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Calcium Catalysed Regioselective (5-exo dig) Tandem Process for the Synthesis of Fully Substituted Furans

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Calcium Catalysed Regioselective (5-exo dig) Tandem Process for the Synthesis of Fully Substituted Furans†

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An efficient and highly regio-selective synthesis of fused & substituted furans has been described using $Ca(OTf)_2$ as the catalyst. This tandem process involves alkylation, 5-exo dig cyclisation and isomerization to furnish densely substituted furans under solvent free conditions. A case study of regioselectivity has been demonstrated.

Furan derivatives are important 5-membered oxygen containing aromatic heterocyclics present in many of the biologically important natural products (Figure 1) and synthetic molecules.[1] Particularly, fused and 2,3-disubstituted furans received special attention due to the structural features and biological activities such as antifungal, antiviral, antidiabetic, antiparasitic and pharmaceutical applications.[2,3] Hence these scaffolds become synthetically intriguing and challenging for the chemists and hence came up with novel synthetic methodologies for their synthesis.[4-7] Although viable synthetic methods are available for their synthesis, most of them suffer from multistep synthesis, regioselectivity, usage of nonavailable starting materials, expensive transition metal catalysts, strong bases or acids.[4-7] Therefore, it is highly desirable to develop a regioselective, solvent free, step and atom economic synthesis of 2,3-disubstituted benzofurans.

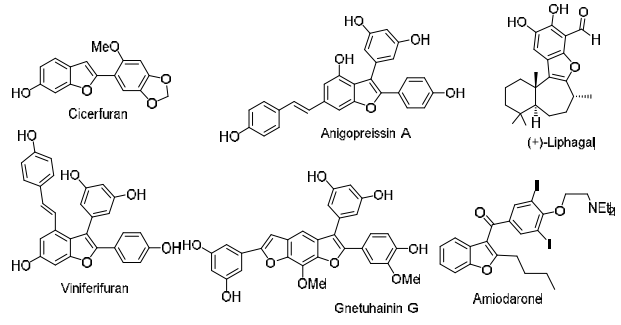

Figure 1. Representatives of biological important natural products with benzofuran moiety

One-pot cascade reactions offer many advantages in terms of economic and environmental point of view.[8] In the recent years calcium salts proved as an alternative Lewis acids due to their abundance and stability towards moisture and air.[9] Our group has also showed the utility of $Ca(OTf)_2$ as a green catalyst in many of the organic transformations during the synthesis of small heterocyclic molecules using the Ritter reaction,[10a] tandem synthesis of pyranocoumarins,[10b] benzo[b]pyrans & benzylpyrazolyl coumarins,[10c] and sp3 C-H functionalization of methyl azaarenes.[10d-10f] In continuation of our research aimed towards the synthesis of medicinally relevant molecules through a sustainable catalysis,[10] herein we report a cascade calcium catalyzed regioselective synthesis of 2,3-disubstituted benzofurans under solvent free conditions.

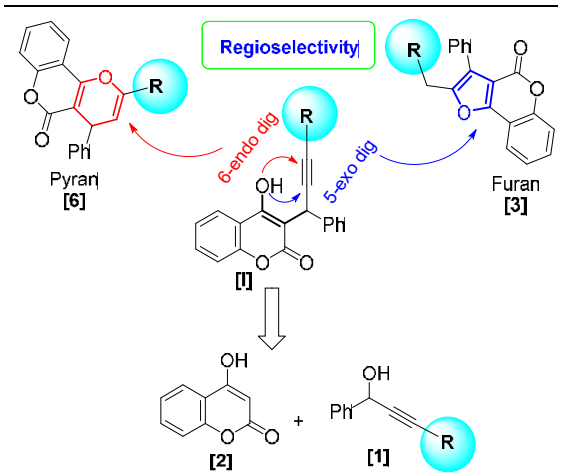

Figure 2. Conceptulization of highly regioselective synthesis of Furan derivatives

Figure 2 represents the conceptualization of our strategy towards the regioselective synthesis of furan derivatives over the Pyran derivatives. 3-benzylated coumarin [**I**] may undergo two possible intramolecular oxacyclisations (i) 5-exo dig cyclisation to form furan moiety (ii) 6-endo dig cyclisation to form pyran moiety. Since the intermediate compound [**I**] is

