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Akimichi Ohtsuki, Shun Sakurai, Mamoru Tobisu,* and Naoto Chatani*

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Nickel-catalyzed Ring-opening Cross-coupling of Cyclic Alkenyl Ethers with Arylboronic Esters via Carbon–Oxygen Bond Cleavage

Akimichi Ohtsuki,1 Shun Sakurai,2 Mamoru Tobisu,*1,2 and Naoto Chatani*,2

¹Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan ²Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

(E-mail: tobisu@chem.eng.osaka-u.ac.jp; chatani@chem.eng.osaka-u.ac.jp)

We have developed a nickel-catalyzed cross-coupling reaction of cyclic alkenyl ethers with arylboronic esters that leads to the formation of unsaturated alcohols via ringopening by the cleavage of a $C(sp^2)$ -O bond. The use of 1,3dicyclohexylimidazol-2-ylidene as the ligand is essential to promote this cross-coupling process.

In the field of cross-coupling chemistry, development of methods that use phenol or its non-activated derivatives (e.g., anisole or phenyl pivalate) as one of the coupling partners has gained considerable attention because phenols are abundant in nature.¹ Alkenyl ethers^{2,3} and esters^{4,5} have also been used as readily available, waste-less alternatives to alkenyl halides in cross-coupling reactions to form substituted alkenes. If these methods can be extended to cyclic alkenyl ethers, such as 2,3dihydrofuran and 3,4-dihydro-2H-pyran (1), unsaturated alcohols would be formed through ring-opening crosscoupling (Scheme 1). In 1979, Wenkert and coworkers first realized this type of ring-opening cross-coupling using ArMgX as a nucleophile in the presence of a nickel catalyst.^{2a} Since then, considerable progress has been made in ringopening Kumada-Tamao-Corriu type cross-coupling of cyclic alkenyl ethers, allowing its application in natural product synthesis,6 and low temperature chemoselective crosscoupling,^{2f} and extension to alkylation^{2h,2j} and alkynylation.^{2g} Rueping reported that an organolithium reagent can also serve as a suitable nucleophile for this ring-opening crosscoupling.2i Herein, we report the use of an organoboron nucleophile for the cross-coupling of cyclic alkenyl ethers.

Scheme 1. Nickel-catalyzed ring-opening cross-coupling of cyclic alkenyl ethers.



During the course of our investigation on the cross-coupling reaction of aryl ethers with organoboron reagents,⁷ we found that alkenyl ethers are also similarly cross-coupled using Ni(cod)₂/PCy₃ as a catalyst.^{2c} Therefore, we initiated our investigation by simply applying the Ni(cod)₂/PCy₃ system to the reaction of **1** with boronic ester **2a** (Table 1). Unfortunately, the desired product **1a** was not formed under

these conditions (Entry 1). Our success in catalytic activation of inert C-O bonds using an NHC ligand^{2g,2h,7b,8} immediately led us to examine a series of NHC ligands in this ring-opening cross-coupling reaction. Although NHC ligands bearing aromatic (Entries 2 and 3) and adamantyl groups (Entries 4 and 5) at their nitrogen atoms failed to give 1a, the use of cyclohexyl-substituted NHC (ICy) led to the formation of 1a in 10% yield (Entry 6). The yield of 1a was markedly increased to 80% by raising the reaction temperature to 140 °C (Entry 7). Interestingly, comparable reactivity was observed even when the reaction was conducted in the absence of a stoichiometric amount of an external base (i.e., CsF) (Entry 8).8f The stereochemistry of the alkene moiety in 1a was determined to be exclusively E based on ¹H NMR analysis. This stereochemical outcome is in sharp contrast to the reactions using Grignard^{2a,2f,2g,2h,2j} and organolithium²ⁱ reagents, in which the Z isomer is selectively formed.

Table 1. Optimization of reaction conditions^a



^aReaction conditions: **1** (0.50 mmol), 2a (0.60 mmol), Ni(cod)₂ (0.050 mmol), ligand (0.10 mmol), and NaO'Bu (0.10 mmol) in toluene (1.5mL) for 12 h. ^bRun in the absence of NaO'Bu. ^cRun in the absence of CsF.

