **7C** having *tert*-butyl group was less effective (entry 3). The complex of iridium and ligand **7D** having phenyl group was a highly active catalyst for the present reaction (entry 4). In this case, the branched

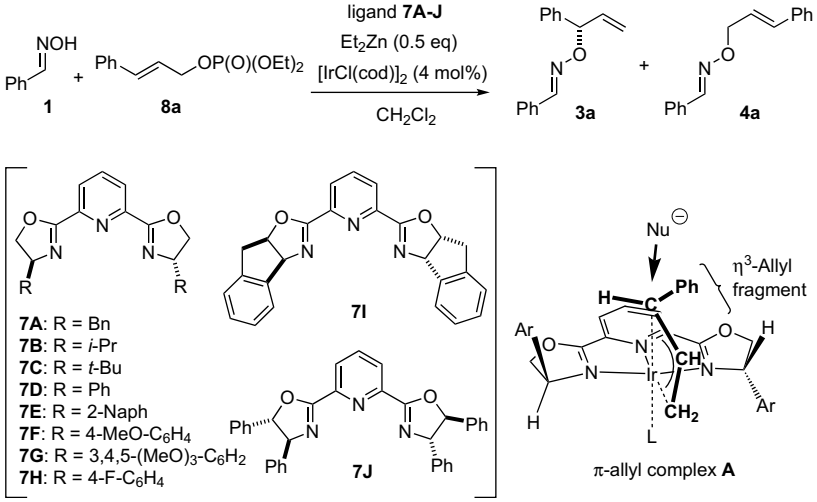
Table 1
Allylic substitution of **8a** with oxime **1** using Et_2Zn[a]

Entry	Ligand	*T* (°C)	Time (h)	% Yield[b] (ratio[c])	% ee[d]
1	**7A**	+20	2	75 (67:33)	43 (*S*)
2	**7B**	+20	2	68 (43:57)	63 (*S*)
3	**7C**	+20	20	6 (86:14)	5 (*S*)
4	**7D**	+20	0.5	81 (69:31)	64 (*S*)
5	**7D**	0	10	77 (74:26)	65 (*S*)
6	**7D**	−20	10	70 (82:18)	80 (*S*)
7	**7D**	−40	48	29 (90:10)	93 (*S*)
8	**7D**	−78	48	Trace	
9	**7D**	−78 to −10	20	80 (84:16)	76 (*S*)
10	**7E**	+20	8	77 (76:24)	50 (*S*)
11	**7F**	+20	8	81 (79:21)	71 (*S*)
12	**7F**	−20	20	71 (90:10)	70 (*S*)
13	**7G**	+20	10	71 (71:29)	61 (*S*)
14	**7H**	+20	4	73 (74:26)	68 (*S*)
15	**7H**	−20	20	64 (84:16)	74 (*S*)
16	**7I**	+20	20	60 (36:64)	43 (*S*)
17	**7J**	+20	8	67 (38:62)	41 (*S*)

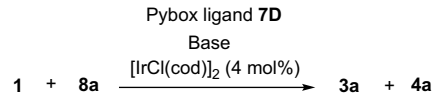
[a] Reactions were carried out in 0.15 M solution by using $[IrCl(cod)]_2$ (4 mol %) in the presence of Et_2Zn (0.5 equiv).
[b] Combined yields of **3a** and **4a**.
[c] Ratio for **3a**:**4a**.
[d] Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H.

oxime ether **3a** was obtained with 64% ee, after being stirred at 20 °C for only 30 min. The degree of regio- and enantioselectivities was shown to be dependent on the reaction temperature (entries 5–9). Thus, changing the temperature from 20 °C to −20 °C led to an increase in regioselectivity to 82:18 and enantioselectivity to 80% ee (entry 6). The reaction proceeded slowly even at −40 °C to afford a 29% yield of oxime ether **3a** with 93% ee in 90:10 ratio (entry 7). Although several aryl pybox ligands **7E**–**J** were evaluated under similar reaction conditions, the iridium–pybox **7D** complex has shown the best activity at low temperature (entries 10–17). Based on Gamasa's study on X-ray crystal structure of π-allyl iridium complex with pybox ligand,[26] the stereochemical feature of our reaction can be rationalized by a pseudooctahedral geometry around the iridium atom, which is bonded to the pybox ligand and to π-allyl fragment as shown in Scheme 1.

We next investigated the reaction of **8a** with **1** catalyzed by the iridium–pybox **7D** complex under different reaction conditions (Scheme 3). In regard to the solvent effect, the replacement of CH_2Cl_2 with toluene or THF led to a decrease in the regio- and enantioselectivities (Table 2, entries 1–3). The concentration influenced the regio- and enantioselectivities (entries 4–7). Both



Scheme 2. Reaction of **8a** with oxime **1** using iridium complex of pybox ligand.



Scheme 3. Reaction of **8a** with oxime **1** using ligand **7D**.

