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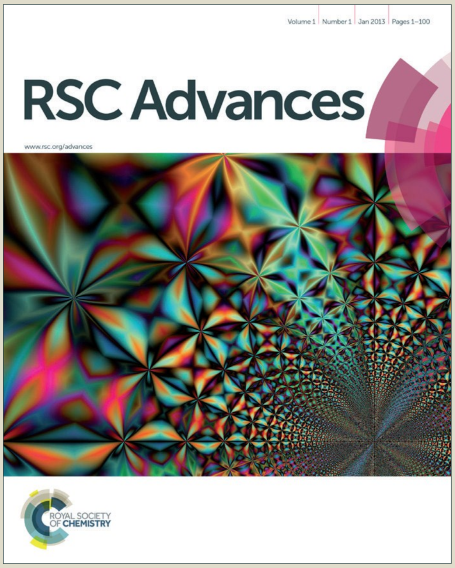

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Journal Name

COMMUNICATION

Sc(OTf)$_3$-Catalyzed Cyclization of α-Allylated 1,3-Dicarbonyls: an Efficient Access to 2,2-Disubstituted 2,3-Dihydrofuran Derivatives

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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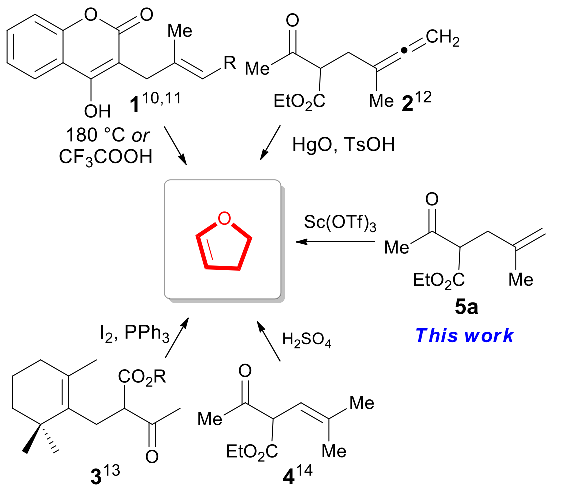
A method to prepare functionalized 2,3-dihydrofurans by Sc(OTf)$_3$-catalyzed cyclization of α-allylated 1,3-dicarbonyl compounds is reported. The reactions were shown to be operationally simplistic and proceed efficiently for a variety of substrates, leading to the formation of 2,2-disubstituted 2,3-dihydrofurans in good to excellent yields.

The 2,3-dihydrofuran derivatives are a class of significant *O*-heterocyclic compounds that can be found in a large number of natural products and biologically active molecules,[1,2] being also widely employed as versatile building blocks in synthetic organic chemistry.[3] Therefore, many synthetic strategies toward 2,3-dihydrofurans have been developed for the synthesis of such types of structures. For example, by these strategies including the [4+1] cycloaddition of enones with diazo compounds,[4] the [3+2] annulations of β-ketosulfides/β-ketosulfones with aldehydes,[5] and ionic[6] or radical[7] reactions of olefins with 1,3-dicarbonyl compounds, as well as cycloisomerization of the but-3-yn-1-ols,[8] the 2,3-dihydrofuran structures could be built efficiently. Even so, more simple and novel approaches are still in great demand.

The reaction of α-propargylated carbonyl derivatives has opened the way to furan scaffolds by employing transition-metal-catalyzed cycloisomerizations during the past years.[9] By instead of the alkyne subunit for alkene, the corresponding 2,3-dihydrofurans should be able to be obtained in an appropriate way. Scheme 1 highlights common methods towards the 2,3-dihydrofuran structure motif from the carbonyl alkene derivatives. For instance, compound **1** could be converted to the corresponding 2,3-dihydrofuran product at high temperature[10] or under acidic conditions.[11] Brönsted acid- and HgO-mediated cyclizations of allenyl-substituted β-ketoesters **2** produced 2,3-dihydrofurans in good yields.[12] The I_2-PPh_3 system could promote the transformation of the carbonyl alkenes **3** to the corresponding 2,3-dihydrofurans under mild conditions.[13] By contrast, the reaction of β,γ-unsaturated ketoesters **4** to 2,3-dihydrofuran framework in excess sulfuric acid proceeded in relatively low efficiency.[14] These methods indeed gave useful 2,3-dihydrofuran motifs, however, suffered from some limitations such as strict reaction conditions, the use of poisonous metals and strong acid or low efficiency. As part of an ongoing program on exploring novel methods to cyclic structure scaffolds,[15] we were interested in developing an approach to 2,3-dihydrofuran motifs which would be of mild conditions and high efficiency. Herein we wish to report a Sc(OTf)$_3$-catalyzed cyclization of the carbonyl alkenes **5** for constructing functionalized 2,3-dihydrofuran derivatives.



