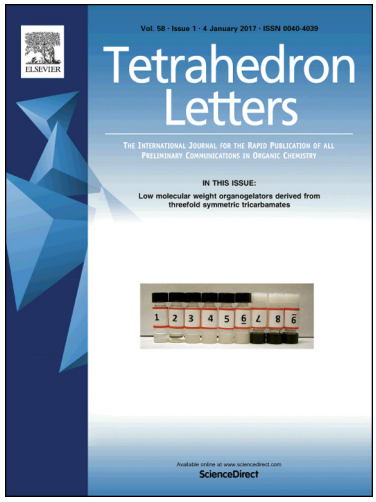

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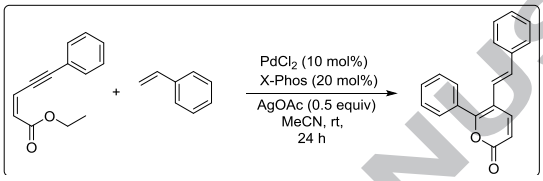

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Palladium-catalyzed convenient one-pot synthesis of multi-substituted 2-pyrones *via* transesterification and alkenylation of enynoates

Ramdas S. Pathare,[a] Shivani Sharma,[a] Kandasamy Gopal,[a] Devesh M. Sawant,[b*] Ram T. Pardasani[a*]

[a]Department of Chemistry, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Bandarsindri, Kishangarh – 305 817, Rajasthan, INDIA.
[b]Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Bandarsindri, Kishangarh – 305 817, Rajasthan, INDIA.

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ABSTRACT

An efficient one-pot protocol for the synthesis of multi-substituted 2-pyrone derivatives from internal alkynes and unactivated alkenes is reported. The methodology involves difunctionalization of internal alkynes by using Pd(II) as a catalyst alongwith X-Phos as ligand *via 6-endo* transesterification and subsequent alkenylation pathway. Notable features include simple and easily available starting materials, including a range of unactivated alkenes, reduced synthetic steps and mild reaction conditions with high efficiency.

Pyrones represent a privileged class of compounds that inherit a wide range of biological activities such as telomerase inhibition, antimicrobial, antifungal, cardiotonic, anti HIV, androgen, pheromonal, phytotoxic effects etc. and is a part of various bioactive natural products (Fig 1).[1] Interestingly, some of the pyrones also exhibit fluorescence properties[2a] and serve as bacterial signaling molecules.[2b] 2-pyrones are versatile building blocks[3] for the synthesis of key intermediates or heterocycles in the field of synthetic organic chemistry and can act as the diene component of a Diels-Alder reaction.[4] Consequently, considerable efforts have been devoted for the construction of 2-pyrones, such as Pd-catalyzed coupling reaction of 2-halobenzoate esters, 2-halobenzoic acids or 2-halobenzonitriles with various alkenes,[5] with vinylic stannanes[6] or with terminal alkynes,[7] C-H activation and functionalization of acrylic acids with alkynes,[8] Rh-catalyzed annulation of maleic acids with alkynes,[9] Ru-catalyzed reaction of unsaturated ketones with silylacetylenes and carbon monoxide,[10] Au-catalyzed coupling reaction of alkynes,[11] iodolactonization of 2-(1-alkynyl)benzoic acids and 5-substituted (2)-*Z*-alken-4-ynoic acids,[12] cyclization reaction of enynoates[13] by using different electrophiles such as I_2, ICl, NIS, PhSeCl. Traditional approaches and organometallic methods involving the lactonization of ketoesters[14], transition-metal-catalysed annulation[15] and cycloaddition[16] reactions have also attracted much attention but limited substrate scope and harsh reaction conditions has restricted the application of these methods. Of these, palladium-catalyzed cascade reactions involving cyclization of enynoates followed by trapping of the resulting □-pyronyl Pd-intermediate with alkenes has emerged as a powerful strategy for the construction of multisubstituted

