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# Palladium(II)-Catalyzed Tandem Intramolecular Aminopalladation of Alkynes and Conjugate Addition. Synthesis of Oxazolidinones, Imidazolidinones, and Lactams

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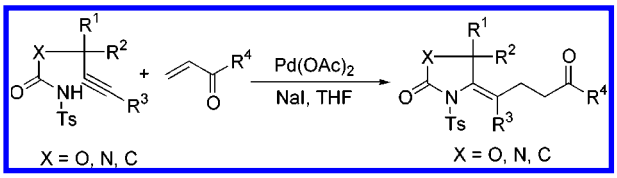
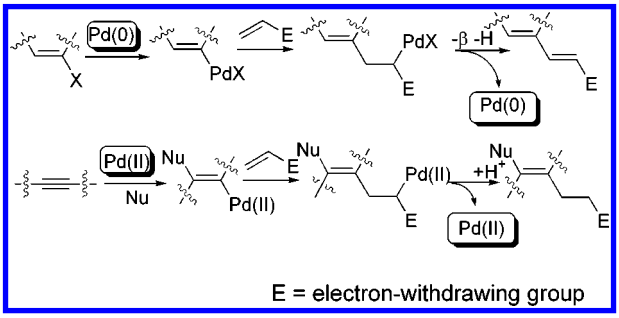
**ABSTRACT**




**Under the catalysis of a divalent palladium species, oxazolidinones, imidazolidinones, or lactams were conveniently obtained with high chemo- and stereoselectivity from the tandem intramolecular aminopalladation of alkynes, followed by insertion of alkenes, and protonolysis of the newly formed carbon–palladium bond.**

The reactions of vinylpalladium intermediates formed from the oxidative addition of Pd(0) with RX have been extensively studied (Scheme 1).[1] However, the reactions of vinylpalladium intermediates which can also easily be obtained from nucleopalladation of alkynes have received only limited attention (Scheme 1).[2] The main reason is that methods of quenching the carbon−palladium bond to regenerate the divalent palladium species are rarely reported,[2c−g] and the carbon−palladium bond is easily quenched by $\beta$-hydride elimination or reductive elimination which in general generates the Pd(0) species, making the catalytic cycle impossible. Thus, a large excess of oxidizing reagents is necessary to recycle the divalent palladium catalyst.[1a] In our previous work, we explored the protonolysis reaction of the carbon−palladium bond in the presence of halide ions, which is an effective method to quench the carbon−palladium bond and regenerate the divalent palladium species (Scheme 1).[3] Palladium(II)-catalyzed tandem

**Scheme 1**




(1) (a) Tsuji, J. *Palladium Reagents and Catalysis: Innovations in Organic Synthesis*; John Wiley: Chichester, 1995. (b) Soderberg, B. C. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: 1995; Vol. 12, Chapter 3.5, p 241.

(2) (a) Mailtis, P. M. *The Organic Chemistry of Palladium*; Academic Press: New York, 1971; Vol. 1, p 79. (b) Maitlis, P. M. *Acc. Chem. Res.* **1976**, *9*, 93−99. (c) Kaneda, K.; Uchiyama, T.; Fujiwarka, Y.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55. (d) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323. (e) Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753. (f) Lu, X.; Zhu, G.; Wang, Z. *Synlett.* **1998**, 115. (g) Lu, X.; Ma, S. New Age of Divalent Palladium Catalysis. In *Transition Metal Catalyzed Reaction*; Murahashi, S.-I., Davies, S. G., Eds.; 1999; Chapter 6, p 133.

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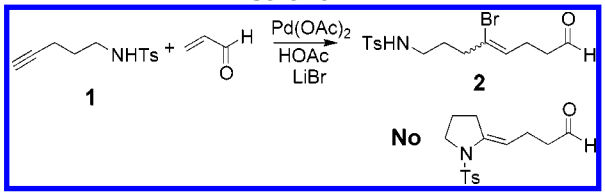
reactions of nucleopalladation (Nu = halogen,[3a,c,d] and oxygen[3b]) of alkynes and conjugate addition have been reported. Here, we wish to report our recent result in the Pd(II)-catalyzed synthesis of oxazolidinones and their analogues via tandem aminopalladation of alkynes and conjugate addition.

