Article

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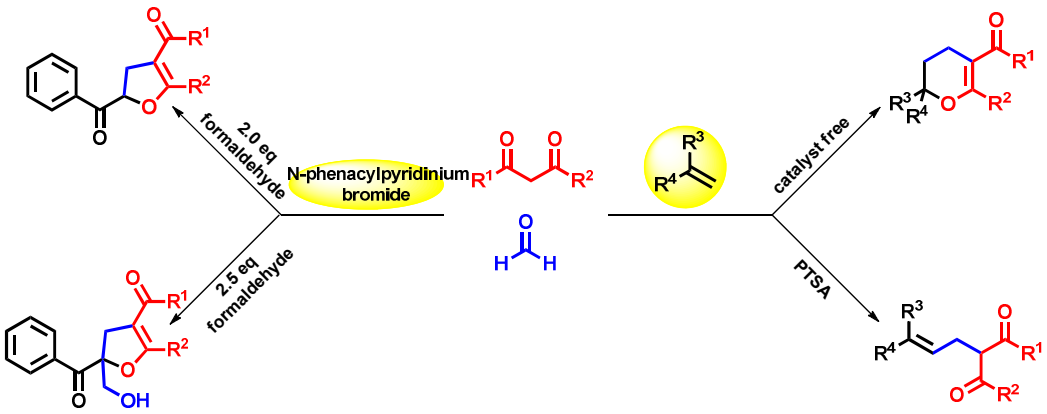
Graphic Abstract



Condition-determined multicomponent reactions of 1,3-dicarbonyl compounds and formaldehyde

Changhui Liu,[a,c] Meng Shen,[a,c] Bingbing Lai,[a] Amir Taheri[a] and Yanlong Gu[a,b*]

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[c] Changhui Liu and Meng Shen contributed equally to this work.

Abstract: By means of changing the reaction parameters, different products could be generated selectively starting from the same combination of substrates involving 1,3-dicarbonyl compound and formaldehyde. This strategy enabled us to access diverse molecules without changing both starting material and reactor, maximizing thus the multi-functionality of the synthetic system. For example, starting from 1,3-dicarbonyl compound, formaldehyde and 1,1-diphenylethylene, two kinds of products could be selectively formed including (i) a densely substituted dihydropyran, and (ii) an C2-cinnamyl substituted 1,3-dicarbonyl compound. A one-pot three-component reaction of phenacylpyridinium salt, 1,3-dicarbonyl compound and formaldehyde was also investigated, which produced either 2,4-diacyl-2,3-dihydrofuran or 2,4-diacyl-2-hydroxylmethyl-2,3-dihydrofuran in good to excellent yield.

Keywords: Multicomponent reactions, diversity-oriented synthesis, condition-determined MCR, combinatorial chemistry

Introduction

Multicomponent reactions (MCRs) are convergent reactions of three or more starting materials, which have emerged as an efficient method for rapidly generating complex molecules with diverse functional substituents.[1] MCRs have often been used to establish expedient and eco-friendly chemical methods for the discovery of new chemical entities required by pharmaceutical and agrochemical industries.[2] The most of MCRs were established by a reaction sequence involving (i) generation of an active intermediate through a reaction of the first two or three components, and (ii) trapping of the intermediate with the same or another component. The generated intermediates generally have a very high reactivity, which enabled us to construct new molecular scaffolds sometimes. Therefore, most of the research interests are focusing on either the exploration of a suitable trapping reagent or derivatization of the intermediate with the hope of establishing a new reaction sequence.[3] However, there is a perceived challenge in the face of the ever increasing demand for novel medicinally active compounds. This forced us to think how to maximize the efficiency of establishing molecule libraries for biological screening.

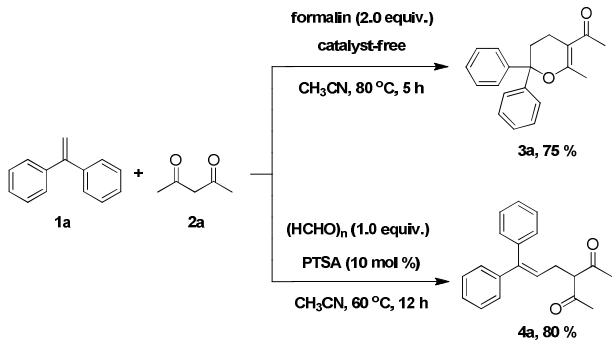
Control of the reaction selectivity, for example, chemo-, stereo-, and region-selectivity, is one of the most important objectives of organic chemistry.[4] Many different reaction parameters such as temperature, pressure, solvent, as well as catalyst type, and other factors can be utilized to modulate the selectivity of organic reactions. Because three or more substrates were involved in a MCR, it is conceivable that by carefully manipulating the reaction parameters, it might be possible to establish two or more MCRs with the same combination of substrates. This strategy can increase the number of MCRs without increasing the number of substrates. Previously, a few reports have disclosed some individual examples on the synthesis of different products from the same substrates.[5] It offered an effective means to us for enriching the diversity of the MCR product libraries, which in turn facilitates biological screening.

We are attracted by the unique advantages of this strategy and started a research

program on this topic some time ago. To utilize this strategy, we have to find a suitable intermediate, which not only has a high reactivity but also is amenable to diversified reaction modes, allowing us to trap it in different reaction pathways. Recently, Knoevenagel reaction of 1,3-dicarbonyl compound and formaldehyde has been used to create MCRs.[6] The generated 2-methylene-1,3-dicarbonyl intermediate not only acts as a *oxo*-diene in Diels-Alder reaction but also serves as Michael acceptor in conjunction with some Michael donors, favoring thus construction of many MCRs.[7] We are attracted by the multifunctionality of this intermediate, and started our MCR investigation with a combination of 1,3-dicarbonyl compound and formaldehyde.

Results and discussion

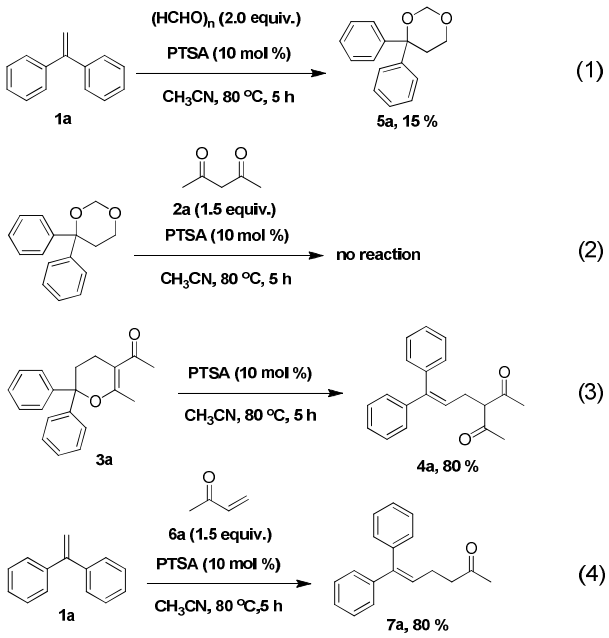
Initially, a three-component reaction of 1,1-diphenylethylene **1a**, acetoacetone **2a** and formaldehyde was investigated. As shown in **Scheme 1**, when formalin was used as HCHO source, a dihydropyran **3a** was obtained in 75 % of yield after 5 hours of reaction at 80 ^{o}C in acetonitrile. The reaction is very clean, and the unreacted 1,1-diphenylethylene can be fully recovered. Interestingly, when paraformaldehyde was used as the HCHO source, a different compound, **4a** was obtained in 80 % of yield in the presence of toluenesulfonic acid (PTSA) at 60 ^{o}C. These results imply that the source of HCHO and the reaction conditions played key role in controlling the reaction selectivity.