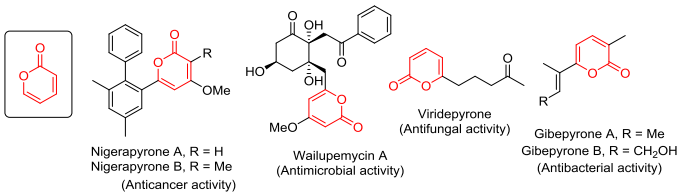
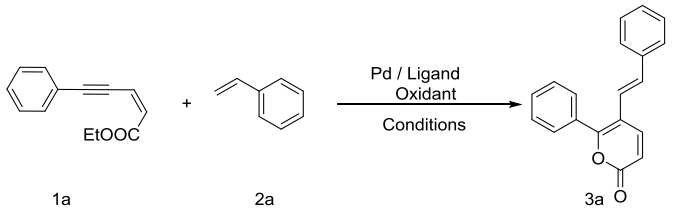


Figure 1: Selected examples of biologically relevant 2-pyrones.

2-pyrones.[17] However this strategy worked well for activated alkenes (such as acrylates), but it furnished poor yields for unactivated alkenes (such as styrenes). In continuation to our efforts to generate bioactive heterocycles,[18] herein we report an efficient synthesis of multifunctionalized 2-pyrones by activation of aryl alkenes using Pd(II)-catalyst along with X-Phos as a ligand for the cyclization and alkenylation of enyonates. The use of phosphine ligand, X-Phos, has remarkably improved the catalytic efficiency of palladium. Thus the overall substrate scope of Pd-catalyzed cascade reaction has been broaden by accommodating unactivated styrene substrate.

We commenced the optimization studies with *Z*-enynoate **1a** and styrene **2a** as model substrate using a series of palladium source with different solvents, oxidants, and ligands under variable reaction conditions as summarized in Table 1 (see the ESI).The desired product **3a** was obtained in 35% yield by using 10 mol% of $Pd(OAc)_2$, 1.0 equiv. of Ag_2O in the presence of DMSO at room temperature for 24 h (entry 1). Moreover, silver acetate was found to be an optimal oxidant for this transformation but other variable oxidants such as $K_2S_2O_8$, CuI,

Table 1: Optimisation of reaction conditions[a]



1a 2a 3a

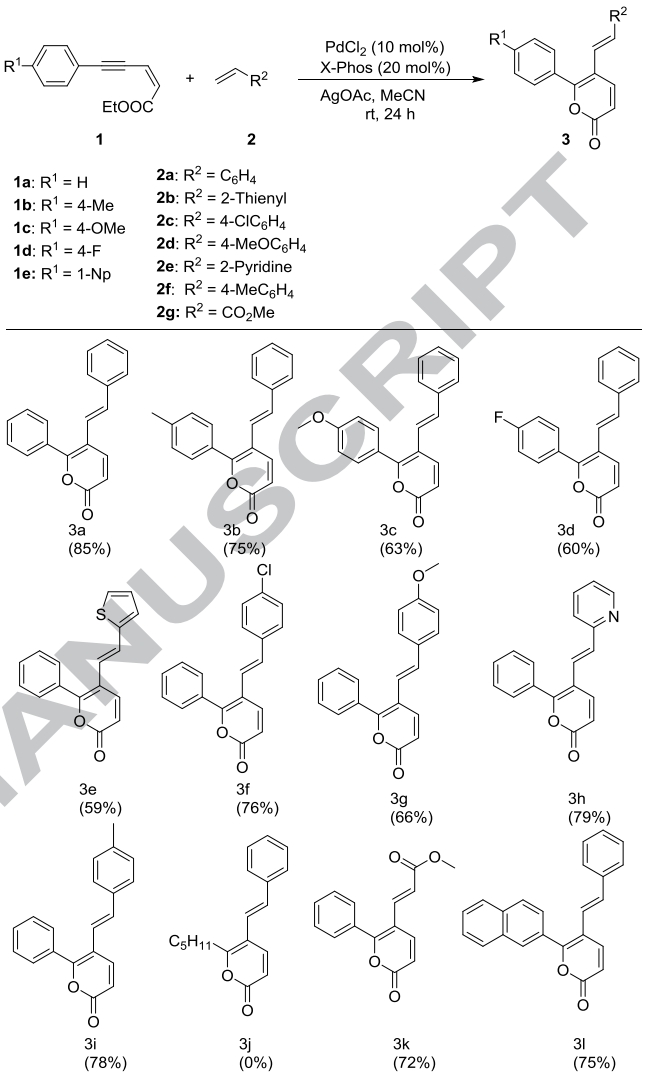
Entry	Catalyst	Ligand	Oxidant	Solvent	Time (h)	Temp (^oC)	Yield (%)[b]
1	$Pd(OAc)_2$	-	Ag_2O	DMSO	24	rt	35
2	$Pd(OAc)_2$	-	$K_2S_2O_8$	DMSO	26	rt	18
3	$Pd(OAc)_2$	-	$K_2S_2O_8$	MeCN	28	rt	20
4	$Pd(OAc)_2$	-	CuI	1,4 dioxane	30	70[c]	<5
5	$Pd(OAc)_2$	-	Oxone	DCE	48	50[c]	<5
6	$Pd(OAc)_2$	-	AgOAc	DMSO	30	rt	30
7	$Pd(OAc)_2$	-	$Cu(OAc)_2$	DMF	48	rt	6
8	$Pd(OAc)_2$	-	AgOAc	MeCN	30	rt	39
9	$PdCl_2$	PPh_3	AgOAc	MeCN	26	rt	45
10	$PdCl_2$	X-Phos	AgOAc	DMSO	48	rt	48
11	$PdCl_2$	Xantphos	AgOAc	MeCN	36	rt	42
12	$Pd(OAc)_2$	X-Phos	AgOAc	MeCN	48	rt	49
13	$Pd_2(dba)_3$	-	AgOAc	MeCN	32	rt	<5
14	$PdCl_2$	X-Phos	AgOAc	DMF	48	rt	nr
15	**$PdCl_2$**	**X-Phos**	**AgOAc**	**MeCN**	**24**	**rt**	**85**
16	$PdCl_2$	X-Phos	AgOAc	Toluene	40	120[c]	nr
17	$PdCl_2$	X-Phos	AgOAc	THF	40	80[c]	nr
18	$PdCl_2$	X-Phos	AgOAc	DCE	48	100[c]	nr
19	$PdCl_2$	X-Phos	AgOAc	MeCN	30	85[c]	trace
20	-	X-Phos	AgOAc	MeCN	30	rt	nr
21	$PdCl_2$	-	AgOAc	MeCN	48	rt	10
22	$PdCl_2$	X-Phos	-	MeCN	30	rt	nr

