Transition-Metal Catalysis

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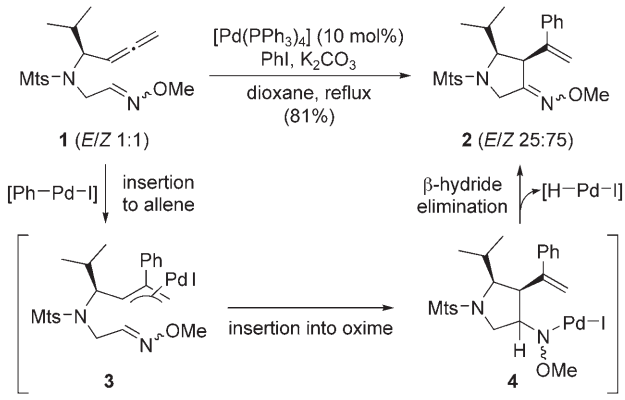
Heck-Type Cyclization of Oxime Ethers: Stereoselective Carbon–Carbon Bond Formation with Aryl Halides To Produce Heterocyclic Oximes**

Hiroaki Ohno, Akimasa Aso, Yoichi Kadoh, Nobutaka Fujii, and Tetsuaki Tanaka**

The insertion of a carbon–carbon multiple bond into a metal–carbon bond is an important step in many palladium-catalyzed transformations. The facile insertion not only of alkenes or alkynes, but also of carbon–nitrogen multiple bonds, has received increasing attention in the past decade. It is well understood from extensive studies by Yamamoto and co-workers that highly nucleophilic bis-π-allylpalladium(II) complexes react with imines to give homoallylic amines by an addition-type reaction.[1–3] Larock and co-workers reported addition-type intra- and intermolecular carbopalladation reactions of nitrile compounds to give aryl ketones.[4,5] Evidence for the insertion of an imine into a palladium–acyl bond[6] to give a palladacycle was presented independently by the research groups of Arndtsen and Sen.[7,8] In contrast, Heck-type insertion–elimination reactions of carbon–nitrogen multiple bonds are extremely limited. Yamamoto and co-workers reported the palladium-catalyzed formation of an indole in a reaction that can be rationalized as the insertion of an imine into a vinylpalladium(II) halide to form a carbon–carbon bond, followed by β-hydride elimination.[9,10] The lack of precedent for the Heck-type reaction of a carbon–nitrogen multiple bond, other than relatively facile indole formation, owes partly to the coordination character of these molecules: Whereas alkenes and alkynes readily form π complexes, which are generally required for the insertion process, the imino ligand is bound to the palladium atom by σ donation of the lone pair of electrons on the nitrogen atom; π complexation of the imine is not favored.[5c,7,8]

During the course of our investigations directed toward the development of novel cyclization reactions of allenic compounds that have an additional multiple bond,[11,12] we observed that the allenic oxime ether **1** underwent unusual palladium-catalyzed carbon–carbon bond formation in the presence of iodobenzene to give the heterocyclic oxime ether **2** (Scheme 1). One rationale for this reaction would be the



Scheme 1. Cyclization of the allenic oxime ether **1**, and a plausible mechanism. Mts = 2,4,6-trimethylphenylsulfonyl.

insertion of phenylpalladium(II) iodide generated in situ into the allenic moiety of **1** followed by an insertion–elimination sequence of the resulting π-allyl palladium intermediate **3**. Although some palladium-catalyzed reactions of imines, such as [2,3] sigmatropic rearrangement,[13] carbon–nitrogen bond formation,[14] carbon–carbon bond cleavage,[15] and oxidative C–H activation,[16] have been reported, the reaction shown in Scheme 1 is the first example of palladium-catalyzed carbon–carbon bond formation with oxime ethers.[17] Herein we describe the first intramolecular Heck-type reaction of oxime ethers. This transformation leads to heterocyclic oxime ethers, such as indole derivatives, which constitute an important class of compounds in medicinal chemistry.

