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Critical ligand and salt effects in organomagnesiate-promoted 3,3′-disubstituted phthalides synthesis from 2-iodobenzoate derivatives

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Abstract: Phthalides, also called isobenzofuranones, are widespread in many biologically active compounds and natural products. To date, most of their synthetic routes are non-convergent. Herein we report a convergent route using a metal halogen exchange (MHE) strategy. Indeed MHE of easily available 2-iodobenzoate derivatives, using the bimetallic organomagnesiate complex (*rac*)-(BIPHEN)BuMgLi, where (*rac*)-BIPHEN is (*rac*)-5,5',6,6'-tetramethyl-3,3'-di-*t*-butyl-1,1'-biphenyl-2,2'-diol, followed by addition of a ketone which lead to an intramolecular cyclisation, and the formation of a series of diverse 3,3'-disubstituted isobenzofuranones in good yield. Among the several MHE agents investigated, (*rac*)-(BIPHEN)BuMgLi was the only one to make such a process possible with full tolerance of various reactive functional substituents useful for subsequent transformations. The synthetic pathway to access the magnesiate has been found to play a prominent role in its reactivity. Therefore, the bimetallic magnesiate complex has been characterized by solution-state ^{1}H, ^{7}Li and ^{1}H DOSY NMR experiments.

Introduction

Phthalides are prevalent in biologically active compounds and natural products.[1–5] In addition, these heterocycles can serve as versatile building blocks for the synthesis of natural and pharmaceutically-important products. Indeed, many patents deal with the syntheses and biological activity of these compounds. Among them, 3,3′-disubstituted phthalides have demonstrated the broad applicability in medicinal chemistry as anti-HIV[6–8] and anticancer agents,[9] protein kinase C modulators[10] or cytosolic phospholipase $A_2\alpha$ inhibitor[11] (Figure 1). They can also have an influence on the innate immune system[12] or as vasodilators.[13]

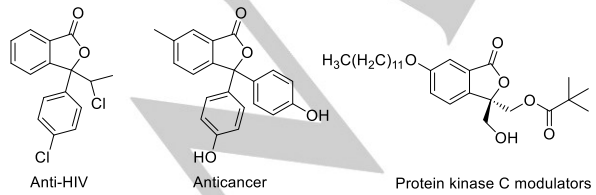
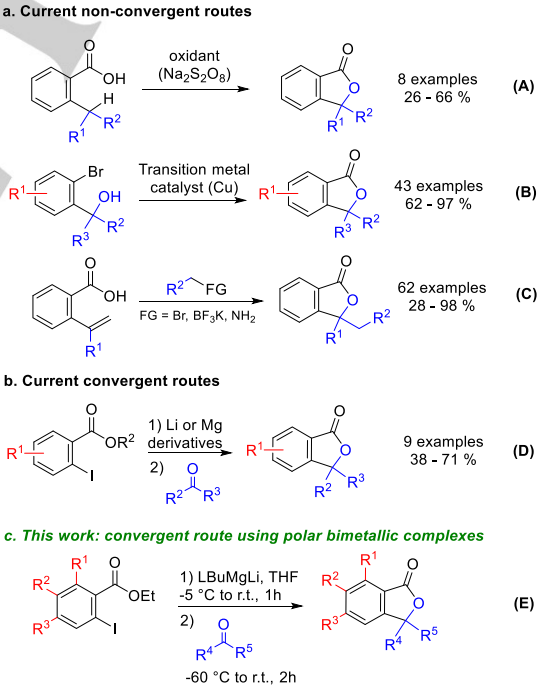


Figure 1. Bioactive 3,3'-disubstituted Isobenzofuranones.

Given their important bioactivities, efforts have been dedicated to the development of new methodologies to prepare 3,3′-disubstituted phthalide derivatives. Many of these methods are non-convergent synthetic routes and rely on intramolecular cyclization, requiring relatively complex syntheses of the starting materials in order to bring diversity to the final phthalides. For instance, as shown in Scheme 1, the first route involved *ortho*-alkyl benzoic acids followed by oxidation of the alkyl chain and ring closing (Scheme 1A[14]).[15–17] The second was a copper-catalyzed cyclization of *ortho*-bromo-benzylalcohols (Scheme 1B).[18] The third methodology used *ortho*-carboxy styrene as starting material (Scheme 1C) *via* a copper-catalyzed reaction involving bromo-derivatives[19] or organotrifluoroborates[20] as coupling partner or *via* an arylation-lactonization sequence involving primary amines.[21]



Scheme 1. Routes to access 3,3-disubstituted Isobenzofuranones.