Scheme 1. Three-component reaction of **1a**, **2a** and formaldehyde.

These results gave us also impetus to investigate the reaction mechanism. It is well

known that **3a** was formed through a tandem Knoevenagel/oxo Diels-Alder reaction pathway, in which **1a** acted as a dienophile to trap the generated 3-methylene-2,4-pantadione (intermediate **I**, **Figure 1**).[8] In order to shed light on the mechanism for the formation of **4a**, several control experiments were then carried out. Firstly, although the Prins cyclization product of **1a** and paraformaldehyde, **5a** could be formed with the aid of PTSA catalyst, it cannot be converted into **4a** under the reaction conditions (**Scheme 2**). Because **3a** could be also detected during the reaction of forming **4a** (**Figure 2**), we therefore treated **3a** with PTSA in acetonitrile. After 5 hours of reaction at 80 ^{o}C, **4a** was formed in 80 % of yield. However, this result is insufficient to lead us to draw a conclusion for the formation of **4a** because kinetic investigation of the reaction between **1a**, **2a** and paraformaldehyde revealed that no significant accumulation of **3a** was observed during the reaction (**Figure S2**). In addition, monitoring of the reaction progress by means of ^{1}H NMR manifested that (i) intermediate **I** was generated quickly in the first 30 minutes of the reaction; then, it's concentration gradually decreased; and (ii) the formation of **4a** occurred in the beginning of the reaction, and it lasted all 12 hours as the concentration of **4a** increased gradually during the reaction. All these results led us to deduce that **4a** might be formed through a direct Michael reaction of the intermediate **I** and **1a**. Because the isolation of pure intermediate **I** is not possible, methyl vinyl ketone **6a** was therefore used as a Michael acceptor, which has a relatively low reactivity than the intermediate **I**. As shown in **Scheme 2**, the expected product **7a** was obtained in 80 % of yield. This result implies that **4a** might be formed through a tandem Knoevenagel/Michael reaction pathway. Incidentally, as Knoevenagel/oxo Diels-Alder reaction is a non-catalytic reaction sequence, formation of **3a** is therefore inevitable during the synthesis of **4a**. A Knoevenagel/oxo Diels-Alder/ring-opening reaction sequence may be also operative for the formation of **4a** (**Figure 1**). The ring-opening reaction pathway is able to convert **3a** into **4a**, ensuring thus a good selectivity of **4a**.



Scheme 2. Control experiments for understanding the mechanism of **4a** formation.

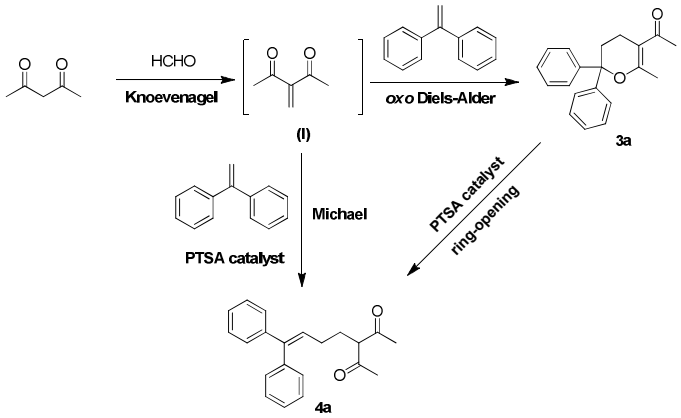


Figure 1. Proposed mechanism for the formations of **3a** and **4a**.

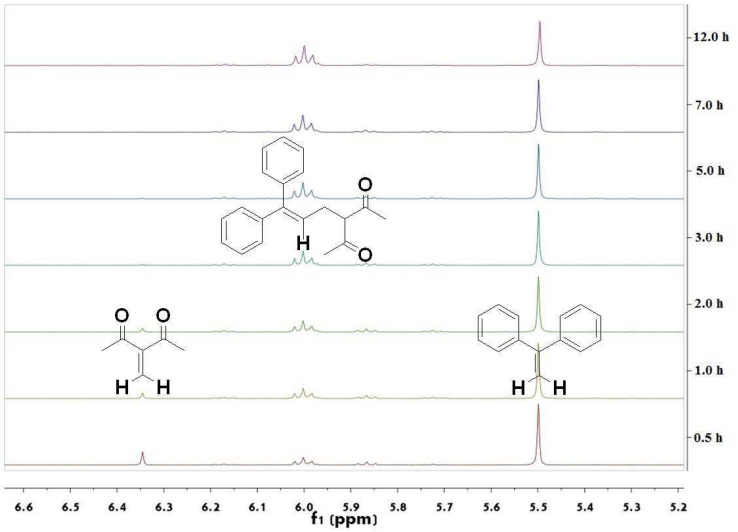


Figure 2. Progress of a PTSA-catalyzed reaction of **1a**, **2a** and paraformaldehyde monitored by ^{1}H NMR.

The PTSA/acetonitrile system was successfully used to establish the three-component reactions of a wide range of 1,3-dicarbonyl compounds, $(HCHO)_n$, and 1,1-diarylethylenes, and the results are shown in **Figure 3**. Many linear β-ketoesters or 1,3-diketones reacted readily with **1a** and paraformaldehyde, affording the corresponding products in generally excellent yields. Cyclopropyl and methoxy groups are tolerable in this system (**4g**). A secondary β-ketoamide can also be used uneventfully (**4i**). Some other 1,1-diphenylethylene derivatives could also be used. Particularly, a diarylethylene with thienyl group participated readily in this reaction as well (**4l**). It is significant to note that **1a** could be replaced by 1,1-diphenylethanol, which is less-expensive as compared with **1a**, in this reaction. This offered a cost-effective alternative route to access **4a**-type product (**Scheme 3**). It should be noted also that, although the same products in **Figure 3** could be synthesized by many reported methods, most of which involve the use of harsh conditions, expensive reagents and suffer from the lack of simplicity and also the yields and selectivities reported are sometimes far from satisfactory. [9] Therefore, the present three-component reaction opened a simple and effective route to access these compounds. However, attempts to use normal 1-arylethylenes, such as

4-methylstyrene and α-methylstyrene, as substrates in PTSA/acetonitrile system were in vain. The reactions suffered from the lack of selectivity as messy mixtures were formed in these cases. By the same token, formaldehyde cannot be replaced by other aliphatic or aromatic aldehyde in this reaction.

