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Tetrahedron Letters 44 (2003) 467–470

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# One-pot synthesis of tetrahydrofuran derivatives via a divalent palladium-catalyzed three-component coupling

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Received 7 October 2002; revised 7 November 2002; accepted 15 November 2002

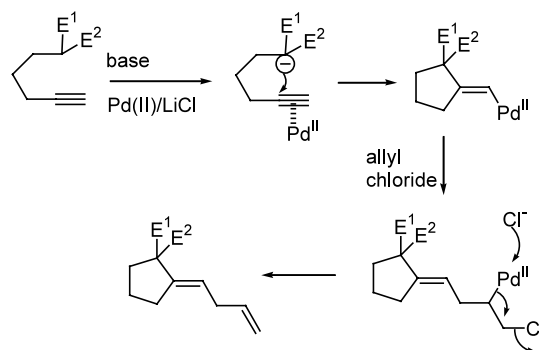
**Abstract**—Under divalent palladium catalysis, a three-component coupling reaction for synthesizing tetrahydrofuran derivatives has been established. The reaction involves the intramolecular carbopalladation of an alkyne with a carbanion which was generated from the addition of an alkoxide ion to an alkene derivative, followed by allylic chloride insertion to the C–Pd bond and quenching the C–Pd bond by  $\beta$ -heteroatom elimination in the presence of excess chloride ions. © 2002 Elsevier Science Ltd. All rights reserved.

Five-membered oxygen heterocycles are important synthetic targets due to their occurrence in numerous natural products, their wide range of biological activities, and their utility as versatile intermediates.<sup>1</sup> A variety of new synthetic methodologies has been developed for this important class of heterocyclic compounds.<sup>2</sup> Recently, free radical and transition-metal catalyzed cyclizations have emerged as powerful tools for the construction of these structures.<sup>3</sup> Over the same period, multi-component condensations have gained considerable attention in the field of heterocycle synthesis.<sup>4</sup>

As part of our ongoing program in divalent Pd-catalyzed reactions, we recently discovered a new Pd(II)-catalyzed tandem reaction which proceeds via the intramolecular carbopalladation of an alkyne and coupling with an allylic chloride (Scheme 1).<sup>5</sup> The reaction mechanism is speculated to be a divalent palladium-catalyzed reaction, involving intramolecular carbopalladation of the alkyne, allyl chloride insertion into the C–Pd bond and quenching the C–Pd bond by  $\beta$ -heteroatom elimination.

This synthetic methodology has now been applied to the synthesis of tetrahydrofuran derivatives. Our strategy is based on the carbopalladation of alkynes by a carbanion formed by the conjugate addition of an alkynoate to an alkylidene-malonate followed by olefin insertion and  $\beta$ -heteroatom elimination (Scheme 2).<sup>6</sup>

The reaction of propargyl alcohol **1a** and the olefin **2a** was examined. Firstly, on treatment of the potassium propargylate generated from **1a** (using <sup>t</sup>BuOK as base, at 0°C) with **2a** in the presence of LiCl (4 equiv.), allyl chloride (5 equiv.) and Pd(OAc)<sub>2</sub> (5 mol%) as the catalyst in THF, the expected product **3a** was obtained in 37% yield (based on **2a**), accompanied with another

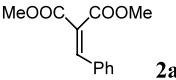

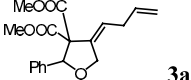
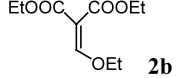
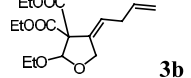
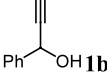
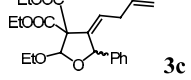
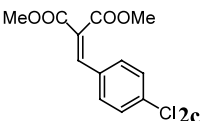
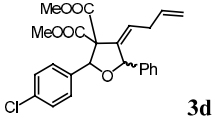
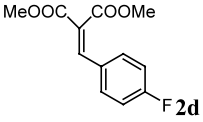
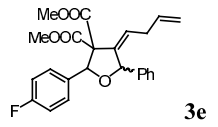
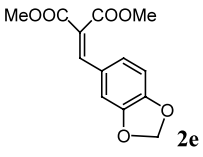
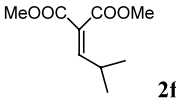
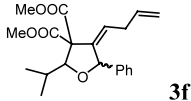
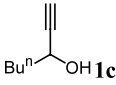
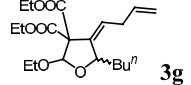

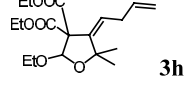
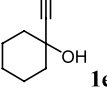
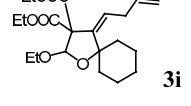

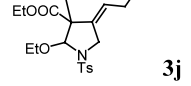


Scheme 1.