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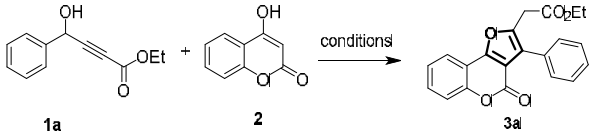
prone to undergo cyclisation in both ways, we propose that if –R group is an electron withdrawing group then β-carbon will be more electron deficient and hence it provokes the intramolecular nucleophilic attack by a 5-exo dig oxacyclisation pathway to furnish the regioselective furan derivatives. We began to implement our idea by refluxing ethyl 4-hydroxy-4-phenylbut-2-ynoate (**1a**, 1 equiv.) with 4-hydroxy coumarin (1.1 equiv) in dichloromethane at 55 °C in presence of $Ca(OTf)_2$ and Bu_4NPF_6 (10 mol%) and isolated the proposed furan compound **3a** in 35% after 5 h (Table 1, entry 1,). Continuing the reaction furthermore could not help in increasing the yields of the product. Various other solvents were studied for enhancing the product yield as showed in Table 1.

Table 1. Optimization studies for the synthesis of 2,3-disubstituted furocoumarin **3a** .



1a 2 3a

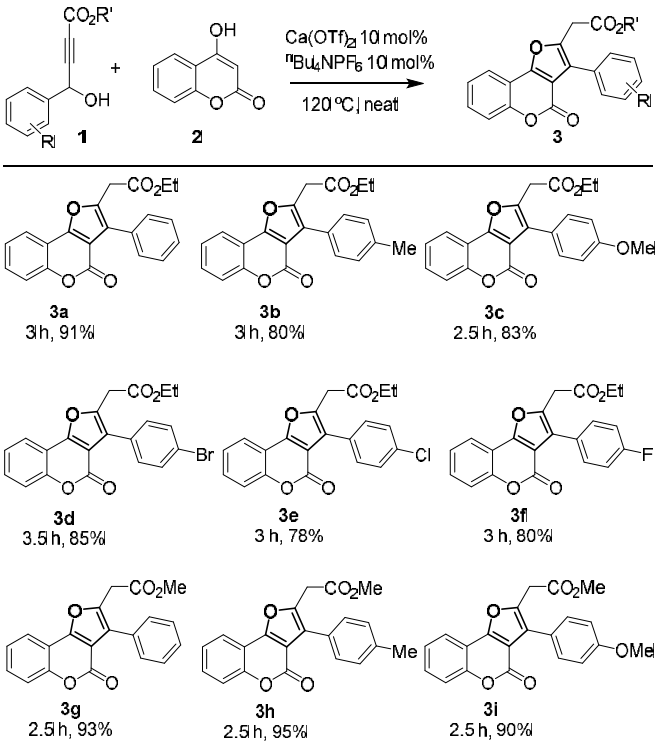
Entry	$Ca(OTf)_2$ (mol%)	Bu_4NPF_6 (mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	10	10	CH_2Cl_2	50	5	35
2	10	10	THF	90	5	25
3	10	10	CH_3CN	90	6	30
4	10	10	$PhCH_3$	120	5	40
5	10	10	H_2O	100	15	5
6[b]	10	10	neat	120	3	91
7	10	-	neat	120	6	45
8	-	10	neat	120	5	57
9	-	20	neat	120	5	61
10	5	5	neat	120	5	73
11	-	-	neat	120	8	trace

[a] Isolated yields. [b] Optimum conditions.

When the same reaction was repeated in THF, acetonitrile, and toluene the product was isolated in 25%, 30% and 40% respectively (Table 1, entries 2-4). Water gave only 5% conversion even after 15 h under reflux. However we were glad to isolate 91% of benzofuran **3a** under solvent free conditions (Table 1, entry 6). After optimizing the solvent case in the reaction we were interested in looking at the catalyst loading. When the reaction was performed in the absence of additive the yield was found to be 45% (Table 1, entry 7) nevertheless we were surprised to notice that when additive alone was used under neat conditions the yield was better 57% (Table 1, entry 8) than the previous case. Therefore we performed the reaction using 20 mol% of additive alone and noticed that the yield was increased to a small extent (Table 1, entries 8, 9). In case of 5 mol% of catalyst and additive loading the isolated yield was 73% only and in the absence of both we only could observe trace of product and hence we concluded that the reaction yields better only when 10 mol% catalyst and additive was used under solvent free conditions (Table 1, entry 6).