Table 2
Allylic substitution of **8a** with oxime **1** using ligand **7D**[a]

Entry	Base	Solvent	*T* (°C)	Time (h)	% Yield[b] (ratio[c])	% ee[d]
1	Et_2Zn	Toluene (0.15 M)	+20	0.5	76 (57:43)	60 (*S*)
2	Et_2Zn	Toluene (0.15 M)	−20	20	64 (60:40)	78 (*S*)
3	Et_2Zn	THF (0.15 M)	+20	20	46 (66:34)	42 (*S*)
4	Et_2Zn	CH_2Cl_2 (0.15 M)	−40	48	29 (90:10)	93 (*S*)
5	Et_2Zn	CH_2Cl_2 (0.29 M)	−40	20	47 (88:12)	91 (*S*)
6	Et_2Zn	CH_2Cl_2 (0.5 M)	−40	20	48 (84:16)	80 (*S*)
7	Et_2Zn	CH_2Cl_2 (1.0 M)	−40	20	58 (83:17)	59 (*S*)
8	Me_2Zn	CH_2Cl_2 (0.15 M)	−20	10	61 (86:14)	78 (*S*)
9	DIBAL	CH_2Cl_2 (0.15 M)	+20	10	NR	
10	PhMgBr	CH_2Cl_2 (0.15 M)	+20	10	Trace	
11	*n*-BuLi	CH_2Cl_2 (0.15 M)	+20	3	40 (66:34)	80 (*S*)
12	KHMDS	CH_2Cl_2 (0.15 M)	+20	3	25 (71:29)	76 (*S*)
13	K_2CO_3	CH_2Cl_2 (0.17 M)	+20	3	64 (89:11)	73 (*S*)
14	CsOAc	CH_2Cl_2 (0.17 M)	+20	3	18 (98:2)	40 (*S*)
15	Cs_2CO_3	CH_2Cl_2 (0.17 M)	+20	2	80 (86:14)	80 (*S*)
16	$CsOH·H_2O$	CH_2Cl_2 (0.17 M)	−20	20	52 (89:11)	85 (*S*)
17	$Ba(OH)_2·H_2O$	CH_2Cl_2 (0.17 M)	+20	1	81 (88:12)	81 (*S*)

[a] Reactions were carried out by using $[IrCl(cod)]_2$ (4 mol %) and ligand **7D**.
[b] Combined yields of **3a** and **4a**.
[c] Ratio for **3a**:**4a**.
[d] Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H.

selectivities were increased under the dilution conditions (entry 4). Next, the effect of bases on reactivity and selectivities was studied (entries 8–17). Amines such as Et_3N and DBU were less effective for the present reaction. The good selectivities and chemical efficiency were obtained when Cs_2CO_3 or $Ba(OH)_2·H_2O$ was employed (entries 15 and 17). In the presence of Cs_2CO_3, the reaction proceeded smoothly to give the oxime ether **3a** in 80% yield with 80% ee even at 20 °C (entry 15). The reaction using $Ba(OH)_2·H_2O$ afforded the oxime ether **3a** with 81% ee within 1 h (entry 17).

Next, the reactions of **8a** with **1** were studied in the presence of Cs_2CO_3 under the several reaction conditions (Table 3). As expected, the degree of regio- and enantioselectivities was shown to be dependent on the reaction temperature (entries 1–3). The reaction at −20 °C gave the oxime ether **3a** with 87% ee in 92:8 ratio (entry 3). When the reaction was carried out in 0.33 M solution, the oxime ether **3a** was obtained with 84% ee (entry 4). The replacement of CH_2Cl_2 with toluene or THF led to a decrease in regioselectivity (entries 5 and 6).

The similar trends were observed in the reaction using $Ba(OH)_2·H_2O$ as a base (Table 4). Changing the temperature from 20 °C to −20 °C led to an increase in regioselectivity to 90:10 and enantioselectivity to 95% ee (entry 2). Under the optimized reaction

Table 3
Allylic substitution of **8a** with oxime **1** using Cs_2CO_3[a]

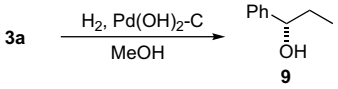
Entry	Solvent	*T* (°C)	Time (h)	% Yield[b] (ratio[c])	% ee[d]
1	CH_2Cl_2 (0.17 M)	+20	2	80 (86:14)	80 (*S*)
2	CH_2Cl_2 (0.17 M)	0	10	82 (88:12)	80 (*S*)
3	CH_2Cl_2 (0.17 M)	−20	20	61 (92:8)	87 (*S*)
4	CH_2Cl_2 (0.33 M)	−20	20	69 (91:9)	84 (*S*)
5	Toluene (0.17 M)	+20	3	67 (73:27)	77 (*S*)
6	THF (0.17 M)	+20	20	48 (74:26)	80 (*S*)

[a] Reactions were carried out by using $[IrCl(cod)]_2$ (4 mol %), ligand **7D** and Cs_2CO_3 (1 equiv).
[b] Combined yields of **3a** and **4a**.
[c] Ratio for **3a**:**4a**.
[d] Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H.

