# A Highly Efficient Synthesis of 2,5-Disubstituted Furans from Enyne Acetates Catalyzed by Lewis Acid and Palladium

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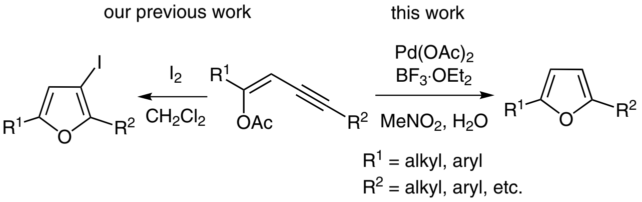
**Abstract:** A highly efficient synthesis of a wide range of 2,5-disubstituted furans from enyne acetates is described. The reactions are conducted by using Lewis acid and palladium catalyst and provide symmetrical and unsymmetrical products in good to excellent yields, with broad substrate scope, including a variety of aromatic and aliphatic substituents in the 2- and 5-position of the furan ring.

**Key words:** furan, enyne acetate, Lewis acid, palladium, synthesis

Furans are one of the most important classes of five-membered heterocycle compounds, and they are found as key structural units in many natural products, pharmaceuticals, and agrochemicals.[1] Substituted furans are also used as building blocks in organic synthesis and material science.[2] The classical approach to furan synthesis is the Paal–Knorr method, in which 1,4-dicarbonyl compounds are converted into furan derivatives.[3] As an alternative to classical furan synthesis, several studies have focused on the development of metal-catalyzed synthesis of furans employing acyclic precursors. These include the cyclization of alkynyl,[4] allenyl,[5] cyclopropenyl,[6] and cyclopropyl[7] ketone derivatives. Alternative strategies involve the cyclization of alkynols,[8] substituted oxiranes,[9] functionalized propargyl vinyl ethers,[10] enynediones,[11] 1,3-diynes,[12] and other substrates.[13]

2,5-Disubstituted furans are important substructures in various drugs and drug candidates.[14] Although a variety of well-established methods have proven to be very effective for the synthesis of 2,5-disubstituted furans,[12,15] the search for efficient routes to substituted furans with flexible substituent patterns is an important goal of organic synthesis. Very recently, we reported a convenient and expedient method for the synthesis of 2,5-disubstituted 3-iodofurans through electrophilic iodocyclization of enyne acetates.[16] As a part of our continuing interest in the construction of furan derivatives, here we report a synthesis of 2,5-disubstituted furans from enyne acetates that is catalyzed by Lewis acid and palladium and is carried out in the presence of water (Scheme 1). The approach is convenient for the construction of both symmetrical and unsymmetrical 2,5-disubstituted furans in good yields with broad functional group compatibilities.



**Scheme 1** Synthesis of substituted furans from enyne acetates by electrophilic iodocyclization and mediated by Lewis acid and palladium

Initial efforts focused on establishing efficient catalysts and suitable reaction conditions in acetonitrile, with enyne acetate **1a** as the model substrate. As shown in Table 1, the reaction did not proceed without catalyst (Table 1, entry 1). Several commonly used metal salts were tested as the catalyst to conduct this reaction and found that whereas iron and silver salts were inactive for the transformation (entries 2 and 3), copper and palladium salts could both smoothly promote the transformation, with palladium acetate being the most efficient (entries 4–10). Previous work on furan synthesis have shown that Lewis or Brønsted acid favored triple bond activation, thus promoting subsequent oxygen attack on the triple bond. Different additives were therefore tried, and we were pleased to find that the inclusion of such acids did promote the reaction. Indeed, furan **2a** was obtained in high conversions and yields when additives were used under the developed conditions (entries 11–14). Compared with Brønsted acid, Lewis acids were more beneficial to the transformation, and $BF_3{\cdot}OEt_2$ was found to be the most suitable additive (entry 14). A control experiment showed that the catalyst was necessary in the present process (entry 15). We then screened the effect of solvent on this reaction, and showed that solvents played an important role in the outcome of the reaction (entries 17–23). Among the solvents used, $MeNO_2$ was established as the solvent of choice for the reaction (entry 22). We considered that the optimized reaction conditions are as follows: **1a** (0.25 mmol), $H_2O$ (1 equiv), $Pd(OAc)_2$ (5 mol%), $BF_3{\cdot}OEt_2$ (30 mol%), and $MeNO_2$ at 80 °C for 10 h (entry 22).

