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Hydroxylamines as Oxygen Atom Nucleophiles in Transition-Metal-Catalyzed Allylic Substitution

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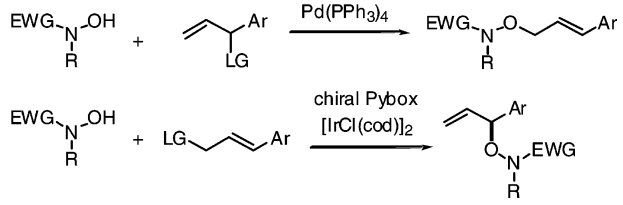

The viability of hydroxylamines as nucleophiles in transition-metal-catalyzed allylic substitutions was examined. We have found that the oxygen atom of hydroxylamines having an *N*-electron-withdrawing substituent (also known as hydroxamic acids) acts as a reactive nucleophile. The palladium-catalyzed *O*-allylic substitution of hydroxylamines with allylic carbonate afforded the linear hydroxylamines. The selective formation of the branched hydroxylamines was observed in iridium-catalyzed reaction. Regio- and enantioselective allylic substitution of the unsymmetrical phosphates with hydroxylamines was studied by using the iridium complex of chiral pybox ligand. The aqueous-medium reaction with hydroxylamines proceeded smoothly in the presence of $Ba(OH)_2 \cdot H_2O$ to give the branched products with good enantioselectivities.

Introduction

Transition-metal-catalyzed allylic substitutions have been developed as fundamentally important cross-coupling reactions.[1] In comparison with allylic amination and alkylation, the corresponding reaction with oxygen nucleophiles has received much less attention due to the poor nucleophilic property of the oxygen atom and also low regioselectivity attained in the reaction.[2] Therefore, *O*-allylic substitution had been largely limited to carboxylate and phenolic nucleophiles, except for the intramoleclar reactions.[2] Recently, synthetically useful studies have been directed toward allylic substitution with alcohols under basic conditions.[3] Our laboratory is interested in developing the effective oxygen nucleophiles for the synthesis of functionalized allylic compounds (Figure 1). For this purpose, we have focused our efforts toward allylic substitution with the oxygen nucleophiles directly connected with heteroatoms. As our first successful results, we have recently reported the utility of oximes and hydroxylamines having an *N*-electron-withdrawing substituent as oxygen nucleophiles in transition-metal-catalyzed allylic substitution.[4,5] These results indicate that oxime and hydroxylamine act as soft

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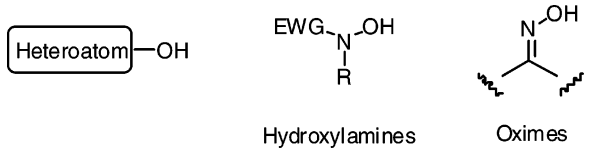

FIGURE 1. Hydroxylamines and oximes as oxygen atom nucleophiles.

nucleophiles due to their equilibrium acidities being enhanced by a C=N bond or electron-withdrawing substituent. In this paper, we describe the in detail study of hydroxylamines as oxygen nucleophiles in palladium or iridium-catalyzed allylic substitutions. We also report the iridium-catalyzed asymmetric reaction.

Hydroxylamine derivatives are the attractive synthetic reagents for allylic substitution because they have nitrogen and oxygen atoms as nucleophiles. However, allylic substitution using hydroxylamines has been limited to palladium-catalyzed amination, as a result of the reaction of an electrophilic π-allyl palladium complex with the nucleophilic nitrogen atom of hydroxylamines.[6] Additionally, procedures for preparing the allylated hydroxylamines often require lengthy linear manipulation.[7] As shown below, this reaction is extremely facile and give allylated hydroxylamines in good yield under mild reaction conditions.