Convergent routes have also been reported; however, unlike the non-convergent strategies, generally a lower level of chemical diversity is possible. These involve metal halogen exchange (MHE) of easily available 2-iodobenzoates followed by addition of a few ketones from the pool and intramolecular addition of the transiently formed alkoxide to the ester function (Scheme 1D).[22,23] However, these reactions suffer from limitations

regarding the starting materials and carbonyl electrophiles. Indeed, in case of the use of a lithium derivative,[22] the ester itself had to be sterically hindered enough to avoid nucleophilic attack prior to the cyclization process. Due to the basicity of the organometallic intermediates, these reactions were generally restricted to the use of non-enolizable ketones.[23]

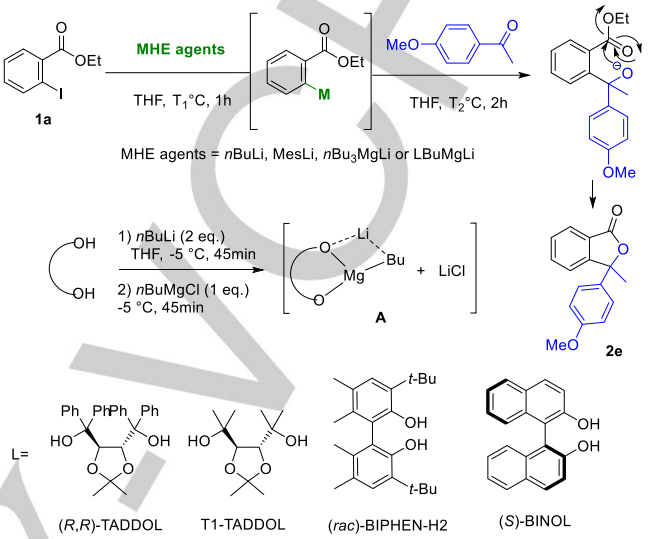
Thus, it appears that a convergent strategy allowing a general access to various 3,3′-disubstituted phthalides is not yet available (Scheme 1E). Our group has shown that the incorporation of an anionic dialkoxide ligand within a lithium magnesiate conferred interesting properties to the metalation agent and formed intermediates with an increased chemoselectivity and reactivity towards electrophiles. Subsequently, this gave rise to the possibility of performing the syntheses of enantioselective secondary alcohols using chiral ligands.[24–26] More recently, we reported that the bimetallic (*S*)-(BIPHEN)BuMgLi reagent promoted the chemo- and enantioselective magnesiation-lactonization of 2-iodo-ethylbenzoate leading to a panel of chiral 3-substituted isobenzofuranones with a good level of enantioselectivity. Among the carbonyl electrophiles used, it was interesting to note that enolizable aldehydes reacted efficiently.[27]

Herein we report our investigation on the synthesis of 3,3′-disubstituted phthalides from enolizable ketones using organomagnesiates bearing dialkoxides ligands. We showed that the homoleptic alkyl bimetallic complex nBu$_3$MgLi is inefficient in such a reaction; however, when the heteroleptic (*rac*)-(BIPHEN)BuMgLi was employed a wide set of 3,3′-disubstituted isobenzofuranones were formed in good yields.

Results and Discussion

In this work, we investigated the magnesiation-lactonization process for the synthesis of 3,3′-disubstituted isobenzofuranones, employing heteroleptic lithium magnesiates. In our first reaction, we studied the reactivity of 2-ethyliodobenzoate and the enolizable *p*-methoxyacetophenone and several potential MHE agents in the presence or absence of dialkoxy/diphenoxy ligands (Scheme 2). The reaction conditions and results are reported in Table 1.