Examination of the time dependence of the E/Z ratio of **1a** revealed that the Z isomer was formed predominantly at the beginning of the reaction and the selectivity for the E isomer increased as the reaction time extended (Table 2). These

results indicate that the cross-coupling reaction proceeds in a Z-selective manner as in the reactions using Grignard or organolithium reagents, but the product can isomerize under the catalytic conditions. To obtain some insight into the factor(s) controlling this isomerization process, we conducted several control experiments using independently synthesized Z-1a (Table 3). Although Z-1a was geometrically stable when heated at 140 °C for 12 h, isomerization occurred when a catalytic amount of either Ni(cod)₂ or ICy·HCl and NaO'Bu were present. Complete isomerization to E-1a took place under the catalytic conditions used for the ring-opening cross-coupling of 1a (Entry 4).⁹

Table 2. Time dependence of the E/Z ratio



Table 3. Isomerization of 1a under various conditions



The scope of the Ni/ICy-catalyzed reaction of 1 with different organoboron reagents was investigated (Table 4). Although we used neopentylglycol-protected boronic ester 2a in our initial optimization studies, pinacolate ester 2b also reacted with comparable efficiency. The reaction did not proceed when arylboronic acid 2c was used. Bulky aryl groups such as the ortho-tolyl moiety in 2d can be introduced successfully. This ring-opening cross-coupling is sensitive to the electronic nature of the boronic esters, with electron-rich boron reagents being generally more reactive. Although the Ni/ICy system is known to promote the cleavage of C-O bonds in methoxyarenes, no byproducts arising from C-OMe cleavage were observed in the reaction using 2g. Carbonyl functionalities including ester 2j and carbamate 2i were compatible with this nickel-catalyzed ring-opening cross-

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coupling. Alkenyl alcohols bearing naphthyl and indolyl groups can also be synthesized by the reaction using **2k** and **2l**, respectively.

Table 4. Scope of boron reagents^a



^aReaction conditions: **1** (0.50 mmol), **2b-1** (0.60 mmol), Ni(cod)₂ (0.050 mmol), ICy·HCl (0.10 mmol), and NaO'Bu (0.10 mmol) in toluene (1.5 mL) at 140 °C for 12 h. Ratios in parentheses refer to the *E/Z* ratio of the product determined by ¹H NMR spectroscopy. ^bRun in the presence of CsF (1.0 mmol) using 1.0 mmol of boronic ester.

This ring-opening cross-coupling was successfully applied to 2,3-dihydrofuran (3), leading to the formation of γ , δ -unsaturated alcohol **3a** (Table 5). The arylation occurred smoothly even when more sterically demanding trisubstituted alkenes, such as **5** and **6**, were used. Unsaturated diol derivatives can also be synthesized by the ring-opening arylation of **7**. Benzofuran was unreactive under these conditions. This protocol was also applicable to acyclic alkenyl ether **8**.

In summary, we developed a nickel-catalyzed ringopening arylation of cyclic alkenyl ethers using organoboron reagents. The ICy ligand is uniquely effective among the ligands examined, demonstrating outstanding activity of ICy for the activation of ether C-O bonds. The current method allows **1** and **3** to serve as readily available, waste-less C4 and C5 sources that can be introduced onto aromatic rings. Further investigation of nickel-catalyzed cross-coupling reactions of ethers is ongoing in our laboratories.

Table 5. Scope of alkenyl ethers^a



^aReaction conditions: alkenyl ether (0.50 mmol), **2a** (0.60 mmol), Ni(cod)₂ (0.050 mmol), ICy·HCl (0.10 mmol) and NaO'Bu (0.10 mmol) in toluene (1.5 mL) at 140 °C for 12 h. Ratios in parentheses refer to the E/Z ratio of the product determined by ¹H NMR spectroscopy. ^bRun using **2a** (1.0 mmol), Ni(cod)₂ (0.10 mmol), ICy·HCl (0.20 mmol) and NaO'Bu (0.20 mmol). °This ratio is that of the *E* and *Z* isomers of **5a** to an exo alkene isomer [*i.e.*, 5-(p-tolyl)hex-5-en-1-ol]. ^dPhenylboronic ester was used instead of **2a** to avoid the complexity associated with the formation of the E/Z isomers.

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Supporting Information is also available electronically on J-Stage.

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