Results and Discussion

Allylic Substitution of Hydroxylamines Having an *N*-Electron-Withdrawing Substituent. Controlling the regioselectivities has been of great importance in allylic substitution of simple acyclic substrates.[8] The iridium-catalyzed regioselective allylic amination giving the branched products was achieved by Takeuchi's group.[9] Therefore, the iridium-catalyzed allylic substitution has been a subject of current interest. The effective iridium-catalyzed etherification of alcohols with allyl acetate was also reported by Ishii's group.[10] The highly regio- and enantioselective allylic substitutions have been recently disclosed by using an iridium-phosphoramidite complex.[11]

As a part of our studies on the iridium-catalyzed reactions,[12] we investigated the iridium-catalyzed allylic substitution of several hydroxylamines **4A**−**E** (Scheme 1). In the presence of $[IrCl(cod)]_2$ (4 mol %), the reactions of hydroxylamines **4A**−**E** with allylic carbonate **1a** were run in MeCN at 20 °C (Table 1, entries 1−5). The *N*-benzylhydroxylamine **4A** worked as a nitrogen nucleophile to give the branched *N*-allylated product **5Aa** in 92% yield without formation of *O*-allylated product **6Aa** (entry 1). In contrast, both nitrogen and oxygen atoms on *N*-Boc-hydroxylamine **4B** and *N*-Cbz-hydroxylamine **4C** acted as nucleophiles to give the *N*-allylated products **5Ba**−**Ca** and *O*-allylated products **6Ba**−**Ca** (entries 2

SCHEME 1

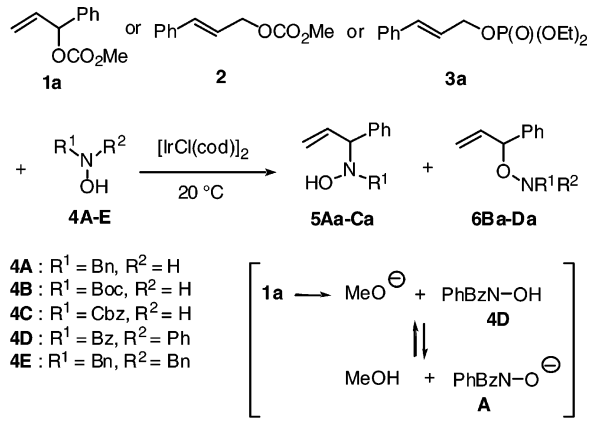

TABLE 1. Iridium-Catalyzed Reaction of Hydroxylamine Derivatives 4A−E[a]

entry	reagent	solvent	hydroxylamine	time	product (% yield)[b] 5	6
1	**1a**	MeCN	**4A**	10 min	**5Aa** (92)	none
2	**1a**	MeCN	**4B**	3 h	**5Ba** (53)	**6Ba** (37)
3	**1a**	MeCN	**4C**	6 h	**5Ca** (34)	**6Ca** (21)
4	**1a**	MeCN	**4D**	10 min	none	**6Da** (98)
5	**1a**	MeCN	**4E**	3 h	no reaction	
6	**1a**	THF	**4D**	3.5 h	none	**6Da** (92)
7	**1a**	CH_2Cl_2	**4D**	3.5 h	none	**6Da** (86)
8	**1a**	toluene	**4D**	3.5 h	none	**6Da** (74)
9	**2**	MeCN	**4D**	24 h	no reaction	
10	**3a**	MeCN	**4D**	24 h		**6Da** (5)

[a] Reactions were carried out using allylic reagents (1 equiv) and hydroxylamine derivatives **4A**−**E** (1 equiv) in the presence of $[IrCl(cod)]_2$ (4 mol %). [b] Isolated yields.