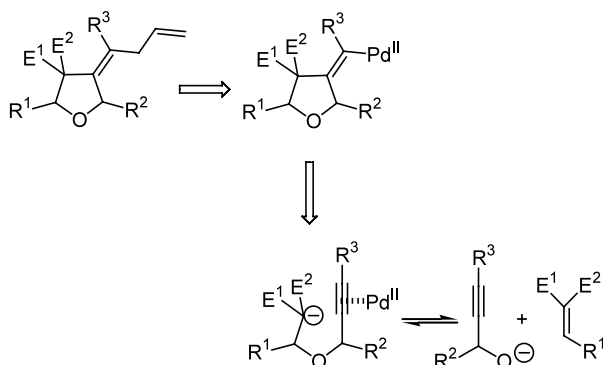
**Keywords:** carbopalladation; coupling reaction; divalent palladium;  $\beta$ -heteroatom elimination; tetrahydrofuran derivatives.

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**Table 1.** Synthesis of tetrahydrofuran derivatives using divalent palladium catalysis<sup>a</sup>

entry	Michael acceptor	Alcohol	Product	Yield % <sup>b</sup> ( <i>cis/trans</i> ) <sup>c</sup>
1	 <b>2a</b>	 <b>1a</b>	 <b>3a</b>	47
2	 <b>2b</b>	<b>1a</b>	 <b>3b</b>	65
3	<b>2b</b>	 <b>1b</b>	 <b>3c</b>	75 (1.1:1)
4	 <b>2c</b>	<b>1a</b>	--	--
5	<b>2c</b>	<b>1b</b>	 <b>3d</b>	56 (1.5:1)
6	 <b>2d</b>	<b>1a</b>	--	--
7	<b>2d</b>	<b>1b</b>	 <b>3e</b>	59 (1.4:1)
8	 <b>2e</b>	<b>1a</b>	--	-- <sup>d</sup>
9	<b>2e</b>	<b>1b</b>	--	-- <sup>d</sup>
10	 <b>2f</b>	<b>1b</b>	 <b>3f</b>	58 (1:1)
11	<b>2b</b>	 <b>1c</b>	 <b>3g</b>	61 (1.1:1)
12	<b>2b</b>	 <b>1d</b>	 <b>3h</b>	65
13	<b>2b</b>	 <b>1e</b>	 <b>3i</b>	53
14	<b>2b</b>	 <b>1h</b>	 <b>3j</b>	21

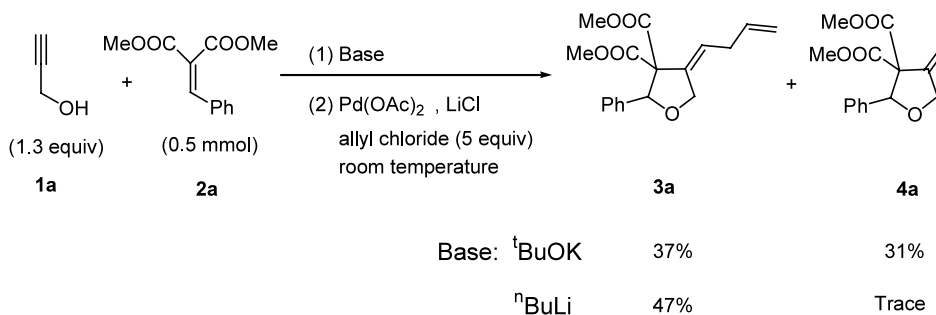
<sup>a</sup>All reactions were carried out from –78 °C to room temperature on a 0.5 mmol scale (referred to the Michael acceptor), and<sup>b</sup>BuLi as the base. <sup>b</sup>Isolated yield. <sup>c</sup>The ratio of *cis/trans* isomers was determined by <sup>1</sup>H NMR of the diastereomeric mixture.<sup>d</sup>No expected cyclization product was formed with recovery of **2e**.



