Furans *versus* 4*H*-pyrans: catalyst-controlled regiodivergent tandem Michael addition–cyclization reaction of 2-(1-alkynyl)-2-alken-1-ones with 1,3-dicarbonyl compounds†

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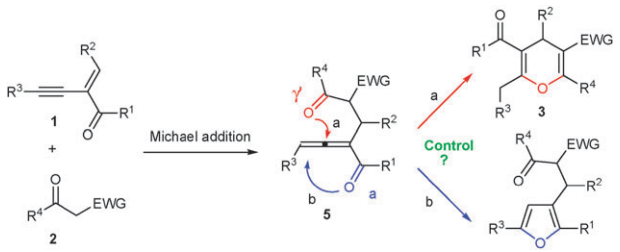
The DBU-catalyzed reaction of 1-(1-alkynyl)-2-alken-1-ones with 1,3-dicarbonyl compounds produces 4*H*-pyrans in moderate to excellent yield, whereas the cationic Pd(II)-catalyzed reaction affords furans regioselectively.

Furans and 4*H*-pyrans are two types of very important and widespread groups of five and six-membered oxygen containing heterocycles. The furan rings are common structural units in many natural biologically active products, pharmaceuticals,[1,2] and versatile building blocks in synthetic organic chemistry.[3,4] 4*H*-Pyrans have been identified as potential and specific IK_{Ca} channel blockers[5] that were proposed as potential therapeutic agents for several diseases such as sickle cell anaemia, secretory diarrhea, cystic fibrosis, autoimmune diseases and restenosis.[6] Thus, it is not surprising that various new synthetic methods have been developed for the assembly of furans[7] or pyrans,[8] and the search for new methodologies proceeding more efficiently from readily available starting materials still remains an active area of research.

On the other hand, one of the challenges of modern synthesis is to create distinct types of complex molecules from identical starting materials based solely on catalyst selection.[9] As a continuation of our interest in exploration of novel regiodivergent reactions,[10] and the chemistry of 2-(1-alkynyl)-2-alken-1-ones,[11] we envisaged that the direct synthesis of 4*H*-pyran **3** or furan **4** might be realized by a one-pot reaction of 2-(1-alkynyl)-2-alken-1-ones **1** with 1,3-dicarbonyl compounds **2** through controlling sequential C–C and C–O bond formation under the proper conditions (Scheme 1). First, the intermolecular Michael addition of the nucleophile **2** and ketone **1** produce intermediate allenyl ketone **5**. There is an obvious regioselectivity issue in further transformations of intermediate **5**, that is, two kinds of C–O bond formation patterns occur *via* the interaction of the allenyl group with two different carbonyl groups (α carbonyl and γ′ carbonyl group) leading to functionalized 4*H*-pyrans **3** (Scheme 1, Path a) or furan **4** (Scheme 1, Path b). Herein we present our recent results on the catalyst-controlled regiodivergent tandem



Scheme 1 The design of direct synthesis of furan or pyran derivatives by a controlled tandem reaction from the same starting materials.

Michael addition–cyclization of 2-(1-alkynyl)-2-alken-1-ones **1** with 1,3-dicarbonyl compounds **2** to give furans or 4*H*-pyrans, respectively. To the best of our knowledge, the selective synthesis of furans or pyrans from the same starting materials by a simple subtle catalyst selection has rarely been reported.[12]

In the course of our current studies focused on the chemistry of electron-deficient 1,3-conjugated enynes, we recently disclosed that DBU (1,8-diazabicyclo[5.4.0]undecen-7-ene) was found to be an efficient base catalyst in the reaction of 2-(1-alkynyl)-2-alken-1-esters with 1,3-dicarbonyl compounds to give 4*H*-pyrans.[11a] This new synthetic methodology to the preparation of novel pyrans can be successfully extended to a variety of 2-(1-alkynyl)-2-alken-1-ones **1** with 1,3-diketones and their analogues. The results are summarized in Tables 1–2. Some points are noteworthy: (1) all atoms of both reactants are incorporated into the desired 4*H*-pyrans, that is, this reaction is 100% atom-economic; (2) the transformation is quite general, and structurally diverse pentasubstituted 4*H*-pyrans could be easily synthesized in moderate to excellent yields *via* this transformation (Table 1, entries 1–5, method A; Table 2, entries 1–9, method (A); (3) it is not only 1,3-diketones such as acetylacetone and dibenzoylmethane but also β-keto esters that can be used as nucleophiles to afford the corresponding highly substituted 4*H*-pyrans (Table 1, entries 1–5, method (A); (4) alkynes bearing aliphatic groups afford relatively higher yields than those bearing aryl groups (Table 2, compare entries 6, 9 to entries 1–5).