No matter which MHE agent or conditions were employed, the iodine-metal exchange reaction proceeded quantitively as confirmed by TLC monitoring. In contrast, noticeable differences were found regarding the second step of the reaction where the arylorganometallic intermediate reacts with the ketone. In the case of *n*BuLi and 2,4,6-trimethylphenyllithium (MesLi) (Entry 1 and 2 – Table 1), no formation of lactone was observed; instead a complex mixture of degradation products was obtained, including ethyl 2-benzoylbenzoate resulting from the self-reaction of the arylorganometallic intermediate (see SI 1.a.). The reaction also failed when using the homoleptic nBu$_3$MgLi reagent under Oshima's conditions at −78°C (Entry 3 - Table 1)[27] leading to mainly the formation of ethylbenzoate as a result of protonation of the unreacted aryl magnesiate after aqueous work-up. Addition of a *n*-butyl moiety from the aryl magnesiate intermediate was also observed leading to the formation of 1-phenylpentan-1-one (see SI 1.b.). Suspecting an insufficient nucleophilicity of the intermediate aryl magnesiate under cryogenic conditions, the reaction was then attempted at room temperature (Entry 4 - Table 1) resulting unfortunately only in the formation of degradation products. These first experiments revealed a lack of reactivity of the intermediate arylorganometallic species towards the ketone and a non-tolerance of the ester functionality.



Scheme 2. Study of the magnesation-lactonization reaction and preparation of reagents containing alkoxide.

Table 1. Screening of MHEA in the magnesation-lactonization process.[a]

Entry	MHEA (eq.)	T$_1$°C[b]	T$_1$°C	**2e** %[c]
1	*n*BuLi (1)	-78	-78[d]	0
2	MesLi (1)	-78	-78[e]	0
3	nBu$_3$MgLi (1.2)[g]	-78	-78[f]	0
4	nBu$_3$MgLi (1.2)[g]	-10 to r.t.	-60 to r.t. [f]	0
5	(*rac*)-(BIPHEN)BuMgLi (2)	-10 to r.t.	-60[d]	0
6	(*rac*)-(BIPHEN)BuMgLi (2)	-10 to r.t.	-40[d]	7
7	(*rac*)-(BIPHEN)BuMgLi (2)	-10 to r.t.	-20[d]	10
8	(*rac*)-(BIPHEN)BuMgLi (2)	-10 to r.t.	-60 to r.t. [d]	75
9	(*R,R*)-(TADDOL)BuMgLi (2)	-10 to r.t.	-60 to r.t. [d]	0
10	T1-(TADDOL)BuMgLi (2)	-10 to r.t.	-60 to r.t. [d]	0
11	(*S*)-(BINOL)BuMgLi (2)	-10 to r.t.	-60 to r.t. [d]	0

[a] Reactions performed on 0.5 mmol of **1a**. [b] Iodine-metal exchange was complete in every case. [c] Isolated yield. The amounts of ketone were as follows: [d] 2 eq., [e] 1.5 eq., [f] 3 eq.. [g] Synthesized from 2 eq. of *n*BuLi and 1 eq. of *n*BuMgCl at -10 °C.

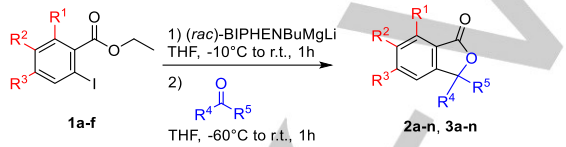
We then considered the introduction of alkoxide ligands, which were expected to favor the release of the aromatic intermediate via a modification of the metal coordination sphere and to have a better tolerance of sensitive functional groups. Thus, we examined the reactivity of magnesiate complex LBuMgLi **A** [L =