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SCHEME 2

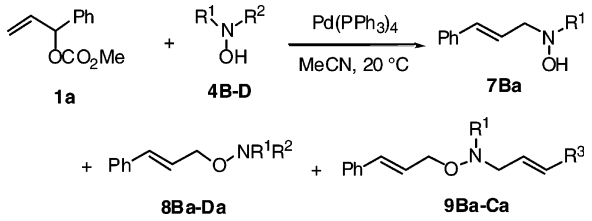


TABLE 2. Palladium-Catalyzed Reaction of Hydroxylamine Derivatives 4B−D

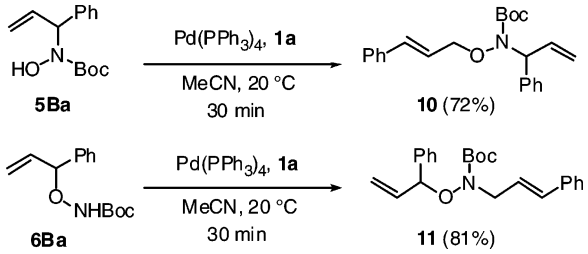
entry	reagent (equiv)	hydroxylamine	time	product (% yield)[a] 7	8	9
1[b]	**1a** (1.0)	**4D**	10 min		**8Da** (93)	
2[b]	**1a** (1.0)	**4B**	30 min	**7Ba** (10)	**8Ba** (67)	**9Ba** (6)
3[b]	**1a** (1.0)	**4C**	1.5 h		**8Ca** (59)	**9Ca** (12)
4[c]	**1a** (2.5)	**4B**	1 h			**9Ba** (76)
5[c]	**1a** (2.5)	**4C**	1 h			**9Ca** (79)

[a] Isolated yields. [b] Reactions were carried out using **1a** (1 equiv) and hydroxylamine derivatives **4B**−**D** (1 equiv) in the presence of $Pd(PPh_3)_4$ (4 mol %). [c] Reactions were carried out using **1a** (2.5 equiv) and hydroxylamine derivatives **4B,C** (1 equiv) in the presence of $Pd(PPh_3)_4$ (4 mol %).

and 3). The *N*-benzoyl-*N*-phenylhydroxylamine **4D** worked well as an oxygen nucleophile to give the branched *O*-allylated product **6Da** in 98% yield after being stirred for 10 min (entry 4). In contrast to hydroxylamines **4B**−**D** having an *N*-electron-withdrawing substituent, the reaction of *N,N*-dibenzylhydroxylamine **4E** did not occur after being stirred at 20 °C for 3 h (entry 5). In our recent studies, the nitrogen atom of guanidine derivatives having two *N*-electron-withdrawing substituents acted as a reactive nucleophile in allylic substitution.[13] On the basis of these observations, it is noted that the stability of conjugate base of hydroxylamines would be an important criteria for the nucleophilic property of an oxygen atom of hydroxylamines. Thus, a rational hypothesis of this reaction is that hydroxylamine **4D** would be effectively activated by methoxide generated from the carbonate **1a** as shown in Scheme 1. Considering the solvent effect, polar solvent such as MeCN gave the best result. The reaction in other solvents such as THF, CH_2Cl_2, and toluene proceeded slowly (entries 6−8). In contrast to allylic carbonate **1a**, a linear carbonate **2** and phosphate **3a** did not work well under the similar reaction conditions (entries 9 and 10).

We next investigated the palladium-catalyzed allylic substitution of several hydroxylamines **4B**−**D** (Scheme 2). The palladium-catalyzed reaction of *N*-benzoyl-*N*-phenylhydroxylamine **4D** with carbonate **1a** afforded the linear *O*-allylated product **8Da** in 93% yield after being stirred for 10 min (Table 2, entry 1). In the case of *N*-Boc-hydroxylamine **4B**, the *O*-allylation was dominant to give the *O*-allylated product **8Ba** in 67% yield, accompanied with a small amount of *N*-allylated product **7Ba** and diallylated product **9Ba** (entry 2). The similar trend was observed in the reaction of *N*-Cbz-hydroxylamine **4C** (entry 3). Since hydroxylamines having an *N*-electron-withdrawing substituent have shown excellent reactivity toward π-allyl palladium complexs, the palladium-catalyzed *N,O*-diallylation of hydroxylamines was examined in latter cases. As expected, the selective formation of *N,O*-diallylated products **9Ba** and **9Ca** was observed in the reaction of *N*-Boc-hydroxylamine **4B** or *N*-Cbz-hydroxylamine **4C** with 2.5 equiv of **1a** (entries 4 and 5).