On the basis of the observed reactivity of the allenic oxime ether **1** (Scheme 1), we envisaged that simpler oxime ethers, such as **7a**, with an aryl halide moiety would serve as useful substrates for the Heck-type carbon–carbon bond-forming reaction. The requisite substrates were prepared readily by alkylation of the *N*-protected 2-halo aniline **5** and related compounds with a 2-hydroxyacetaldehyde *O*-alkyl oxime, such as **6**,[18] under Mitsunobu conditions (Scheme 2).

The treatment of **7a** (*E*/*Z* 30:70) with a catalytic amount of $[Pd(PPh_3)_4]$ in the presence of K_2CO_3 (2 equiv) in dioxane at reflux gave the desired indolin-3-one *O*-methyl oxime **8a** in 89% yield (Table 1, entry 1). Interestingly, whereas the

[*] Dr. H. Ohno, Prof. Dr. N. Fujii
Graduate School of Pharmaceutical Sciences
Kyoto University
Sakyo-ku, Kyoto 606-8501 (Japan)
Fax: (+81) 75-753-4570
E-mail: hohno@pharm.kyoto-u.ac.jp
A. Aso, Y. Kadoh, Prof. Dr. T. Tanaka
Graduate School of Pharmaceutical Sciences
Osaka University
1-6 Yamadaoka, Suita, Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-8214
E-mail: t-tanaka@phs.osaka-u.ac.jp

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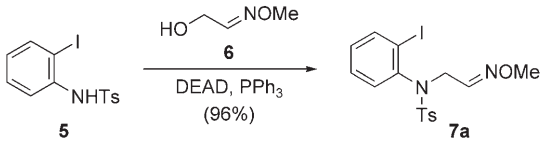
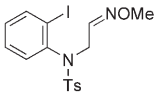
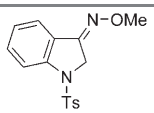
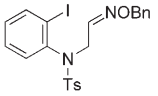
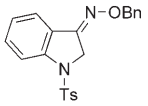
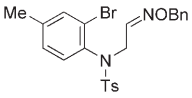
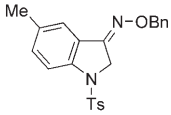
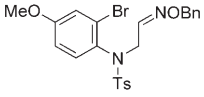
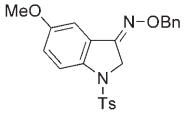
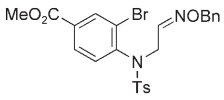
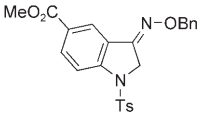
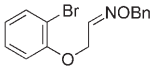
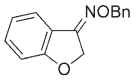


Scheme 2. Representative synthesis of substrates derived from aniline. DEAD = diethyl azodicarboxylate, Ts = *p*-toluenesulfonyl.

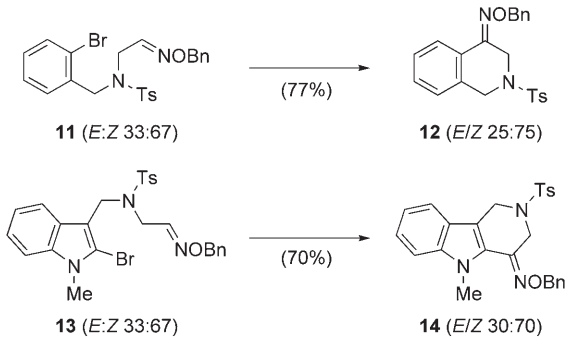
Table 1: Heck-type cyclization of oxime ethers that contain a halogenated aryl group.[a]