Table 4
Allylic substitution of **8a** with oxime **1** using $Ba(OH)_2·H_2O$[a]

Entry	Solvent	*T* (°C)	Time (h)	% Yield[b] (ratio[c])	% ee[d]
1	CH_2Cl_2 (0.17 M)	+20	1	81 (88:12)	81 (*S*)
2	CH_2Cl_2 (0.17 M)	−20	20	87 (90:10)	95 (*S*)
3	CH_2Cl_2 (0.33 M)	−20	20	90 (88:12)	94 (*S*)
4	Toluene (0.17 M)	+20	5	73 (52:48)	80 (*S*)
5	THF (0.17 M)	+20	20	59 (62:38)	73 (*S*)

[a] Reactions were carried out by using $[IrCl(cod)]_2$ (4 mol %), ligand **7D** and $Ba(OH)_2·H_2O$ (1 equiv).
[b] Combined yields of **3a** and **4a**.
[c] Ratio for **3a**:**4a**.
[d] Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H.

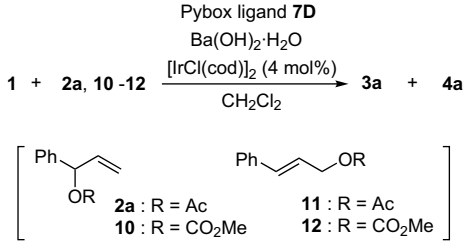


Scheme 4. Conversion of **3a** into **9**.

conditions, the formation of nitrones **5a** and **6a** was not observed (entry 2). The absolute configuration of oxime ether **3a** was determined to be *S* by converting **3a** into authentic alcohol (*S*)-**9** (Scheme 4).[27] The reduction of C=C and N–O bonds of **3a** was achieved by hydrogenolysis using $Pd(OH)_2$–C.

To gain further insight into the reaction mechanism, the other allylic reagents were tested under the optimized reaction conditions using $Ba(OH)_2·H_2O$ (Scheme 5). At first, racemic branched reagents **2a** and **10** were employed (Table 5). The reaction of branched reagents **2a** and **10** with oxime **1** proceeded with excellent regioselectivities to afford the branched oxime ether **3a** without the formation of the linear oxime ether **4a** (entries 1–4). However, these enantioselectivities were poor. Treatment of acetate **2a** with **1** at −20 °C gave the oxime ether **3a** with 32% ee (entry 1). Surprisingly, the high reaction temperature improved the enantioselectivity. Reaction at +60 °C gave the oxime ether **3a** with 55% ee (entry 3). The reaction of carbonate **10** with oxime **1** gave the nearly racemic oxime ether **3a** (entry 4). In contrast to the reaction of linear phosphate **8a**, the reaction did not proceed effectively when cinnamyl acetate **11** and cinnamyl methyl carbonate **12** were employed (entries 5 and 6). Thus, the linear phosphates such as cinnamyl phosphate **8a** are highly promising electrophiles for the present iridium-catalyzed reaction.

The observed effect of allylic reagents can be explained by two different iridium complexes **A** and **B** as shown in Scheme 6. The above results suggest that the formation of π-allyl complex **A** is important to achieve high enantioselectivity and the conversion of σ-complex **B** into π-allyl complex **A** is relatively slow. In contrast to the predominant formation of π-allyl complex **A** from phosphate **8a**, the use of branched reagents **2a** and **10** gave σ-complex **B**, which allows two competitive pathways.[28] The S_N2' type reaction of σ-complex **B** with nucleophile proceeded with excellent regioselectivity and low enantioselectivity. Additionally, it assumes that the high reaction temperature promoted the conversion of



Scheme 5. Reaction of allylic reagents **2a** and **10**–**12** with oxime **1**.

Table 5
Allylic substitution of **2a**, **10**–**12** with oxime **1** using $Ba(OH)_2 \cdot H_2O$[a]

Entry	Reagent	T (°C)	Time (h)	% Yield[b] (ratio[c])	% ee[d]
1	**2a**	−20	15	66 (>98:2)	32 (*S*)
2	**2a**	+20	0.5	85 (>98:2)	42 (*S*)
3	**2a**	+60	0.5	82 (>98:2)	55 (*S*)
4	**10**	+20	0.5	75 (>98:2)	Racemic
5	**11**	+20	20	NR	
6	**12**	+20	20	Trace	

[a] Reactions were carried out in CH_2Cl_2 by using $[IrCl(cod)]_2$ (4 mol %), ligand **7D** and $Ba(OH)_2 \cdot H_2O$ (1 equiv).
[b] Combined yields of **3a** and **4a**.
[c] Ratio for **3a**:**4a**.
[d] Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H.

σ-complex **B** into π-allyl complex **A**, leading to the improvement of enantioselectivity.