[a]Reaction condition: all reactions (0.3 mmol scale) were performed under open air using 1:2:0.5 ratio of **1a**:**2a**:oxidant, $PdCl_2$ (10 mol %), ligand (20 mol%) in 1.0 mL of solvent (rt: room temperature, 35° C; nr: no reaction). [b]Isolated yield. [c]Failed to initiate the reaction even at higher temperatures.

Oxone (composed of 50% oxidizing agent $KHSO_5$) and $Cu(OAc)_2$ afforded the desired product **3** in lower yield (entries 2-8). To improve the yield and efficiency, different ligands with Pd(II) catalysts were tried (entries 9-12). Among them X-phos was the most efficient ligand (entry 10). On the other hand, solvent screening studies demonstrated that acetonitrile appeared to be the most suitable solvent among various solvents used (entry 14-18). The reaction failed to initiate in the absence of catalyst, ligand or oxidant (entries 20-22). Thus all three components were critical for the success of this reaction. Increasing the reaction temperature, to our delight, afforded negligible yield of the product **3a** (Table 1, entries 4-5 and 16-19). Based on these results, we concluded that **1a** (1 equiv), **2a** (2 equiv), Pd catalyst (10 mol%), X-phos ligand (20 mol%) and AgOAc as oxidant (0.5 equiv) in acetonitrile at room temperature in the presence of open air atmosphere for 24 hours was the best optimum set of conditions for this reaction and produced the excellent result with 85% isolated yield of **3a** (entry 15).

With the optimized reaction conditions for (*E*)-6-phenyl-5-styryl-2*H*-pyran-2-one **(3a)** in hand, we next focused our attention on investigating the substrate scope, a diverse range of (*E*)-6-phenyl-5-styryl-2*H*-pyran-2-one (**3a-3l**) were prepared and subjected to the variable set of optimized reaction conditions.

Scheme 1: Pd(II) catalyzed cyclization and alkenylation of enynoates **1** with electron-deficient alkenes **2** [a,b]



[a]Reaction condition: optimized reaction condition (entry 15, Table 1) is followed and yields are given as isolated yield.