With the optimized conditions in hand, we next focused on the scope of the reaction (Scheme 2). In general, all of the substrates tested could form the corresponding 2,5-disubstituted furans in good to excellent yields. Substitution at the 2-position of the aromatic ring reduced the yields slightly (**2h**, **2j**, and **2s**). The reaction conditions

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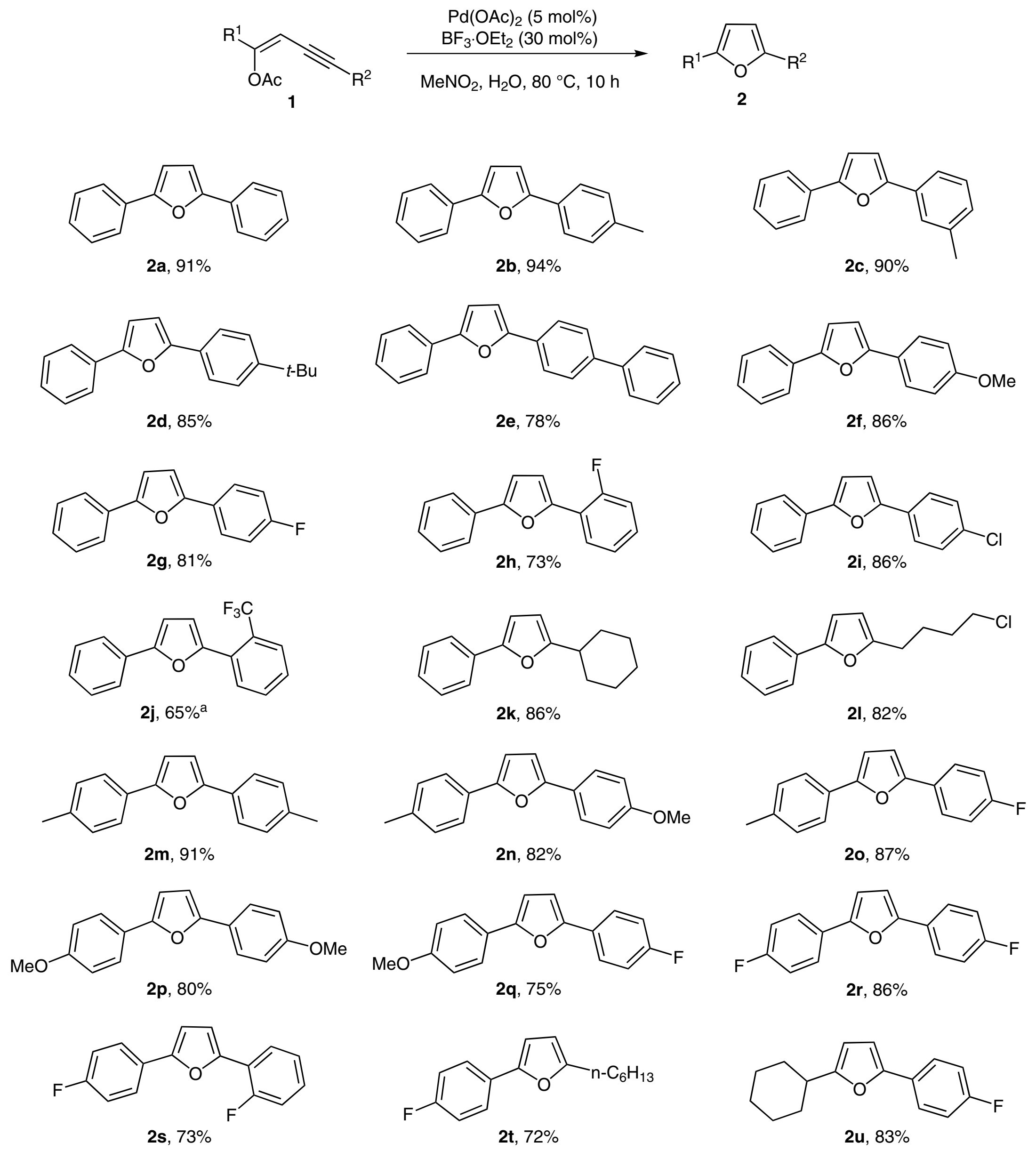