Having optimum conditions set for the regioselective synthesis of 2,3-disubstituted furocoumarins,[11] we were interested to check the scope of various other propargylic alcohols as the electrophilic counter parts against 4-hydroxy coumarin (Table 2).

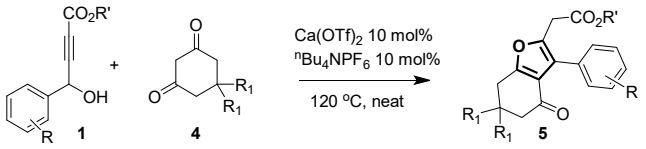
Table 2. Scope of propargylic alcohols as the electrophilic counter parts against 4-hydroxy coumarin in the synthesis of 2,3-disubstituted furocoumarins (3)

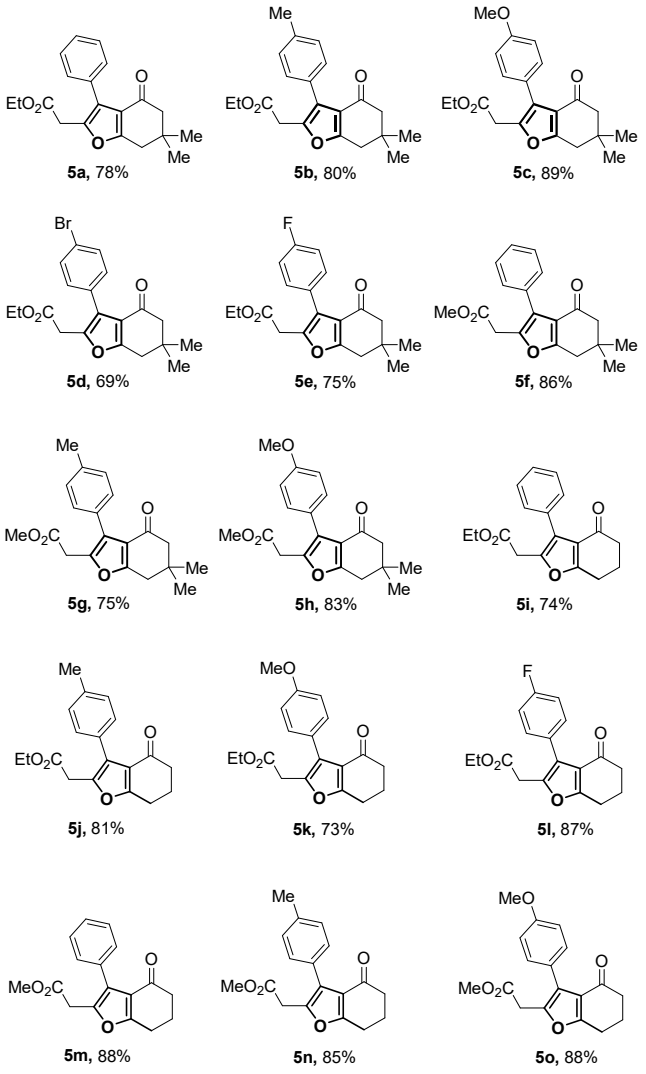


[a] All reactions were carried out using alkyne **1** (1 mmol) and coumarin **2** (1.1 mmol) with catalytic amount of $Ca(OTf)_2$ and Bu_4NPF_6 (10 mol%) each under solvent free condition at 120 °C

