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Pd(II)-Catalyzed Sequential C–C/C–O Bond Formations: A New Strategy to Construct Trisubstituted Furans

Meifang Zheng, Liangbin Huang, Wanqing Wu, and Huanfeng Jiang*

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P.R. China

jianghf@scut.edu.cn

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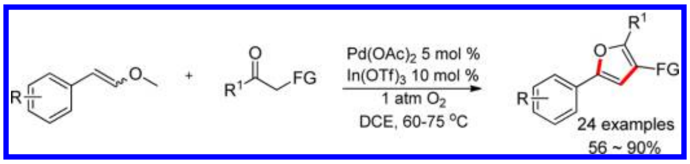
ABSTRACT



Palladium-catalyzed oxidative difunctionalization of enol ethers with 1,3-dicarbonyl compounds to construct trisubstituted furans in one step under mild conditions is described. The reaction is thought to proceed through a C–C bond formation along with a C–O bond closing the ring structure. Oxygen is the sole oxidant regenerating the Pd(II) catalyst.

Bond formation through transition-metal-catalyzed functionalization of unsaturated hydrocarbons continues to be a fantastic research arena due to its great potential for applications in natural product and bioactive compound synthesis.[1] Because of this potential, increasing effort has been devoted to the Pd-catalyzed difunctionalization of alkenes, such as carboamination,[2] carboetherification,[3] carbohalogenation,[4] and carboesterification[5] of alkenes. Most of these reactions employed terminal alkenes as the substrates, and strong oxidants are needed. However, literature reports on oxidative difunctionalization of the internal alkenes have not been prevalent.[6] As a subclass method of alkene difunctionalization, carboetherificated decoration of an alkene enables the formation of a C–O bond during ring closure along with a C–C bond adjacent to the ring,[7] which adds considerable utility in the construction of related heterocycles. Aryl-substituted enol

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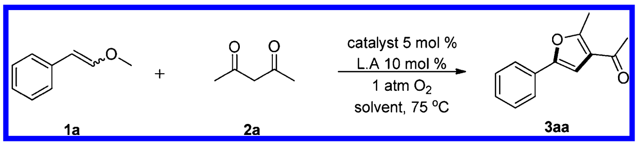
ethers, as readily available and versatile substrates, have seldom been employed because of their self-intramolecular Friedel–Crafts cyclizations.[8] In addition, the utilization of molecular oxygen as a green and inexpensive oxidant is one of the most important goals in oxidation chemistry.[9] Herein, we report a palladium-catalyzed highly selective oxidative carboetherification of alkyl enol ethers with 1,3-dicarbonyl compounds, which illustrates an efficient example of achieving trisubstituted furans in one step under mild conditions.

The furan moiety represents a key structural unit that occurs ubiquitously in biologically active natural and pharmaceutical compounds.[10] Thus, the development of a practical and efficient synthetic method for furans is of significant importance. Although diverse approaches toward the synthesis of furans have been exploited, improvement is still needed for a mild and efficient synthetic method of high regioselectivity.[11] In recent years, our group has developed efficient methods for the construction of functionalized furan derivatives via Cu-, Ag-, Fe-catalyzed intramolecular procedures.[12] Evidently, an oxidative cross-coupling reaction between enol ethers and 1,3-carbonyl compounds to construct trisubstituted furans, using oxygen as the sole oxidant, would be a fascinating approach.

Table 1. Optimization of Reaction Conditions[a]

