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Selective Synthesis of Allylated Oxime Ethers and Nitrones Based on Palladium-Catalyzed Allylic Substitution of Oximes

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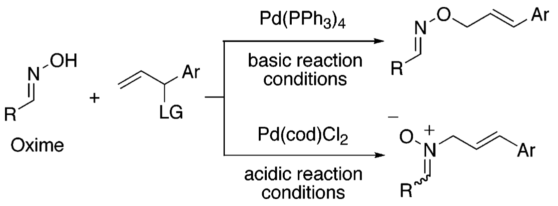

The viability of oximes as nucleophiles in transition-metal-catalyzed allylic substitution was examined. The oxygen atom of oxime acted as a reactive nucleophile in the reaction of a π-allyl palladium complex. In the presence of $Pd(PPh_3)_4$, the allylic substitution of oximes with allylic carbonate afforded the linear O-allylated oxime ethers selectively without a base. In contrast, the palladium-catalyzed reaction with allylic acetate proceeded smoothly in the presence of K_2CO_3 or Et_2Zn as a base. Selective formation of nitrones was achieved by using palladium(II) catalyst. In the presence of $Pd(cod)Cl_2$, the allylic substitution of oximes with allylic acetate afforded the N-allylated nitrones under solvent-free conditions, as a result of the reaction with the nitrogen atom of oximes.

Introduction

Oximes are attractive synthetic reagents for allylic substitution since they have both nitrogen and oxygen atoms as nucleophiles (Figure 1). However, the utility of oximes in transition-metal-catalyzed allylic substitution has not been investigated, except for the palladium-catalyzed reaction of oximes with butadiene.[1,2] Therefore, the viability of oximes as nucleophiles in allylic substitution is our initial focusing efforts. Particularly, our laboratory is interested in controlling the reactivity of the nitrogen and oxygen atoms of oxime by simply changing the reaction conditions. As our first successful result, we have recently reported the utility of oximes as oxygen nucleophiles in transition-metal-catalyzed allylic substitution to give oxime ethers selectively.[3] In this paper, we describe the in detail study of the selective synthesis of oxime ethers and nitrones by changing the palladium catalysts.

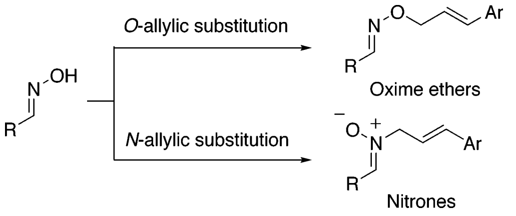

FIGURE 1. Allylic substitution of oximes.

Results and Discussion

Synthesis of Oxime Ethers Based on Palladium(0)-Catalyzed Allylic Substitution. Oxime ether has recently emerged as a valuable substrate for nucleophilic addition of organometallic reagents or radical species.[4,5] In general, oxime ether is prepared from *O*-alkyl hydroxylamine and its corresponding aldehyde. The direct preparation of oxime ethers from oximes has been commonly limited to the reaction of oxime with alkyl halide

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(1) Baker, R.; Nobbs, M. S. *Tetrahedron Lett.* **1977**, 3759.

(2) In a related study, the palladium-catalyzed deprotection of *O*-allyl oxime ethers and its application were reported. See: (a) Yamada, T.; Goto, K.; Mitsuda, Y.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 4557. (b) Suzuki, O.; Hashiguchi, Y.; Inoue, S.; Sato, K. *Chem. Lett.* **1988**, 291.

(3) (a) Miyabe, H.; Matsumura, A.; Yoshida, K.; Yamauchi, M.; Takemoto, Y. *Synlett* **2004**, 2123. (b) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 4631.

10.1021/jo050632+ CCC: $30.25

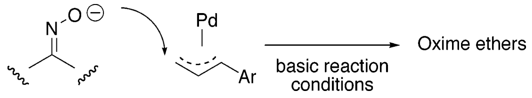

FIGURE 2. Oximes as oxygen atom nucleophiles.

