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Nucleophile-assisted Pt-catalyzed cyclization of enynones: an access to synthesis of highly substituted furans

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Abstract—A new and efficient Pt-catalyzed hydroxy- or alkoxy cyclization of 2-(1-alkynyl)-2-alkene-1-ones offers a general synthetic pathway to a wide range of highly substituted furans in good to excellent yields.

Substituted furan derivatives are important synthetic intermediates[1] and are found as structural units in many natural products such as pheromones[2] or polyether antibiotics.[3] Because of their many applications in pharmaceutical fields, synthetic investigations to furan derivatives have continuously attracted attentions to many organic chemists.[4] Among various strategies, catalytic transformation by means of transition metal catalysts such as essential palladium-catalyzed processes is one of the modern approaches for the syntheses of substituted furan derivatives from cyclization of alkyne- or allene-containing substrates.[5]

Activating alkynes by coordination to electrophilic transition-metal complexes has a lead to the development of a variety of catalytic cyclization reactions involving a carbon–carbon or carbon–heteroatom bond formation.[6] The potential of late-transition metal-based Lewis acid has recently been witnessed for synthetic versatility including total synthesis of natural products.[7] Recently, Echavarren and his coworkers extended the scope of this reaction in detail for hydroxyl- or alkoxy cyclization of enynes, which was particularly attractive because it allowed the sequential formation of a C–C and a C–O bond from enynes.[8] Nevertheless, there is room for the implementation of new partners in this process.

It is particularly important to find highly effective reactivity profile of metal catalysts for these tandem nucleophile-trapped cyclization reactions. Larock and his coworkers reported a novel method of highly substituted furans by $AuCl_3$-catalyzed nucleophilic addition followed by cyclization reaction, although it was limited to specific substrate classes.[9] To circumvent such substrate limitation and enhance the scope of the reaction, we have elected to investigate Pt(II) complexes for our preliminary studies. Herein we wish to report that certain Pt complexes are highly effective catalysts for the hydroxyl- or alkoxy cyclization of 2-(1-alkynyl)-2-alkene-1-ones.

In our initial study, we examined the reaction of enynone **1a** with several Pt catalysts in various reaction solvents as summarized in Table 1. The use of Pt(0) complexes like $Pt(PPh_3)_4$ and $Pt(CH_2{=}CH_2)(PPh_3)_2$ did not show the reactivity for this transformation (entries 1–2). Gratifyingly, treatment of **1a** with 5 mol % of Pt(II) catalyst in MeOH solvent afforded the corresponding methoxy-incorporated furan derivative **2aa** in high yields. Utilization of nonpolar solvents such as toluene was to be unsuccessful for this transformation (entry 6). More conveniently, however, the same protocol could be performed in the presence of a nucleophile (MeOH, 2 equiv) in toluene resulting in formation of **2aa** with only marginal yield erosion (entry 7). Under these reaction conditions various alcoholic solvents such as methanol, *n*-butanol, *i*-propanol, allyl alcohol, and propargyl alcohol were incorporated well affording the corresponding alkoxy substituted furan derivatives in 91, 74, 78, 67, and 76% yields, respectively (entries 8–12).[10] Additionally, this method could provide a variety of amine derivatives by utilizing amine nucleophiles. Thus, we applied this reaction with aniline to afford

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Keywords: Platinum; Nucleophile; Cyclization; Furan.

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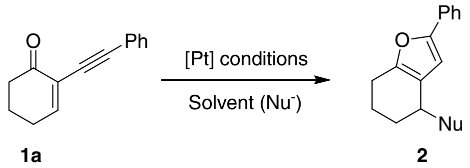
Table 1. Pt-catalyzed cyclization of enynone **1a** under various reaction conditions



(1)

