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Palladium/carboxylic acid-catalyzed Alkenylation of Furfural and its Derivatives Using Alkynes

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Abstract: Furfural and its derivatives underwent alkenylation with alkynes via α-C–H activation in the presence of a palladium/carboxylic acid catalyst to give the corresponding single and double alkenylated products. The reactive aldehyde group remained intact during this reaction. This catalytic system allowed selective alkenylation of furan substrates having electron-withdrawing substituents.

Effective uses of biomass and its derivatives are of growing importance in attaining sustainable development. Furfural is one of the important products derived from cellulosic biomass, and is utilized extensively for the preparation of organic acids such as maleic acid. Furfural is composed of a furan ring with an aldehyde group at the α position. The furan ring is a useful and versatile building block and a key component for functional molecules such as pharmaceuticals, bioactive natural products, and emissive materials.[1,2,3] Thus, development of a straightforward catalytic functionalization method of furfural and its derivatives may contribute to advances in syntheses of high-value added chemicals from biomass as a means of diminishing our dependence on fossil fuel resources.

At present, catalytic C–C bond-forming reaction via inert C–H bond cleavages is regarded as the most important and effective method for the facile construction of various highly functionalized molecules with atom- and step-economies. In fact, several examples of those reactions employing furyl C–H bonds in furfural were reported,[4,5] in which the reactive aldehyde group was left intact.[6] Among them, alkenylation of arenes using alkynes via a C–H bond cleavage is a straightforward method to construct π-conjugated arylene-vinylene units without byproduct formation.[7] However, to the best of our knowledge, only one example of the alkenylation of furfural using alkynes was reported by Hong and co-workers.[4] They showed that an excess amount of furfural underwent α-alkenylation with alkynes using a ruthenium catalyst under CO pressure at high temperature (Figure 1A). Recently, we demonstrated that a simple palladium(0)/carboxylic acid catalyst system is highly effective for alkenylation of an equimolar amount of thiophenes and electron-deficient arenes using alkynes, which gives variously substituted alkenylated (hetero)arenes (Figure 1B).[8,9] We expected that this palladium(0)/acid catalyst system has the potential to employ furfural for alkenylation by alkynes without excess use of substrates under mild conditions and avoid any reactions involving the reactive aldehyde group. Herein, we report the facile alkenylation of furfural and its analogues using alkynes to form α-alkenylated products (Figure 1C).

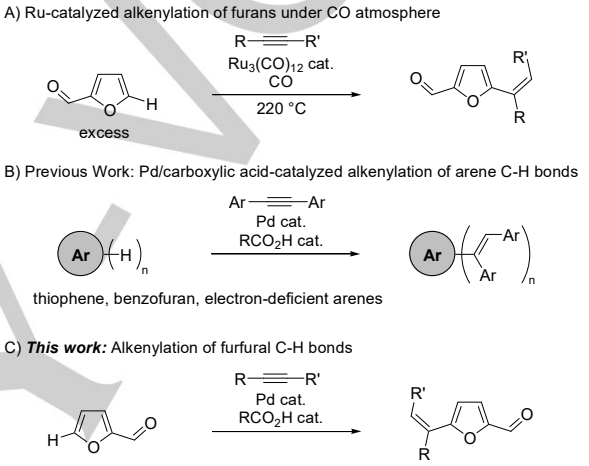
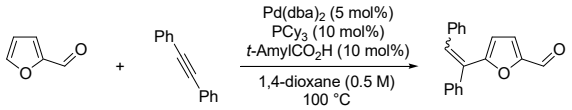