SCHEME 1

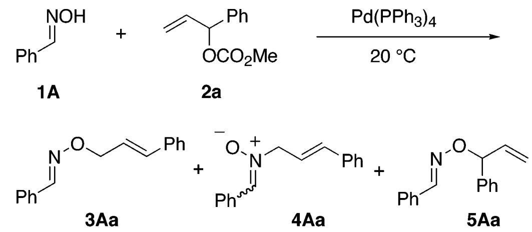

TABLE 1. Palladium(0)-Catalyzed Reaction of 1A with Carbonate 2a[a]

entry	solvent	time (h)	yield (%)[b]	ratio **3Aa**:**4Aa**:**5Aa**
1	EtOH	12	97	87:7:6
2	MeCN	1	98	84:7:9
3	THF	0.5	99	86:6:8
4	CH_2Cl_2	0.2	99	85:10:5

[a] Reactions were carried out using **1A** (1 equiv) and carbonate **2a** (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (4 mol %) at 20 °C. [b] Combined yields.

under basic conditions.[6] We have newly investigated an alternative direct approach based on transition-metal-catalyzed allylic substitution of oximes to address the O-allylated oxime ethers under basic reaction conditions (Figure 2).

Transition-metal-catalyzed allylic amination and alkylation have been developed as fundamentally important cross-coupling reactions.[7] In contrast, the corresponding reaction with oxygen nucleophiles has received much less attention due to the poor nucleophilic property of the oxygen atom,[8] although the useful allylic substitutions with alcohols under basic conditions have been recently reported.[9] We recently reported the utility of hydroxylamines having an N-electron-withdrawing substituent as oxygen nucleophiles in allylic substitution.[10] These results indicate that oxime would act as a soft nucleophile due to enhancing the acidity by a C=N bond.

As a preliminary experiment, the transition metal of choice was $Pd(PPh_3)_4$ since it has shown an excellent reactivity in allylic substitution of various nucleophiles.[7] We employed the *E*-oximes, after the separation of *E*- and *Z*-isomers. In the presence of $Pd(PPh_3)_4$ (4 mol %), a reaction of aldoxime **1A** with allylic carbonate **2a** was run at 20 °C (Scheme 1). As expected, oxime **1A** exhibited an excellent reactivity toward an electrophilic π-allyl palladium complex. The reaction in EtOH proceeded slowly to give linear oxime ether **3Aa**, linear nitrone **4Aa**, and branched oxime ether **5Aa** in 97% combined yield in an 87:7:6 ratio, after being stirred for 12 h (Table 1, entry 1). While in the case of the reaction in MeCN, the formation of products **3Aa**–**5Aa** was observed after being stirred for only 1 h (entry 2). With regard to the solvent effect, the replacement of EtOH by THF and CH_2Cl_2 also gave good results (entries 3 and 4). In our previous studies, the oxygen atom of hydroxylamines having an N-electron-withdrawing substituent and the nitrogen atoms of guanidine derivatives having two N-electron-withdrawing substituents acted as a reactive nucleophile in allylic substitution.[10,11] On the basis of these observations, it is noted that the stability of the conjugate base of oxime **1A** would be an important criteria for the nucleophilic property of an oxygen atom. Thus, a rational hypothesis of this reaction is that oxime **1A** would be effectively activated by methoxide generated from the carbonate **2a**.[12]

We next investigated the palladium-catalyzed reaction of oxime **1A** with allylic acetate **6a** (Scheme 2). The reaction with allylic acetate **6a** in THF proceeded slowly to give the products **3Aa**–**5Aa** in 20% combined yield,

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(4) For some examples of the addition of organometallic nucleophiles to the oxime ethers, see: (a) Cooper, T. S.; Laurent, P.; Moody, C. J.; Takle, A. K. *Org. Biomol. Chem.* **2004**, *2*, 265. (b) Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *Synlett* **1997**, 659. (c) Marco, J. A.; Carda, M.; Murga, J.; González, F.; Falomir, E. *Tetrahedron Lett.* **1997**, *38*, 1841. (d) Hanessian, S.; Lu, P.-P.; Sanceau, J.-Y.; Chemla, P.; Gohda, K.; Fonne-Pfister, R.; Prade, L.; Cowan-Jacob, S. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 3160. (e) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5273. (f) Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6745. (g) Dieter, R. K.; Datar, R. *Can. J. Chem.* **1993**, *71*, 814.