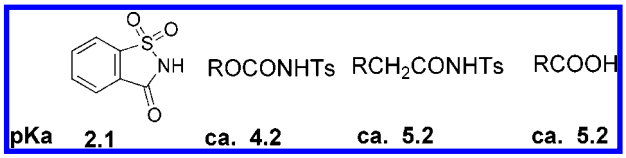
In the literature, the aminopalladation was reported using amines substituted with electron-withdrawing groups as observed in the catalytic cyclization of *o*-allylanilines, carbamates, and sulfonamides.[1a,4,5] Thus, we initiated our studies with *N*-tosyl-protected 4-pentynylamine **1**. The reaction of compound **1** (1 mmol) and acrolein (15 mmol) in the presence of LiBr (4 mmol) and $Pd(OAc)_2$ (0.05 mmol) in HOAc afforded the product **2** initiated by halopalladation instead of the expected product initiated by intramolecular aminopalladation (Scheme 2), indicating that the halopalladation reaction is competitive with the expected aminopalladation reaction.

**Scheme 2**



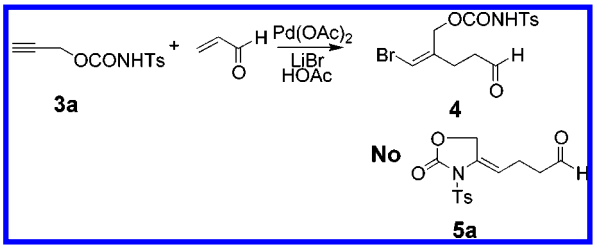

With the aim of exploring the divalent palladium-catalyzed reaction utilizing protonolysis of the carbon−palladium bond as the key step in regenerating the divalent palladium species, halide ions and acidic conditions for protonolysis are necessary.[3] Therefore, the nucleophile should be still able to work properly even under acidic conditions. From our previous work on the intramolecular oxypalladation of alkynoic acids,[3a,b,e] it was known that carboxylic acids can serve as effective nucleophiles in acetic acid. On comparing the p$K_a$ values of carboxylic acid and different kinds of amides (Scheme 3), we learned that the p$K_a$ values of *N*-tosyl carbamates and *N*-tosylamides[6] are comparable with that of carboxylic acids. Thus, we chose *N*-tosyl carbamate **3a** to examine the possibility of the aminopalladation reaction.[7]

**Scheme 3**



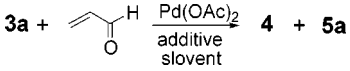

However, the reaction of compounds **3a** (1.0 mmol) and acrolein (15 mmol) in the presence of LiBr (4 mmol) and $Pd(OAc)_2$ (0.05 mmol) in HOAc still produced the halopalladation−insertion−protonolysis product **4** rather than the expected aminopalladation−insertion−protonolysis product **5a** (Scheme 4).

**Scheme 4**




No reaction occurred when the bromide ion was changed to iodide ion in HOAc as solvent (Table 1, entries 2−4).

**Table 1.** Reaction of **3a** with Acrolein under Different Conditions[a]




| | | | product (yield)[b] | |
|---|---|---|---|---|
| entry | solvent | additive | **4** | **5a** |
| 1 | HOAc | LiBr | 59 | |
| 2 | HOAc | $Bu_4NI$ | | |
| 3 | HOAc | LiI | | |
| 4 | HOAc | LiI/LiOAc | | |
| 5 | THF | LiI/LiOAc | | 70 |
| 6 | THF | LiI | | 70 |
| 7 | THF | NaI | | 70 |
| 8 | THF | LiBr | | 68 |
| 9 | THF | LiCl | | 61 |

[a] Reaction conditions: **3a** (1.0 mmol), acrolein (15 mmol), $Pd(OAc)_2$ (0.05 mmol), and LiX (2.0 mmol) in solvent (5 mL) at room temperature. [b] Isolated yields.

However, the aminopalladation−insertion−protonolysis product **5a** did form when THF was used instead of HOAc as the solvent (Table 1, entries 5−7). Use of either bromide or chloride ions gave similar results (Table 1, entries 8 and 9).

A wide range of substituted carbamates **3** were examined under similar conditions (Scheme 5 and Table 2), and they

(3) (a) Wang, Z.; Lu, X. *Chem. Commun.* **1996**, 535. (b) Wang, Z.; Lu, X. *J. Org. Chem.* **1996**, *61*, 2254. (c) Wang, Z.; Lu, X. *Tetrahedron, Lett.* **1997**, *38*, 5213. (d) Wang, Z.; Lu, X.; Lei, A.; Zhang, Z. *J. Org. Chem.* **1998**, *63*, 3806. (e) Wang, Z.; Zhang, Z.; Lu, X. *Organometallics* **2000**, *19*, 775.