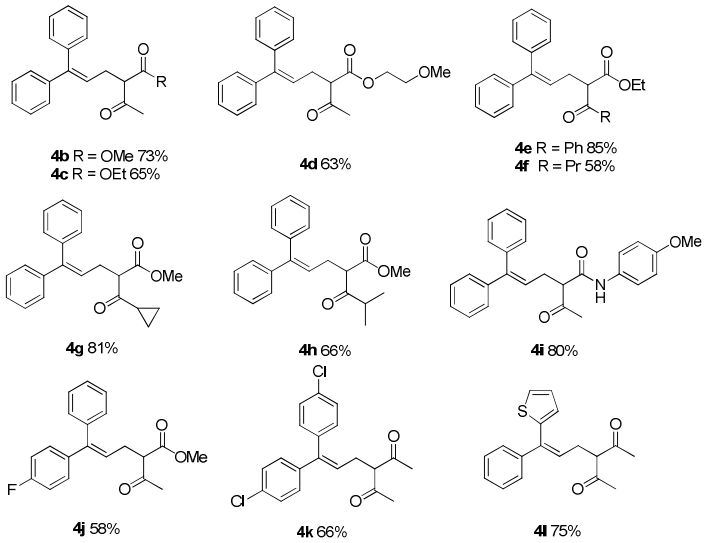
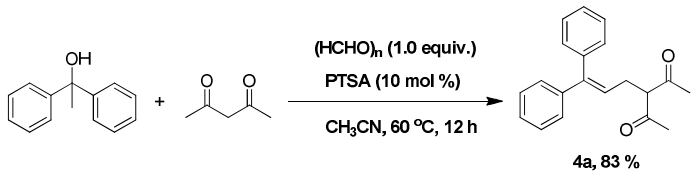


Figure 3. PTSA-catalyzed three-component reaction of 1,1-diarylethylene, 1,3-dicarbonyl compound and $(HCHO)_n$.



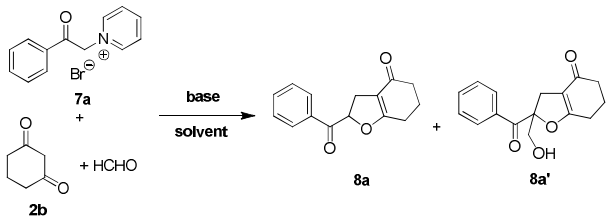
Scheme 3. PTSA-catalyzed three-component reaction of 1,1-diphenylethanol, **2a** and paraformaldehyde.

The above-mentioned results demonstrated that the development of condition-determined MCRs based on a combination of 1,3-dicarbonyl compound and formaldehyde is indeed possible. Encouraged by these results, we then investigated the condensation reaction of N-phenacylpyridinium bromide **7a**, 1,3-cyclohexanedione **2b** and formaldehyde, which can hopefully produce a 2,4-diacyl-2,3-dihydrofuran derivative, **8a** through a cascade Knoevenagel / [4+1] annulation reaction under appropriate conditions.[10] The reaction was also triggered by a Knoevenagel condensation of **2b** with formaldehyde, which generated a 2-methylene-1,3-cyclohexanedione intermediate (**II**) that can be trapped by

phenacylpyridinium salt through [4+1] annulation reaction (**Figure 4**). As shown in **Table 1**, a product was indeed formed in the presence of an inorganic base, $K_2HPO_4{\cdot}3H_2O$, in DMSO, however, it was the hydroxymethylation product of the expected one, **8a'**. Because compound **8a** was also detected at the end of the reaction, we therefore deduced that **8a'** might be formed through a cascade Knoevenagel / [4+1] annulation / hydroxymethylation reaction (**Figure 4**). Indeed, treatment of **8a** in DMSO in the presence of paraformaldehyde resulted in an evident formation of **8a'** (**Scheme 4**). To our great delight, the quasi four-component reaction was found to be very efficient, and the yield of **8a'** reached 83 % after 4 hours of reaction at 80 ^{o}C (entry 1). This observation encouraged us to scrutinize the effects of reaction parameters including base, solvent and reaction temperature. No or only trace amount of product was obtained with inorganic bases, such as $K_3PO_4{\cdot}3H_2O$ and K_2CO_3 (entries 2 and 3). Organic bases like NEt_3 and DBU were also ineffective for this reaction (entries 4 and 5). Among different solvents tested in the reaction, DMSO clearly stood out, producing **8a'** with the highest yield, with DMF and acetonitrile in a distant second place (*ca*. 40 % yields). PEG400, ionic liquid $[BMIm]BF_4$, and water resulted in significantly lower efficiency of the reaction (entries 8 to 10). Ratio of **7a**/**2b**/HCHO can also significantly affect the yield of **8a'**, and the best is **7a**/**2b**/HCHO = 1.0/2.0/2.5. Poor yields were obtained with much excess amount of **2b** or HCHO, which might result from an extensive formation of a by-product through Knoevenagel / Michael reaction of **2b** and HCHO (entries 11 and 12). Interestingly, when ratio of **7a**/**2b**/HCHO was changed to 1.0/1.5/2.0, **8a** was produced as a major product, and **8a'** was formed only in tiny amount (entry 13). These results imply that substrate ratio has a subtle influence on the reaction selectivity, and amounts of **2b** and formaldehyde are both important to determine the reaction selectivity. It offered us a possible means to control the reaction selectivity by tuning the reaction parameters. It should be noted that, in all the previous reports on Knoevenagel / [4+1] annulation sequential reaction of phenacylpyridinium salt, the use of aromatic aldehyde is mandatory in order to facilitate controlling of the reaction selectivity.[11]

The present synthesis of **8a**-like 2,3-dihydrofuran represents the first example of using non-aromatic aldehyde as substrate. Additionally, the reaction was also affected by temperature and reaction time, and the maximum yield of **8a'** was obtained at 80 ^{o}C after 4 hours of reaction (entries 14 to 16). It is worthwhile to note that, under the optimal conditions, effort to replace paraformaldehyde with either formalin (37 wt %) or trioxymethylene was in vain (entries 17 and 18).