Figure 1. A) Hong's study. B) Our previous study. C) This work

We first examined the reaction of furfural (**1a**, 1.0 equiv) with diphenylacetylene (**2a**, 1.0 equiv) under typical conditions ($Pd(dba)_2$ (5 mol%), tricyclohexylphosphine (PCy_3) (10 mol%), and 2,2-dimethylbutanoic acid (*t*-AmylCO_2H) (10 mol%) as catalysts) at 100 °C for 17 h.[8a] The reaction occurred to give the desired adduct, 5-(1,2-diphenylethenyl)-furfural (**3a**) (*Z*/*E* = 1.2/1), in moderate yield (Table 1, Run 1).[10] To enhance the yield of the product, we optimized the conditions (Runs 2-6). As a result, the reaction using 4 equivalents of **1a** at a longer reaction time gave **3a** in good yield with *Z*-selectively (Run 5). In this scenario, the reactive aldehyde group was retained during the alkenylation, and did not interfere with the addition reaction. In fact, this stereoselectivity is in contrast to the previous case[8a] in which *syn*-addition proceeds to form the *E*-adduct kinetically, and the subsequent isomerization occurred to provide the *Z*-form smoothly.[4] The catalyst loading was successfully reduced to 1 mol% with a comparable yield (Run 7). No reaction occurred in the absence of *t*-AmylCO_2H (Run 8), PCy_3 (Run 9), or both $Pd(dba)_2$ and PCy_3 (Run 10), showing that the combination of $Pd(dba)_2$, PCy_3, and *t*-AmylCO_2H is essential for this reaction. Use of $Pd(OAc)_2$ instead of $Pd(dba)_2$ and *t*-AmylCO_2H decreased the yield (Run 11). Notably, although an excess amount of **1a** was required for enhancing the yield of **3a**, residual **1a** remained intact after the reaction. This starting material could be recovered by an isolation procedure.

Table 1. Optimization of the conditions[a]



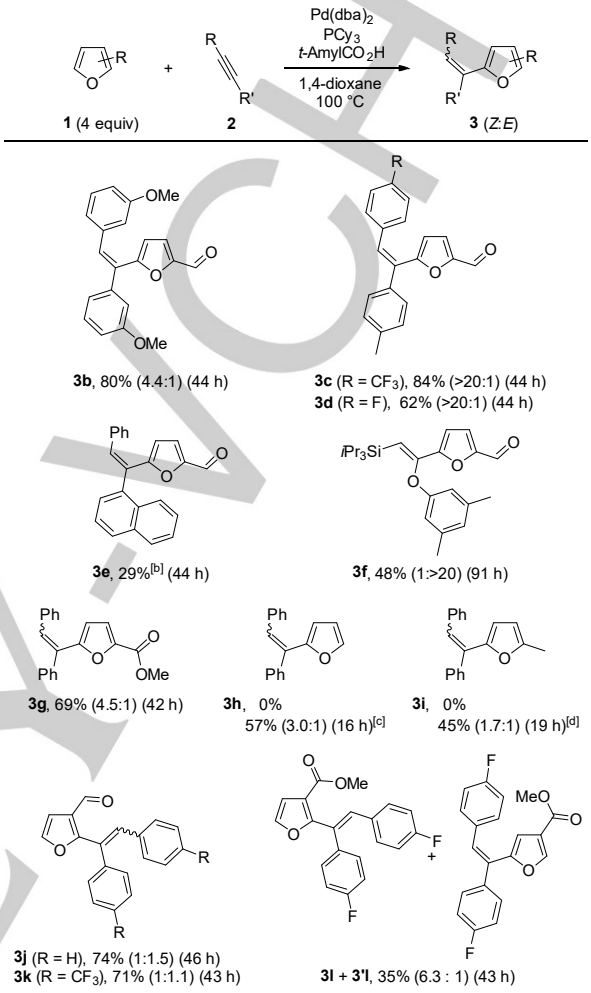
1a (X equiv) **2a** (1 equiv) **3a**

Run	X (equiv. of **1a**)	Temp (°C)	Time (h)	**3a**, Yield (*Z*/*E*)[b]
1	1	100	17	52% (1.2:1)
2	0.5	100	17	31% (1.2:1)
3	2	100	16	70% (4.1:1)
4	4	100	16	79% (9.4:1)
5	4	100	35	83% (>20:1)
				74% (>20:1)[c]
6	4	80	17	48% (8.7:1)
7[d]	4	100	17	82% (12:1)
8[e]	4	100	21	0%
9[f]	4	100	21	0%
10[g]	4	100	16	0%
11[h]	4	100	17	41% (2.0:1)