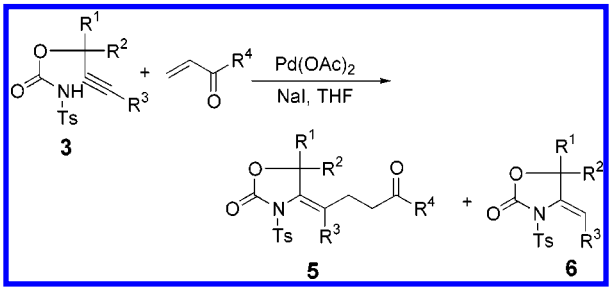
(4) (a) Utimoto, K.; Miwa, H.; Nozaki, H.; *Tetrahdron, Lett.* **1981**, *22*, 4277. (b) Pugin, B.; Venanzi, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 6877.

(5) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994, and references therein.

(6) Schaaf, T. K.; Hess, H. J. *J. Med. Chem.* **1979**, *22*, 1340.

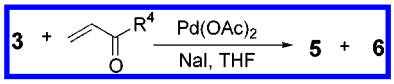
(7) *N*-Tosyl carbamates could be used as the efficient nucleophiles in the aminopalladation reaction of alkenes or alkynes. (a) Trost, B. M.; Vranken, D. L.-V. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228. (b) Tamaru, Y.; Kimura, M. *Synlett* **1997**, 749. (c) Bando, T.; Harayama, H.; Fukazawa, Y.; Shiro, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1994**, *59*, 1465. (d) Kimura, M.; Wakamiya, Y.; Horino, Y.; Tamaru, Y. *Tetrahedron Lett.* **1997**, *38*, 3963. (e) Arcadi, A. *Synlett* **1997**, 941.

**Scheme 5**




all gave exclusively the products initiated by aminopalladation.[8] It was found that the substituents in **3** played an important role in the reaction. With the disubstituted **3f** or **3h**, oxazolidinone **6** was also formed as a byproduct together with the expected product **5** (Table 2, entries 6−9).

**Table 2.** Reaction of Substituted **3** with Alkenes under Pd(II) Catalysis[a]




| | 3 | | | | | product (%)[b] | |
|---|---|---|---|---|---|---|---|
| entry | **3** | $R^1$ | $R^2$ | $R^3$ | $R^4$ | **5** | **6** |
| 1 | **3a** | H | H | H | H | 85 (**5a**) | |
| 2 | **3a** | H | H | H | Me | 50 (**5b**) | |
| 3 | **3c** | H | Et | H | H | 61 (**5c**) | |
| 4 | **3c** | H | Et | H | Me | 72 (**5d**) | |
| 5 | **3e** | H | Ph | H | Me | 83 (**5e**) | |
| 6 | **3f** | Me | Me | H | H | 68 (**5f**) | 32 (**6f**) |
| 7 | **3f** | Me | Me | H | Me | 54 (**5g**) | 46 (**6f**) |
| 8 | **3h** | Me | *n*-$C_5H_{11}$ | H | H | 31 (**5h**) | 22 (**6h**) |
| 9 | **3h** | Me | *n*-$C_5H_{11}$ | H | Me | 39 (**5i**) | 33 (**6h**) |
| 10 | **3j** | H | H | Me | H | 72 (**5j**) | |
| 11 | **3j** | H | H | Me | Me | 63 (**5k**) | |

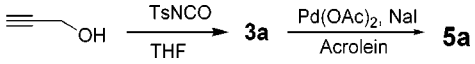
[a] Reaction conditions: **3** (1.0 mmol), electron-deficient alkenes (15 mmol), $Pd(OAc)_2$ (0.05 mmol), and LiBr (2.0 mmol) at room temperature. [b] Isolated yields.

The structures of oxazolidinones **5** were characterized using NMR, IR, MS, and elementary analysis. The stereochemistry of exocyclic double bonds in oxazolidinones **5** was in the (*E*)-configuration as determined by comparing the chemical shifts of the vinylic protons with literature values[9] or by NOESY spectra (for **5j**[10]).

(8) **Typical procedure: 3a** (1.0 mmol) was reacted with acrolein (15 mmol) in THF (5 mL) in the presence of $Pd(OAc)_2$ (0.05 mmol) and NaI (2.0 mmol) at room temperature. After the reaction was complete as monitored by TLC, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 4/1−2/1) to give product **5a** in 85% yield: oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.73 (s, 1H), 7.84 (d, $J$ = 8.5 Hz, 2H), 7.28 (d, $J$ = 8.1 Hz, 2H), 5.79 (tt, $J$ = 2.6, 7.9 Hz, 1H), 4.82 (t, $J$ = 2.6 Hz, 2H), 2.59 (t, $J$ = 6.8 Hz, 2H), 2.38 (s, 3H), 2.13 (dt, $J$ = 8.3, 6.8 Hz, 2H); IR (neat) $\nu$ 2852, 2747, 1792, 1725, 1692, 1391, 1160, 1089, 1060 cm$^{-1}$; MS *m/e* 310 ($M^+$ + 1), 309 ($M^+$), 253, 228, 155, 138, 91 (100), 65. Anal. Calcd for $C_{14}H_{15}NO_5S$: C, 54.36; H, 4.89; N, 4.53. Found: C, 54.33; H, 5.02; N, 4.73.