Table 1. Three-component reaction of N-phenacylpyridinium bromide, acetylacetone and formaldehyde under different conditions.[a]



entry	base	solvent	ratio of **7a**/**2b**/HCHO	temp. (^{o}C)	yield (%)	
					8a	**8a′**
1	$K_2HPO_4{\cdot}3H_2O$	DMSO	1.0/2.0/2.5	80	<5	**83**
2	$K_3PO_4{\cdot}3H_2O$	DMSO	1.0/2.0/2.5	80	<5	<5
3	K_2CO_3	DMSO	1.0/2.0/2.5	80	0	0
4	Et_3N	DMSO	1.0/2.0/2.5	80	8	5
5	DBU	DMSO	1.0/2.0/2.5	80	0	0
6	$K_2HPO_4{\cdot}3H_2O$	DMF	1.0/2.0/2.5	80	<5	36
7	$K_2HPO_4{\cdot}3H_2O$	CH_3CN	1.0/2.0/2.5	80	<5	39
8	$K_2HPO_4{\cdot}3H_2O$	PEG400	1.0/2.0/2.5	80	<5	<5
9	$K_2HPO_4{\cdot}3H_2O$	$[BMIm]BF_4$	1.0/2.0/2.5	80	9	<5
10	$K_2HPO_4{\cdot}3H_2O$	H_2O	1.0/2.0/2.5	80	8	<5
11	$K_2HPO_4{\cdot}3H_2O$	DMSO	1.0/1.0/2.0	80	<5	67
12	$K_2HPO_4{\cdot}3H_2O$	DMSO	1.0/2.5/3.0	80	9	22
13	$K_2HPO_4{\cdot}3H_2O$	DMSO	1.0/1.5/2.0	80	**80**	<5
14	$K_2HPO_4{\cdot}3H_2O$	DMSO	1.0/2.0/2.5	50	0	5
15	$K_2HPO_4{\cdot}3H_2O$	DMSO	1.0/2.0/2.5	100	5	10
16[b]	$K_2HPO_4{\cdot}3H_2O$	DMSO	1.0/2.0/2.5	80	24	51
17[c]	$K_2HPO_4{\cdot}3H_2O$	DMSO	1.0/2.0/2.5	80	< 5	11
18[d]	$K_2HPO_4{\cdot}3H_2O$	DMSO	1.0/2.0/2.5	80	0	0

[a]: **1a**: 1.0 mmol, paraformaldehdye was used as HCHO source, solvent: 1.0 ml, reaction time: 4 h.

[b]: reaction time: 2 h.

[c]: aqueous solution of formaldehyde was used as HCHO source.

[d]: trioxymethylene was used as HCHO source.

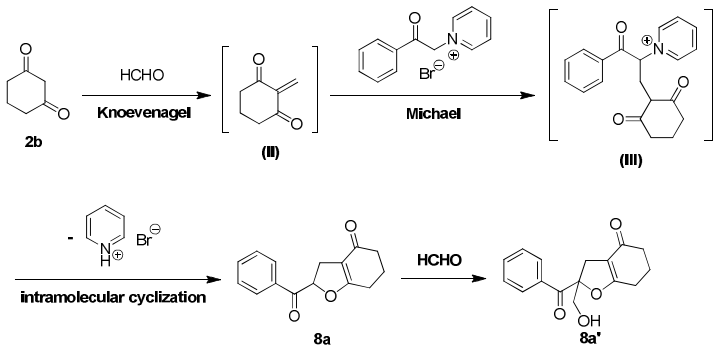
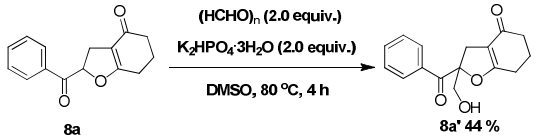


Figure 4.Proposed mechanism for the formations of **8a** and **8a'**.

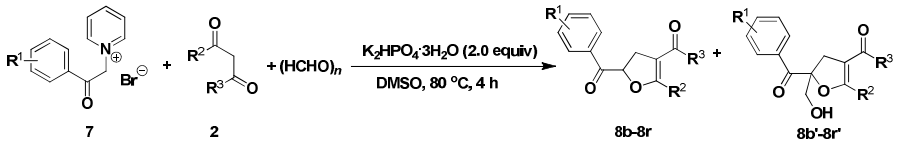


Scheme 4. Hydroxymethylation of **8a** to **8a'**.

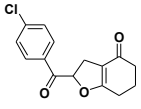
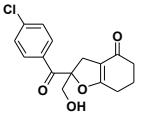
We also probed the scope of the reaction with respect to both the pyridinium bromide and the 1,3-dicarbonyl compounds. As evidenced by the results in **Table 2**, N-phenacylpyridinium bromides with both electron-donating and moderately electron-withdrawing groups smoothly reacted with **2b**, producing 2-hydroxymethylated 2,3-dihydrofurans derivatives in generally good yields (entries 1 to 5). By means of decreasing the ratio of **7**/**2**/HCHO, we are able to suppress the hydroxymethylation. Particularly, when N-(4-methoxyphenacyl)pyridinium bromide was used, yield of the tandem Knoevenagel/[4+1] annulation product, **8e**, reached 95 % with the ratio of **7**/**2**/HCHO = 1.0/1.5/2.0. However, increasing the ratio to 1.0/2.0/2.5 was in vain to obtain its hydroxymethylated counterpart, **8e'**. In this case, much excess amount of paraformaldehyde has to be used in order to get a good yield of **8e'** (entry 4). Acetoacetone **2a** reacted readily with **7a** and formaldehyde, however, extra effort has to be paid to control the reaction selectivity because change of the substrate ratio cannot alter significantly the product distribution. Addition of solvent amount of xylene, which constructed a biphasic system along with DMSO, was proved to be an effective way to suppress the hydroxymethylation reaction of **8g** (entry 6). In order to get **8g'**, the reaction has to be performed at 30 ^{o}C. Fortunately, when the other N-phenacylpyridinium bromide derivatives were used to react with **2a**,

