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An exceptional palladium-catalyzed alkenylation of silyl enol ether in the absence of a fluoride additive

Hiroki Shigehisa, Takaaki Jikihara, Osamu Takizawa, Hiromasa Nagase, Toshio Honda *

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

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Abstract

An exceptional intramolecular palladium-catalyzed alkenylation of silyl enol ether in the absence of a fluoride additive was developed, and this reaction led to the construction of bicyclo[3.3.1]nonane ring system in reasonable yield. In this type of reactions, trialkylamines were employed as additives instead of previously indispensable fluoride additives.

Keywords: Palladium-catalyzed alkenylation; Intramolecular C–C bond formation; Silyl enol ether; Bicyclo[3.3.1]nonane; Trialkylamine

Palladium-catalyzed direct arylation or alkenylation of ketones in the presence of a strong base, such as a metal alkoxide, has been well established and widely used in the past decade for the synthesis of polycyclic compounds, including natural products.[1–4] On the other hand, the chemistry of a similar carbon–carbon bond formation for silyl enol ether or ketene silyl acetal instead of a carbonyl compound under mild basic conditions is still in the development stage,[5] and is a challenging subject in synthetic organic chemistry. Since the report by Kuwajima and Urabe of palladium-catalyzed arylation of silyl enol ether in 1982,[6] several groups have been interested in this chemistry, especially for arylation, and have developed the generality of this protocol.[7,8] Despite the great utility of this type of reaction, there have been few applications of this approach to alkenylation.[9,10] Palladium-catalyzed arylation or alkenylation for silyl enol ether or ketene silyl acetal is generally conducted with silicon activators such as a fluoride additive. We report herein a remarkable example of palladium-catalyzed intramolecular alkenylation of silyl enol ether in the absence of a fluoride additive. It should be noted that trialkylamines were employed in this new type of reaction as additives instead of previously indispensable fluoride additives.

Compounds **8** and **9**, readily prepared from commercially available 1,4-cyclohexanedione monoethylene acetal (**1**), were chosen as the key precursors for the palladium-catalyzed carbon–carbon bond formation. Ester **2**, prepared in two steps from **1** based on the known procedure,[11] was transformed into diethyl malonate derivative **3**. The requisite ketone **6** was provided from **3** by allylation with 2,3-dibromopropene and subsequent hydrolysis of acetal of **4**. Ketone **7** was also synthesized from **3** using 3,4-dibromo-2-methyl-2-butene[4d] instead of 2,3-dibromopropene in the same manner. Finally, treatment of **6** or **7** with TESOTf–$^{i}Pr_2NEt$ gave the corresponding triethylsilyl enol ether **8** or **9**, respectively (Scheme 1).

With the requisite starting materials available, a study was carried out to find the best conditions for palladium-catalyzed alkenylation of **9** by changing the reaction parameters, such as additive, ligand, solvent, concentration and temperature, since the product of **9** should have higher stability than that of the product of **8** (Table 1). In all attempted reactions, the desired product **10** together with **11** and uncyclized diene **12** were obtained in various ratios depending on the reaction conditions. To try to improve

* Corresponding author. Tel.: +81 3 5498 5791; fax: +81 3 3787 0036.
E-mail address: honda@hoshi.ac.jp (T. Honda).

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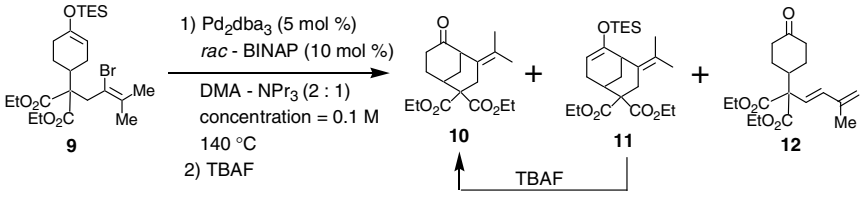
Table 1
Optimization of palladium-catalyzed alkenylation of silyl enol ether **9**



Entry	Changed factor from standard conditions	Yield of **10** + **12**[a] (%)	Ratio (10:12)
1	Solvent = DMA–NPr_3 (19:1)	92	2:1
2	Solvent = DMA–NPr_3 (9:1)	93	4:1
3	Solvent = DMA–NPr_3 (2:1)	99	8.3:1
4	Solvent = DMA–NPr_3 (1:2)	99	10:1
5	Solvent = DMF–NPr_3 (2:1)	99	3.3:1
6	LIGAND = DPPF	87	4.4:1
7	Temperature = 120 °C	90	8:1[b]
8	Temperature = 100 °C	NR	

[a] ratios and yields were obtained based on NMR analysis.
[b] 10% of ketone **7** was observed in its NMR spectrum.