Ethyl 4-hydroxy-4-(p-tolyl)but-2-ynoate gave 80% furocoumarin **3b** after 3 h. Similarly ethyl 4-hydroxy-4-(4-methoxyphenyl)but-2-ynoate yielded 83% of **3c** in 2.5 h only. Other propargylic alcohols (**1**) bearing p-halo substitutions on the phenyl ring like bromo, chloro and fluoro yielded the respective furocoumarins **3d, 3e** and **3f** in 85%, 78% and 80% yields. Methyl 4-hydroxy-4-phenylbut-2-ynoate and its 4-methyl and 4-methoxy derivatives furnished the furan derivatives **3g, 3h** and **3i** in 93%, 95% and 90% yields respectively. After describing the scope of electrophilic partners in the furan synthesis, we further investigated the scope of nucleophilic partners other than 4-hydroxy coumarin (Table 3). We choose 5,5-dimethyl-cyclohexane 1,3-dione (**4a**) and cyclohexane 1,3-dione (**4b**) as the nucleophilic partners because they can undergo further cyclization through enolic –OH group. As planned 5,5-dimethyl-cyclohexane 1,3-dione (**4a**) was treated with ethyl 4-hydroxy-4-phenylbut-2-ynoate (**1a)** at 120 °C for 4 h and isolated the benzofuran **5a** in 78% yield. *para*-phenyl derivatives of **1a** such as *p*-methyl, methoxy, bromo and fluoro compounds furnished the corresponding 2,3-disubstituted benzofurans **5b, 5c, 5d** and **5e** in good yields (Table 3). Similar way methyl 4-hydroxy-4-phenylbut-2-ynoate and its *para*-phenyl derivatves yielded benzofurans **5f**, **5g** and **5h** in good yields. Third nucleophilic counterpart cyclohexane-1,3-dione (**4b**) was equally competent and reacted with variety of propargylic systems and furnished the respective benzofurans in good to excellent yields (Table 3, 5i-5o).

Table 3. Substrate scope of 2,3-disubstituted benzofurans

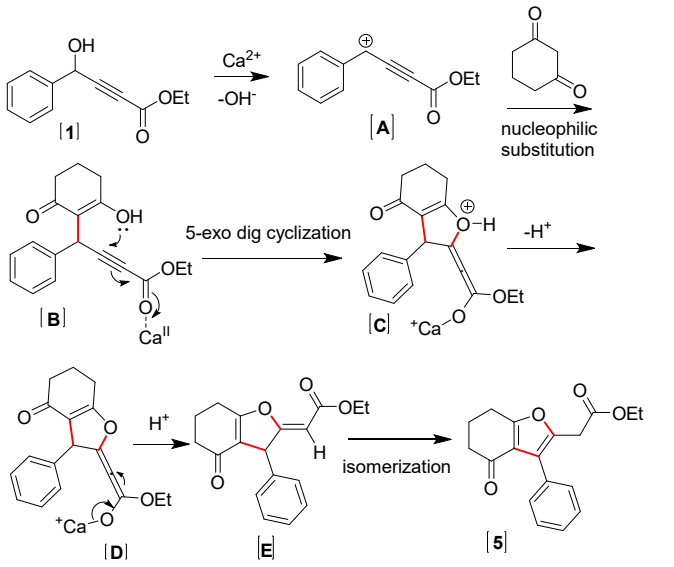




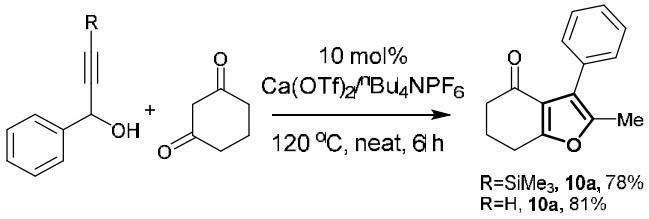
[a] All reactions were carried out using **1** (1 mmol) and **4** (1.1 mmol) with catalytic amount of $Ca(OTf)_2$ and Bu_4NPF_6 (10 mol%) each under solvent free condition.

A plausible mechanism for the Ca(II) catalyzed regioselective synthesis of furan derivatives is described in the Scheme 1. Initially, propargylic alcohol reacts with calcium triflate and generates the carbocation then nucleophilic substitution takes place through a carbocation intermediate [**A**] to form alkyl substituted compound [**B**]. In the next stage a regioselective oxa-cyclization takes place through a 5-exo dig passion to form the intermediate [**E**], because of having electron withdrawing group (-CO_2Et) attached to alkyne the β-carbon become more electrophilic and hence it drives to the formation of five membered cyclization in preference to the six membered. Finally compound [**E**] isomerizes to yield the thermodynamically stable furan compound [**5**].