(5) For some examples of radical addition to oxime ethers, see: (a) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131. (b) Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569. (c) Miyabe, H.; Shibata, R.; Ushiro, C.; Naito, T. *Tetrahedron Lett.* **1998**, *39*, 631. (d) Miyabe, H.; Ushiro, C.; Naito T. *Chem. Commun.* **2000**, 1789. (e) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631. For reviews, see: (f) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (g) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140.

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(7) For some reviews, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (b) Trost, B. M. *Chem. Rev.* **1996**, *96*, 395. (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, pp 833–884. (e) Trost, B. M.; Lee, C. B. In *Catalytic Asymmetric Synthesis II*; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; pp 593–650. (f) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. (g) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(8) For some selected examples, see: (a) Stork, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073. (b) Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964. (c) Keinan, E.; Sahai, M.; Roth, Z. *J. Org. Chem.* **1985**, *50*, 3558. (d) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931. (e) Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585. (f) Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4877. (g) Trost, B. M.; Tang, W.; Schulte, J. L. *Org. Lett.* **2000**, *2*, 4013. (h) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2000**, *122*, 5012. (i) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **2001**, *66*, 6634. (j) Konno, T.; Nagata, K.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2002**, *67*, 1768.

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SCHEME 2

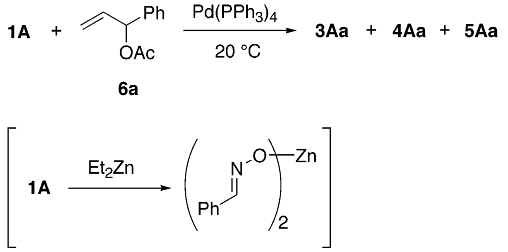


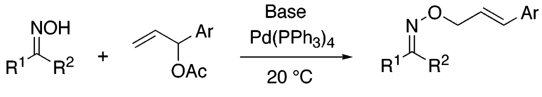
TABLE 2. Palladium(0)-Catalyzed Reaction of 1A with Acetate 6a

entry	solvent	base (1 equiv)	time (h)	yield (%)^a	ratio **3Aa**:**4Aa**:**5Aa**
1^b	THF	none	20	20	88:6:6
2^b	THF	K_2CO_3	6	82	90:4:6
3^b	THF	Et_3N	20	23	85:7:7
4^b	THF	DBU	20	21	88:0:2
5^b	THF	Et_2Zn	10	89	100: 0:0
6^c	CH_2Cl_2	none	24	27	94:3:3
7^c	CH_2Cl_2	K_2CO_3	7	86	96:2:2
8^c	CH_2Cl_2	Et_3N	24	38	90:5:5
9^c	CH_2Cl_2	DBU	24	48	92:8:0
10^c	CH_2Cl_2	Et_2Zn	24	74	92:8:0

^{a} Combined yields. ^{b} Reactions were carried out using **1A** (1 equiv) and acetate **6a** (1.5 equiv) in THF in the presence of $Pd(PPh_3)_4$ (8 mol %). ^{c} Reactions were carried out using **1A** (1 equiv) and acetate **6a** (1.5 equiv) in CH_2Cl_2 in the presence of $Pd(PPh_3)_4$ (6 mol %).

after being stirred for 20 h in the absence of base (Table 2, entry 1). This observation suggested that an acetoxy anion, generated from acetate **6a**, is less effective for activation of oxime **1A** as a base. Thus, several bases were employed to study the effect of bases (entries 2−5). In the presence of K_2CO_3, the reaction proceeded smoothly to give good yield of allylated products **3Aa**−**5Aa** within 6 h (entry 2). Amines, such as Et_3N and DBU, were less effective for this reaction (entries 3 and 4). Recently, a mild and an efficient method for allylic etherification using zinc alkoxides was reported by Lee's group.[9e] To test the viability of zinc alkoxides generated from oximes (Scheme 2), the reaction of oxime **1A** was investigated in the presence of Et_2Zn. As expected, the selective formation of the linear oxime ether **3Aa** was observed by using Et_2Zn as a base (entry 5). With regard to the solvent effect, the reactions also proceeded smoothly in CH_2Cl_2, and the similar trend was observed (entries 6−10).