Scheme 2.

product **4a** (31% yield) (Scheme 3). When  $n$ BuLi was used as the base, the reaction gave a higher yield of **3a** (47%) and only a trace of **4a**. Various bases such as NaH,  $t$ BuOK and  $n$ BuLi were used,  $n$ BuLi proved to be the best for this reaction. The palladium catalyst was found to be essential for the reaction:  $\text{Pd}(\text{OAc})_2$  and  $\text{PdCl}_2(\text{PhCN})_2$  were both effective, but  $\text{PdCl}_2(\text{PPh}_3)_2$  and other  $\text{Ph}_3\text{P}$ -containing palladium species were not effective. In order to explore the scope and generality of this reaction, different Michael acceptors and propargylic alcohols were examined using the optimized procedure.<sup>7</sup> The results are shown in Table 1.

A range of tetrahydrofuran derivatives were obtained in moderate yields. The reaction tolerated various substitution patterns of the  $\alpha,\beta$ -unsaturated ester, giving comparable results for both aryl (**2a**, **2c**, **2d**) and alkyl (**2f**) substituents (entries 1, 5, 7 and 10). However, the reaction of **2e**, which has an electron-donating group in the benzene ring, did not occur (entries 8 and 9). In comparison with the aryl and alkyl substituents, the alkoxy substituted substrate (**2b**) gave better results (entries 2 and 3). For the activated olefin **2b**, even the much more hindered propargylic nucleophiles gave similar yields (entries 2, 3, and 11–13). Finally, when the tosyl protected propargylamine **1h** was reacted with **2b** under the same reaction conditions, the substituted tetrahydropyrrole **3j** was obtained, but only in a poor yield (Table 1, entry 14).



Scheme 3.

In summary, a three-component reaction for synthesizing tetrahydrofuran derivatives has been developed, which combines a conjugate addition and tandem palladium(II)-catalyzed carbopalladation–cyclization in one step. The methodology is extremely convenient, practical and versatile in that a range of readily available propargylic alcohols, allyl chloride, and activated olefins can be used.

### Acknowledgements

This work was funded by the Major State Basic Research Program (Grant No. G2000077502-A). We thank the National Natural Sciences Foundation of China and Chinese Academy of Sciences for financial support.

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6. A similar strategy has been used to synthesize tetrahydrofuran derivatives under Pd(0) catalysis, see: (a) Monteiro, N.; Balme, G. *J. Org. Chem.* **2000**, *65*, 3223; (b) Bottex, M.; Cavicchioli, M.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, *66*, 175.
7. Typical procedure for synthesizing tetrahydrofuran derivatives **3**: Alcohol **1** (0.75 mmol) was stirred with <sup>n</sup>BuLi (0.6 mmol) at –78°C for 10 min, then **2** (0.5 mmol), allyl chloride (2.5 mmol), LiCl (2.0 mmol) and Pd(OAc)<sub>2</sub> (5 mol%) were added successively. The mixture was allowed to warm and then stirred at room temperature for 1 h. H<sub>2</sub>O (10 mL) was added and the reaction mixture was extracted with diethyl ether (2×20 mL). The combined

extracts were dried, filtered, and evaporated. The crude oil was purified by column chromatography on silica gel (ethyl acetate/petroleum ether=1/15) to give **3**. All the products were characterized by spectral data. Spectroscopic data for **3a**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44–7.40 (m, 2H), 7.33–7.27 (m, 3H), 5.88–5.82 (m, 2H), 5.70 (s, 1H), 5.09 (d, *J*=16.4 Hz, 1H), 5.05 (d, *J*=10.2 Hz, 1H), 4.85 (d, *J*=13.1 Hz, 1H), 4.52 (d, *J*=13.1 Hz, 1H), 3.83 (s, 3H), 3.21 (s, 3H), 2.80 (m, 2H); IR (neat) ν 1732, 1638, 1435, 1263, 1070, 978 cm<sup>–1</sup>; MS (*m/z*): 316 (M<sup>+</sup>), 256, 210, 178, 146, 121, 105 (100), 91, 77; HRMS, calcd for C<sub>18</sub>H<sub>20</sub>O<sub>5</sub>, 316.1311. Found: 316.1326. The stereochemistry of **3a** was determined by NOESY spectra.