SCHEME 3



SCHEME 4

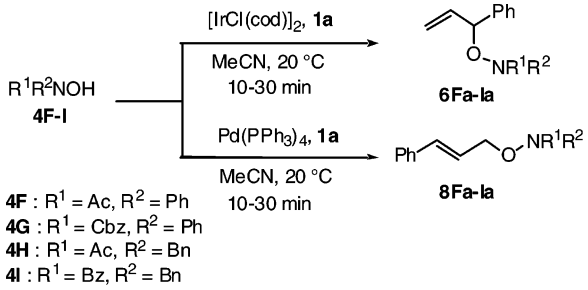


TABLE 3. Reaction of 1a with Hydroxylamine Derivatives 4F−I

entry	hydroxylamine	catalyst	product	yield (%)[a]
1[b]	**4F**	$[IrCl(cod)]_2$	**6Fa**	82
2[b]	**4G**	$[IrCl(cod)]_2$	**6Ga**	87
3[b]	**4H**	$[IrCl(cod)]_2$	**6Ha**	86
4[b]	**4I**	$[IrCl(cod)]_2$	**6Ia**	85
5[c]	**4F**	$Pd(PPh_3)_4$	**8Fa**	96
6[c]	**4G**	$Pd(PPh_3)_4$	**8Ga**	98
7[c]	**4H**	$Pd(PPh_3)_4$	**8Ha**	95
8[c]	**4I**	$Pd(PPh_3)_4$	**8Ia**	93

[a] Isolated yields. [b] Reactions were carried out using **1a** (1 equiv) and hydroxylamine derivatives **4F**−**I** (1 equiv) in MeCN in the presence of $[IrCl(cod)]_2$ (4 mol %). [c] Reactions were carried out using **1a** (1 equiv) and hydroxylamine derivatives **4F**−**I** (1 equiv) in MeCN in the presence of $Pd(PPh_3)_4$ (4 mol %).

We also investigated the additional allylation of the branched hydroxylamines **5Ba** and **6Ba** prepared from the iridium-catalyzed reaction (Scheme 3). Although the iridium-catalyzed allylation of **5Ba** and **6Ba** did not proceed probably as a result of the low activity of iridium catalyst, the palladium-catalyzed allylation gave the *N,O*-diallylated products **10** and **11**. In the presence of $Pd(PPh_3)_4$, the *O*-allylation of **5Ba** proceeded smoothly to give the diallylated product **10**, which has the *O*-linear and *N*-branched substituents. The palladium-catalyzed *N*-allylation of **6Ba** also proceeded smoothly to give the *N*-linear and *O*-branched product **11** in 81% yield.

To study the effect of a *N*-electron-withdrawing substituent, several hydroxylamines **4F**−**I** were employed (Scheme 4). As expected, hydroxylamines **4F**−**I** having a *N*-electron-withdrawing substituent worked well as oxygen atom nucleophiles (Table 3). In the presence of $[IrCl(cod)]_2$, the reactions of **4F**−**I** proceeded smoothly to give the branched product **6Fa**−**Ia** with excellent regi-

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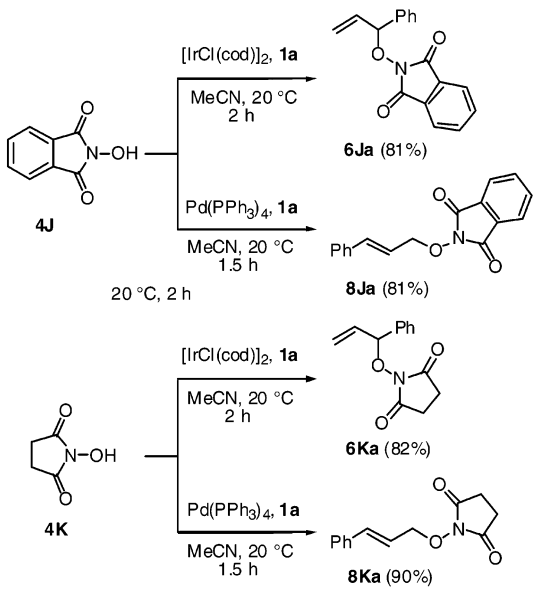
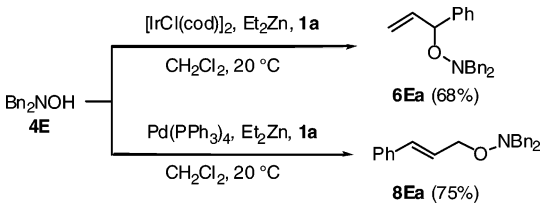
SCHEME 5



SCHEME 6



oselectivities (entries 1−4). The palladium-catalyzed reactions afforded the linear *O*-allylated product **8Fa**−**Ia** in good yields (entries 5−8).