[a] A mixture of **1a**, **2a** (1 equiv), $Pd(dba)_2$ (5 mol%), PCy_3 (10 mol%), *t*-$AmylCO_2H$ (10 mol%), and 1,4-dioxane (0.5 M) was stirred. [b] Determined by ^1H NMR. [c] Isolated yield. [d] $Pd(dba)_2$ (1 mol%), PCy_3 (2 mol%), and *t*-$AmylCO_2H$ (2 mol%). [e] Absence of *t*-$AmylCO_2H$. [f] Absence of PCy_3. [g] Absence of both $Pd(dba)_2$ and PCy_3. [h] Use of $Pd(OAc)_2$ instead of $Pd(dba)_2$ and *t*-$AmylCO_2H$.

Under the optimized conditions, we examined the scope of alkynes, and the results are summarized in Table 2. Substituted diarylalkynes having methoxy, trifluoromethyl, or fluorine groups reacted with **1a** to give corresponding adducts **3b**-**3d** in good yields. Unsymmetrical 1-(1-naphthyl)-2-phenylethyne underwent the reaction to afford *Z*-**3e** as a main product containing a 1-naphthyl group at the α-position of the alkenyl moiety. Moreover, when the electronically and sterically biased aryloxy(triisopropylsilyl)ethyne was used, the reaction took place with complete regioselectivity to give the *syn*-addition product *Z*-**3f** in a manner similar to that from the previously reported hydroarylation.[8a] We next investigated the scope of furan substrates as shown in Figure 2. Methyl furan-2-carboxylate (**1b**) reacted with **2a** to form the product **3g** with the *Z*-isomer being favored. In the case of normal furan (**1c**), no reaction was observed under the optimized conditions. On the other hand, the reaction using neat furan as a solvent underwent the reaction at the C2 position to afford the corresponding product **3h**. The same tendency was observed in the reaction employing 2-methylfuran (**1d**), which provided **3i** in a moderate yield. These results showed that furans having an electron-withdrawing group are highly reactive substrates in this catalytic system. This trend is in contrast to the previous alkenylation reaction using furan derivatives.[4,7h] 3-Furancarboxaldehyde (**1e**) underwent the reaction with alkynes via selective cleavage of the 2-C–H bond[5d,11] to give 2-alkenylated products **3j** and **3k**. The 3-aldehyde group acted as a directing group to affect the selective 2-C–H bond cleavage. The poor ratios of stereoselectivities of **3j** and **3k** are likely due to steric repulsion between the 3-aldehyde group and the β-aryl group on the alkenyl moiety. Methyl furan-3-carboxylate (**1f**) also reacted at the 2-position in preference to the 5-position to form *E*-**3l** as a major product. The methoxy carbonyl group, that is bulkier than the aldehyde group, at the C3 position probably prefers the *syn*-addition product.

Table 2. Scope of the alkenylation[a]



[a] A mixture of **1** (4 equiv), **2** (1 equiv), $Pd(dba)_2$ (5 mol%), PCy_3 (10 mol%), *t*-$AmylCO_2H$ (10 mol%), and 1,4-dioxane (0.5 M) was stirred at 100 °C. Isolated yields based on **2**. [b] In a crude mixture, four regio- and stereo-mixtures were observed (64 : 21 : 10 : 5). However, no isomers except the major product *Z*-**3e** were isolated in substantial amounts. [c] Furan (**1c**, 28 equiv) was used as a solvent instead of 1,4-dioxane. [d] 2-Methylfuran (**1d**, 27 equiv) was used as a solvent instead of 1,4-dioxane.