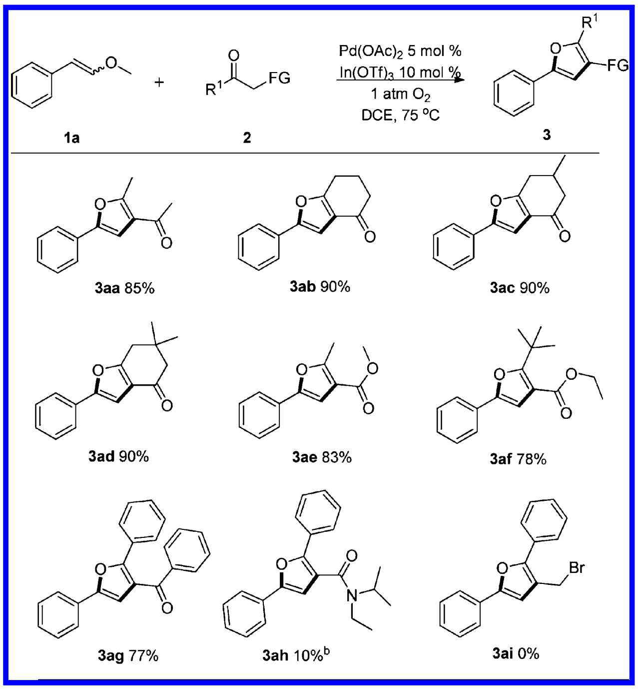


entry	catalyst	additive	solvent	yield[c] (%)
1[b]	$Pd(OAc)_2$	$Zn(OTf)_2$	DCE	51
2	$Pd(OAc)_2$	$FeCl_2$	DCE	22
3	$Pd(OAc)_2$	$SnCl_4$	DCE	19
4	$Pd(OAc)_2$	$In(OTf)_3$	DCE	91 (85)[d]
5	$Pd(OAc)_2$	$Sc(OTf)_3$	DCE	66
6	$Pd(OAc)_2$	$MgClO_4$	DCE	47
7	$Pd(OAc)_2$	$ZnCl_2$	DCE	trace
8	$Pd(OAc)_2$	$Yb(OTf)_3$	DCE	trace
9	$Pd(OAc)_2$	–	DCE	N.P.
10	–	$In(OTf)_3$	DCE	trace
11	$Pd(OAc)_2$	HOTf	DCE	trace
12	$PdCl_2$	$In(OTf)_3$	DCE	12
13	PdI_2	$In(OTf)_3$	DCE	20
14	$Pd(OAc)_2$	$In(OTf)_3$	CH_3CN	N.P.
15	$Pd(OAc)_2$	$In(OTf)_3$	DMA	trace
16	$Pd(OAc)_2$	$In(OTf)_3$	dioxane	61
17[e]	$Pd(OAc)_2$	$In(OTf)_3$	DCE	78
18[f]	$Pd(OAc)_2$	$In(OTf)_3$	DCE	N.P.

[a] Reaction conditions: unless otherwise noted, the reaction was carried out with 0.05 mmol of methoxystyrene and 1.2 equiv of acetyl acetone in solvent (0.5 mL) at 75 °C in 1 atm O_2 balloon for 18 h. [b] The reaction was performed in the open air. [c] Determined by GC–MS. [d] Isolated yield. [e] The reaction was performed at 50 °C for 18 h. [f] Under N_2.

The reaction of 2-methoxyvinylbenzene (**1a**) and acetyl acetone (**2a**) was initially employed in the presence of 5 mol % $Pd(OAc)_2$ and 10 mol % $Zn(OTf)_2$ in 1 mL of DCE. As we expected, carboetherification of **1a** indeed preceded readily under 1 atm air at 75 °C to give the furan product **3aa** in moderate yield (Table 1, entry 1). To further improve the yield, we examined a range of acids, and $In(OTf)_3$ was found to be the most effective, while other Lewis acids were either poorly effective [$FeCl_2$, $SnCl_2$, $Sc(OTf)_3$, $MgClO_4$, $Sc(OTf)_3$ (entries 2–3 and entries 5–6)] or entirely ineffective [$ZnCl_2$, $Yb(OTf)_3$ (entries 7–8)]. The reaction did not proceed at all in the absence of acid additives or palladium catalyst (entries 9–10). When a Brønsted acid, such as HOTf, was added for this transformation, phenylacetaldehyde was the main product through hydrolysis (entry 11). It must be noted that with the same amounts of $PdCl_2$ and PdI_2 as the catalyst the reaction took place in 12% and 20% yield, respectively (entries 12–13). The examination of the solvent effect revealed that DCE was the best choice for this system (entry 4), while other solvents were less efficient (entries 15–16) or even totally ineffective (entry 14). At a lower temperature (50 °C), the conversion of **1a** decreased and gave only 78% of **3aa** (entry 17). Moreover, the reaction could not occur without oxygen atmosphere (entry 18).

Table 2. Scope of 1,3-Diketones[a]



[a] The reaction was carried out with 0.3 mmol of 2-methoxyvinylbenzene and 1.2 equiv of acetyl acetone in DCE (0.5 mL) at 75 °C in 1 atm O_2 balloon for 18 h [b] Determined by GC–MS.

With optimized reaction conditions established, we started to investigate other 1,3-carbonyl compounds in this Pd-catalyzed, oxidative cyclization reaction (Table 2).

