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Carbene Catalyzed Access to 3,6-Disubstituted α-Pyrones via Michael Addition/Lactonization/Elimination Cascade

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Abstract: The first direct transition metal-free access to 3,6-disubstituted α-pyrones from α-chloro aldehydes and β-tosyl enones is reported. The reactions proceed *via* the Michael addition/lactonization/elimination cascade. The regioselective addition of NHC-bound enolates/homoenolates to the enones bearing a bulkier functionality such as tosyl group at the β-position has remained challenging. The 3,6-disubstituted α-pyrones could be converted to valuable products such as 1,2,3,4-tetrasubstituted benzenes, 1,4-disubstituted naphthalenes as well as anthracenes and 6,13-disubstituted dihydro-etheno-pentacenes in a simple operation.

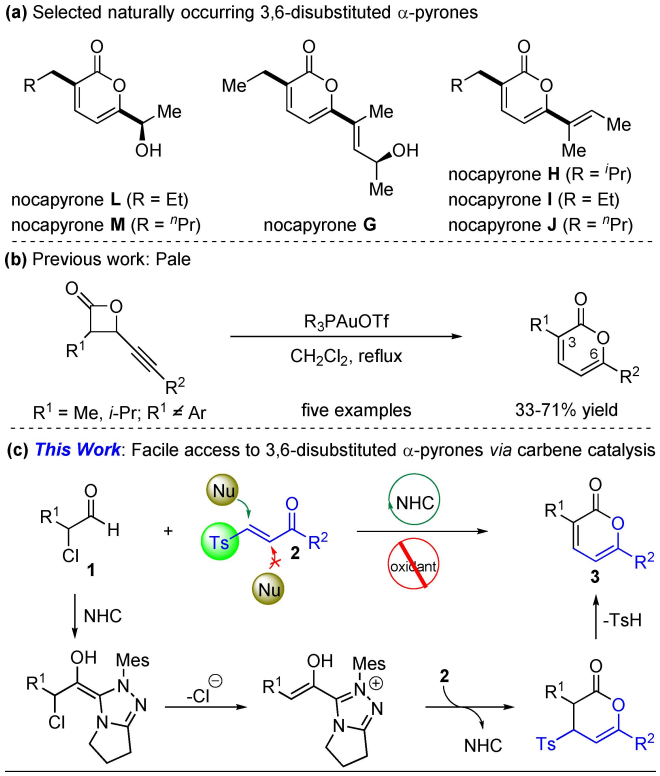
Keywords: α-Pyrones; β-Tosyl enones; Cascade; Carbenes

α-Pyrones with a diverse backbone are highly abound in nature and pharmacologically active compounds.[1] They also serve as the versatile building blocks for preparing complex targets due to multiple reactive sites.[2] Consequently, a considerable effort has been devoted on developing synthetic methods. Typically, they are accessed using transition metal-catalysts *via* cycloaddition, ring expansion and annulation reactions.[3] Recently, several organocatalytic methods have also been explored for the synthesis of α-pyrones by Kwon, Smith, Chi and Studer.[4] 3,6-Disubstituted α-pyrones are essential skeleton in numerous marine natural products exhibiting potent biological activities like neuro-protective effects, NO production inhibition, antibacterial, pro-inflammatory factor inhibition, etc. (Scheme 1a).[5] Despite this, their synthetic methods are scarcely available. In 2010, Pale and co-workers reported an elegant gold(I) catalyzed cycloisomerization of β-alkynylpropiolactones to produce 3,6-functionalized α-pyrones (Scheme 1b).[6]

However, this transition metal-based method using relatively unstable β-lactones as the substrate has remained limited to a few substrates. It was found to be unsuitable for α-aryl-substituted substrates (R^1 = Ar), whereas a poor yield was observed when R^1 was not a methyl group (up to 33% yield). Therefore, the development of a new operationally simple organocatalytic method with a wide substrate scope is highly desired.

With our group's core objective of developing organocatalytic methods, we were interested to develop an *N*-Heterocyclic Carbene (NHC) catalyzed oxidant-free method to access these valuable targets.[7,8] We envisioned that enolates in reaction with the enones bearing a leaving group would eventually produce 3,6-disubstituted α-pyrones *via* the Michael addition-lactonization-elimination cascade (Scheme 1c).[9] Accordingly, we chose to use the widely accessible α-chloro aldehydes and β-tosyl enones as the substrates. It is worth mentioning that enones bearing a bulkier β-substituent has remained challenging under carbene catalysis. Very recently, Fu, Huang and co-workers achieved [4+2] cycloaddition using β-trimethylsilyl enones whereas the corresponding reaction with phosphorylated enones was reported by our group.[10] On the other hand, β-tosyl enones have yet remained beyond the scope of carbene catalysis.