Scheme 1. Plausible mechanism for the Ca(II) catalyzed regioselective synthesis of densely substituted Furans



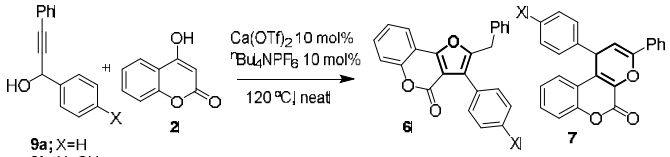
When we tried a reaction with 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-ol along with cylcohexane 1,3-dione under the same reaction conditions we could isolate the 2-methylbenzofuran **10a** in 78% after 6h. (Scheme 2). Surprisingly the TMS group was cleaved during the process and this could be due to the presence of fluoride ions in the reaction in the form of additive. When another propargyl alcohol with a terminal alkyne 1-phenylprop-2-yn-1-ol was used we still got the same benzofuran product as expected (**10a**).[12]



Scheme 2. reaction of cyclohexane 1,3-dione with silyl and terminal alkynes

In order to validate the conceptualization proposed in the Figure 2, we choose 1,3-diphenylprop-2-yn-1-ol (**9a**) as the electrophilic partner instead of methyl 4-hydroxy-4-phenylbut-2-ynoate (**1a**) against 4-hydroxy coumarin and subjected under same reaction conditions. After 2 h, we could isolate the mixture of both furan and Pyran (**6a**/**7a**)[13] in 1:9.08 ratios with an overall yield of 93%. Similarly when 3-phenyl-1-(p-tolyl)prop-2-yn-1-ol (**9b**) treated with 4-hydroxy coumarin we observed the mixture of furan and pyran (**6b**/**7b**) in 1:8 ratios. It is true with 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (**9c**) also and yielded 85% of **6c**/**7c** in 1:13.3 ratios as described in the Scheme 3.[7b, 7c] Which is strongly supporting our conceptualization that if there is a powerful electron

withdrawing group α-to the alkyne that drives the reaction through a 5-exo dig pathway in preference to the 6-endo dig pathway. Probably that could be the main reason why we got only furan compounds with the propargylic ester **1** (Table 2 and 3).

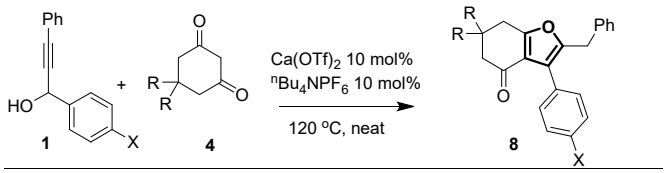


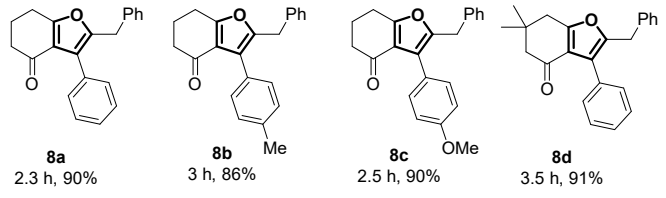
Entry	product	distribution (6/7)	time (h)	Yield (%)
1.	X = H;	**6a/7a** 1.0 : 9.08	2	93
2.	X = CH_3	**6b/7b** 1.0 : 8.00	2.5	88
3.	X = OCH_3	**6c/7c** 1.0 : 13.32	2.5	85

Scheme 3. Case study of regioselectvity in the synthesis of furan verses pyran

When the same regioselective study was performed with dione **4** and propargylic alcohols **9a, 9b** and **9c** (Table 4) it is still evidenced the same observation. But in this case we observed the furans as the major isomers and the selectivity is very high over the pyrans. For example the ratios of furan/pyran for **8a, 8b, 8c** & **8d** are 1/0.06, 1/0.05, 1/0.04 & 1/0.03 respectively. Nevertheless this observation still supports our conceptualization (Figure 2), probably aromatic and non-aromatic nature of nucleophilic enols (4-hydroxycoumarin and cyclohexane 1,3- dione) could be deciding the ratios.

Table 4. 1,3-diphenylprop-2-yn-1-ol and its derivatives in the regioselective synthesis of benzofurans





8a 2.3 h, 90%
8b 3 h, 86%
8c 2.5 h, 90%
8d 3.5 h, 91%

Conclusions

In summary, we are successful in developing a one-pot cascade synthesis of fully functionalized furans under solvent free conditions using eco-friendly & highly abundant calcium catalyst. Step economy & atom economy of the methodology are delineated as the advantages compared to the two-step syntheses reported earlier. Regioselectivity, substrate scope and high yields are proved this methodology as one of the remarkable in the furans synthesis. Application this strategy for the synthesis of novel related heterocyclics is currently under progress in our laboratory.