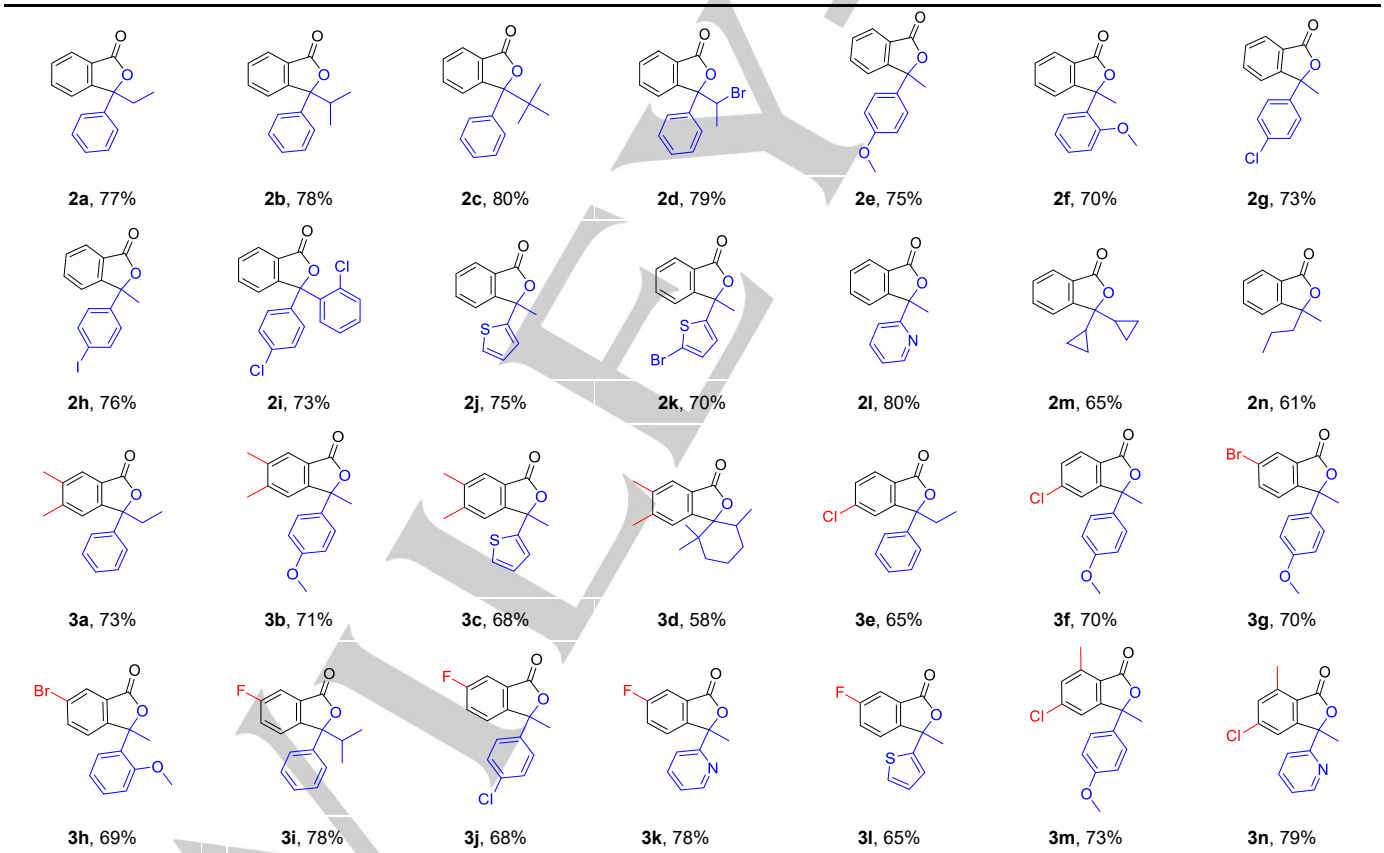
(*rac*)-BIPHEN, (*R,R*)-TADDOL, T1-TADDOL or (*S*)-BINOL] reagents. The reagents were obtained by reacting the doubly lithiated dialkoxide with *n*BuMgCl (Scheme 2).

From previous works, it has been reported that the iodine-magnesium exchange required two equivalents of magnesiate complex LBuMgLi **A** for its completion. This was explained by the reaction of one equivalent of LBuMgLi **A** with the reactive iodobutane formed during the exchange process leading to the formation of a molecule of octane.[28] Indeed, we showed that one equivalent of aldehyde (relative to ethyl-2-iodobenzoate) was found sufficient to trap the intermediate arylmagnesiate quantitatively. This is only possible in the absence of free butyl magnesiate after the metal-halogen exchange step. Applying such a stoichiometry (1:2 ethyl-2-iodobenzoate:LBuMgLi **A**), we were pleased to see that the introduction of the (*rac*)-BIPHEN ligand produced the target lactone **2e** in 75 % isolated yield when used at room temperature (Entry 8 – Table 1). However, attempts to decrease the temperature of the ketone quenching step (Entries 5-7 – Table 1) dramatically reduced the reaction yield showing that magnesiate can be easily used in non-cryogenic conditions. Other dialkoxide type ligands were also investigated (Entries 9-11 – Table 1) but these led to mainly ethylbenzoate after the work-up instead of **2e** signifying an insufficient nucleophilicity of the aryl magnesiate towards the ketone.