SCHEME 3



1A-G **6a-i** **3Ab-Ga**

A : R^1 = Ph, R^2 = H
B : R^1 = 4-F_3C-C_6H_4, R^2 = H
C : R^1 = 4-MeO-C_6H_4, R^2 = H
D : R^1 = 2-Py, R^2 = H
E : R^1 = Ph, R^2 = Ph
F : R^1 = R^2 = $(CH_2)_5$
G : R^1 = CO_2Me, R^2 = H

a : Ar = Ph
b : Ar = 4-F_3C-C_6H_4
c : Ar = 4-MeO-C_6H_4
d : Ar = 1-Naph
e : Ar = 2-Naph
f : Ar = 4-F-C_6H_4
g : Ar = 3-Cl-C_6H_4
h : Ar = 4-Cl-C_6H_4
i : Ar = 4-Me-C_6H_4

TABLE 3. Palladium(0)-Catalyzed Reaction of 1A−G with Acetates 6a−i in the Presence of Et_2Zn^{a}

entry	reagent	substrate	time (h)	product	yield (%)^b
1	**6b**	**1A**	10	**3Ab**	89
2	**6c**	**1A**	10	**3Ac**	79
3	**6d**	**1A**	10	**3Ad**	91
4	**6e**	**1A**	10	**3Ae**	94
5	**6f**	**1A**	10	**3Af**	92
6	**6g**	**1A**	10	**3Ag**	89
7	**6h**	**1A**	10	**3Ah**	79
8	**6i**	**1A**	10	**3Ai**	89
9	**6a**	**1B**	5	**3Ba**	78
10	**6a**	**1C**	10	**3Ca**	95
11	**6a**	**1D**	20	**3Da**	37
12	**6a**	**1E**	15	**3Ea**	88
13	**6a**	**1F**	20	**3Fa**	78
14	**6a**	**1G**	5	**3Ga**	53

^{a} Reactions were carried out using **1A**−**G** (1 equiv) and acetate **6a**−**i** (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (8 mol %) and Et_2Zn (1 equiv) in THF. ^{b} Isolated yields of linear oxime ethers **3Ab**−**Ga**.

To examine the effect of allylic reagents, we next investigated the palladium-catalyzed reactions of **1A** with allylic acetates **6b**−**i** bearing a variety of substituents (Scheme 3). The reactions were carried out in THF in the presence of Et_2Zn (Table 3, entries 1−8). As expected, allylic reagents having electron-withdrawing or electron-donating substituents on the aromatic ring also worked well. The reaction with bulky allylic reagents having 2-naphthyl or 1-naphthyl substituents also gave good yields of oxime ethers **3Ad** and **3Ae**, allowing a facile incorporation of structural variety (entries 3 and 4). To access the scope of the allylation, we also studied the reaction with aliphatic allylic acetates. Although ^{1}H NMR analysis of the roughly purified product seemed to indicate the formation of oxime ether, the corresponding oxime ether was not isolated as a pure form after purification. We next studied the effect of oximes (entries 9−14). The reaction of aldoxime **1B** containing an electron-withdrawing substituent proceeded smoothly to give the product **3Ba** after being stirred for only 5 h, probably due to the extra stabilization of conjugate base of **1B** by an electron-withdrawing substituent (entry 9). The aldoxime **1C** containing an electron-donating substituent, which was assumed to be less reactive than **1A**, also produced an excellent yield of oxime ether **3Ca** (entry 10). However, a modest yield was observed in the reaction of aldoxime **1D** containing a basic 2-pyridinyl group (entry 11). It should be noted that a bulky ketoxime **1E** also worked well under similar reaction conditions to give the product **3Ea** in 88% yield (entry 12). Additionally, aliphatic ketoxime **1F**, which would be the most unreactive,[12] also worked well to give 78% yield of the product **3Fa**, after being stirred for 20 h (entry 13). These results supported the idea that the nucleophilic property and reactivity of oximes were dependent on the stability of the conjugate base of oximes. Although glyoxylic oxime **1G** has shown high reactivity due to a neighboring

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(13) Ryu and Komatsu reported that Et_2Zn can serve as a radical initiator in the absence of O_2. See: (a) Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335. For studies on Et_2Zn-induced radical reactions, see: (b) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. (c) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951. (d) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito T. *J. Org. Chem.* **2000**, *65*, 176. (e) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443.