2.2. Regio- and enantioselective allylic substitution of several phosphates

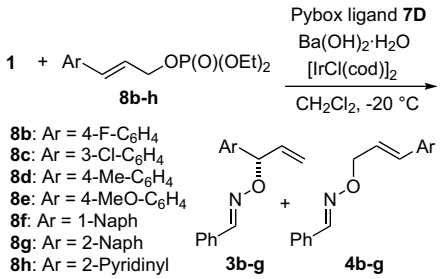
Finally, several phosphates **8b**–**h** were tested under the optimized reaction conditions (Scheme 7). The phosphates **8b** and **8c** having electron-withdrawing substituents on aromatic ring showed the low reactivity toward the allylic substitution (Table 6, entries 1–4). Good yields were observed when 8 mol % of $[IrCl(cod)]_2$ was employed (entries 2 and 4). In contrast, the reaction of phosphate **8d** having tolyl group proceeded smoothly to give a 90% ee of oxime ether **3d** with good regioselectivity (entry 5). However, the reaction of phosphate **8e** having an electron-donating substituent on aromatic ring gave the low yield of oxime ether **3e**, due to instability of phosphate **8e** under reaction conditions (entry 6). The phosphates **8f** and **8g** having bulky 1-naphtyl or 2-naphtyl substituents worked well, allowing facile incorporation of structural variety (entries 7–10). On the other hand, the phosphate **8h** having basic 2-pyridinyl group did not work (entry 11). The absolute configuration of oxime ethers **3b**–**g** was assigned to be *S*, since their high performance liquid chromatography analyses and optical rotations showed similarity with those of oxime ether (*S*)-**3a**.

In summary, we have demonstrated that regio- and enantioselectivities in *O*-allylic substitution of oximes are achieved by using an iridium–pybox complex. In addition to the enantioselective *O*-allylic substitution with hydroxylamines,[14b] the allylic substitution with oximes disclosed a broader aspect of the utility of the oxygen nucleophiles directly connected with heteroatoms for the synthesis of various types of functionalized allylic compounds.

3. Experimental

3.1. General

Melting points were taken on a YANAGIMOTO micromelting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 500 MHz and at 125 MHz, respectively. IR spectra were recorded on a JASCO FT/IR-410 Fourier-transfer infrared spectrometer. Low and high resolution mass spectra were obtained by EI method. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$). Optical rotations were recorded on a JASCO DIP-360 polarimeter.



Scheme 7. Reaction of phosphates **8b**–**h** with oxime **1**.

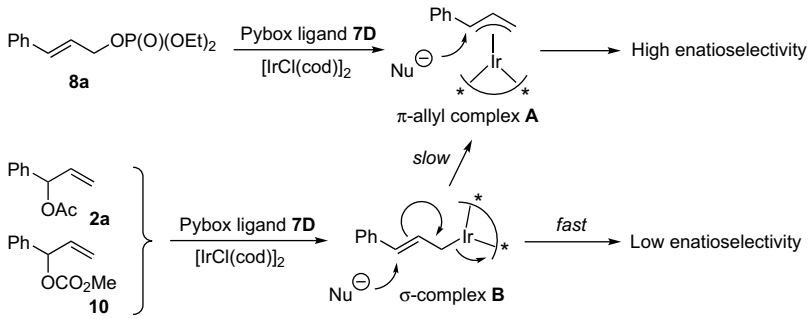
Table 6
Allylic substitution of **8b**–**h** with oxime **1**[a]

Entry	Reagent	Mol % of $[IrCl(cod)]_2$	Time (h)	% Yield[b] (ratio[c])	% ee[d]
1	**8b**	4	20	48 (69:31)	83
2	**8b**	8	40	89 (69:31)	90
3	**8c**	4	20	38 (74:26)	90
4	**8c**	8	40	86 (76:24)	92
5	**8d**	4	20	84 (83:17)	90
6	**8e**	4	20	35 (84:16)	70
7	**8f**	4	20	38 (95:5)	91
8	**8f**	8	35	83 (94:6)	90
9	**8g**	4	20	70 (82:18)	92
10	**8g**	6	30	81 (83:17)	89
11	**8h**	4	20	NR	

[a] Reactions were carried out in CH_2Cl_2 by using $[IrCl(cod)]_2$, ligand **7D** and $Ba(OH)_2 \cdot H_2O$ (1 equiv).
[b] Combined yields of **3b**–**g** and **4b**–**g**.
[c] Ratio for **3b**–**g**:**4b**–**g**.
[d] Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H.