Having realized path a from reaction intermediate **5** to produce pyrans **3** using a basic catalyst, we next examined another envisioned reaction pathway associated with tuning the regioselectivity of reaction intermediate **5** for furan synthesis (Path b) by using a metal catalyst. To identify the optimal reaction conditions for the reaction, a number of metal catalysts, including $AuCl_3$,[13] $PdCl_2(CH_3CN)_2$,[11b,c] cationic Pd(II),[14] and several different organic solvents and

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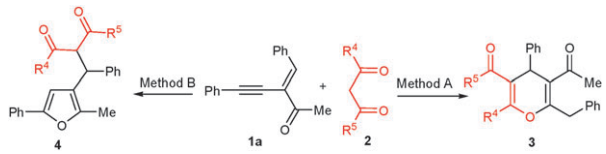
Table 1 Catalyst-controllable selective synthesis of 4*H*-pyrans **3** or furans **4** from **1a** and 1,3-dicabonyl compounds **2**[a]



Entry	Substrate **2** R^4/R^5	Method A **3** (time, yield)	Method B **4** (time, yield, d.r.)[b]
1	Me/Me(**2a**)	**3aa** (4 h, 83%)	**4aa** (7 h, 99%, —)
2	Ph/Ph(**2b**)	**3ab** (4 h, 51%)	**4ab** (20 h, 51%, —)[c]
3	Me/OMe(**2c**)	**3ac** (4 h, 78%)	**4ac** (15 h, 96%, 1.6/1)
4	Ph/OEt(**2d**)	**3ad** (4 h, 62%)	**4ad** (16 h, 82%, 1.8/1)
5	isopropyl/OMe(**2e**)	**3ae** (4 h, 72%)	**4ae** (10 h, 94%, 1.2/1)

[a] Method A: The reaction was carried out by using **1** (0.25 mmol) and **2** (0.375 mmol, 1.5 equivalents), DBU (5 mol%) in 1 mL of DMF at 100 °C. Method B: unless, otherwise specified, The reaction was carried out by using **1** (0.25 mmol) and **2a** (0.375 mmol, 1.5 equivalents), $[Pd(dppp)(H_2O)_2](OTf)_2$ (5% mol) in 1 mL of $ClCH_2CH_2Cl$ at rt. [b] d.r. = diasteroisomer ratio. [c] The reation was run at 40 °C.

ligands were examined in the reaction of (*E*)-3-benzylidene-5-phenylpent-4-yn-2-one **1a** with acetylacetone **2a** (for details see the ESI†). Optimization of the reaction conditions revealed that the reaction proceeded efficiently when $[Pd(dppp)(H_2O)_2](OTf)_2$ and 1,2-dichloroethane were used as catalyst and solvent, respectively, the desired furan **4aa** was obtained in quantitative yield (99%). The screening of different solvents showed that the solvent has a significant influence on the reaction, 1,2-dichloroethane (DCE) was found to be quite successful for present transformation. The screening of different catalysts showed that a cationic Pd(II) catalyst with stronger Lewis acidity generally gave superior results when compared to $AuCl_3$, $PdCl_2(CH_3CN)_2$ and Pd(μ-OH)dppp catalysts with weaker Lewis acidity in terms of conversion and yield. It is well documented that cationic Pd(II) catalysts that efficiently catalyze 1,3-dicarbonyl compounds undergo Michael reactions, aldol-type reactions and Mannich-type reactions;[14] the present results showed that cationic Pd(II) catalysts can also efficiently catalyze the reaction of 1,3-dicarbonyl compounds with ketones **1** to give furans.

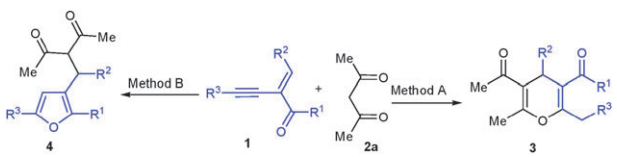
With the optimized reaction conditions in hand, we next studied the reaction of **1a** with various 1,3-dicarbonyl compounds **2** to determine the scope of this transformation, and the results are listed in Table 1, method B. Several points are noteworthy: (1) the reaction is also 100% atom-economic; (2) when the reaction was examined with β-keto esters, the desired furans were obtained as an inseparable mixture of two diastereomers in excellent yields with moderate diastereoselectivity (Table 1, method B, entries 3–5); (3) the reaction of **1a** with low reactive dibenzoylmethane **2b** gives a relatively lower yield and requires an elevated temperature (Table 1, entry 2).

The generality of the method for furan synthesis can be successfully extended to a variety of ketones **1** leading to the corresponding trisubstituted functionalized furans in 43–99% yield (Table 2, method B, entries 1–9). This procedure displays toleration of the presence of aryl and alkyl substituents at both the carbonylic carbon (R^1) and the triple bond position (R^3) (Table 2, method B, entries 1–3, 6, 8–9). The substituents attached to the double bond (R^2) have a major impact on the yield of the reaction. For example, the reaction of **1h** with acetylacetone **2a** gives a relatively lower yield (43%) and requires more nucleophile loading (Table 2, method B, entry 7). The structure of furan **4ca** was further confirmed by single-crystal X-ray diffraction analysis (for details see the ESI†).

In order to determine our envisioned reaction pathway proceeding through allenyl ketone **5**, some further control experiments were performed using **1a** and dimethyl malonate **2f** as representative substrates (Scheme 2).

