O-Allylic Substitution of Hydroxylamine Derivatives Having an N-Electron-Withdrawing Substituent

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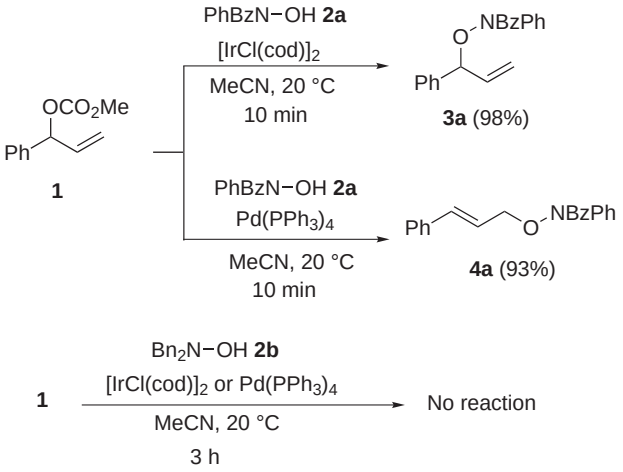
Abstract: The O-allylic substitution of hydroxylamines having an N-electron-withdrawing substituent proceeded smoothly to afford O-allylated products by using $[IrCl(cod)]_2$ or $Pd(PPh_3)_4$.

Key words: allylations, iridium, palladium, cyclizations, metathesis

Transition metal-catalyzed allylic amination and alkylation have been developed as a fundamentally important cross-coupling reaction.[1] In contrast, the corresponding reaction with oxygen nucleophiles has not been widely studied due to the poor nucleophilic property of the oxygen atom and poor regioselectivity attained in the reaction.[2] Therefore, O-allylic substitution is largely limited to carboxylate and phenolic nucleophiles.[2] Recently, a few studies have been directed toward allylic substitution with alcohols under basic conditions.[3] Herein, we now report the utility of hydroxylamines having an N-electron-withdrawing substituent as an oxygen nucleophile in transition metal-catalyzed allylic substitution. We also report the N,O-diallylation of hydroxylamines and an application to novel cyclization.[4]

Hydroxylamine derivatives would be an attractive synthetic reagent for allylic substitution, since they have nitrogen and oxygen atoms as a nucleophile. 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.[5] In the presence of $[IrCl(cod)]_2$ (4 mol%), a reaction of allylic carbonate **1** with *N*-benzoyl-*N*-phenylhydroxylamine (**2a**) was run in MeCN at 20 °C for 10 min (Scheme 1). The *N*-benzoyl-*N*-phenylhydroxylamine (**2a**) worked well as an oxygen nucleophile to give the branched O-allylated product **3a** in 98% yield with excellent regioselectivity.[6] In contrast, the palladium-catalyzed reaction afforded the linear product **4a** in 93% yield. In these reactions, the solvent influenced the reactivity of *N*-benzoyl-*N*-phenylhydroxylamine (**2a**). A polar solvent such as MeCN gave the best result, while nonpolar solvents such as benzene and toluene gave poor yields of the products. We also investigated the iridium and palladium-catalyzed reactions of **1** with *N*,*N*-dibenzylhydroxylamine **2b** under similar reaction conditions. However, practically no reaction of **1** with *N*,*N*-dibenzylhydroxylamine (**2b**) occurred after being stirred at 20 °C for 3 h. These observations suggest that the *N*-electron-withdrawing substituent would be important for the nucleophilic property of an oxygen atom on hydroxylamine. A rational hypothesis of these reactions is that hydroxylamine **2a** would be effectively activated by methoxide generated from **1**.



Scheme 1

We next studied the reaction of **1** with *N*-Boc-hydroxylamine (**2c**) (Scheme 2). In the case of **2c**, both nitrogen and oxygen atoms on hydroxylamine acted as a nucleophile. The iridium-catalyzed reaction afforded 37% yield of O-allylated product **3c** and 53% yield of N-allylated product **5**, after being stirred at 20 °C for 3 h. In the case of the palladium-catalyzed reaction, the O-allylation was mainly observed to give the O-allylated product **4c** in 67% yield, accompanied with a small amount of N-allylated product **6**.