3.2. General procedure for allylic substitution of 8a using Et_2Zn and ligands 7A–J in 0.15 M solution

To a solution of oxime **1** (121 mg, 1.0 mmol) in CH_2Cl_2 (4.0 mL) was added Et_2Zn (1.0 M in hexane, 0.50 mL, 0.50 mmol) under argon atmosphere at 20 °C. After being stirred at the same temperature for 10 min, a solution of phosphate **8a** (405 mg, 1.5 mmol), $[IrCl(cod)]_2$ (26.8 mg, 0.040 mmol), and pybox ligand **7A–J** (0.080 mmol) in CH_2Cl_2 (2.0 mL) was added to the reaction mixture at the temperature indicated in Table 1. After the reaction was completed, the reaction mixture was diluted with saturated aqueous potassium sodium (+)-tartrate and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under



Scheme 6. Possible reaction pathway.

reduced pressure. The ratio of products was determined by ^{1}H NMR analysis of crude products. Purification of the residue by preparative TLC (hexane/AcOEt=20:1, twofold development) afforded the products **3a** and **4a**.

3.3. General procedure for allylic substitution of 8a–h using Cs_2CO_3 or $Ba(OH)_2\cdot H_2O$ in 0.17 M solution

A mixture of oxime **1** (121 mg, 1.0 mmol) and Cs_2CO_3 or $Ba(OH)_2\cdot H_2O$ (1.0 mmol) in CH_2Cl_2 (4.0 mL) was stirred under argon atmosphere at 20 °C for 10 min. To the reaction mixture was added a solution of phosphate **8a**–**h** (1.5 mmol), pybox **7D** (0.080–0.16 mmol), and $[IrCl(cod)]_2$ (0.040–0.080 mmol) in CH_2Cl_2 (2.0 mL) at −20 °C. After the reaction was completed, the reaction mixture was diluted with saturated aqueous NH_4Cl and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The ratio of products was determined by ^{1}H NMR analysis of crude products. Purification of the residue by preparative TLC (hexane/AcOEt=5:1 to 25:1, twofold development) afforded the products **3a**–**g** and **4a**–**g**.

3.3.1. (E)-(S)-O-(1-Phenylprop-2-enyl)benzaldehyde oxime (*3a*)

A colorless oil. IR ($CHCl_3$) 2908, 1494, 1450, 1414 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.18 (1H, s), 7.60–7.50 (2H, m), 7.45–7.23 (8H, m), 6.16 (1H, ddd, J=17.1, 10.5, 6.3 Hz), 5.71 (1H, d, J=6.3 Hz), 5.34 (1H, d, J=17.1 Hz), 5.29 (1H, d, J=10.5 Hz). ^{13}C NMR ($CDCl_3$) δ 149.2, 140.1, 137.6, 132.3, 129.8, 128.6, 128.4, 127.9, 127.4, 127.1, 117.3. MS (EI$^+$) m/z: 237 (M$^+$, 0.2), 117 (100). HRMS calcd for $C_{16}H_{15}NO$: 237.1154, Found: 237.1156. HPLC (Chiralcel OD-H, hexane/2-propanol=90:10, 0.5 mL/min, 254 nm) t_r (*S*)=8.8 min, t_r (*R*)=13.2 min. A sample of 95% ee (*S*) by HPLC analysis gave $[\alpha]^{26}_D$ −62.3 (*c* 1.03, $CHCl_3$).

3.3.2. (E)-O-(3-Phenylprop-2-enyl)benzaldehyde oxime (*4a*)

A colorless oil. IR ($CHCl_3$) 2926, 1494, 1448 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.13 (1H, s), 7.63–7.48 (2H, m), 7.46–7.16 (8H, m), 6.67 (1H, d, J=15.9 Hz), 6.42 (1H, dt, J=15.9, 6.2 Hz), 4.83 (2H, d, J=6.2 Hz). ^{13}C NMR ($CDCl_3$) δ 148.9, 136.6, 133.5, 132.2, 129.8, 128.7, 128.5, 127.8, 127.1, 126.6, 125.1, 74.9. MS (EI$^+$) m/z: 237 (M$^+$, 1.5), 117 (100). HRMS calcd for $C_{16}H_{15}NO$: 237.1154, Found: 237.1155.

3.3.3. (E)-(S)-O-[1-(4-Fluorophenyl)prop-2-enyl]benzaldehyde oxime (*3b*)

A colorless oil. IR ($CHCl_3$) 2906, 1509, 1447, 1415 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.17 (1H, s), 7.58–7.53 (2H, m), 7.40–7.32 (5H, m), 7.08–7.02 (2H, m), 6.13 (1H, ddd, J=17.0, 10.6, 6.2 Hz), 5.68 (1H, d, J=6.2 Hz), 5.32 (1H, d, J=17.0 Hz), 5.31 (1H, d, J=10.6 Hz). ^{13}C NMR ($CDCl_3$) δ 162.4 (d, J=246 Hz), 149.3, 137.4, 136.0, 132.2, 129.9, 129.1 (d, J=7.2 Hz), 128.6, 127.1, 117.5, 115.3 (d, J=20.7 Hz), 85.3. MS (EI$^+$) m/z: 255 (M$^+$, 0.2), 135 (100). HRMS calcd for $C_{16}H_{14}FNO$: 255.1059, Found: 255.1065. HPLC (Chiralcel OD-H, hexane/2-propanol=90:10, 0.5 mL/min, 254 nm) t_r (*S*)=8.6 min, t_r (*R*)=12.8 min. A sample of 90% ee (*S*) by HPLC analysis gave $[\alpha]^{28}_D$ −53.7 (*c* 1.04, $CHCl_3$).