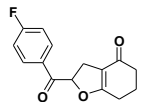
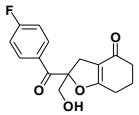
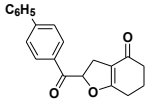
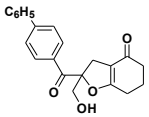
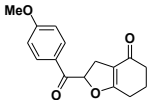
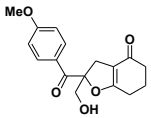
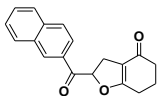
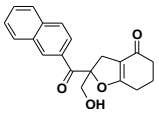
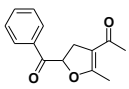
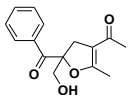
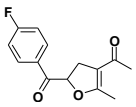
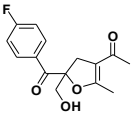
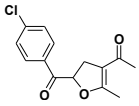
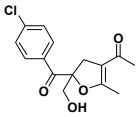
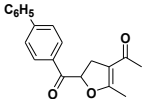
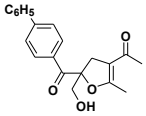
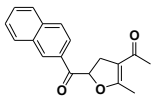
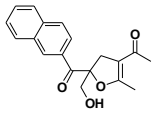
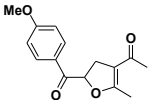
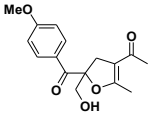
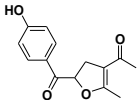
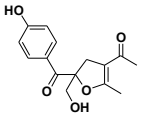
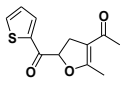
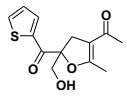
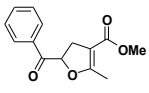
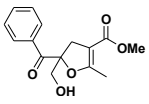
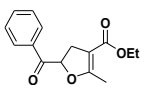
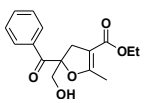
it is quite easy to control the reaction selectivity. In the presence of a large excess amount of paraformaldehyde, the hydroxymethylated product will be preferentially formed as usual. Whereas, the major products are the non-hydroxymethylated 2,3-dihydrofurans when the ratio of **7**/**2b**/HCHO is 1.0/2.0/2.5 (entries 7 to 14). This strategy is particularly effective for tuning the selectivity of condensation between N-(4-phenylphenacyl)pyridinium bromide, **2a** and formaldehyde. Both hydroxymethylated and non-hydroxymethylated products could be obtained in more than 90 % of yields in this case (entry 10). 1-(2-Naphthoylmethyl)pyridinium bromide was also proved to be an eligible substrate that reacted smoothly with either **2b** or **2a**, providing both hydroxymethylated and non-hydroxymethylated products in good yields (entries 5 and 11). It should be noted that OH group in the phenacylpyridinium salt can be delivered uneventfully (entry 12). This facilitates further conversions of the obtained 2,3-dihydrofurans. Heterocyclic group, such as thienyl, is also tolerable in the present reaction (entry 13). Reactions with β-ketoesters proceeded also very well, and the products succeeded the ester moieties without any damage (entries 14 to 17). Ether fragment in 2-methoxyethyl acetoacetate is also tolerable. Due to an insusceptibility of the reaction toward the change of the substrate ratio, DMSO/xylene biphasic system was employed when methyl isobutyrylacetate and 2-methoxyethyl acetoacetate were used to react with **7a** (entries 16 and 17). It should be noted that when an aqueous solution of acetaldehyde was used instead of paraformaldehyde, no expected substituted dihydrofuran derivative was formed.

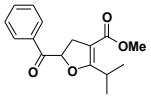
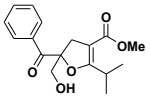
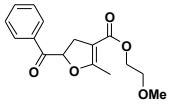
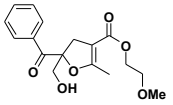
Table 2. Substrate scope of three-component reaction of N-phenacylpyridinium bromides, 1,3-dicarbonyl compounds and paraformaldehyde.[a]



7 2 8b-8r 8b'-8r'

entry	**1**/**2**/HCHO	major product		yield (%)[b]	**1**/**2**/HCHO	major product		Yield (%)[b]
1	1.0/1.5/2.0		**8b**	74 (12)	1.0/2.0/2.5		**8b'**	60 (14)

2	1.0/1.5/2.0		**8c**	62 (9)	1.0/2.0/2.5		**8c'**	68 (13)
3	1.0/1.5/2.0		**8d**	70 (8)	1.0/2.0/2.5		**8d'**	70 (10)
4	1.0/1.5/2.0		**8e**	95 (< 1)	1.0/2.0/7.0		**8e'**	71 (19)
5	1.0/1.5/2.0		**8f**	86 (7)	1.0/2.0/7.0		**8f'**	76 (14)
6	1.0/2.0/2.5		**8g**	82[c] (6)	1.0/2.0/2.5		**8g'**	85[d] (7)
7	1.0/2.0/2.5		**8h**	69 (16)	1.0/2.0/7.0		**8h'**	70 (11)
8	1.0/2.0/2.5		**8i**	73 (8)	1.0/2.0/7.0		**8i'**	51 (9)
9	1.0/2.0/2.5		**8j**	94 (< 5)	1.0/2.0/7.0		**8j'**	93 (< 5)
10	1.0/2.0/2.5		**8k**	72 (12)	1.0/2.0/7.0		**8k'**	57 (18)
11	1.0/2.0/2.5		**8l**	65 (17)	1.0/2.0/7.0		**8l'**	62 (15)
12	1.0/2.0/2.5		**8m**	75 (11)	1.0/2.0/7.0		**8m'**	50 (13)
13	1.0/2.0/2.5		**8n**	81 (10)	1.0/2.0/7.0		**8n'**	61 (16)
14	1.0/2.0/2.5		**8o**	49 (8)	1.0/2.0/7.0		**8o'**	54 (< 5)
15	1.0/2.0/2.5		**8p**	60 (14)	1.0/2.0/7.0		**8p'**	71 (7)

16	1.0/2.0/2.5		**8q**	50[c] (9)	1.0/2.0/2.5		**8q'**	76 (13)
17	1.0/2.0/2.5		**8r**	50[c] (11)	1.0/2.0/2.5		**8r'**	97 (< 1)

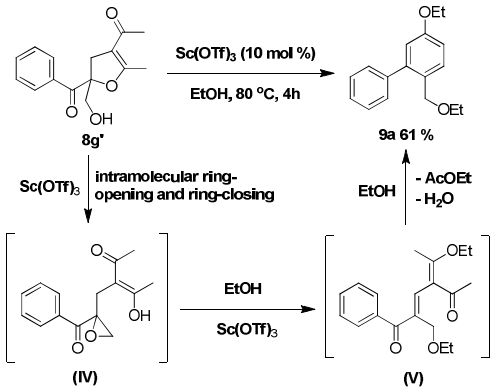
[a]: N-phenacylpyridinium bromide: 0.5 mmol, DMSO: 1.0 ml; $K_2HPO_4 \cdot 3H_2O$: 1.0 mmol; 80 °C, 4 h.

[b]: value in parentheses is the yield of the minor product.

[c]: xylene was added.

[d]: 30 °C.

Because the hydroxymethylated products contain some reactive groups, we therefore suspected that these molecules might be susceptible under acidic conditions. As we expected, treatment of **8g'** in ethanol in the presence of $Sc(OTf)_3$ resulted in selective formation of diphenyl derivative **9a** (**Scheme 5**). The existence of hydroxyl group in **8g'** was proved to be crucial for rendering this reaction possible because no reaction was observed when **8g** was used as substrate under the identical conditions. Initial step of the reaction might be an intramolecular ring-opening and ring-closing reaction of **8g'** with the aid of acid catalyst, which generated an epoxide intermediate (**IV**). The following ring-opening of (**IV**) with ethanol produced an intermediate (**V**) that underwent an intramolecular aldol reaction[12] and subsequent retro-Claisen condensation[13] to form the final product **9a**. This reaction not only displayed an interesting reaction sequence but also offered us the first example that can get aromatic ether from five-member ring heterocycles without oxidation.[14]



Scheme 5. Conversion of **8g'** to **9a**.