Entry	Substrate	*t* [h]	Product	Yield[b] [%]
1	 **7a** (*E*/*Z* 30:70)	13	 **8a** (*E*/*Z* = 6:94)	89
2	 **7b** (*E*/*Z* 40:60)	24	 **8b** (*E*/*Z* 2:>98)	80
3	 **7c** (*E*/*Z* 30:70)	23	 **8c** (*E*/*Z* 2:>98)	56
4	 **7d** (*E*/*Z* 30:70)	17	 **8d** (*E*/*Z* 8:92)	68
5	 **7e** (*E*/*Z* 35:65)	13	 **8e** (*E*/*Z* 4:96)	59
6	 **9** (*E*/*Z* 45:55)	14	 **10** (*E*/*Z* 20:80)	72

[a] All reactions were conducted with $[Pd(PPh_3)_4]$ (10 mol%) and K_2CO_3 (2 equiv) in dioxane at reflux. [b] Yield of the isolated product. Bn = benzyl.

formation of the pyrrolidine derivative **2** from the allenic oxime ether **1** proceeded with only moderate stereoselectivity (*E*/*Z* 25:75), the reaction of the halide **7a** gave the indolin-3-one derivative **8a** in a highly *Z*-selective manner (*E*/*Z* 6:94).[19] The more sterically hindered *O*-benzyl oxime **7b** underwent cyclization to give (*Z*)-**8b** as the sole isolable isomer in 80% yield (Table 1, entry 2). Similarly, the aniline derivatives **7c** and **7d** with an electron-donating substituent and **7e** with an electron-withdrawing substituent were converted into the corresponding indolin-3-one oxime ethers **8c**–**e** with good stereoselectivities (Table 1, entries 3–5). Benzofuran-3-one *O*-benzyl oxime (**10**) was synthesized readily from the *o*-bromophenol-derived oxime ether **9** by the same protocol (Table 1, entry 6); however, the *E*/*Z* selectivity of the reaction was relatively low (*E*/*Z* 20:80).

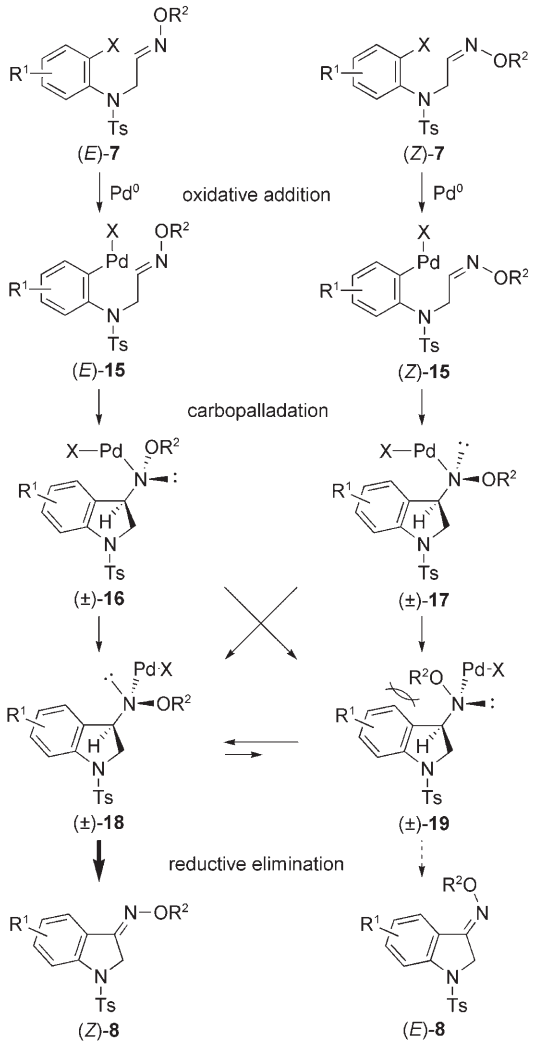
Next, we investigated six-membered-ring formation by this Heck-type cyclization. The benzylamine-derived substrate **11**, which has a longer tether than that of the aniline-derived substrates **7**, was prepared in a similar way by the Mitsunobu reaction of *N*-protected 2-bromobenzylamine with 2-hydroxyacetaldehyde *O*-benzyl oxime. The treatment of **11** with $[Pd(PPh_3)_4]$ in the presence of K_2CO_3 in dioxane at reflux for 48 h produced the desired 2,3-dihydroisoquinolin-4-one derivative **12** in 77% yield (Scheme 3). Similarly, the bromoindole-derived substrate **13** was transformed into the dihydropyridine-fused indole oxime ether **14** in 70% yield.