3.3.4. (E)-O-[3-(4-Fluorophenyl)prop-2-enyl]benzaldehyde oxime (*4b*)

A colorless crystal. Mp 54–57 °C (hexane). IR ($CHCl_3$) 2926, 1509, 1447, 1414 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.14 (1H, s), 7.63–7.57 (2H, m), 7.42–7.34 (5H, m), 7.05–6.97 (2H, m), 6.65 (1H, d, J=15.8 Hz), 6.34 (1H, dt, J=15.8, 6.1 Hz), 4.82 (2H, d, J=6.1 Hz). ^{13}C NMR ($CDCl_3$) δ 162.5 (d, J=247 Hz), 149.0, 132.8, 132.3, 132.2, 129.8, 128.7, 128.1 (d, J=8.3 Hz), 127.1, 124.9, 115.4 (d, J=21.7 Hz), 74.7. MS (EI$^+$) m/z: 255 (M$^+$, 0.5), 135 (100). HRMS calcd for $C_{16}H_{14}FNO$: 255.1059, Found: 255.1062. Anal. Calcd for $C_{16}H_{14}FNO$: C, 75.28; H, 5.53; N, 5.49; F, 7.44. Found: C, 75.33; H, 5.72; N, 5.45; F, 7.46.

3.3.5. (E)-(S)-O-[1-(3-Chlorophenyl)prop-2-enyl]benzaldehyde oxime (*3c*)

A colorless oil. IR ($CHCl_3$) 2911, 1476, 1448, 1429 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.18 (1H, s), 7.59–7.50 (2H, m), 7.40–7.23 (7H, m), 6.10 (1H, ddd, J=17.2, 10.6, 6.1 Hz), 5.66 (1H, d, J=6.1 Hz), 5.33 (1H, d, J=17.2 Hz), 5.30 (1H, d, J=10.6 Hz). ^{13}C NMR ($CDCl_3$) δ 149.6, 142.4, 137.0, 134.3, 132.1, 130.0, 129.7, 128.7, 128.0, 127.5, 127.2, 125.5, 117.9, 85.3. MS (EI$^+$) m/z: 271 (M$^+$, 1), 151 (100). HRMS calcd for $C_{16}H_{14}ClNO$: 271.0764, Found: 271.0767. HPLC (Chiralcel OD-H, hexane/2-propanol=90:10, 0.5 mL/min, 254 nm) t_r (*S*)=8.8 min, t_r (*R*)=12.1 min. A sample of 90% ee (*S*) by HPLC analysis gave $[\alpha]^{28}_D$ −65.0 (*c* 1.05, $CHCl_3$).

3.3.6. (E)-O-[3-(3-Chlorophenyl)prop-2-enyl]benzaldehyde oxime (*4c*)

A colorless oil. IR ($CHCl_3$) 2925, 1477, 1447, 1425 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.13 (1H, s), 7.63–7.56 (2H, m), 7.43–7.33 (4H, m), 7.28–7.17 (3H, m), 6.59 (1H, d, J=15.9 Hz), 6.42 (1H, dt, J=15.9, 5.5 Hz), 4.82 (2H, d, J=5.5 Hz). ^{13}C NMR ($CDCl_3$) δ 149.1, 138.6, 134.5, 132.2, 131.8, 129.9, 129.8, 128.7, 127.7, 127.1, 126.9, 126.5, 124.8, 74.5. MS (EI$^+$) m/z: 271 (M$^+$, 3), 151 (100). HRMS calcd for $C_{16}H_{14}ClNO$: 271.0764, Found: 271.0764.

3.3.7. (E)-(S)-O-[1-(4-Methylphenyl)prop-2-enyl]benzaldehyde oxime (*3d*)

A colorless oil. IR ($CHCl_3$) 2945, 1513, 1493, 1448, 1413 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.17 (1H, s), 7.58–7.52 (2H, m), 7.35–7.32 (3H, m), 7.29 (2H, d, J=7.9 Hz), 7.18 (2H, d, J=7.9 Hz), 6.16 (1H, ddd, J=17.4, 10.5, 6.3 Hz), 5.67 (1H, d, J=6.3 Hz), 5.33 (1H, d, J=17.4 Hz), 5.28 (1H, d, J=10.5 Hz), 2.34 (3H, s). ^{13}C NMR ($CDCl_3$) δ 149.1, 137.8, 137.6, 137.2, 132.4, 129.8, 129.1, 128.6, 127.4, 127.1, 117.1, 86.0, 21.1. MS (EI$^+$) m/z: 251 (M$^+$, <0.1), 131 (100). HRMS calcd for $C_{17}H_{17}NO$: 251.1310, Found: 251.1306. HPLC (Chiralcel OD-H, hexane/2-propanol=90:10, 0.5 mL/min, 254 nm) t_r (*S*)=8.0 min, t_r (*R*)=11.0 min. A sample of 90% ee (*S*) by HPLC analysis gave $[\alpha]^{28}_D$ −72.9 (*c* 1.01, $CHCl_3$).