Conclusion

Some condition-determined MCRs of 1,3-dicarbonyl compound and formaldehyde were reported. Reaction of 1,3-dicarbonyl compound, formaldehyde and 1,1-diphenylethylene produced either a densely substituted 3,4-dihydropyran or a C2-cinnamyl substituted 1,3-dicarbonyl compound. A pseudo four-component reaction of N-phenacylpyridinium bromide, 1,3-dicarbonyl compound and formaldehyde was also developed, which involved a hitherto unreported Knoevenagel/[4+1] annulation/hydroxymethylation reaction sequence. All these examples demonstrated that the concept of condition-determined MCR is indeed useful for divergence-oriented organic synthesis.

Experimental Section

General

Melting points were determined by microscopic melting pointmeter and were uncorrected. IR spectra were recorded on a FT-IR Bruker (EQUINOX 55) using KBr pellets or neat liquid technology. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400. Chemical shifts are expressed in ppm relative to Me_4Si in solvent. All chemicals used were of reagent grade and were used as received without further purification. All reactions were conducted in a 10 mL of V-type flask equipped with triangle magnetic stirring.

Reaction of 1,1-diarylethylene, 1,3-dicarbonyl compound and $(HCHO)_n$

In a typical reaction, 1,3-dicarbonyl compound (0.2 mmol) was mixed with paraformaldehyde (0.2 mmol), 1,1-diarylethylene (0.25 mmol) and PTSA (0.02 mmol, 3.8 mg, 10 % mol) in acetonitrile (1.0 mL), The mixture was then stirred at 60 ^{o}C for 12 hours. After reaction, the mixture was cooled to room temperature, and the product was obtained by isolation with preparative TLC (eluting solution: petroleum ether / ethyl acetate = 5 / 1 (v/v)). Tests for substrate scope were all performed with an analogous procedure.

Three-component reaction of N-phenacylpyridinium bromides, 1,3-dicarbonyl

compounds and $(HCHO)_n$

N-Phenacylpyridinium bromide (0.25 mmol) was mixed with 1,3-dicarbonyl compound (0.375 mmol), and paraformaldehyde (0.5 mmol), The mixture was then stirred at 80 ^oC for 4 hours. After reaction, the mixture was cooled to room temperature, and the product 2,4-diacyl-2,3-dihydrofuran derivative was obtained by isolation with preparative TLC (eluting solution: petroleum ether / ethyl acetate = 10 / 1 (v/v)). Tests for substrate scope were all performed with an analogous procedure. The hydroxymethylation product was obtained only change the ratio of N-phenacylpyridinium bromide, 1,3-dicarbonyl compound and paraformaldehyde to 1.0/2.0/2.5.

Synthesis of 9a from 8g′

8g′ (52 mg, 0.2 mmol) and $Sc(OTf)_3$ (10 mg, 10 % mol) was added to ethanol (1 mL), and the mixture was then stirred at 80 ^oC for 4 hours. After reaction, the product **9a** was obtained by isolation with preparative TLC (eluting solution: petroleum ether / ethyl acetate = 20 / 1 (v/v)) with yield 61 %.

Acknowledgements

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References

1 (a) Toure, B. B.; Hall, D. G., Natural product synthesis using multicomponent reaction strategies. *Chem. Rev*. **2009**, *109* (9), 4439-4486. (b) Sunderhaus, J. D.; Martin, S. F., Applications of multicomponent reactions to the synthesis of

diverse heterocyclic scaffolds. *Chem-Eur. J.* **2009**, *15* (6), 1300-1308. (c) Ganem, B., Strategies for innovation in multicomponent reaction design. *Acc. Chem. Res.* **2009**, *42* (3), 463-472. (d) Jiang, B.; Rajale, T.; Wever, W.; Tu, S. –J.; Li, G., Multicomponent reactions for the synthesis of heterocycles. *Chem. Asian J.* **2010**, *5* (11), 2318-2335. (e) Yu, J.; Shi, F.; Gong, L. –Z., Brønsted-acid-catalyzed asymmetric multicomponent reactions for the facile synthesis of highly enantioenriched structurally diverse nitrogenous heterocycles. *Acc. Chem. Res.* **2011**, *44* (11), 1156-1171. (f) de Graaff, C.; Ruijter, E.; Orru, R. V. A., Recent developments in asymmetric multicomponent reactions, *Chem. Soc. Rev*. **2012**, *41* (10), 3969-4009.

2 (a) Ramazani, A.; Kazemizadeh, A. R., Preparation of stabilized phosphorus ylides via multicomponent reactions and their synthetic applications, *Curr. Org. Chem*. **2011**, *15* (23), 3986-4020. (b) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J., 1,3-Dicarbonyl compounds in stereoselective domino and multicomponent reactions, *Tetrahedron: Asymmetry*, **2010**, *21*(9-10), 1085-1109. (c) Willy, B.; Mueller, T. J. J., Multicomponent heterocycle syntheses via catalytic generation of alkynones, *Curr. Org. Chem*. **2009**, *13* (18), 1777-1790. (d) Isambert, N.; Lavila, R., Heterocycles as key substrates in multicomponent reactions: the fast lane towards molecular complexity, *Chem. – Eur. J*. **2008**, *14* (28), 8444-8454. (e) Cioc, R. C.; Ruijter, E.; Orru, R. V. A. Multicomponent reactions: advanced tools for sustainable organic synthesis, *Green Chem*. **2014**, *16* (6), 2958-2975.

[3] (a) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A., Multicomponent reaction design in the quest for molecular complexity and diversity, *Angew. Chem. Int. Ed*. **2011**, *50*, 6234-6246. (b) Bhunia, A.; Biju, A. T., Employing arynes in transition-metal-free, N-heterocycle-initiated multicomponent reactions, *Synlett*, **2014**, *25* (5), 608-614. (c) See also the *Chemical Society Reviews* issue on the Rapid formation of molecular complexity in organic synthesis: *Chem. Soc. Rev.* **2009**, *38*, 2969-3276.