**Scheme 2** Preparation of 2,5-disubstituted furans from enyne acetates (isolated yields). *Reagents and conditions*: **1** (0.25 mmol), $Pd(OAc)_2$ (5 mol%), $BF_3{\cdot}OEt_2$ (30 mol%), $H_2O$ (1 equiv), $MeNO_2$ (1 mL), 80 °C, 10 h. [a] Reacted for 16 h.

were compatible with alkyl, alkyloxy, aryl, fluoro, chloro, bromo, and trifluoromethyl groups (**2b**–**u**). Initially, a set of substituents at the terminal alkyne moiety were evaluated in the standard conditions (**2b**–**j**). Substrates with either electron-donating or electron-withdrawing groups on the benzene ring could be used to generate the corresponding products (**2b**–**j**). A substrate with the bulky *tert*-butyl group afforded the product in 85% yield (**2d**). The presence of a $CF_3$ group on the 2-position of benzene ring led to prolonged reaction time (**2j**). It should be pointed out that carbon–halogen bonds were well tolerated and the products containing halogen groups were afforded smoothly. Especially, the aryl chloride could be further functionalized (**2i**). Alkynes bearing aliphatic substituents were compatible with the reaction system (**2k** and **2l**). We then evaluated the $R^1$ groups on the double bond under the standard conditions (**2m**–**u**). Substrates with either electron-rich groups (methyl and methoxy) or the electron-deficient group (fluoro) attached to the benzene ring could produce the 2,5-disubstituted furans in satisfactory yields (**2m**–**s**). Gratifying, the standard conditions were compatible with the cyclohexyl group and gave the desired product in 83% yield (**2u**).

A possible mechanism was proposed as outlined in Scheme 3 on the basis of the reported mechanism[17] and the present results. First, triple-bond coordination to Pd(II) occurs to give a π-complex **A**. The nucleophilic oxygen then attacks the Pd-activated triple bond to give 3-furylpalladium intermediate **B**. Finally, **B** undergoes protodepalladation to afford 2,5-disubstituted furans **2**. We

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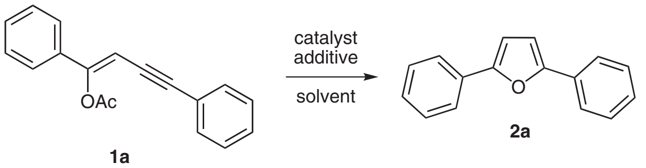
**Table 1** Optimization of Reaction Conditions for the Synthesis of 2,5-Disubstituted Furan[a]