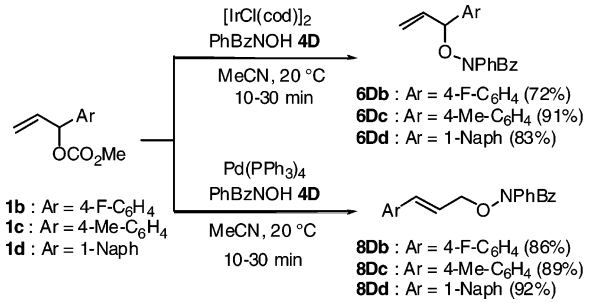
As hydroxylamines having two *N*-electron-withdrawing substituents, *N*-hydroxyphthalimide **4J** and *N*-hydroxysuccinimide **4K** were employed (Scheme 5). These hydroxylamine derivatives worked well. The iridium- and palladium-catalyzed reactions afforded the branched and linear products, respectively.

Recently, a mild and efficient method for allylic etherification using zinc alkoxides was reported by Lee's group.[3e] To test the viability of zinc alkoxide generated from hydroxylamine, the reaction of *N*,*N*-dibenzylhydroxylamine **4E** was investigated in the presence of Et_2Zn as shown in Scheme 6. Although the reaction of **4E** did not proceed without base (Table 1, entry 5), the iridium-catalyzed *O*-allylation of **4E** afforded the branched product **6Ea** by using Et_2Zn as a base. In the presence of $Pd(PPh_3)_4$ and Et_2Zn, a 75% yield of the linear product **8Ea** was obtained.

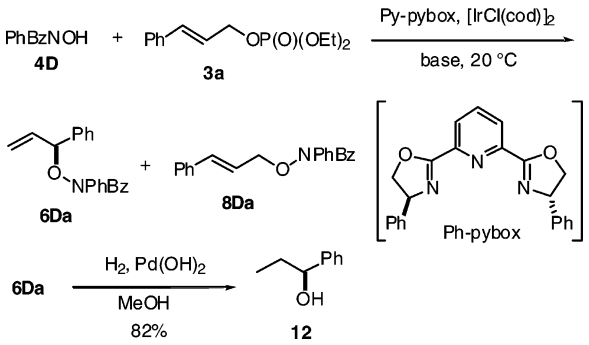
Finally, we examined the *O*-allylation of hydroxylamine **4D** with allylic carbonates **1b**−**d** bearing a variety of substituents (Scheme 7). Allylic reagents having an electron-withdrawing substituent or bulky 1-naphthyl groups worked well. The iridium- and palladium-catalyzed reactions proceeded with excellent regioselectivities to afford the branched products **6Db**−**Dd** and linear products **8Db**−**Dd**, respectively.

Enantioselective Allylic Substitution of Hydroxylamines. The development of regio- and enantioselective allylic substitution has attracted much recent attention,[8,11] and thus, a variety of chiral ligands have been

SCHEME 7



SCHEME 8



employed. However, the utility of C_2-symmetric pybox ligand in transition-metal-catalyzed allylic substitution has not been widely invesitigated.[14] We have recently demonstrated that an iridium−pybox complex has the potential to control regio- and enantiostereochemistry in allylic substitution with oximes and amines.[5b] As a part of our program directed toward the development of reactions catalyzed by the iridium−pybox complex, we next investigated the enantioselective allylic substitution with the oxygen atom of hydroxylamines. Recently, the iridium−idane−pybox catalyst was also used in a reductive aldol reaction.[15]