[4] See some examples: (a) Bocokić, V.; Kalkan, A.; Lutz, M.; Spek, A. L.; Gryko, D. T.; Reek, J. N. H., Capsule-controlled selectivity of a rhodium hydroformylation catalyst, *Nat. Commun*. **2013**, 4, 2670; (b) Xu, X.; Zhou, J.; Yang, L.; Hu, W., Selectivity control in enantioselective four-component reactions of aryl

diazoacetates with alcohols, aldehydes and amines: an efficient approach to synthesizing chiral β-amino-α-hydroxyesters, *Chem. Commun*. **2008**, 6564-6566; (c) Shawali, A. S. Chemoselectivity in 1,3-Dipolar Cycloaddition Reactions of Nitrilimines with Multifunctionalized Dipolarophiles, *Curr. Org. Chem*. **2014**, *18*, 598-614.; (d) Ji, J.; Zhang, X.; Zhu, Y.; Qian, Y.; Zhou, J.; Yang, L.; Hu, W., Diastereoselectivity switch in cooperatively catalyzed three-component reactions of an aryldiazoacetate, an alcohol, and a β,γ-unsaturated α-keto ester, *J. Org. Chem*. **2011**, *76*, 5821-5824; (e) Shawali, A. S.; Abdelhamid, A. O., Synthesis of spiro-heterocycles via 1,3-dipolar cycloadditions of nitrilimines to exoheterocyclic enones. site-, regio- and stereo-selectivities overview, *Curr. Org. Chem*. **2012**, *16*, 2673-2689.

[5] See some recent examples: (a) Gao, H.; Sun, J.; Yan, C. –G., Selective synthesis of functionalized spiro[indoline-3,2′-pyridines] and spiro[indoline-3,4′-pyridines] by lewis acid catalyzed reactions of acetylenedicarboxylate, arylamines, and isatins, *J. Org. Chem*. **2014**, *79*, 4131-4136; (b) Zhou, F.; Liu, X.; Zhang, N.; Liang, Y.; Zhang, R.; Xin, X.; Dong, D., Copper-catalyzed three-component reaction: solvent-controlled regioselective synthesis of 4-amino- and 6-amino-2-iminopyridines, *Org. Lett*. **2013**, *15*, 5786-5789; (c) Jaegli, S.; Dufour, J.; Wei, H. –L.; Piou, T.; Duan, X. –H.; Vors, J. –P.; Neuville, L.; Zhu, J., Palladium-catalyzed carbo-heterofunctionalization of alkenes for the synthesis of oxindoles and spirooxindoles, *Org. Lett.* **2010**, *12*, 4498-4501; (d) Li, J.; Wang, N.; Li, C.; Jia, X., Multicomponent reaction to construct spirocyclic oxindoles with a Michael (triple Michael)/cyclization cascade sequence as the key step, *Chem. Eur. J*. **2012**, *18*, 9645-9650; (f) Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Knyazeva, I. V.; Groth, U.; Glasnov, T. N.; Kappe, C. O., Tuning of chemo- and regioselectivities in multicomponent condensations of 5-aminopyrazoles, dimedone, and aldehydes, *J. Org. Chem.* **2008**, *73*, 5110-5118; (g) Elders, N.; Ruijter, E.; de Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A., Selective formation of 2-imidazolines and 2-substituted oxazoles by using a three-component reaction, *Chem. Eur. J.* **2008**, *14*, 4961-4973; (h) Karapetyan, G.; Dang, T. T.; Sher, M.; Ghochikyan, T. V.; Saghyan, A.; Langer, P., Diversity-oriented synthesis of functionalized phenols by regioselective [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with

3-alkoxy-2-en-1-ones and related substrates, *Curr. Org. Chem*. **2012**, *16*, 557-565. (i) He, H.; Sharif, M.; Neumann, H.; Beller, M.; Wu, X. –F., A convenient palladium-catalyzed carbonylative synthesis of 4(3*H*)-quinazolinones from 2-bromoformanilides and organo nitros with $Mo(CO)_6$ as a multiple promoter, *Green Chem*. **2014**, *16*, 3763-3767; (j) Chen, J.; Neumann, H.; Beller, M.; Wu, X. –F., Palladium-catalyzed synthesis of isoindoloquinazolinones *via* dicarbonylation of 1,2-dibromoarenes, *Org. Biomol. Chem.*, **2014**, *12*, 5835-5838; (k) Chen, J.; Natte, K.; Spannenberg, A.; Neumann, H.; Beller, M.; Wu X. –F., Efficient palladium-catalyzed double carbonylation of *o*-dibromobenzenes: synthesis of thalidomide, *Org. Biomol. Chem.*, **2014**, *12*, 5578-5581. (l) Li, H.-Q; Li,W.-F; Spannenberg, A.; Baumann, W.; Neumann, H.; Beller, M.; Wu, X.-F., A Novel Domino Synthesis of Quinazolinediones by Palladium-Catalyzed Double Carbonylation, *Chem. Eur. J.* **2014**, *20*, 8541-8544; (m) Chen, J.; Natte, K.; Spannenberg, A.; Neumann, H.; Langer, P.; Beller, M.; Wu, X-F., Base-Controlled Selectivity in the Synthesis of Linear and Angular Fused Quinazolinones by a Palladium-Catalyzed Carbonylation/Nucleophilic Aromatic Substitution Sequence, *Angew. Chem. Int. Ed.* **2014**, *53*, 7579-7583; (n) He, L; Li, H.-Q; Neumann, H; Beller, M; Wu, X.-F, Highly Efficient Four-Component Synthesis of 4(3H)-Quinazolinones: Palladium-Catalyzed Carbonylative Coupling Reactions, *Angew. Chem. Int. Ed.* **2014**, *53*, 1420-1424.

[6] (a) Gu, Y.; de Sousa, R.; Frapper, G.; Bachmann, C.; Barrault, J.; Jérôme, F., Catalyst-free aqueous multicomponent domino reactions from formaldehyde and 1,3-dicarbonyl derivatives, *Green Chem*. **2009**, *11*, 1968-1972; (b) Gu, Y.; Barrault, J.; Jérôme, F., Trapping of active methylene intermediates with alkenes, indoles or thiols: towards highly selective multicomponent reactions, *Adv. Synth. Catal*. **2009**, *351*, 3269-3278; (c) Tan, J. –N.; Li, H.; Gu, Y., Water mediated trapping of active methylene intermediates generated by IBX-induced oxidation of Baylis–Hillman adducts with nucleophiles, *Green Chem*. **2010**, *12*, 1772-1782; (d) Li, M.; Chen, C.; He, F.; Gu, Y., Multicomponent reactions of 1,3-cyclohexanediones and formaldehyde in glycerol: stabilization of paraformaldehyde in glycerol resulted from using dimedone as substrate, *Adv. Synth. Catal*. **2010**, *352*, 519-530; (e) Tan, J. –N.; Li, M.; Gu, Y., Multicomponent reactions of 1,3-disubstituted 5-pyrazolones and formaldehyde

in environmentally benign solvent systems and their variations with more fundamental substrates, *Green Chem*. **2010**, *12*, 908-914.