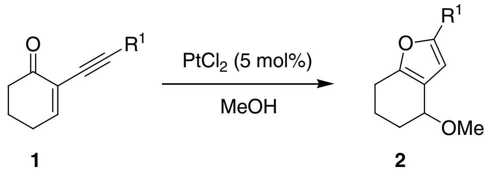
	Pt catalysts (mol %)	Solvents (nucleophile)	Temperature (°C)/time (h)	Products	Isolated yield[a] (%)
1	$Pt(PPh_3)_4$ (5)	MeOH (**A**)	Reflux/14	—	No reaction
2	$Pt(CH_2{=}CH_2)(PPh_3)_2$ (5)	MeOH	Reflux/14	—	No reaction
3	$Pt(Phen)Cl_2$ (5)	MeOH	rt/10	**2aa**	73
4	$Pt(MeCN)_2Cl_2$ (5)	MeOH	rt/8	**2aa**	68
5	$PtCl_2$(5)/$AgSbF_6$ (10)	MeOH	rt/3	**2aa**	74
6	$PtCl_2$ (5)	Toluene	40/24	—	No reaction
7	$PtCl_2$ (5)	Toluene/MeOH (2 equiv)	40/8	**2aa**	85
8	**$PtCl_2$ (5)**	**MeOH (A)**	**40/8**	**2aa**	**91**
9	$PtCl_2$ (5)	*n*-BuOH (**B**)	rt/5	**2ab**	74
10	$PtCl_2$ (5)	*i*-PrOH (**C**)	rt/6	**2ac**	78
11	$PtCl_2$ (5)	Allyl alcohol (**D**)	40/8	**2ad**	67
12[a]	$PtCl_2$ (5)	Propargyl alcohol (**E**)	40/10	**2ae**	76
13	$PtCl_2$ (5)	Aniline (**F**)	40/10	**2af**	65
14	$PtCl_2$ (5)	Acetic acid (**G**)	40/10	**2ag**	71
15[b]	$PtCl_2$ (5)	Water/acetone (**H**)	40/8	**2ah**	71
16[c]	$PtCl_2$ (5)/$AgSbF_6$ (10)	1,3-Diphenyl acetone (**I**)	Reflux/12	**2ai**	68

[a] Propargyl alcohol (2 equiv) was used as a nucleophile in toluene solvent.

[b] Water/acetone (v/v = 10:1).

[c] 1,3-Diphenylacetone (1.2 equiv) was used as a nucleophile in CH_2Cl_2 solvent.

Table 2. Pt-catalyzed tandem nucleophile assisted cyclization of 2-(alkylethynyl)-2-cyclohexenones in MeOH

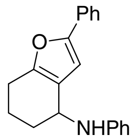


(2)

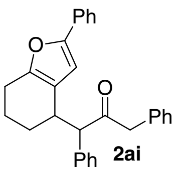
	Substrates (R^1)		Temperature (°C)/ time (h)	Products	Isolated yield (%)
1	Cyclohexenyl	**1b**	rt/7	**2ba**	83
2	TMS	**1c**	40/8	**2ca**	67[a]
3	H	**1d**	40/10	**2da**	30
4	*n*-Propyl	**1e**	40/10	**2ea**	82
5	*t*-Butyl	**1f**	40/10	**2fa**	78
6	$NC(CH_2)_3$	**1g**	40/10	**2ga**	72

[a] Yield of TMS-deprotected product 2 (R^1 = H).

the corresponding furan **2af** in 65% yield. And the acetate functionality could be readily incorporated to give the resulting furan derivative **2ag** in 71% yield. The use of water as solvent has many advantages in organic synthesis from both economical and environmental points of view;[11] thus the reaction in aqueous medium of water/acetone (10:1) provided the alcoholic furan derivative **2ah** in 71% yield.



2af

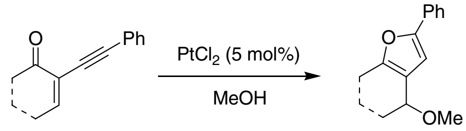


Furthermore, the beneficial effect of this new reaction condition of **1a** with carbon nucleophile should allow for the simultaneous formation of C–C and C–O bond from the corresponding enynone (entry 16). Thus, these new conditions appeared to be far more efficient than those previously used Au procedures. And in the presence of cationic Pt complexes ($PtCl_2$ plus $AgSbF_6$) we were also pleased to observe that the enynone **1a** gave the corresponding products (entries 5 and 16).