The use of water as a solvent has many advantages in organic synthesis from both economical and environmental points of view.[16] In our recent study,[5b] the iridium−pybox complex catalyzed reaction in organic solvent. Therefore, utility of the iridium−pybox complex in aqueous media has been the new focus of our efforts. We investigated the aqueous-medium reaction of **3a** with **4D** under several reaction conditions (Scheme 8). As expected, the chiral iridium complex of pybox ligand exhibited a good activity even in aqueous media. Additionally, the water-resistant phosphate **3a** participated in the present aqueous-medium reaction even under basic reaction conditions, although the reaction of phosphate **3a** did not proceed effectively in the absence of the base. To a solution of hydroxylamine **4D** and $Ba(OH)_2 \cdot H_2O$ in THF−H_2O was added a solution of the phosphate **3a**,

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TABLE 4. Reaction of 3a with 4D in the Presence of $Ba(OH)_2 \cdot H_2O$[a]

entry	solvent	time (h)	% yield[b] (ratio[c])	% ee[d]
1	THF−H_2O (10:1)	3	95 (37:63)	80
2	toluene−H_2O (10:1)	3	37 (45:55)	35
3	CH_2Cl_2−H_2O (10:1)	3	96 (65:35)	82
4	$PhCF_3$−H_2O (2:1)	4	70 (80:20)	87
5	$PhCF_3$−H_2O (1:2)	4	65 (77:23)	84

[a] Reactions were carried out in the presence of $Ba(OH)_2 \cdot H_2O$ (1 equiv). [b] Combined yields. [c] Ratio for **6Da**:**8Da**. [d] Enantiostereoselectivities were determined by HPLC analysis.

TABLE 5. Effect of Base on Reaction of 3a with 4D in $PhCF_3$−H_2O[a]

entry	base	time (h)	% yield[b] (ratio[c])	% ee[d]
1	none	20	trace	
2	$BaCO_3$	15	10 (>95:5)	60
3	$CsOH \cdot H_2O$	15	30 (82:18)	67
4	Cs_2CO_3	15	30 (85:15)	56
5	NaOH	15	33 (82:18)	65
6	NaOH, TBAB	5	67 (71:29)	86
7	$Ca(OH)_2$	0.2	85 (50:50)	88

[a] Reactions were carried out in $PhCF_3$−H_2O (2:1, v/v). [b] Combined yields. [c] Ratio for **6Da**:**8Da**. [d] Enantiostereoselectivities were determined by HPLC analysis.

$[IrCl(cod)]_2$ (6 mol %), and chiral ligand (12 mol %) in THF, and then the reaction mixture was stirred at 20 °C for 3 h (Table 4, entry 1). This monophasic reaction proceeded smoothly to give good yields of the products **6Da** and **8Da**, although a low regioselectivity was observed. Enantiomeric excess of **6Da** was determined to be 80% ee by high performance liquid chromatography analysis using Chiralcel AD-H. In contrast, the palladium-catalyzed reaction using Ph-pybox gave the linear product as major products. The replacement of THF−H_2O with toluene−H_2O led to a decrease in the enantioselectivity (entry 2). The biphasic reaction in CH_2Cl_2−H_2O also proceeded smoothly to give **6Da** in 82% ee (entry 3). The use of $PhCF_3$−H_2O (2:1, v/v) as a biphasic solvent led to an increase in regioselectivity to 80:20 and enantioselectivity to 87% ee (entry 4). The similar result was observed in $PhCF_3$−H_2O (1:2, v/v) (entry 5). Although the reaction using anhydrous MeCN as solvent proceeded smoothly to give the good yields of the products, a low enantioselectivity was observed. The absolute configuration of product **6Da** was determined to be *S* by converting **6Da** into authentic alcohol (*S*)-**12**.[17] The reduction of C=C and N−O bonds of **6Da** was achieved by hydrogenolysis in the presence of $Pd(OH)_2$.