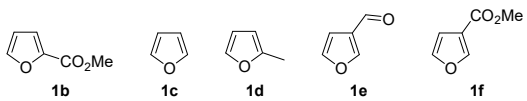
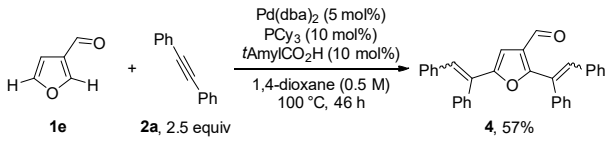


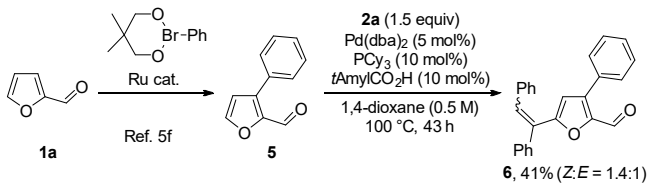
Figure 2. Furan substrate **1**

Double alkenylation was examined by using **1e** and 2.5 equivalents of **2a**. Although the conditions for double alkenylations were not optimized, the desired double adduct **4** was successfully produced (Scheme 1).[12]



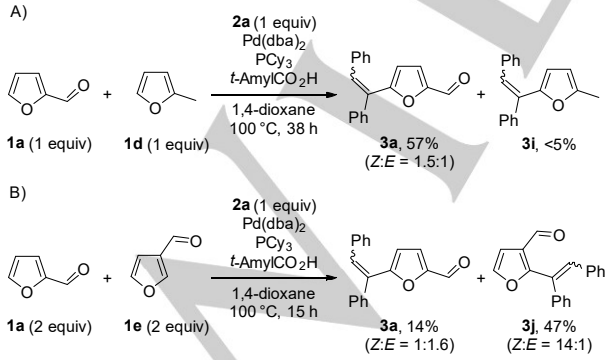
Scheme 1. Double alkenylation of **1e**

The present α-alkenylation was used in the sequential functionalization of furfural. According to Oble and Poli's report,[5f] we prepared 3-phenylated furfural **5**, and then subjected it to the present alkenylation to produce the 5-alkenylation product **6** (Scheme 2).



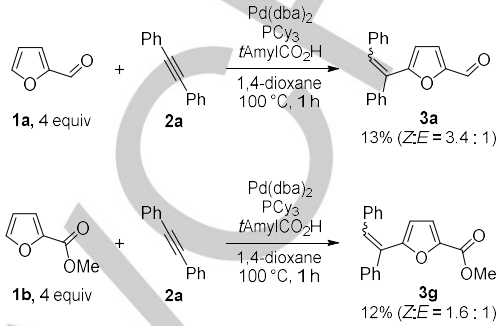
Scheme 2. Sequential introduction of furfural

As shown above, furan derivatives having electron-withdrawing substituents are effective substrates in this reaction rather than normal furan and electron-rich furans. Since it is highly advantageous to use substrates selectively, we performed a competition experiment between furfural (**1a**) and 2-methylfuran (**1d**) under the optimized conditions. Indeed, **1a** underwent the reaction preferentially and **3i** was hardly formed (Scheme 3A).[13] This result suggests that the C–H bond cleavage proceeds not via an attack of the furan to the alkyne mediated by a metal complex[14,15] but by a concerted-metalation-deprotonation (CMD) pathway.[16] Moreover, a competition reaction of equimolar mixtures of **1a** and 3-furancarboxaldehyde (**1e**) was conducted, which gave **3j** in preference to **3a** (Scheme 3B). This result suggests that an electron-deficient directing group enhanced the reactivity of the 2-C–H bond over other substrates having less-hindered α-C–H bonds.