The results are summarized in Scheme 1. Evidently a broad range of structurally and electronically diversified substituents across the alkyne aryne ring (R^1) and electron deficient alkene ring (R^2) were well tolerated and generated the desired product **3** in moderate to good yields. Under similar conditions, diversely substituted internal alkynes (**1a-1e)** were successfully involved in the cyclization and alkenylation using readily available electron deficient alkenes **2a-2g** (Scheme 1). A series of substituents on phenyl ring of enynoates including *p*-Me, *p*-F, *p*-OMe etc. were well tolerated and corresponding 5,6-disubstituted 2-pyrone derivatives were obtained in good to excellent yield. The feasibility of the reaction was also evaluated by using both electron withdrawing and electron donating vinyl arenes to generate corresponding products in good yields. Different heterocyclic vinyl arenes such as thiophenes, pyridines were also well tolerated and gave good yields of **3e** and **3h**. Aliphatic alkene was unable to cyclize because of electron donating nature which decreased the electrophilicity of alkyne **(3j)**. Bulky substituent such as naphthyl was also well tolerated and produced **3l** in good yield. A plausible reaction mechanism is shown in Figure 2.[19] To start with, the alkyne **1a** is activated by coordination of active Pd(II) species **A**, to form complex **B**. which may undergo transesterification process through base

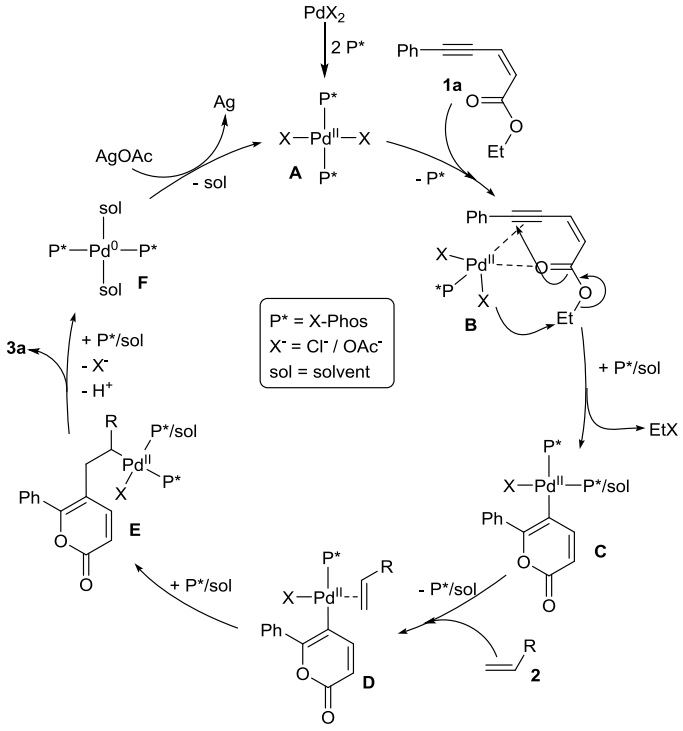


Figure 2: Plausible reaction mechanism

mediated ethyl cleavage and formed the key organometallic intermediate **C** in 6-*endo-dig* fashion. Subsequently, coordination and insertion of olefin into the intermediate **C** forms another organometallic intermediate **E** which undergoes reductive elimination to produce the desired product **3** and Pd(0) species **F**. Finally the catalytic cycle is completed by regeneration of the active Pd(II) species **A** through the oxidation of **F** with the help of oxidant AgOAc.

In summary we have demonstrated tandem one pot Pd(II) catalyst with X-Phos as a ligand to improve the efficiency of the catalyst to get highly regioselective and efficient 6-*endo-dig* cyclization strategies for the syntheses of multisubstituted 2-pyrone derivetives with good and excellent yields. This methodology may exhibit wide range of applications in the construction of biologically active complex heterocycles.

Acknowledgments

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[a]Department of Chemistry, [b]Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Bandarsindri, Kishangarh – 305 817, Rajasthan, INDIA.

Highlights:

1. Synthesis of multisubstituted 2-pyrone by one-pot Pd-catalyzed alkenylation of enynoates
2. Phosphine ligand, X-Phos plays a crucial role for the reaction involving unactivated alkenes
3. Notable features: mild reaction condition and open air reactions