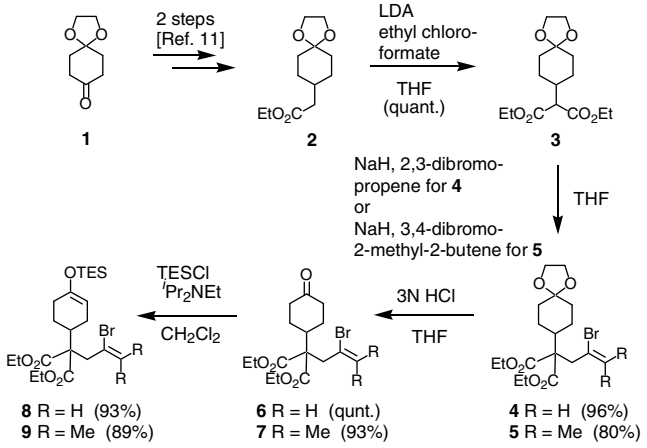
the ratio of cyclized product **10** to uncyclized product **12**, the reaction mixture was treated with TBAF (1 equiv), after the disappearance of the starting material **9** on TLC, to convert **11** to **10**. Since difficulties were encountered in isolation of **10** and **12** from the reaction mixture as pure forms, the ratio of **10** and **12** was obtained on the basis of NMR analysis as shown in Table 1.

By investigation of a suitable base for this conversion, we found that an amine additive is essential for this reaction. Significant enhancement of the **10/12** ratio was achieved by increasing the volume ratio of NPr_3. Although the best result was obtained in entry 4 in terms of yield and products ratio, removal of the amine used was found to be troublesome. Thus, we decided to employ the reaction conditions of entry 3 for the following experiments. The use of NEt_3 and $^iPr_2NEt$ exhibited lack of reproducibility, probably due to their low boiling points. The products (**10**–**12**) were not obtained without the presence of amine bases such as NPr_3, NEt_3 and $^iPr_2NEt$. Other amine bases (pyridine, lutidine, DBU, DABCO) and an inorganic base (K_2CO_3) examined did not give **10**–**12**. By screening of readily available ligands, BINAP was selected as the optimum ligand for the desired reaction. Other phosphine ligands (DPPM, DPPE, DPPP, DPPB, PPh_3) did not give the desired product **10** or **11**. Using the suitable ligand and additive, a systematic screening of other reaction parameters was undertaken. Among the common solvents usually used for this type of reaction, it was revealed that only *N*,*N*-dimethylacetamide (DMA) and *N*,*N*-dimethylformamide (DMF) afforded the desired product **10**. It was also revealed that the optimum temperature was 140 °C. In general, improvement of yields for the desired product is observed at a low substrate concentration; however, we used 0.1 M solution for this reaction by reason of its easy handling. Regarding the silyl group on enol ether, a triethylsilyl group gave the best results. When this reaction was applied to trimethylsilyl enol ether, the ratio of **10/12** was decreased, and the starting material remained unchanged, even after longer reaction time, when *tert*-butyldimethylsilyl enol ether was used.

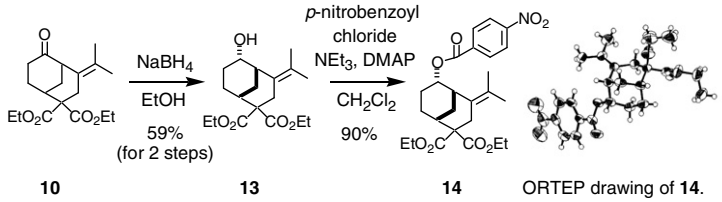
Under the optimum reaction conditions described above,[12] a similar reaction was carried out without treatment of the crude products with TBAF in order to isolate the corresponding silyl enol ether. The reaction of **9** under the same reaction conditions as those for entry 3 provided 46% (isolated yield) of **11** as the major product together with 26% of **10** and 15% of **12**.