Since the π-allyl palladium complex has shown excellent reactivity toward hydroxylamines, we next studied the palladium-catalyzed N,O-diallylation of hydroxylamines (Scheme 3). As expected, the formation of N,O-diallylated products **7c** and **7d** was observed in the reaction of **1** (2.5 equiv) with *N*-Boc-hydroxylamine (**2c**) or *N*-Cbz-hydroxylamine (**2d**). The additional allylation of the branched hydroxylamines **3c** and **5**, prepared from the iridium-catalyzed reaction, was also tested (Scheme 2). In

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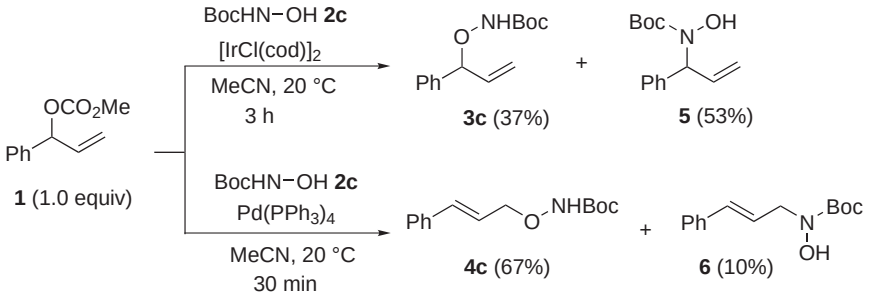
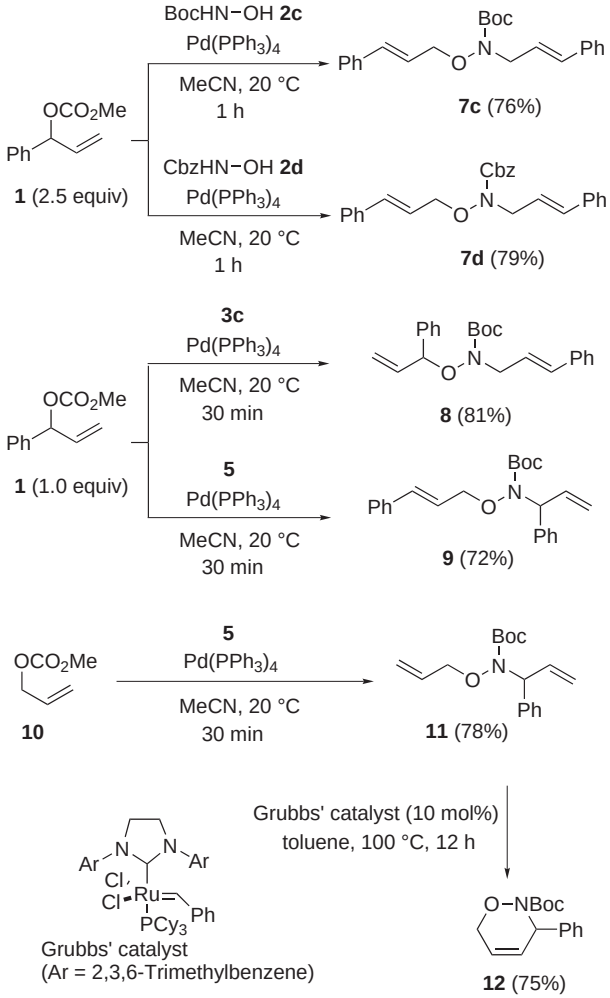