[7] (a) Kumar, A.; Kumar, M.; Gupta, M. K., An efficient organocatalyzed multicomponent synthesis of diarylmethanes via Mannich type Friedel–Crafts reaction, *Tetrahedron Lett*. **2009**, *50*, 7024-7027; (b) Kumar, A.; Sharma, S.; Maurya, R. A., A novel multi-component reaction of indole, formaldehyde, and tertiary aromatic amines, *Tetrahedron Lett*. **2009**, *50*, 5937-5940; (c) Ferreira, S. B.; Gonzaga, D. T. G.; de Carvalho da Silva, F.; de Lima Araújo, K. G.; Ferreira, V. F., Synthesis of new *o*-quinone methides from β-lapachone analogues, *Synlett*, **2011**, 1623-1625; (d) Massa, A., Recent advances in the chemistry of active methylene compounds, *Curr. Org. Chem*. **2012**, *16*, 2159-2159; (e) Di Mola, A.; Palombi, L.; Massa, A., Active methylene compounds in the synthesis of 3-substituted isobenzofuranones, isoindolinones and related compounds, *Curr. Org. Chem*. **2012**, *16*, 2302-2320.

[8] Frapper, G.; Bachmann, C.; Gu, Y.; de Sousa, R. C.; Jérôme, F., Mechanisms of the Knoevenagel hetero Diels–Alder sequence in multicomponent reactions to dihydropyrans: experimental and theoretical investigations into the role of water, *Phys. Chem. Chem. Phys.* **2011**, *13*, 628-636.

[9] (a) Safi, M.; Sinou, D., Palladium(0)-catalyzed substitution of allylic substrates in a two-phase aqueous-organic medium, *Tetrahedron Lett.* **1991**, *32*, 2025-2028; (b) Maity, A. K.; Chatterjee, P. N.; Roy, S., Multimetallic Ir–Sn_3-catalyzed substitution reaction of π-activated alcohols with carbon and heteroatom nucleophiles, *Tetrahedron*, **2013**, *69*, 924-956; (c) Wahl, B.; Giboulot, S.; Mortreux, A.; Castanet, Y.; Sauthier, M.; Liron, F.; Poli, G., Straightforward synthesis of allylated keto esters: the Palladium-catalysed haloketone alkoxycarbonylation/allylation domino reaction, *Adv. Synth. Catal*. **2012**, *354*, 1077-1083; (d) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A., Efficient metal-catalyzed direct benzylation and allylic alkylation of 2,4-pentanediones, *Org, Lett*. **2007**, *9*, 825-828.

[10] (a) Chuang, C. –P.; Chen, K. –P.; Hsu, Y. –L.; Tsai, A. -I.; Liu, S. –T., α-Nitro carbonyl compounds in the synthesis of 2,3-dihydrofurans, *Tetrahedron*, **2008**, *64*, 7511-7516; (b) Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K. –I.; Shioiri, T., Stereoselective synthesis of dihydrofurans under phase-transfer catalyzed

conditions, *Tetrahedron Lett*. **1998**, *39*, 9739-9742; (c) Chuang, C. P.; Tsai, A. –I., Pyridinium ylides in the synthesis of 2,3-dihydrofurans, *Synthesis*, **2006**, 675-679; (d) Indumathi, S.; Perumal, S.; Anbananthan, N., A facile eco-friendly three-component protocol for the regio- and stereoselective synthesis of functionalized *trans*-dihydrofuro[3,2-*c*]-quinolin-4(2*H*)-ones, *Green Chem*. **2012**, *14*, 3361-3367; (e) Gunasekaran, P.; Balamurugan, K.; Sivakumar, S.; Perumal, S.; Menéndez, J. C.; Almansour, A. I., Domino reactions in water: diastereoselective synthesis of densely functionalized indolyldihydrofuran derivatives, *Green Chem*. **2012**, *14*, 750-757; (f) Chuang, C. –P.; Chen, K. –P., *N*-Phenacylpyridinium bromides in the one-pot synthesis of 2,3-dihydrofurans, *Tetrahedron*, **2012**, *68*, 1401-1406; (g) Wang, Q. -F.; Hou, H.; Hui, L.; Yan, C. -G., Diastereoselective synthesis of *trans*-2,3-dihydrofurans with pyridinium ylide assisted tandem reaction, *J. Org. Chem*. **2009**, *74*, 7403-7406; (h) Yang, Z.; Fan, M.; Mu, R.; Liu, W.; Liang, Y., A facile synthesis of highly functionalized dihydrofurans based on 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed reaction of halides with enones, *Tetrahedron*, **2005**, *61*, 9140-9146; (i) Vitale, P.; Scilimati, A., Five-membered ring heterocycles by reacting enolates with dipoles, *Curr. Org. Chem*. **2013**, *17*, 1986-2000.

[11] Literature survey stated that while sulfonium ylide and imidazolium ylide enabled the use of aliphatic aldehyde, the reactions with pyridium ylide are still not amenable to aliphatic aldehyde: (a) Jiang, Y.; Ma, D., Synthesis of enantiopure substituted dihydrofurans via the reaction of (*S*)-glyceraldehyde acetonide- or Garner aldehyde acetonide-derived enones with sulfonium ylides. *Tetrahedron: Asymmetry*, **2002**, *13*, 1033-1038; (b) Kumar, A.; Srivastava, S.; Gupta, G., Cascade [4 + 1] annulation *via* more environmentally friendly nitrogen ylides in water: synthesis of bicyclic and tricyclic fused dihydrofurans, *Green Chem*. **2012**, *14*, 3269-3272.

[12] (a) Chen, L.; Luo, S.; Li, J.; Li, X.; Cheng, J. –P., Organocatalytic kinetic resolution *via* intramolecular aldol reactions: Enantioselective synthesis of both enantiomers of chiral cyclohexenones, *Org. Biomol. Chem*. **2010**, *8*, 2627-2632; (b) Jin, T.; Yamamoto, Y., Gold-catalyzed intramolecular carbocyclization of alkynyl ketones leading to highly substituted cyclic enones, *Org. Lett*. **2007**, *9*, 5259-5262.

[13] Biswas, S.; Maiti, S.; Jana, U., An efficient iron-catalyzed carbon–carbon single-bond ceavage via Retro-Claisen Condensation: a mild and convenient approach to synthesize a variety of esters or ketones, *Eur. J. Org. Chem*. **2010**, 2861-2866.

[14] Synthesis of aromatic ether from non-aromatic precursor has just been established by means of oxidative condensation of alcohol and 2-cyclohexenone: Simon, M. –O.; Girard, S. A.; Li, C. –J., Catalytic aerobic synthesis of aromatic ethers from non-aromatic precursors, *Angew. Chem. Int. Ed*. **2012**, *51*, 7537-7540.