3.3.8. (E)-O-[3-(4-Methylphenyl)prop-2-enyl]benzaldehyde oxime (*4d*)

A colorless crystal. Mp 70–72 °C (hexane). IR ($CHCl_3$) 2925, 1512, 1493, 1448, 1414 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.14 (1H, s), 7.63–7.56 (2H, m), 7.40–7.34 (3H, m), 7.31 (2H, d, J=7.9 Hz), 7.12 (2H, d, J=7.9 Hz), 6.65 (1H, d, J=15.9 Hz), 6.38 (1H, dt, J=15.9, 6.4 Hz), 4.83 (2H, d, J=6.4 Hz), 2.34 (3H, s). ^{13}C NMR ($CDCl_3$) δ 148.9, 137.7, 133.9, 133.5, 132.3, 129.8, 129.3, 128.7, 127.1, 126.5, 124.0, 75.0, 21.1. MS (EI$^+$) m/z: 251 (M$^+$, 1.4), 131 (100). HRMS calcd for $C_{17}H_{17}NO$: 251.1310, Found: 251.1314. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.54; H, 6.92; N, 5.53.

3.3.9. (E)-(S)-O-[1-(4-Methoxyphenyl)prop-2-enyl]benzaldehyde oxime (*3e*)

A colorless oil. IR ($CHCl_3$) 2935, 1512, 1463, 1446, 1416 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, s), 7.58–7.51 (2H, m), 7.40–7.29 (5H, m), 6.90 (2H, d, J=8.0 Hz), 6.16 (1H, ddd, J=17.0, 10.6, 6.2 Hz), 5.66 (1H, d, J=6.2 Hz), 5.32 (1H, d, J=17.0 Hz), 5.28 (1H, d, J=10.6 Hz), 3.80 (3H, s). ^{13}C NMR ($CDCl_3$) δ 159.4, 149.1, 137.8, 132.4, 132.2, 129.8, 128.8, 128.6, 127.1, 117.0, 113.8, 85.7, 55.2. MS (EI$^+$) m/z: 267 (M$^+$, <0.1), 147 (100). HRMS calcd for $C_{17}H_{17}NO_2$: 267.1259, Found: 267.1258. HPLC (Chiralcel OD-H, hexane/2-propanol=90:10, 0.5 mL/min, 254 nm) t_r (*S*)=10.0 min, t_r (*R*)=15.9 min. A sample of 70% ee (*S*) by HPLC analysis gave $[\alpha]^{28}_D$ −60.4 (*c* 1.04, $CHCl_3$).

3.3.10. (E)-O-[3-(4-Methoxyphenyl)prop-2-enyl]benzaldehyde oxime (*4e*)

A colorless oil. IR ($CHCl_3$) 2935, 1512, 1464, 1445 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.14 (1H, s), 7.63–7.57 (2H, m), 7.40–7.28 (5H, m), 6.84 (2H, d, J=8.6 Hz), 6.63 (1H, d, J=15.9 Hz), 6.29 (1H, dt, J=15.9, 6.5 Hz),

4.81 (2H, d, J=6.5 Hz), 3.78 (3H, s). ^{13}C NMR ($CDCl_3$) δ 159.4, 148.8, 133.3, 132.3, 129.8, 129.4, 128.7, 127.8, 127.1, 122.7, 113.9, 75.1, 55.2. MS (EI$^+$) m/z: 267 (M^+, 6), 147 (100). HRMS calcd for $C_{17}H_{17}NO_2$: 267.1259, Found: 267.1253.

*3.3.11. (E)-(S)-O-[1-(1-Naphthyl)prop-2-enyl]benzaldehyde oxime (**3f**)*

A colorless oil. IR ($CHCl_3$) 2944, 1511, 1447 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.21 (1H, s), 8.20 (1H, d, J=11.0 Hz), 7.85 (1H, d, J=7.9 Hz), 7.80 (2H, d, J=8.3 Hz), 7.61–7.44 (6H, m), 7.34–7.28 (3H, m), 6.43 (1H, d, J=5.5 Hz), 6.35 (1H, ddd, J=17.0, 9.2, 5.5 Hz), 5.37 (1H, d, J=17.0 Hz), 5.34 (1H, d, J=9.2 Hz). ^{13}C NMR ($CDCl_3$) δ 149.3, 137.1, 135.6, 134.0, 132.3, 131.2, 129.8, 128.8, 128.7, 128.6, 127.2, 126.1, 125.6, 125.5, 125.3, 124.3, 117.8, 83.6. MS (EI$^+$) m/z: 287 (M^+, 0.2), 167 (100). HRMS calcd for $C_{20}H_{17}NO$: 287.1310, Found: 287.1313. HPLC (Chiralcel OD-H, hexane/2-propanol=90:10, 0.5 mL/min, 254 nm) t_r (S)=12.0 min, t_r (R)=13.6 min. A sample of 90% ee (S) by HPLC analysis gave $[\alpha]^{28}_D$ −17.1 (c 1.04, $CHCl_3$).