The base dramatically influenced the reactivity, regioselectivity and enantioselectivity (Table 5). In the absence of base, the reaction did not proceeded (entry 1). When $BaCO_3$, $CsOH \cdot H_2O$, Cs_2CO_3 and NaOH were employed as a base, the reactions proceeded slowly to give the low yields of **6Da** with moderate enantioselectivities (entries 2−5). In the presence of TBAB, the reaction using NaOH gave the 86% ee of branched product **6Da** with a 75:25 regioselectivity (entry 6). In the presence of $Ca(OH)_2$, the branched product **6Da** was obtained with 88% ee within 0.2 h, although a significant amount of the linear product **8Da** was obtained (entry 7). Nevertheless,

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SCHEME 9

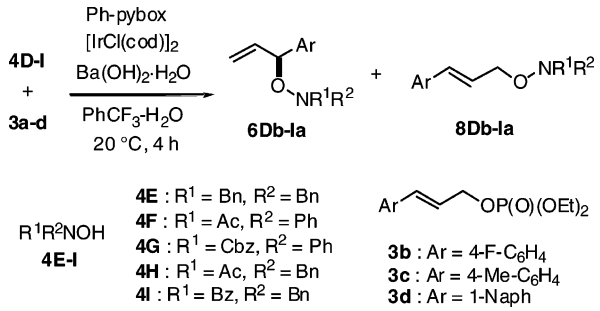

TABLE 6. Reaction of 3a−d with 4D−K in $PhCF_3$−H_2O[a]

entry	nucleophile	reagent	% yield[b] (ratio[c])	% ee[d]
1	**4E**	**3a**	no reaction	
2	**4F**	**3a**	75 (77:23)	82
3	**4G**	**3a**	63 (64:36)	68
4	**4H**	**3a**	70 (76:24)	82
5	**4I**	**3a**	68 (80:20)	87
6	**4D**	**3b**	61 (72:28)	62
7	**4D**	**3c**	67 (79:21)	72
8	**4D**	**3d**	60 (94:6)	78

[a] Reactions were carried out in $PhCF_3$−H_2O (2:1, v/v) in the presence of $Ba(OH)_2 \cdot H_2O$ (1 equiv). [b] Combined yields. [c] Ratio for **6Db**−**Ia**:**8Db**−**Ia**. [d] Enantiostereoselectivities were determined by HPLC analysis.

good ee values were obtained at lower reaction times with low regioselectivity, whereas the opposite effect had been noticed at longer reaction times using the bases shown in Table 5.

Next, several hydroxylamines **4D**−**I** and phosphates **3a**−**d** were employed under the optimized reaction conditions using $Ba(OH)_2 \cdot H_2O$ (Scheme 9). The reaction of **3a** with hydroxylamines **4F**−**I** containing an electron-withdrawing substituent proceeded smoothly to give the products **6Fa**−**Ia** and **8Fa**−**Ia** (entries 2−5). It is important to note that practically no reaction with *N*,*N*-dibenzyl hydroxylamine **4E** occurred under the similar reaction conditions (entry 1). These results indicate that the stabilization of conjugate base of hydroxylamines by an electron-withdrawing substituent is important for the iridium−pybox complex-catalyzed enantioselective allylic substitution as well as racemic reactions. Phosphates **3b**−**d** worked well, allowing facile incorporation of structural variety (entries 6−8).

Conclusions

We have clearly demonstrated that the oxygen atom of hydroxylamines acts as a reactive nucleophile in transition-metal-catalyzed allylic substitutions. The electron-withdrawing substituents on the nitrogen atom of hydroxylamine increased the acidity of the proton on the oxygen atom to generate an *O*-anion and decreased the nucleophilicity of the nitrogen atom. The linear *O*-allylated products were obtained in the palladium-catalyzed allylic substitution of allylic carbonates. The selective formation of the branched products was also observed in iridium-catalyzed reaction. In addition to the enantioselective allylic substitution with oximes,[5b] the enantioselective reaction with hydroxylamines disclosed a broader aspect of the utility of the iridium−pybox complex in allylic substitutions.

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Supporting Information Available: Experimental procedures and characterization data for all obtained compounds and ^{1}H and ^{13}C NMR spectra of all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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