Scheme 1 The access to 2,3-dihydrofuran motif from the alkylated β-ketoesters.

The readily available α-allylated β-ketoester **5a** was chosen as the model substrate. We examined in detail the cyclized reaction of **5a** with different metal salts as well as with

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Electronic Supplementary Information (ESI) available: Experimental procedures and analysis data for the substrates and 2,3-dihydrofuran compounds were provided in the ESI. See DOI: 10.1039/x0xx00000x

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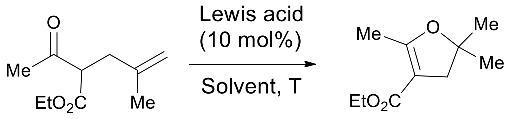
DOI: 10.1039/C6RA14051G

$BF_3·Et_2O$, and the results were listed in Table 1. Among the assayed Lewis acids, $Sc(OTf)_3$ (10 mol%) was proved to be the best catalyst, giving the desired 2,3-dihydrofuran **6a** in 89% yield with 1,2-dichloroethane as a solvent at 80 ˚C (Table 1, entry 8).[16] The low yields or slow reactions were obtained with the others catalysts such as $FeCl_3$ and $Cu(OTf)_2$, whereas with Ag(I) salts, the reactions did not proceed (Table 1, entries 1-7). When $BF_3·Et_2O$ was selected as the catalyst, a decomposed mixture was obtained (Table 1, entry 3). By contrast, indium (III) triflate is also an alternative Lewis acid for the formation of 2,3-dihydrofuran **6a** (Table 1, entry 5). Subsequently, the various solvents were screened. It could be found that tetrahydrofuran, toluene and acetonitrile were not good solvents for the present transformation (Table 1, entries 9-11). Additionally, decreasing the temperature to 60 ˚C could afford **6a** in 91% isolated yield (Table 1, entry 12), whereas the reaction was low efficient at 40 ˚C (Table 1, entry 13). The catalyst loading was not decreased or prolonged reaction time was required (Table 1, entry 14). Notably, all of the reactions could be performed in air. Finally, the optimized system consisting of 10 mol% of $Sc(OTf)_3$ at 60 ˚C in 1,2-dichloroethane was established (Table 1, entry 12).

Table 1 Optimization of the reaction conditions[a]



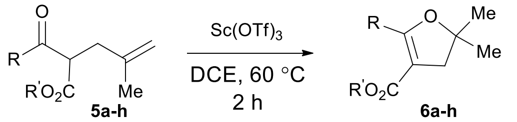
5a **6a**

Entry	Catalyst	Solvent	Temp. (˚C)	Time (h)	Yield (%)[b]
1	$AgSbF_6$	DCE	80	1.5	0
2	$AgBF_4$	DCE	80	1.5	0
3	$BF_3·Et_2O$	DCE	80	1.5	0
4	$FeCl_3$	DCE	80	1.5	34
5	$In(OTf)_3$	DCE	80	1.5	80
6	$InCl_3$	DCE	80	1.5	19
7	$Cu(OTf)_2$	DCE	80	1.5	10
8	$Sc(OTf)_3$	DCE	80	1.5	89
9	$Sc(OTf)_3$	THF	80	1.5	38
10	$Sc(OTf)_3$	toluene	80	1.5	55
11	$Sc(OTf)_3$	CH_3CN	80	1.5	32
12	**$Sc(OTf)_3$**	**DCE**	**60**	**2**	**91**
13	$Sc(OTf)_3$	DCE	40	12	46
14[c]	$Sc(OTf)_3$	DCE	60	12	80