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11 **General experimental procedure for the Ca(II)-catalysed synthesis of fully substituted furans:** Suitable propargylic alcohol (1mmol) and 4-hydroxycoumarin (1.1 mmol) were heated at 120 ^{o}C in presence of $Ca(OTf)_2$ (10 mol%) and $^{n}Bu_4NPF_6$. After completion (reaction progress was monitored by TLC), reaction mixture was brought to room temperature diluted with water and extracted into ethyl acetate thrice. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Finally the crude mass was purified through column chromatography using petroleum ether and ethyl acetate as the eluents to obtain the desired furan 3 & 5. Spectral data of selected compounds: **Ethyl 2-(4-oxo-3-(p-tolyl)-4*H*-furo[3,2-*c*]chromene-2-yl)acetate (3b):** Brown solid, m.p. 107 ^{o}C, 66.4 mg, 80% yield, (eluent: Petroleum ether: EtOAc 88:12); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8 Hz, 1H), 7.52-7.50 (m, 1H), 7.46-7.43 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8 Hz, 2H), 4.26 (q, *J* = 7.25 Hz, 2H), 3.87 (s, 2H), 2.43 (s, 3H), 1.32 (t, *J* = 7.25 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 157.6, 157.1, 152.5, 147.1, 138.2, 130.7, 129.6, 129.1, 126.2, 124.4, 123.4, 120.9, 117.1, 112.6, 109.6, 61.7, 32.9, 21.3, 14.2 ppm; HRMS (ESI) *m/z* calcd. for $C_{22}H_{19}O_6$ $[M + H]^+$ 379.1176; found 379.1194; **Ethyl 2-(3-(4-methoxyphenyl)-4-oxo-4*H*-furo[3,2-*c*]chromene-2-yl)acetate (3c):** Yellow solid, m.p. 109.2 ºC, 67.6 mg, 83 % yield, (eluent: Petroleum ether: EtOAc 88:12); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (dd, *J* = 7.5 Hz, *J* = 7.5 Hz, 1H), 7.53-7.44 (m, 4H), 7.37-7.34 (m, 1H), 7.03-7.01 (m, 2H), 4.26 (q, *J* = 7 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 2H), 1.32 (t, *J* = 7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 159.6, 157.1, 152.5, 146.9, 131.0, 130.7, 124.4, 123.2, 121.3, 120.9, 117.1, 113.9, 112.7, 109.6, 61.7, 55.3, 32.9, 14.2 ppm; HRMS (ESI) *m/z* calcd. for $C_{22}H_{18}NaO_5$ $[M + Na]^+$ 385.1046; found 385.1062; **Ethyl 2-(3-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl) acetate (5c):** Yellow liquid, 72.5 mg, 89% yield; (eluent: Petroleum ether: EtOAc 80:20); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 169.4, 165.8, 159.0, 144.5, 130.9, 123.0, 121.7, 118.5, 113.5, 61.4, 55.2, 52.9, 37.6, 34.8, 32.5, 28.6, 14.1 ppm; HRMS (ESI) *m/z* calcd. for $C_{21}H_{24}O_5$ $[M + H]^+$ 365.1364; found 365.1348; **Ethyl 2-(3-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)acetate (5k):** Brown liquid, 51.6 mg, 73 % yield; (eluent: Petroleum ether: EtOAc 80:20); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 9 Hz, 2H), 6.92 (d, *J* = 9 Hz, 2H), 4.20 (q, *J* = 7.25 Hz, 2H), 3.83(s, 3H), 3.63 (s, 2H), 2.91 (t, *J* = 6 Hz, 2H), 2.49 (t, *J* = 7 Hz, 2H), 2.19 (t, *J* = 6.5 Hz, 2H), 1.29-1.25 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.0, 169.5, 166.6, 159.0, 144.2, 130.8, 123.1, 121.9, 119.7, 113.5, 61.4, 55.2, 38.6, 32.4, 23.7, 22.4, 14.1 ppm; HRMS (ESI) *m/z* calcd. for $C_{19}H_{20}NaO_5$ $[M + Na]^+$ 351.1208; found 351.1262.

12 We thank one of the reviewers for suggesting to make this example.

13 The isomeric ratio was taken based on ^{1}H NMR recorded for the crude reaction mixture.