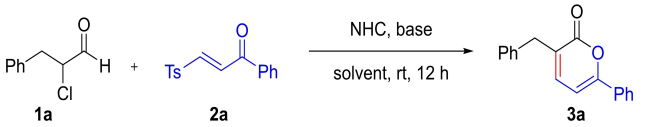
At the outset, we examined 2-chloro-3-phenyl-propanal **1a** and 1-phenyl-3-tosylprop-2-en-1-one **2a** as the model substrates for this cascade reaction in the



Scheme 1. 3,6-Disubstitued α-Pyrones: Naturally Occurring Bioactive Scaffolds and Synthetic Methods.

presence of DBU as a base in THF (Table 1). Different NHC precatalysts were evaluated under this condition. Among them, imidazolium salt **A** was found to be ineffective and the thiazolium salt **B** gave the desired product **3 a** in a trace amount (entries 1 and 2). The use of pyrrolidinone-based triazolium salt **C** bearing *N*–C_6F_5 group produced the desired product in 23% yield (entry 3). Switching to the corresponding *N*-Mes protected catalyst **D** produced **3 a** in a decent yield of 54% (entry 4). A higher yield with catalyst **D** in comparison to **C** may be attributed to the irreversible addition of the former to **1 a**, thereby accelerating the formation of the Breslow intermediate.[11] We next screened various organic and inorganic bases using catalyst **D**. The use of other organic bases such as TMG and DABCO furnished **3 a** in a reduced yield (entries 5 and 6). Among the different inorganic bases employed, Cs_2CO_3 provided **3 a** in an improved yield of 72% (entries 7 and 8). We next tested different solvents such as CH_3CN, toluene, CH_2Cl_2, $CHCl_3$ and $(CH_2Cl)_2$ (entries 9–13). Gratifyingly, a number of chlorinated solvents were found to be equally good for this reaction and **3 a** was obtained in an excellent yield of 97% in CH_2Cl_2 (entry 11). A reduced loading of Cs_2CO_3 from 200 mol% to 100 mol% led to the formation of **3 a** with a diminished yield (65%, entry 14). A control experiment in the absence of any

Table 1. Optimization of the Reaction Condition.[a]



1a 2a 3a

S. No.	NHC	Base	Solvent	Yield (%)[b]
1	**A**	DBU	THF	0
2	**B**	DBU	THF	12
3	**C**	DBU	THF	23
4	**D**	DBU	THF	54
5	**D**	TMG	THF	51
6	**D**	DABCO	THF	38
7	**D**	K_2CO_3	THF	65
8	**D**	Cs_2CO_3	THF	72
9	**D**	Cs_2CO_3	CH_3CN	54
10	**D**	Cs_2CO_3	toluene	76
11	**D**	**Cs_2CO_3**	**CH_2Cl_2**	**97**
12	**D**	Cs_2CO_3	$CHCl_3$	91
13	**D**	Cs_2CO_3	$(CH_2Cl)_2$	90
14[c]	**D**	Cs_2CO_3	CH_2Cl_2	65
15	–	Cs_2CO_3	CH_2Cl_2	0