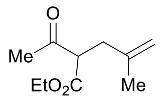
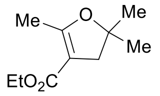
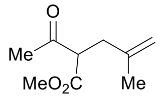
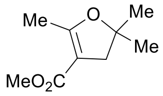
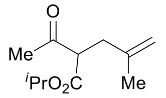
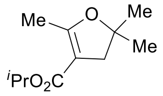
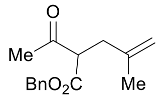
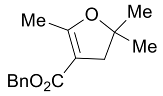
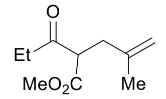
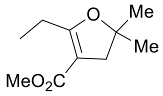
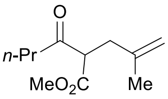
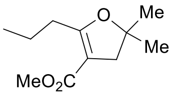
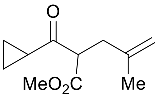
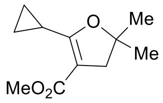
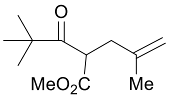
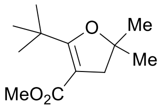
[a] Reaction conditions: 0.2 mmol of substrate **5a** with 10 mol% of catalyst in the indicated solvent (2.0 mL) in air. [b] Isolated yields after column chromatography. [c] 5 mol% of catalyst was used.

Using the optimized system, the scope of substrates with alkyl-β-ketoesters **5** was firstly evaluated (Table 2). In general, complete conversions were observed for substrates **5a-h**, leading to the expected 2,3-dihydrofuran products **6a-h** in moderate to good yields. The carbonyl alkenes **5a-d** bearing different ester functionality could afford the corresponding products **6a-d** in 76-91% yields (Table 2, entries 1-4). Sterically demanding ethyl, propyl, cyclopropyl, and tert-butyl substituents on the ketone subunit were also well tolerated (Table 2, entries 5-8). It should be noted that when ethyl 2-acetylpent-4-enoate was subjected to the reaction conditions, no formation of the expected 2,3-dihydrofuran product was observed.

Table 2 The substrate scope for alkyl-β-ketoesters[a,b]



5a-h **6a-h**

Entry	Substrate		Product		Yield (%)
1		**5a**		**6a**	91
2		**5b**		**6b**	84
3		**5c**		**6c**	86
4		**5d**		**6d**	76
5		**5e**		**6e**	79
6		**5f**		**6f**	67
7		**5g**		**6g**	78
8		**5h**		**6h**	65

[a] Reaction conditions: 0.2 mmol of substrate **5** with 10 mol% of $Sc(OTf)_3$ in DCE (2.0 mL) at 60 ˚C in air. [b] Isolated yields after column chromatography.

We next turn to expand the scope of $Sc(OTf)_3$-catalyzed cyclization of aryl ketones for the formation of 2,3-dihydrofurans under the optimized conditions. As shown in Table 3, a variety of aromatic ketone-derived alkenes could be efficiently converted to the cyclic products in moderate to good yields (56-93%). Substrates having electron-donating substituents on the aryl ring moiety could produce the 2,3-dihydrofuran derivatives in good yields (Table 3, entries 2-3 and 7). Substrates with electron-deficient fluoro-, chloro, and bromoarenes were also suitable for the present

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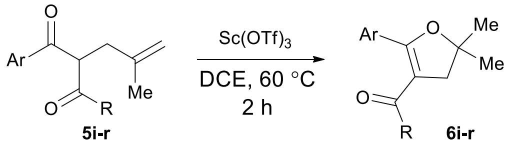
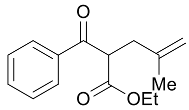
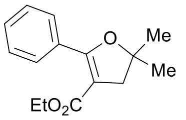
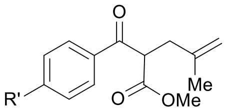
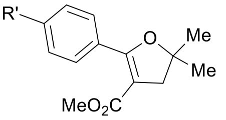
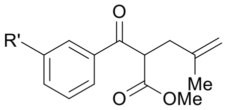
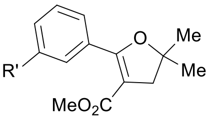
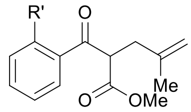
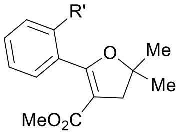
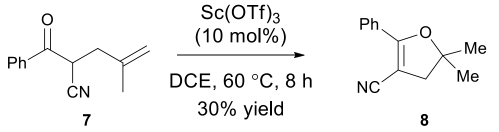
transformation, giving the 2,3-dihydrofuran products in high yields (Table 3, entries 4-6 and 8). Furthermore, the carbonyl alkenes bearing sterically demanding ortho-methyl- and bromo-arenes could achieve the transformations to the desired products albeit in diminished yields (Table 3, entries 9-10).