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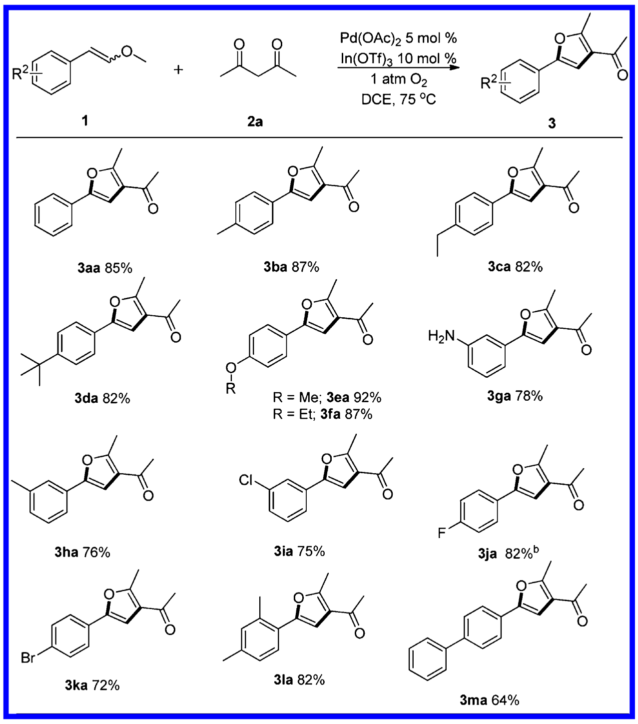
A series of furans could be obtained in good to excellent yields from different 1,3-diketones. Compared with unsymmetrical 1,3-carbonyls, the symmetrical ones provided higher furan yields. When the cyclohexane-1,3-dione was used under standard conditions, 2-phenyl-6,7-dihydrobenzofuran-4(5*H*)-one (**3ab**) was obtained in excellent yield. Moreover, the 5-methyl- or 5-dimethyl-substituted cyclohexane-1,3-diones were also incorporated, delivering the corresponding furans regioselectively (**3ac** and **3ad**). In an expansion of the substrates, β-keto esters **2e** and **2f** were used in the reaction with 2-methoxyvinylbenzene (**1a**), and the corresponding products **3ae** and **3af** could be obtained successfully in high yields and consistent chemoselectivity. Notably, when both R^1 and FG were aryl groups, the target furans were provided as isomers in lower yields (**3ag**). The 1,3-dicarbonyl compound bearing an amide group was also reacted with **1a** and afforded the furan product **3ah** in 10% yield. Unfortunately, 2-bromo-1-phenylethanone was not a suitable substrate for the reaction under the current conditions (**3ai**).

Next, a variety of methoxystyrene compounds were evaluated in this Pd-catalyzed, oxidative cyclization reaction (Table 3). Both electron-donating and -withdrawing groups could be tolerated on the aromatic moieties to access the 2,3,5-trisubstituted furans, including alkyl (**3ba**−**3da**, **3ha**, and **3la**), alkoxyl (**3ea**, **3fa**), halogen (**3ia**−**3ka**), amine (**3ga**), and aromatic (**3ma**) groups. 1-Methyl-, 1-ethyl-, and 1-*tert*-butyl-substituted (2-methoxyvinyl)benzenes underwent cyclization preferentially at the less hindered position to afford the corresponding furans with a single regioisomer in excellent yields (87%, 82%, and 82% respectively). Substituents at the meta positions of 2-methoxyvinyl-derived moieties (**1g**−**1i**) were tolerated, delivering good yields of the corresponding furans (**3ga**−**3ia**). Impressively, in the case of 3-(2-methoxyvinyl)aniline (**1g**), 78% of the carboetherification product, 1-(5-(3-aminophenyl)-2-methylfuran-3-yl)ethanone (**3ga**), was isolated, which clearly demonstrated that a meta substitution effect caused by the NH_2- group also existed in the present transformation. A similar reactivity trend for 5-(biphenyl-4-yl)-2-methyl-3-acetate-furan (**3ma**) was observed during our investigations on the usage of 4-phenylmethoxystyrene. When 4-fluoro-methoxylstyrene was employed, 5-(4-fluorophenyl)-2-methyl-3-acetate-furan (**3ja**) was obtained with excellent yield and exclusive regioselectivity. For example, substrates bearing an electron-rich substituent all gave good conversions and chemoselectivity (**3ea** and **3fa**). Generally, compared with halogen substituents, the electron-rich groups on the aromatic ring improved this procedure (**3ba**−**3fa**, **3ga**−**3ha**, and **3la**), favoring the chemoselectivity of the products (**3ia**−**3ka**). This might reveal that the electronic nature of the substituents on the phenyl ring has a pronounced effect on the overall efficiency of the process.

Table 3. Scope of β-Methoxystyrenes[a]



[a] The reaction was carried out with 0.3 mmol of 2-methoxyvinylbenzene and 1.2 equiv of acetyl acetone in DCE (0.5 mL) at 75 °C in 1 atm O_2 balloon for 18 h. [b] The reaction was performed at 60 °C.