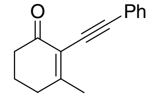
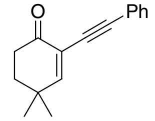
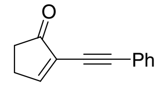
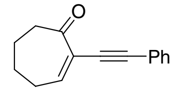
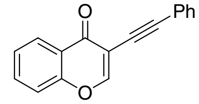
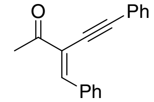
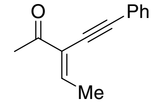
The preliminary data prompted to us to investigate different substituents with respect to the R^1 at alkyne terminus aimed at favoring tandem nucleophile-assisted cyclized products as shown in Table 2.

At first, the cyclohexenyl group at alkyne terminus reacted well under above reaction conditions and the TMS substituent produced the corresponding TMS deprotected furan derivative in 67% yield and the terminal free alkyne was rather sluggish under the above reaction conditions to give the corresponding furan derivative in only 30% yield (entries 2 and 3). Despite these draw backs, we were excited to observe the formation of furan derivatives in high yields when the internal alkynes **1e**, **1f**, and **1g** were subjected to these reaction conditions (entries 4–6). However, in contrast with the broad scope and excellent reproducibility of Pt(II)-catalyzed cyclizations, $AuCl_3$ failed in the cyclization of these enynones such as **1e**, **1f**, and **1g** probably because of the hygroscopic nature of this metal chloride. Indeed, Pd catalysts also failed to exhibit useful catalytic activity presumably due to competing reduction of Pd(II) to Pd(0).

Table 3. Pt-catalyzed tandem nucleophile assisted cyclization of various enynones in MeOH



(3)

Entry	Enynones		Temperature (°C)/time (h)	Products	Isolated yield (%)
1		**3**	40/10	**4a**	85
2		**5**	40/5	**6a**	73
3		**7**	Reflux/24	—	No reaction
4		**8**	40/10	**9a**	72
5		**10**	40/10	**11a**	78
6		**12**	40/12	**13a**	88
7		**14**	40/12	**15a**	76

Given the success of this new observation, we further investigated the scope of this reaction with a wide range of substrates as summarized in Table 3. Cyclic enynones (**3**–**8**) were readily prepared from the known literature procedures.[12] Varying the steric demand on cyclohexene ring did not diminish the efficiency of this present protocol (entries 1 and 2). Disappointingly, the reaction of five-membered enynone **7** has failed to afford the expected cyclized product even after a longer reaction time. In contrast, the seven-membered enynone **8** reacted well under our catalytic condition to furnish the furan **9a** in 71% yield. A similar outcome was observed in the cyclization trapping reaction of benzopyran derived enynone **10**. To our delight, subjection of acyclic enynones such as **12** and **14** into these cyclization conditions afforded to the corresponding products **13a** and **15a** in 88% and 76% yields, respectively.

These cyclization reactions proceeded in maximum atom economics under neutral and relatively mild conditions and were environmentally benign. These hydroxy- or alkoxy cyclizations of enynones catalyzed by Pt(II) were of particular interest, because these transformations allowed for the simultaneous formation of the two C–O bonds from the enynones. Additionally, it showed a greater tolerance for alkylated substituents at alkyne terminus than related Au-catalyzed cyclization.

In conclusion, a new approach to the synthesis of fused bicyclic furan derivatives has been developed under Pt(II)-catalysis. Extension to asymmetric variants[13] and one pot arylative cyclizations[14] of the present method is currently under active investigation.

Acknowledgements

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10. A typical procedure for the Pt-catalyzed cyclization of 2-(phenylethynyl)-2-cyclohexenone **1a** in MeOH is shown. To a mixture of 2-(phenylethynyl)-2-cyclohexenone **1a** (0.4 mmol) and 5 mol % of $PtCl_2$, MeOH (1.2 mL) was added as both a nucleophile and a reaction medium. The resulting suspension was stirred at ambient temperature for 10 min. After heating for the time specified, the reaction mixture was allowed to cool to room temperature. The excess solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography. All the product (**2aa**–**15a**) have been characterized by ^{1}H, ^{13}C NMR, IR and HRMS.
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