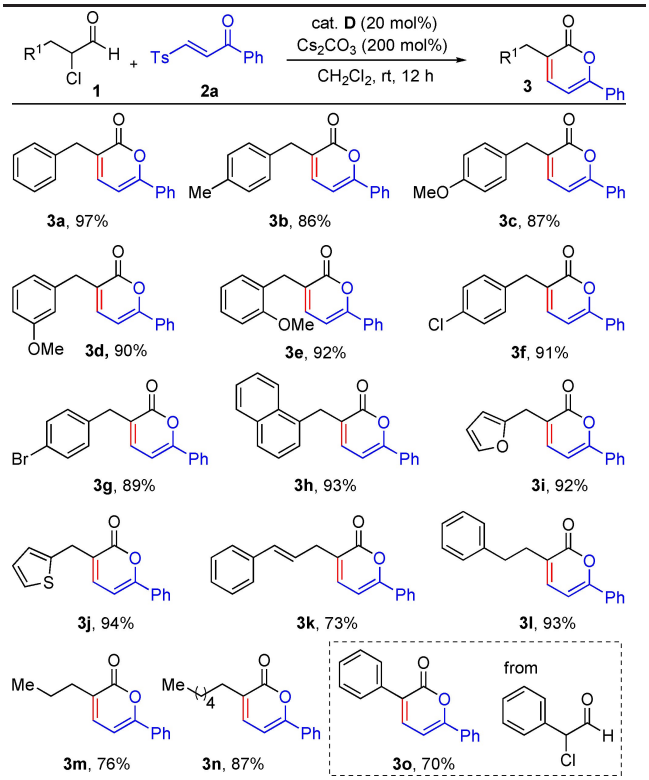
A B C D

[a] Standard reaction condition, unless otherwise specified: **1 a** (0.2 mmol), **2 a** (0.1 mmol), NHC **A**–**D** (20 mol%), Cs_2CO_3 (200 mol%), solvent (1.5 mL) at rt for 12 h.
[b] Isolated yield of **3 a**.
[c] 100 mol% of Cs_2CO_3 used. DBU = 1,8-Diazabicycloundec-7-ene, DABCO = 1,4-Diazabicyclo [2.2.2] octane, TMG = 1,1,3,3-Tetramethyl guanidine.

NHC catalyst failed to produce the product (entry 15). The use of other enolate precursors like cinnamaldehyde and its saturated analogue in the presence of 3,3′,5,5′-tetra-*tert*-butyldipheno-quinone as an oxidant, cyclopropanecarbaldehyde or 4-nitrophenyl-3-phenyl-propanoate instead of **1 a** was found to be inefficient under the optimized reaction condition.

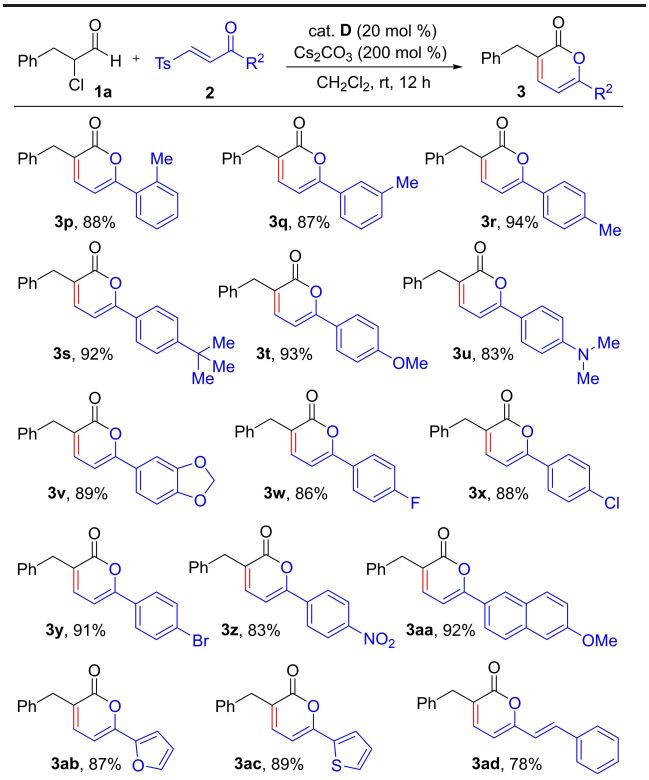
With a set of optimal reaction condition in hand, we moved on to evaluate the scope of this NHC-catalyzed cascade reaction with respect to α-chloro aldehydes **1** in reaction with tosyl enone **2 a** (Table 2). The β-aryl aldehydes **1** with an electron-donating substituent such as methyl or methoxy groups at *para*, *meta* or *ortho*-position reacted well to produce **3 b**-**3 e** in an excellent yield. Likewise, electron-withdrawing substituents on the aryl ring were well tolerated, giving the desired α-pyrones in 89–91% yields (**3 f**–**3 g**). Replacing the β-phenyl substituent with either a naphthyl or heteroaryl unit did not affect the yield (**3 h**–**3 j**). The reaction condition was amenable to the presence of an unsaturated moiety, affording **3 k** in a good yield. We next investigated aliphatic aldehydes with a varied carbon chain length. Pleasantly, chloro aldehydes

Table 2. Scope of α-Chloro aldehydes.[a]



[a] Standard reaction condition as in entry 11, Table 1. Yields are the isolated yields after column chromatography.

Table 3. Scope of β-Tosyl enones.[a]



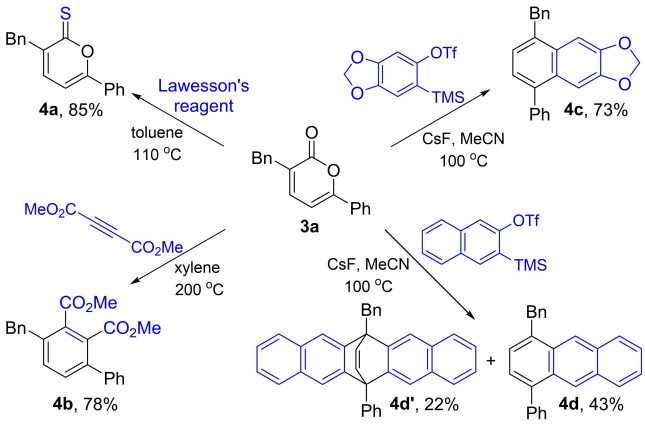
[a] Standard reaction condition as in entry 11, Table 1. Yields are the isolated yields after column chromatography.