*3.3.12. (E)-O-[3-(1-Naphthyl)prop-2-enyl]benzaldehyde oxime (**4f**)*

A colorless oil. IR ($CHCl_3$) 2925, 1507, 1493, 1446 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.17 (1H, s), 8.12 (1H, d, J=7.9 Hz), 7.82 (1H, d, J=6.4 Hz), 7.75 (1H, d, J=8.2 Hz), 7.68–7.55 (3H, m), 7.51–7.30 (7H, m), 6.44 (1H, dt, J=15.8, 6.1 Hz), 4.94 (2H, d, J=6.1 Hz), 3.78 (3H, s). ^{13}C NMR ($CDCl_3$) δ 149.0, 134.5, 133.6, 132.3, 131.2, 130.6, 129.9, 128.7, 128.5, 128.4, 128.1, 127.1, 126.1, 125.8, 125.6, 124.1, 123.8, 75.0. MS (EI$^+$) m/z: 287 (M^+, 10.1), 167 (100). HRMS calcd for $C_{20}H_{17}NO$: 287.1310, Found: 287.1311.

*3.3.13. (E)-(S)-O-[1-(2-Naphthyl)prop-2-enyl]benzaldehyde oxime (**3g**)*

A colorless oil. IR ($CHCl_3$) 2944, 1507, 1446 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.21 (1H, s), 7.90–7.77 (4H, m), 7.58–7.42 (5H, m), 7.35–7.26 (3H, m), 6.24 (1H, ddd, J=17.0, 10.5, 6.0 Hz), 5.87 (1H, d, J=6.0 Hz), 5.38 (1H, d, J=17.0 Hz), 5.32 (1H, d, J=10.5 Hz). ^{13}C NMR ($CDCl_3$) δ 149.3, 137.7, 137.6, 133.3, 133.1, 132.3, 129.8, 128.6, 128.2, 128.1, 127.7, 127.2, 126.4, 126.1, 126.0, 125.3, 117.6, 86.2. MS (EI$^+$) m/z: 287 (M^+, <0.1), 167 (100). HRMS calcd for $C_{20}H_{17}NO$: 287.1310, Found: 287.1308. HPLC (Chiralcel OD-H, hexane/2-propanol=90:10, 0.5 mL/min, 254 nm) t_r (S)=9.9 min, t_r (R)=16.3 min. A sample of 89% ee (S) by HPLC analysis gave $[\alpha]^{28}_D$ −76.3 (c 1.00, $CHCl_3$).

*3.3.14. (E)-O-[3-(2-Naphthyl)prop-2-enyl]benzaldehyde oxime (**4g**)*

A colorless crystal. Mp 70–73 °C (hexane). IR ($CHCl_3$) 2927, 1506, 1446 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, s), 7.83–7.75 (4H, m), 7.66–7.58 (3H, m), 7.49–7.34 (5H, m), 6.85 (1H, d, J=15.9 Hz), 6.56 (1H, dt, J=15.9, 6.1 Hz), 4.90 (2H, d, J=6.1 Hz). ^{13}C NMR ($CDCl_3$) δ 149.0, 134.1, 133.6, 133.1, 132.2, 129.9, 128.7 (2C), 128.2, 128.0, 127.7, 127.1, 126.7, 126.3, 126.0, 125.5, 123.6, 75.0. MS (EI$^+$) m/z: 287 (M^+, 5.5), 167 (100). HRMS calcd for $C_{20}H_{17}NO$: 287.1310, Found: 287.1312. Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.72; H, 5.97; N, 4.83.

3.4. Reduction of oxime ether 3a

A suspension of oxime ether **3a** (119 mg, 0.50 mmol) and 20% $Pd(OH)_2$–C (30 mg) in MeOH (2.5 mL) was stirred under a hydrogen atmosphere at 20 °C for 3 h. After the reaction mixture was filtered, the filtrate was concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt=5:1) afforded product **9** (47.6 mg, 70%). A colorless oil. IR ($CHCl_3$) 3428, 2969, 1493, 1455, 1380 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.37–7.20 (5H, m), 4.55 (1H, t, J=6.6 Hz), 2.12 (1H, br s), 1.84–1.67 (2H, m), 0.89 (3H, t, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 144.6, 128.4, 127.4, 126.0, 75.9, 31.7, 10.0. MS (EI$^+$) m/z: 136 (M^+, 9.0), 91 (100). HRMS calcd for $C_9H_{12}O$: 136.0888, Found: 136.0888. A sample of 95% ee gave $[\alpha]^{26}_D$ −49.0 (c 1.01, hexane).

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