TABLE 4. Palladium(0)-Catalyzed Reaction of 1A–G with Acetates 6a–f in the Presence of K_2CO_3[a]

entry	reagent	substrate	product	yield (%)[b]
1	**6b**	**1A**	**3Ab**	80
2	**6c**	**1A**	**3Ac**	71
3	**6f**	**1A**	**3Af**	72
4	**6a**	**1E**	**3Ea**	67
5	**6a**	**1G**	**3Ga**	75

[a] Reactions were carried out using **1A–G** (1 equiv) and acetate **6a–f** (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (6 mol %) and K_2CO_3 (1 equiv) in CH_2Cl_2 for 7 h. [b] Isolated yields of linear oxime ethers **3Ab–Ga**.

electron-withdrawing substituent, a modest yield was observed in the presence of Et_2Zn, as a result of competitive ethyl radical addition to product **3Ga** (entry 14).[13]

Several examples of the palladium-catalyzed reactions using K_2CO_3 as a base in CH_2Cl_2 are shown in Table 4. Allylic reagents **6b**, **6c**, and **6f** having electron-withdrawing or electron-donating substituents and a bulky ketoxime **1E** worked well (entries 1–4). Compared to the reaction of glyoxylic oxime **1G** using Et_2Zn, the reaction of **1G** using K_2CO_3 afforded a good yield of product **3Ga** because no competitive radical addition reaction occurred (entry 5). All oxime ethers **3** and **5** were obtained as *E*-isomers. According to our previous studies on oxime ethers,[5,14] *E*- and *Z*-configurations of oxime ethers were assigned by ^1H NMR spectroscopy. In general, the signals due to the imino hydrogen of the *E*-oxime ethers are shifted downfield by the influence of the alkoxy group of the oxime ether moiety.[15]

Synthesis of Nitrones Based on Palladium(II)-Catalyzed Allylic Substitution. Nitrones are well-known to be reactive substrates for 1,3-dipolar cycloaddition reactions, nucleophilic addition of organometallic reagents, and so on.[16,17] Nitrones have also evolved as a useful trap for short-lived reactive radicals.[18] Recently, the synthetically useful radical reactions of nitrones have been reported.[19] For the selective synthesis of nitrones, we have next focused our efforts toward N-allylic substitution of oximes.

N-Alkylation of oximes has been found to be the most useful for the synthesis of nitrones as well as the condensation between a carbonyl compound and N-substituted hydroxylamine.[16] The nitrogen lone pair on the oxime is considered to be more nucleophilic than the oxygen lone pairs; however, mixtures of N-alkylated and O-alkylated products are often still obtained.[20] Recently, Kanemasa reported that the conjugate addition of oximes took place at a nitrogen atom of oxime in the presence of Lewis acid to afford the nitrones.[21] Therefore, we considered that the selective synthesis of nitrones would be achieved under the acidic reaction conditions (Figure 3).

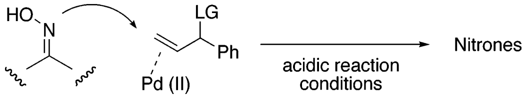
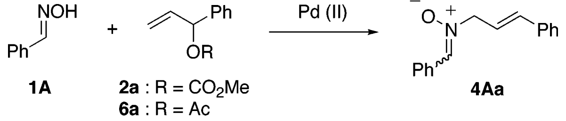


FIGURE 3. Oximes as nitrogen atom nucleophiles.

SCHEME 4



Palladium(II)-catalyzed reactions are important in organic transformations.[22] Palladium(II) catalysts form a complex with π-electrons of alkene or alkyne multiple bonds, facilitating the nucleophilic attack to carbon–carbon multiple bonds to give an organopalladium intermediate.[23] Recently, the novel palladium(II)-catalyzed intramolecular allylic substitution was reported.[24] Thus, the palladium(II)-catalyzed intermolecular allylic substitution is a challenging problem. Next, the allylic substitution of oxime **1A** was examined by using a palladium(II) catalyst having a Lewis acidic property, and the selective formation of nitrones was observed. (Scheme 4).