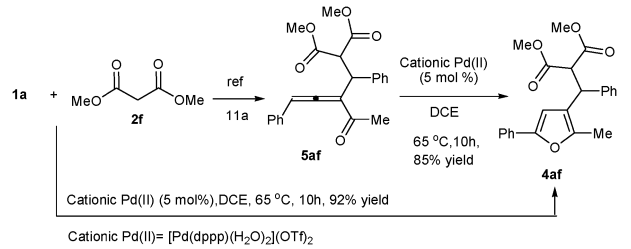
Allenyl ketone **5af** was synthesized according to our previously reported method[11a] which could undergo cycloisomerization readily to afford furan **4af** in 85% isolated yield

Table 2 Selective synthesis of 4*H*-pyrans **3** or furans **4** from various 2-(1-alkynyl)-2-alken-1-ones **1** and acetylacetone **2a**

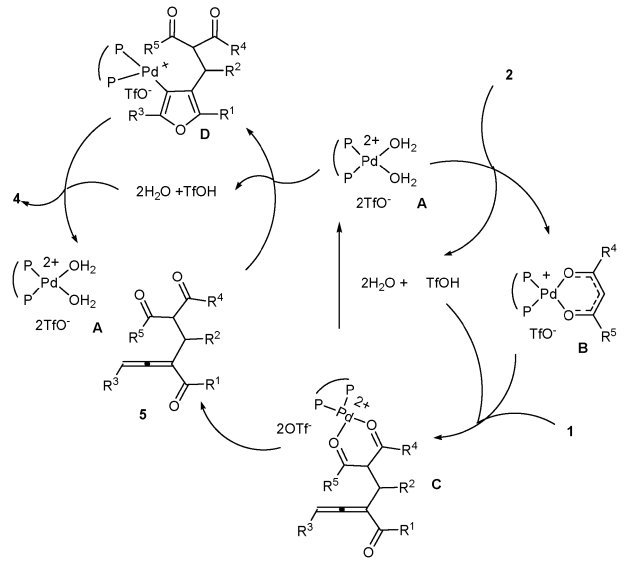


Entry	Substrate **1** $R^1/R^2/R^3$	Method A **3** (time, yield)	Method B **4** (time, yield)
1	Me/4-MeOC_6H_4/Ph (**1b**)	**3ba** (5 h, 50%)	**4ba** (7 h, 99%)
2	Me/Ph/4-MeOC_6H_4 (**1c**)	**3ca** (5 h, 51%)	**4ca** (5 h, 96%)
3	Me/4-MeOC_6H_4/4-MeOC_6H_4 (**1d**)	**3da** (6 h, 56%)	**4da** (5 h, 85%)
4	Me/Ph/1-Naphthyl(**1e**)	**3ea** (5 h, 46%)	**4ea** (40 h, 61%)[a]
5	Me/4-MeOC_6H_4/1-Naphthyl(**1f**)	**3fa** (5 h, 56%)	**4fa** (48 h, 68%)[a]
6	Me/Ph/*n*-C_4H_9(**1g**)	**3ga** (4 h, 98%)	**4ga** (4 h, 99%)
7	Me/*n*-C_4H_9/Ph (**1h**)	**3ha** (5 h, 55%)	**4ha** (4 h, 43%)[b]
8	Ph/Ph/Ph (**1i**)	**3ia** (5 h, 83%)	**4ia** (3 h, 99%)
9	Ph/Ph/*n*-C_4H_9(**1j**)	**3ja** (4 h, 98%)	**4ja** (5 h, 99%)

[a] Additional 5 mol% of catalyst was added after the reaction was stirred for 24 h. [b] 3.0 equivalents of acetylacetone **2a** was used.



Scheme 2 Cationic Pd(II) catalyzes the reaction of **1a** and dimethyl malonate **2f**.



Scheme 3 Proposed catalytic cycle for direct furan syntheses.

catalyzed by 5 mol% cationic Pd(II) at 65 °C. Indeed, the reaction of **1a** with dimethyl malonate **2f** under the same conditions directly affords furan **4af** in 92% isolated yield.

On the basis of the above results, a plausible mechanism for direct synthesis of furan catalyzed by cationic Pd(II) is outlined in Scheme 3. The initial reaction of cationic Pd(II) catalyst **A** with 1,3-dicarbonyl compound **2** gives the palladium enolate **B**,[15a] a strong protic acid (TfOH) and two molecules of water ($2H_2O$). The water contributes to complete the catalytic cycle, because no furan is obtained when molecular sieves (1.5 equiv.) are added to the reaction mixture. The palladium enolate **B** could undergo Michael reaction with the aid of TfOH[15b] to furnish the addition product **C**, which upon hydrolysis affords allenyl ketone **5** and regenerates cationic Pd(II) catalyst **A**. Allenyl ketone **5** is ready to undergo cycloisomerization to final furan **4**.

In summary, the chemistry described herein provides an efficient catalyst-controlled regiodivergent synthesis of furans and 4*H*-pyrans from two simple, readily available starting materials. The regioselective introduction of substituents to the furans or pyrans arises from the appropriate choice of 2-(1-alkynyl)-2-alken-1-ones or β-keto compounds. Further studies on the asymmetric version of these reactions are underway in our laboratory.

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