Notably, polysubstituted furans could also be acquired via oxidative C−C/C−O formations under this catalytic system. To further investigate the property of the methoxyl group of methoxystyrene, several experiments were conducted under the standard conditions with alternative substrates instead of 2-methoxyvinylbenzene (Scheme 1). Interestingly, 1-chloro-2-(2-methoxyvinyl)benzene which possessed the ortho site gave the other regioselective carboetherification product **3na** in lower yields, which might be due to the steric hindrance. Note that when ethyl acetoacetate was used instead of acetylacetone, the same positioned substituted furan **3nf** was obtained in good yield (eq 1 in Scheme 1). Neither buta-1,3-dienylbenzene[13] nor styrene could carry out the carboetherification effectively (eq 2 in Scheme 1). Furthermore, although the styrenyl

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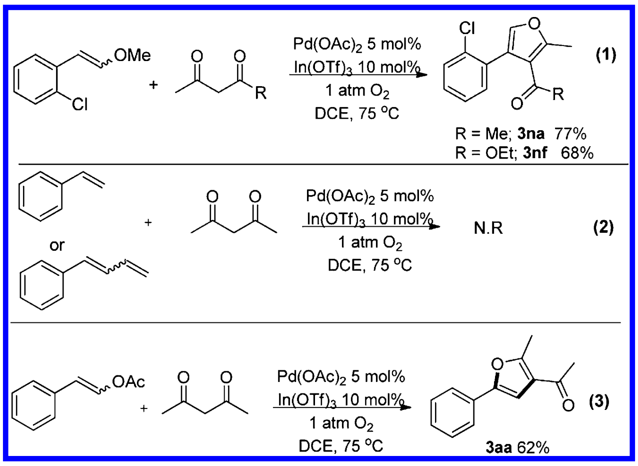
Scheme 1. Control Experiments

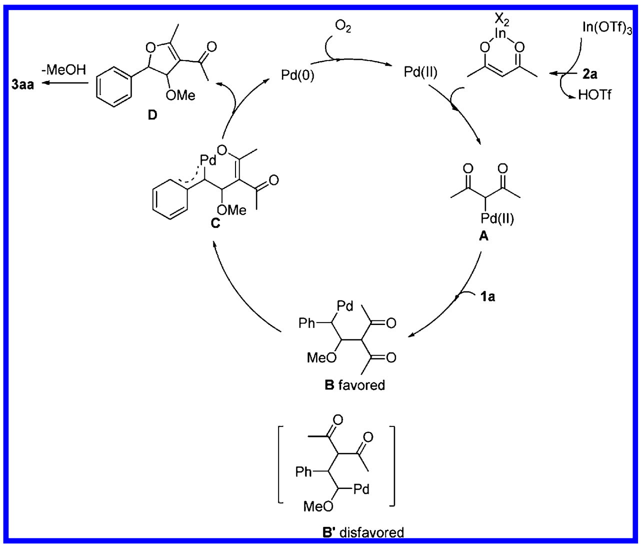


acetate could be successfully converted to the desired furan in 62% yield, conversion was lower than that of the β-methoxystyrene (eq 3 in Scheme 1).

On the basis of the above results, a tentative mechanism for the Pd(II)-catalyzed oxidative coupling between 2-methoxyvinylbenzenes and 1,3-diketones is proposed (Scheme 2). First, $In(OTf)_3$ reacts with the enolized form of a β-diketone to generate the In(III) intermediate and release triflic acid which then effects transmetalation with $Pd(OAc)_2$, furnishing an alkylpalladium complex **A**.[14] **A** then inserts into the styrenyl methyl ether to form **B** instead of **B′** because of the electronic property of the −OMe group governing the more stable intermediate. The subsequent oxypalladation gives palladacycle **C**.[15] Reductive elimination of **C** leads to precursor **D**, followed by the extrusion of methanol to deliver the target product **3aa**. Finally, Pd(0) is oxidized by O_2 to regenerate the Pd(II) catalyst.

In conclusion, we have developed a new Pd-catalyzed method for the formation of $C(sp^2)-C(sp^3)$ and C−O bonds through carboetherification of enol ethers with 1,3-carbonyls, which allows the facile synthesis of

Scheme 2. Possible Reaction Mechanism



multisubstituted furans. This catalytic cyclization process with the use of oxygen as the sole oxidant, has a broad substrate scope and affords furan derivatives in good to excellent yields. Ongoing research involves the extension of substrate scope, and further investigations of the synthetic application as well as detailed mechanistic studies are underway in our labortary.

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Supporting Information Available. Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.