At first, several palladium(II) catalysts were tested (Table 5). In the presence of $Pd(MeCN)_2Cl_2$ (10 mol %), treatment of oxime **1A** with allylic acetate **6a** at 20 °C

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(14) (a) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397. (b) Miyabe, H.; Kanehira, S.; Kume, K.; Kandori, H.; Naito, T. *Tetrahedron* **1998**, *54*, 5883. (c) Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618.

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TABLE 5. Palladium(II)-Catalyzed Reaction of 1A with Carbonate 2a or Acetate 6a[a]

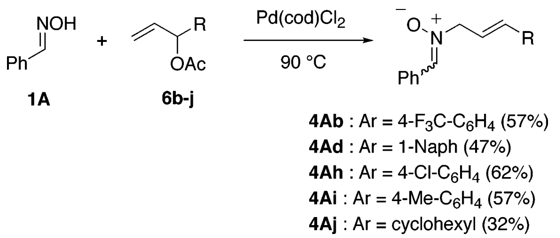
entry	catalyst	reagent	*T* (°C)	time (h)	% yield (ratio)[b]
1	$Pd(MeCN)_2Cl_2$	**6a**	20	24	14 (1:1.4)
2	$Pd(MeCN)_2Cl_2$	**6a**	50	24	37 (1:0.9)
3	$Pd(MeCN)_2Cl_2$	**6a**	90	6	64 (1:0.5)
4	$Pd(MeCN)_2Cl_2$	**2a**	90	6	37 (1:0.2)
5	$Pd(PhCN)_2Cl_2$	**6a**	90	6	37 (1:0.5)
6	$Pd(OCOCF_3)_2$	**6a**	90	6	18 (1:1)
7	Pd(cod)Cl_2	**6a**	90	6	65 (1:0.5)
8	Pd(cod)Cl_2	**2a**	90	6	53 (1:0.4)

[a] Reactions were carried out using **1A** (1 equiv) and reagent **6a** or **2a** (1.5 equiv) in the presence of the Pd(II) catalyst (10 mol %). [b] Isolated yields of **4Aa**. Ratio is for *Z*:*E*-isomers.

under solvent-free conditions led to the isolation of nitrone **4Aa** in 14% yield as an *Z*/*E* mixture, and the starting material **1A** was recovered in 73% yield (entry 1). The stereochemistry of nitrone **4Aa** is assigned on the basis of nOe studies.[25] The reaction temperature dramatically influenced the reactivity. When the reaction was carried out at 90 °C, the reaction proceeded smoothly to give 64% yield of **4Aa** (entry 3). The reaction of **1A** with allylic carbonate **2a** resulted in a decrease in the yield of product (entry 4). Although the use of $Pd(PhCN)_2Cl_2$ and $Pd(OCOCF_3)_2$ decreased the yield of products (entries 5 and 6), Pd(cod)Cl_2 showed good catalytic activity (entries 7 and 8). In the case of alkylation of oximes, it is known that the geometry of the oxime affects the stereoselectivity of the subsequent nitrone-forming reaction, with *anti*-aryloximes affording nitrones, whereas *syn*-aryloximes favor the formation of oxime ethers.[20a] It is noteworthy that the selective formation of nitrone **4Aa** was achieved in the palladium(II)-catalyzed allylation of *anti*-aryloxime (*E*-oxime) **1A**. Additionally, the isomerization between *E*-nitrone and *Z*-nitrone was observed under the reaction conditions. Initially, the palladium(II) catalyst activated the C=C bond of **6a**, and then, the nucleophilic nitrogen of oxime **1A** added to the palladium(II) complex to give nitrone **4Aa**.[24] O-Allylated oxime ether is known to undergo a reversible formal [2,3]-sigmatropic shift giving N-allylated nitrone.[26] Therefore, we also tested the [2,3]-sigmatropic rearrangement of oxime ether **3Aa** under the present reaction conditions. However, the formation of nitrone was not observed; thus, the [2,3]-sigmatropic rearrangement is not an important reaction pathway giving nitrone.[27]

Next, the reaction of **1A** with various allylic acetates **6b**−**j** was examined in the presence of Pd(cod)Cl_2 (10 mol %) (Scheme 5). All experiments were carried out under solvent-free conditions at 90 °C for 6 h. The palladium(II)-catalyzed allylic substitution tolerated substitution on aromatic ring. The nitrones **4Ab**, **4Ah**, and **4Ai** were obtained in 57−62% yields as *Z*/*E* mixtures, although the reaction with acetate **6d** having a bulky 1-naphthyl group decreased the yield of product **4Ad**. The aliphatic acetate **6j** also worked, although a moderate yield of product **4Aj** was observed, probably due to less stability of **4Aj**.