derived from 4-phenyl butanal, pentanal and octanal led to the products **3 l**–**3 n** in excellent yields. The use of 2-phenyl chloroacetaldehyde generated 3-aryl substituted pyrone **3 o**, albeit with a slightly lower yield under the optimal reaction condition. A gram scale synthesis (1.0 g, 3.5 mmol, of **2 a**) was also performed to obtain **3 a** in 89% isolated yield.

Encouraged by the scope of the reaction for a wide range of chloro aldehydes, we next strived to expand the generality of this cascade reaction using a variety of tosyl enones **2** in reaction with **1 a** (Table 3). The electron-rich aryls, bearing a methyl substituent at *ortho*, *meta* or *para*-position, were well tolerated, leading to the formation of α-pyrones in 87–94% yields (**3 p**–**3 r**). A bulkier *tert*-butyl group on the ring did not affect the yield (92%, **3 s**). The enones incorporating other high-electron donating groups like methoxy, *N,N*-dimethylamine or even disubstitution on the aryl ring smoothly converted to the pyrones in 83–93% yield (**3 t**–**3 v**). Behaving similar to electron-rich aryls, the electron-deficient aryls loaded with flouro, chloro, bromo and nitro groups were also compatible under the reaction condition (**3 w**–**3 z**, 83–91% yield). We subjected naphthyl as well as heteroaryl-derived substrates to the standard condition to obtain **3 aa**–**3 ac** in excellent yields. Pleasantly, the enones **2 ad** having a competing conjugated olefin functionality, reacted chemoselectively to furnish **3 ad** in 78% yield. A more sterically challenging β-phenyl substituted enone **2** did not react under this condition.

The *3,6*-disubstituted α-pyrones make unique building blocks for the preparation of molecules that are difficult to access otherwise. They were transformed to a variety of highly functionalized arenes and polyaromatic hydrocarbons (PAHs) (Scheme 2). For instance, the reaction of **3 a** with Lawesson's reagent in toluene afforded 3,6-disubstituted pyran-2-thione **4 a** in 85% yield. A highly substituted benzene **4 b** could be obtained in 78% yield *via* Diels-Alder reaction of **3 a** with dimethylacetylene dicarboxylate, followed by decarboxylation. The treatment of **3 a** with a benzyne precursor in CH_3CN gave 5,8-disubstituted naphtho-1,3-dioxol **4 c** in 73% yield. Interestingly, the use of 2,3-naphthynes instead of sesamol-derived benzyne provided a separable mixture of 1,4-disubstituted anthracene **4 d** and 6,13-disubstituted dihydroethenopentacene **4 d′**.

In conclusion, we have developed the first direct organocatalytic method for the preparation of 3,6-disubstituted α-pyrones *via* Michael addition-lactonization-elimination cascade from α-chloro aldehydes and β-tosyl enones. The sterically hindered β-tosyl enones



Scheme 2. Transformation of **3 a**.

that remained beyond the scope of NHC-catalysis till now, reacted smoothly to give the desired products in good to excellent yield. This method greatly improves the availability of the 3,6-functionalized pyrones, hitherto limited to a few, in terms of substitution pattern on the ring. The products could be easily transformed to 1,2,3,4-tetrasubstituted benzenes, 5,8-disubstituted naphtho-1,3-dioxol, 1,4-disubstituted anthracenes and 6,13-disubstituted dihydro-ethenopentacenes in a simple operation. Further application of *β*-tosyl enones under NHC catalysis is being explored in our lab.

Experimental Section

General Procedure for the Synthesis of 3,6-Disubstituted *α*-Pyrones

To an oven-dried Schlenk tube equipped with a magnetic stirring bar, was added NHC-pre-catalyst **D** (0.02 mmol, 20 mol%), *β*-tosyl enones **2** (0.1 mmol, 1.0 equiv.) under an argon atmosphere. The tube was sealed with a septum, evacuated and refilled with argon (3 cycles). Dichloromethane (1.5 mL), *α*-chloro aldehyde **1** (0.2 mmol, 2.0 equiv.) and Cs_2CO_3 (0.2 mmol, 2.0 equiv.) were added and the reaction mixture was stirred at room temperature for 12 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography using hexane/ethyl acetate as eluent to afford the desired product **3**.

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COMMUNICATIONS

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