Scheme 3. Heck-type cyclization of oxime ethers to form six-membered rings. Reaction conditions: $[Pd(PPh_3)_4]$ (10 mol%), K_2CO_3 (2 equiv), dioxane, reflux, 48 h.

In all cases, the *E*/*Z* ratio of the substrate was not reflected in the product. This observation can be rationalized by an insertion–elimination mechanism that includes pyramidal inversion of the nitrogen atom (Scheme 4). The insertion of the aryl palladium(II) halide (*E*)-**15**, which results from the oxidative addition of (*E*)-**7** to palladium(0), into the carbon–nitrogen double bond in a *syn*-selective manner gives the palladium amide intermediate **16**. Similarly, (*Z*)-**15** (derived from (*Z*)-**7**) undergoes an insertion step to give **17**. If *syn* β-hydride elimination proceeds through **18** or **19** without stereomutation, the isomeric ratio of the starting materials ((*E*)-**7**/(*Z*)-**7**) should be reflected in the product distribution ((*Z*)-**8**/(*E*)-**8**). Although it is known that the energy barrier to the pyramidal inversion of a nitrogen atom is increased when the nitrogen atom is bonded to an oxygen atom,[20,21] the interconversion of the palladium amide intermediates, such as **18** and **19**, through generally facile pyramidal inversion of the nitrogen atom[21,22] would be one rationale for the observed *Z* selectivity: Elimination proceeds preferentially from the more abundant conformer **18** to give the sterically less hindered product (*Z*)-**8**.[23]

In conclusion, we have developed a novel Heck-type cyclization of oxime ethers that leads to indolin-3-one derivatives with good *Z* selectivity (up to >98:2). The reaction has wide applicability, including the construction of benzofuran-3-ones, dihydroisoquinolin-4-ones, and fused indole derivatives. This study demonstrates that aryl halides can undergo a simple Heck-type reaction with a carbon–nitrogen multiple bond.



Scheme 4. Proposed mechanism of the Heck-type cyclization.

Experimental Section

Typical procedure: A mixture of **7a** (*E*/*Z* 30:70; 50.4 mg, 0.113 mmol), $[Pd(PPh_3)_4]$ (13.1 mg, 0.0113 mmol), and K_2CO_3 (31.2 mg, 0.226 mmol) in dioxane (1.1 mL) was heated at reflux for 13 h. The resulting mixture was diluted with ether and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography over silica gel (*n*-hexane/EtOAc 10:1) to afford the desired product **8a** (*E*/*Z* 4:96; 32.0 mg, 89%) as colorless crystals. M.p.: 129–131 °C (*n*-hexane/EtOAc); IR (KBr): $\tilde{\nu}$ = 1597 (C=N), 1358 (SO_2N), 1169 cm^{-1} (SO_2N); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3H, CCH_3), 3.96 (s, 3H, OCH_3), 4.51 (s, 2H, CH_2), 7.07 (td, J = 7.5, 0.9 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.37–7.44 (m, 1H), 7.56 (dd, J = 7.2, 0.9 Hz, 1H), 7.67–7.71 (m, 2H), 7.82 ppm (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.5, 50.7, 62.6, 115.0, 121.8, 123.8, 124.0, 127.1 (2C), 129.9 (2C), 132.0, 133.6, 144.6, 146.1, 152.4 ppm; MS (FAB): *m*/*z* (%): 317 (85) $[M+H]^+$, 154 (100); HRMS (FAB): *m*/*z* calcd for $C_{16}H_{17}N_2O_3S$ $[M+H]^+$: 317.0960; found: 317.0960.

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