SCHEME 5



SCHEME 6

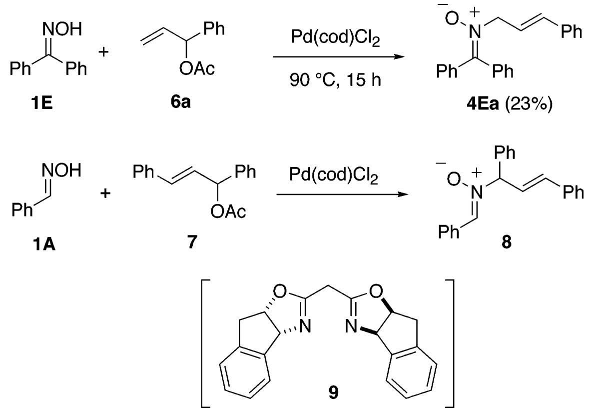


TABLE 6. Palladium(II)-Catalyzed Reaction of 1A with Acetates 7[a]

entry	additive	*T* (°C)	time (h)	yield (%)[b]
1		90	6	14
2	ligand **9**	90	3	34
3	ligand **9**	20	24	68

[a] Reactions were carried out using **1A** (1 equiv) and acetate **7** (1.5 equiv) in the presence of Pd(cod)Cl_2 (10 mol %). [b] Isolated yields of nitrone.

Reaction scope was assessed by employing the bulky ketoxime **1E** and diphenyl allylic acetate **7** (Scheme 6). The overall difference in steric factor was important for the palladium(II)-catalyzed allylic substitution of oximes. The steric congestion around the carbon−nitrogen double bond of oxime **1E** affected the reaction time and yield of the product. The desired nitrone **4Ea** was obtained only in 23% yield, accompanying the recovered oxime **1E** in 42% yield, after being stirred at 90 °C for 15 h.

The structure of allylic acetate also had a substantial effect on the yield of product. To test the reactivity, the racemic substrate **7** was employed. After several investigations, it was found that the ligand was necessary for an efficient reaction of **1A** with the bulky diphenyl allylic acetate **7** (Table 6). On the other hand, the reaction without ligand proceeded in only 14% yield (entry 1), and the reaction proceeded effectively in the presence of box ligand **9** (entries 2 and 3). Notably, the use of ligand **9** at 20 °C resulted in an improvement of product yield, furnishing a 68% yield of reaction product **8** after being stirred for 24 h (entry 3). Although several other chiral box ligands were tested, no enantioselectivity of **8** was

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[25] The irradiation of the allylic −CH_2N proton of *Z*-nitrone **4Aa** effected an enhancement on the imino CH=N proton. See: Figure 1 in Supporting Information.

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[27] The 2,3-sigmatropic shift of oxime ether **3Aa** was also tested under Grigg's reaction conditions. However, the 2,3-sigmatropic shift was not observed, and oxime ether **3Aa** was completely recovered, probably due to the highly stabilized cinnamyl moiety on **3Aa** by resonance effect with the phenyl group.

observed. We also tested the kinetic resolution of the racemic substrate **7** with 0.5 equiv of oxime by using chiral ligand **9**. However, the racemic nitrone **8** was obtained with low chemical efficiency. In the reaction with **7**, only a single *Z*-isomer was obtained due to steric factors.

Conclusions

We have clearly demonstrated that the oxygen atom of oxime acts as a reactive nucleophile in palladium(0)-catalyzed allylic substitution. The O-allylated oxime ethers were selectively obtained in the reaction with allylic carbonates or acetates. The allylic substitution with the nitrogen atom of oxime was achieved by using a palladium(II) catalyst having a Lewis acidic property. The selective formation of N-allylated nitrones was observed in the reaction mainly under solvent-free conditions.

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

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