| Entry | Catalyst | Solvent | Additive | Conv. (%)[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | – | MeCN | – | – | – |
| 2 | $FeCl_3$ | MeCN | – | – | – |
| 3 | $AgNO_3$ | MeCN | – | – | – |
| 4 | CuI | MeCN | – | 12 | 8 |
| 5 | $PdCl_2$ | MeCN | – | 39 | 36 |
| 6 | $Pd(OAc)_2$ | MeCN | – | 55 | 51 |
| 7 | Pd/C | MeCN | – | 12 | 12 |
| 8 | $Pd(PPh_3)_4$ | MeCN | – | 24 | 23 |
| 9 | $PdCl_2(PPh_3)_2$ | MeCN | – | 40 | 35 |
| 10 | $Pd(MeCN)_2Cl_2$ | MeCN | – | 42 | 39 |
| 11 | $Pd(OAc)_2$ | MeCN | LiCl | 92 | 73 |
| 12 | $Pd(OAc)_2$ | MeCN | $ZnCl_2$ | 98 | 68 |
| 13 | $Pd(OAc)_2$ | MeCN | $AlCl_3$ | 85 | 59 |
| 14 | $Pd(OAc)_2$ | MeCN | $BF_3\cdot OEt_2$ | 100 | 89 |
| 15 | – | MeCN | $BF_3\cdot OEt_2$ | 55 | – |
| 16 | $Pd(OAc)_2$ | MeCN | HOAc | 100 | 40 |
| 17 | $Pd(OAc)_2$ | DMF | $BF_3\cdot OEt_2$ | 96 | 62 |
| 18 | $Pd(OAc)_2$ | DMSO | $BF_3\cdot OEt_2$ | 95 | 52 |
| 19 | $Pd(OAc)_2$ | THF | $BF_3\cdot OEt_2$ | 88 | 79 |
| 20 | $Pd(OAc)_2$ | DCE | $BF_3\cdot OEt_2$ | 96 | 83 |
| 21 | $Pd(OAc)_2$ | toluene | $BF_3\cdot OEt_2$ | 96 | 80 |
| 22 | $Pd(OAc)_2$ | $MeNO_2$ | $BF_3\cdot OEt_2$ | 100 | 94<br>(91) |
| 23 | $Pd(OAc)_2$ | dioxane | $BF_3\cdot OEt_2$ | 100 | 86 |

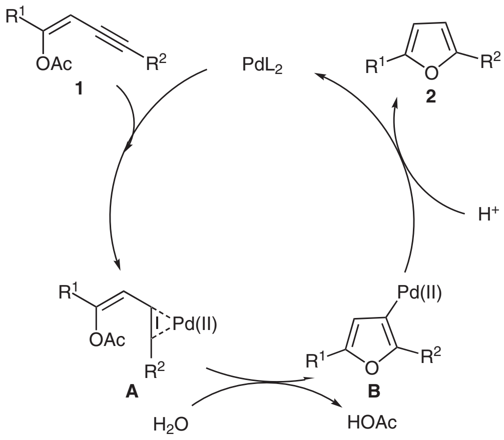
[a] Reaction conditions: **1a** (0.25 mmol), catalyst (5 mol%), additive (30 mol%), $H_2O$ (1 equiv), and solvent (0.5 mL), 80 °C, 10 h.

[b] Determined by GC analysis.

[c] Determined by GC analysis. Isolated yield of **2a** given in parentheses.

supposed that Lewis acid could promote the substrate deacylation in situ in the presence of water, favoring the cyclization step.

In conclusion, we have presented a general and facile method for the synthesis of 2,5-disubstituted furans from enyne acetates, which can be prepared from terminal alkynes.[18] The approach is convenient for the construction of both symmetrical and unsymmetrical products in good to excellent yield. The results also indicate that the Lewis acid/palladium catalyzed cyclization reaction tolerates a wide range of functional groups. Further synthetic applications and studies of the mechanism of the reaction are underway in our laboratory.



**Scheme 3** Possible reaction mechanism

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(18) **Preparation of 2,5-Disubstituted Furans from Enyne Acetates; Typical Procedure:** To a mixture of (*Z*)-1,4-diphenylbut-1-en-3-yn-1-yl acetate (**1a**; 0.25 mmol) and MeNO$_2$ (1.0 mL), Pd(OAc)$_2$ (5 mol%), BF$_3$·OEt$_2$ (30 mol%), and H$_2$O (1 equiv) were added. The mixture was stirred at 80 °C for 10 h, then H$_2$O (10 mL) was added and the solution was extracted with EtOAc (3 × 8 mL). The combined extract was dried with anhydrous MgSO$_4$, the solvent was removed, and the residue was separated by column chromatography (petroleum ether–EtOAc, 30:1) to give the desired product **2a.**

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