Table 3 The substrate scope for aryl-β-ketoesters[a,b]



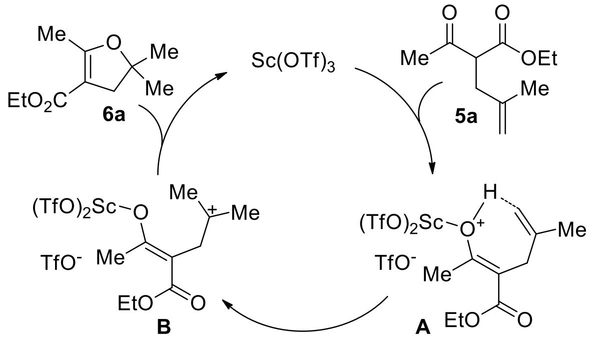
Entry	Substrate		Product		Yield (%)
1		**5i**		**6i**	80
					
2	R' = OMe	**5j**		**6j**	76
3	R' = Me	**5k**		**6k**	88
4	R' = F	**5l**		**6l**	81
5	R' = Cl	**5m**		**6m**	84
6	R' = Br	**5n**		**6n**	83
					
7	R' = Me	**5o**		**6o**	83
8	R' = Cl	**5p**		**6p**	93
					
9	R' = Me	**5q**		**6q**	75
10	R' = Br	**5r**		**6r**	56

[a] Reaction conditions: 0.2 mmol of substrate **5** with 10 mol% of Sc(OTf)$_3$ in DCE (2.0 mL) at 60 ˚C in air. [b] Isolated yields after column chromatography.



Scheme 2 Reaction of the ketoester analog **7**.

In subsequent study, we evaluated the possibility of transformation from the analog **7** to 2,3-dihydrofuran **8** (Scheme 2). Pleasingly, the desired cyclic product **8** was obtained smoothly albeit in low yield.



Scheme 3 Proposed catalytic cycle.

A possible mechanism for this annulation was proposed in Scheme 3.[16] The scandium-enolate intermediate **A** was generated from the coordination of Sc(OTf)$_3$ to ketone-oxygen of **5a** after enolization. The transfer of the acidic proton to the allyl moiety allowed the formation of the carbocation intermediate, which was captured by the enolate nucleophile to form the desired 2,3-dihydrofuran product **6a**. Alternatively, the activation of alkene subunit by Sc(OTf)$_3$ and subsequent nucleophilic attack of the carbonyl oxygen would led to the formation of 2,3-dihydrofuran structure.

In summary, we have developed an efficient Sc(OTf)$_3$-catalyzed cyclization of readily accessible α-allylated 1,3-dicarbonyl compounds that allows the access to functionalized 2,3-dihydrofurans in good to excellent yields. This transformation is operationally simplistic, and efficient with mild conditions. The application for synthesis of some interesting 2,3-dihydrofuran products is underway in our lab.

Acknowledgements

This work was financially supported by the NSFC (21402106, 21475075 and 21475074), Shandong Natural Science Foundation (ZR2014BQ024), and the Project-sponsored by SRF for ROCS, SEM, Shandong Higher Educational Science and Technology Program (J15LA02), and Research Start-up Foundation of Qufu Normal University (bsqd20130115). R. Zhang thanks the funding from National Undergraduate Innovative Training Project.

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DOI: 10.1039/C6RA14051C

Sc(OTf)$_3$-Catalyzed Cyclization of α-Allylated 1,3-Dicarbonyls: an Efficient Access to 2,2-Disubstituted 2,3-Dihydrofuran Derivatives

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A Sc(OTf)$_3$-catalyzed cyclization of α-allylated 1,3-dicarbonyls is reported. By the reaction, a variety of 2,2-disubstituted 2,3-dihydrofurans were obtained in good yields.