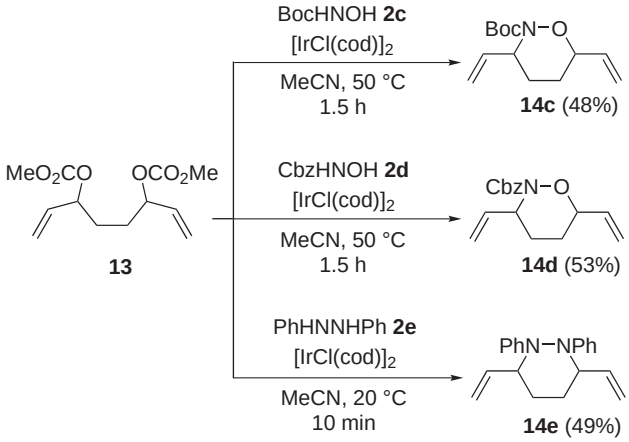
Scheme 2

the presence of $Pd(PPh_3)_4$, the N-allylation of **3c** proceeded smoothly to give the N,O-diallylated product **8**, which has the N-linear and O-branched substituents. The O-allylation of **5** also proceeded smoothly to give the O-linear and N-branched product **9** in 72% yield. We next studied the utility of the O,N-disubstituted hydroxylamine for a temporary tether in the ring-closing metathesis.[7] The N,O-disubstituted hydroxylamine **11** was prepared from the reaction of **10** with **5**. Treatment of **11** with Grubbs' catalyst in toluene furnished the cyclic product **12** in 75% yield.[8]



Scheme 3

The iridium-catalyzed allylation using hydroxylamines was successfully applied to a novel tandem cyclization of **13** (Scheme 4). In the presence of $[IrCl(cod)]_2$, the reaction of **13** with *N*-Boc-hydroxylamine (**2c**) proceeded smoothly to give the six-membered product **14c** in 48 yield, after being stirred at 50 °C for 1.5 hours.[9] The reaction of **13** with *N*-Cbz-hydroxylamine (**2d**) afforded the cyclic product **14d** in 53% yield. In contrast, the reaction of **13** with *N*-benzylhydroxylamine did not give a cyclic product. For comparison with hydroxylamines, the reaction of **13** with hydrazines was studied. In contrast to hydroxylamines, the hydrazines having N-electron-withdrawing substituents such as *N*,*N*′-di-Boc-hydrazine did not work. The effective formation of cyclic product **14e** was observed when *N*,*N*′-diphenylhydrazine (**2e**) was employed.



Scheme 4

In conclusion, the oxygen atom of hydroxylamines having an N-electron-withdrawing substituent acted as a reactive nucleophile in the iridium- or palladium-catalyzed allylic substitution.

A mixture of **13** (100 mg, 0.388 mmol), hydroxylamines **2c** or **2d** (0.388 mmol), and $[IrCl(cod)]_2$ (10 mg, 0.0155 mmol) in MeCN (1.0 mL) was stirred under argon atmosphere at 50 °C for 1.5 h. The reaction mixture was concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane–EtOAc, 10:1) afforded **14c** or **14d**.

Major isomer of **14c**: IR ($CHCl_3$) 1698 cm^{-1}; ^1H NMR (500 MHz , $CDCl_3$) δ 6.06–5.90 (2 H, m), 5.29–5.12 (4 H, m), 4.48 (2 H, br s),

2.03 (2 H, m), 1.56 (2 H, m), 1.43 (9 H, s); ^{13}C NMR (125 MHz , $CDCl_3$) δ 154.8, 136.4, 135.6, 117.0, 115.9, 80.9, 79.1, 56.9, 28.3, 23.9, 23.6; HRMS: Calcd for $C_{13}H_{21}NO_3$ (M^+): 239.1521, Found: 239.1525.

Major isomer of **14d**: IR ($CHCl_3$) 1697 cm^{-1}; ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.37–7.30 (10 H, m), 5.95–6.08 (4 H, m), 5.12–5.33 (12 H, m), 4.63–4.64 (2 H, m), 4.55 (2 H, br s), 1.61–2.15 (8 H, s); ^{13}C NMR (125 MHz , $CDCl_3$) δ 155.3, 136.1, 135.9, 135.0, 128.3, 127.9 (2 C), 117.4, 116.4, 79.4, 67.2, 56.6, 23.6, 23.2; HRMS: Calcd for $C_{16}H_{19}NO_3$ (M^+): 273.1365, Found: 273.1358.

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(9) The cyclic products **14c**–**e** were obtained as a diastereomeric mixture in about 10:1 ratio by ^{1}H NMR, although these stereochemistries have not be determined.