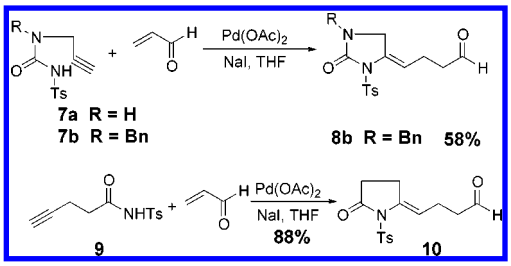
In addition, the reaction can be carried out in a one-pot manner via in situ formation of *N*-tosyl carbamates from the corresponding alkynols,[9a] followed by a Pd(II)-catalyzed reaction, as exemplified by the preparation of aldehyde **5a** from propargyl alcohol in 82% overall yield with the in situ formation of *N*-tosyl carbamate **3a** (Scheme 6).

**Scheme 6**



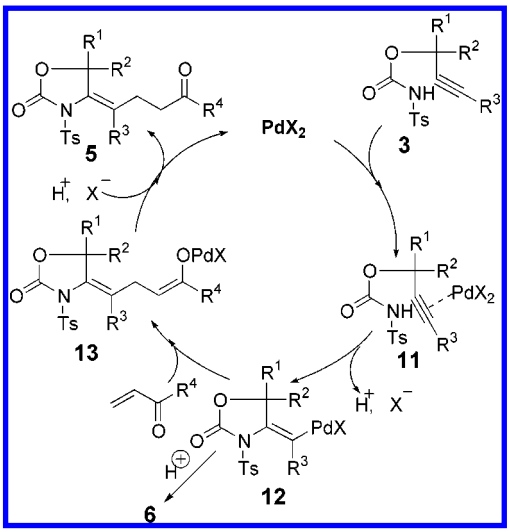

A similar reaction could also occur in an analogous way, e.g., the oxygen atom in carbamate **3** could be replaced by a nitrogen atom or a methylene group. Imidazolidinone **8b** could be obtained in 58% yield from urea **7b**, but no expected product was obtained with urea **7a** under the same conditions. In addition, lactam **10** could be obtained from amide **9** in 88% yield (Scheme 7).

**Scheme 7**




The following mechanism was proposed: First, the Pd(II) species coordinated with the triple bond of carbamate **3**. *Trans* attack of the tosyl amide anion to the coordinated triple bond afforded (*E*)-vinylpalladium intermediate **12** (amino-

**Scheme 8**



palladation),[5,7e] followed by insertion of alkenes and protonolysis of the newly formed carbon−palladium bond in palladium enolate **13** in the presence of halide ions to yield aldehyde or ketone **5** and regenerate the divalent palladium species to complete the catalytic cycle (Scheme 8).[3] The key point is that the $\beta$-hydride elimination reaction is inhibited in the presence of excess halide ions.[3e] In this reaction, the source of proton for protonolysis may be the ionization of tosyl amide in **3**. The possible depression of the ionization of tosylamide in HOAc may result in the preference of THF as solvent for the reaction. The direct protonolysis of intermediate **12** yielded the byproduct **6**.

(9) (a) Tamaru, Y.; Kimura, M.; Tanaka, S.; Kure, S.; Yoshida, Z. *Bull. Chem. Soc. Jpn*. **1994**, *67*, 2838. (b) Gaudemer, A. Determination of Configuration by NMR Spectroscopy. In *Stereochemistry, Fundamentals and Methods*; Kagan, H. B., Ed.; Georg Thieme: Stuggart, 1977; Vol. 1, p 44.

(10) There is strong NOE between two allylic protons in the NOESY spectra of compound **5j**.

In summary, we developed an efficient method for the synthesis of oxazolidinones, imidazolidinones, or lactams with high chemo- and stereoselectivity from alkynol carbamates and $\alpha,\beta$-unsaturated carbonyls. This Pd(II)-catalyzed reaction involves tandem intramolecular aminopalladation, olefin insertion, and protonolysis of the carbon−palladium bond.

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**Supporting Information Available:** Spectral and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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