Scheme 3. Competition experiments

To obtain information about the stereochemistry of this addition, we monitored the *Z*/*E* ratios of the product **3a** at the early stage of this reaction. More *E*-isomer, the *syn*-adduct of **3a**, was observed than in the cases in Table 1, Runs 4 and 5 (Scheme 4). The same trend was observed in the reaction using **1b**. Supported by the *syn*-conformation of **3f** derived from the bulky silylethynyl ether, these results suggest that *syn*-addition proceeds and the subsequent stereoisomerization occurs under thermodynamic control.[17]



Scheme 4. Early stage of this reaction

Based on results from previous reports,[8,9] we propose the reaction mechanism shown in Figure 3. After coordination of the alkyne to the palladium(0) complex forms **7**, the carboxylic acid reacts to generate alkenylpalladium carboxylate **8**.[18] The regioselectivity is probably derived from a steric repulsion between bulky substituents on the alkynyl carbon and the palladium center and the polarization of the carbon-carbon triple bonds.[19] Subsequent C–H bond activation of **1** proceeds via the CMD pathway to give alkenylarylpalladium **9**.[16] Reductive elimination produces the *syn*-addition product and regenerates the palladium(0) complex. The *syn*-adduct is isomerized to the *anti*-adduct possibly mediated by the carboxylic acid.

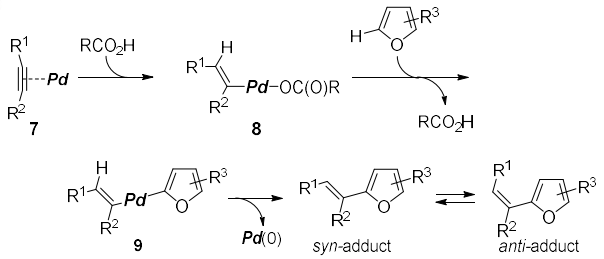


Figure 3. Plausible reaction mechanism

In conclusion, the alkenylation of furfural and similar furan derivatives using alkynes was made possible under a simple palladium/carboxylic acid catalyst via α-C–H bond cleavage. Various furan substrates were used in this reaction to form the corresponding α-alkenylated products. This catalytic method enabled the selective transformation of furans having electron-withdrawing groups such as furfural. Site-selective α-C–H bond cleavage was also achieved by using carbonyl-directing groups at the β position.

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Keywords: Alkynes • C–H activation • Heterocycles • Insertion • Palladium

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[12] The isolated **4** was the mixture of 2(*E*)-5(*E*), 2(*E*)-5(*Z*), and 2(*Z*)-5(*Z*) isomers (1.00:0.97:0.63), which were determined by the proton signals in ^{1}H NMR. See the supporting information for details.

[13] Additionally, the competition reaction using **1a** and **1b** under the reaction with **2a** was carried out and gave **3a** (47%) in preference over **3g** (27%). Moreover, when the similar competition experiment between **1c** and **1d** was attempted, **3h** (11%) was formed slightly higher than **3i** (7%). These results support the reactivity of furan substrates was derived from the electronic nature of substituents on the furan ring.

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[15] We attempted the reaction of **1d** (4 equiv) and **2a** with *t*-AmylCO_2H (10 mol%) at 100 °C under neat conditions. As a result, no reaction occurred, showing that the addition of **1d** do not proceed via an attack to alkynes mediated by carboxylic acids like reference 7a.

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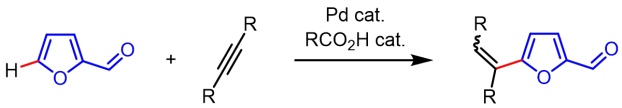

- α-C–H selective alkenylation
- formyl group remaining intact
- atom- and step-economical

Furfural and its derivatives underwent alkenylation with alkynes via α-C–H activation in the presence of a simple palladium/carboxylic acid catalyst with atom- and step-economies. The corresponding single and double alkenylated products were obtained. In the case of furfural, the reactive formyl group was retained during the reaction. This catalytic system allowed selective alkenylation of furan substrates having electron-withdrawing substituents.