The structure of **10** was unambiguously determined by X-ray crystallographic analysis of the corresponding *p*-nitrobenzoate **14** (recrystallized from AcOEt–hexane), derived from **10** via reduction with $NaBH_4$ in EtOH and subsequent benzoylation of alcohol **13** with *p*-nitrobenzoyl chloride. An ORTEP drawing of **14** is shown in Scheme 2.[13]

Application of the palladium-catalyzed alkenylation to silyl enol ether **8** gave the desired cyclized product **15**

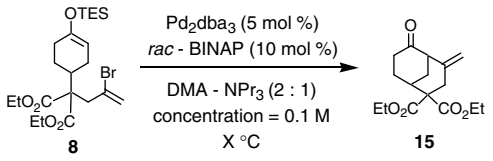


Scheme 1. Synthesis of **8** and **9**.



Scheme 2. Confirmation of relative configuration.

Table 2
Palladium-catalyzed alkenylation of **8**



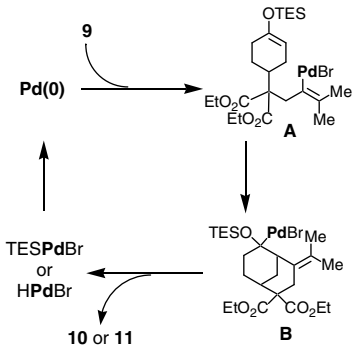
Entry	Temp. (x °C)	Yield[a] (%)
1	80	NR
2	100	54
3	120	51

[a] Isolated yields after chromatography.

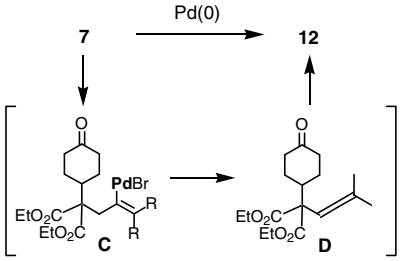
together with a complex product mixture, although the yield of **15** was not satisfactory (when **8** was completely consumed, TBAF was added) (Table 2). The decreased yield would be due to H–Pd elimination of active hydrogen on sp^2 carbon.

The formation of **10** and **11** is consistent with the mechanistic proposal provided for Heck reaction of allylsilane by Tietze and co-worker as shown in Scheme 3.[14,15] The palladium complex **A**, generated by oxidative addition of Pd(0) to alkenyl bromide moiety, would lead to bicyclic compound **B** by migratory insertion of a C–Pd bond into silyl enol ether. The subsequent elimination step of TES-Pd or H–Pd to afford **10** or **11** would be competitive. In the case of allylsilane, Tieze and co-workers also reported analogous competitive elimination depending on the conditions.

A plausible mechanism for the generation of **12** is also shown in Scheme 4. Palladium complex **C**, generated by oxidative addition of Pd(0) to the alkenyl bromide moiety,



Scheme 3. A plausible mechanism for generation of product **10** or **11**.



Scheme 4. A plausible mechanism for generation of diene **12**.

was transformed to allene **D** in the absence of a silyl enol ether moiety. The allene moiety in **D** would be subsequently isomerized into diene **12**. Indeed, when ketone **7** was treated under identical conditions, diene **12** was obtained as the major product in 78% yield without the formation of a detectable amount of **10**.

In summary, palladium-catalyzed alkenylation of silyl enol ether was achieved in an intramolecular manner to furnish a bicyclo[3.3.1]nonane ring system in reasonable yield. This exceptional reaction was developed using an amine base instead of a fluoride silicon activator. The scope and limitation of this methodology are now under investigation in our laboratory.

Acknowledgements

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13. *X-ray crystallographic data for* **14**: Mp 110–111 °C. Space group: triclinic $P\bar{1}$ (#2). $a = 11.5036(15)$ Å, $b = 12.560(4)$ Å, $c = 8.8959(13)$ Å. $\alpha = 101.680(18)°$, $\beta = 101.306(11)°$, $\gamma = 87.381(17)°$, $V = 1234.3(5)$ Å^3, $Z = 2$, $R = 0.088$, $Rw = 0.107$.
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