Encouraged by the excellent chemoselectivity and efficiency of (*rac*)-(BIPHEN)BuMgLi (**A1**) as a MHE agent, we next examined the scope of the magnesiation-lactonization process with several iodobenzoates derivatives and enolizable ketones (Table 2).

Table 2. Scope of the magnesiation-lactonization from **1a-f:** Synthesis of unsymmetrical 3,3'-disubstituted phthalides[a]





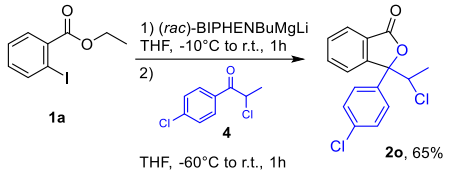
[a] *Reaction conditions*: ethyl-2-iodobenzoate derivatives (0.25 mmol, 0.5 equiv), ketone (0.8 equiv), (*rac*)-(BIPHEN)BuMgLi **A1** (1 equiv), THF (3.5 mL).

As shown in Table 2, the expected lactones **2a-n** and **3a-n** were obtained in good to excellent yields. The reaction proceeded smoothly with aromatic, heteroaromatic and aliphatic ketones most of the latter being enolizable. In particular, the lactone **2n** was obtained in a 61 % yield from the highly enolizable aliphatic 2-pentanone. This indicated a high nucleophilicity versus basicity of the organometallic aryl intermediate. Moreover, various reactive functional substituents, which may be useful for subsequent transformations, were tolerated either on ethyl-2-iodobenzoate derivatives **1** or ketones. This included the sensitive C-bromine bond in **2d**, **2k**, **3g** and **3h** and C-iodine bound in **2h**. Reactive heterocycles as the electrophilic pyridine

(**2l**, **3n**, **3k**) and thiophene (**2j**, **2k**, **3c**, **3l**) nucleus were also well tolerated. Table 2 also illustrates the diversity of the benzoates employed in the reactions. Electron-withdrawing and electron-donating groups were tolerated with no influence on the reactivity of the organometallic aryl intermediate.

Moreover, C-halogen bonds were also tolerated including the C-Br one (**3g-h**) demonstrating the chemoselectivity of (*rac*)-(BIPHEN)BuMgLi (**A1**) towards iodinated substrates and allowing further transformation of the lactone. Interestingly, a wide range of fluorine-containing lactones (**3i-l**) have been obtained in good yields which could be useful from the biological point of view for structure-activity relationship studies when molecular design requires strong electron-withdrawing effects without affecting the steric hindrance in the compound. A spiro lactone (**3d**) was also obtained in moderate yield (58 %) from the enolizable 2,2,6-trimethylcyclohexanone.

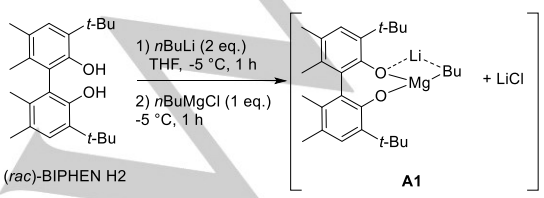
This methodology was successfully applied to the synthesis of an anti-HIV molecule **2o**[6] (Figure 1) with 65 % yield using commercially available **1a** and enolizable chloro-ketone **4** easily synthesized in one step by α-chlorination[29] of the commercially available 4'-chloropropiophenone with 82 % yield. Our methodology allows the synthesis of **2o** with a better yield than that described in the literature (45 %) which uses chlorolactonisation reaction of a non-commercial styrene-type carboxylic acid in the presence of DABCO (1,4-diazabicyclo[2,2,2]octane).[6]



Scheme 3. Preparation of an anti-HIV molecule **2o**.

From this study, we were able to show that (*rac*)-(BIPHEN)BuMgLi **A1** was the best choice for performing the magnesiation-lactonization reactions.

As structure is inextricably linked to reactivity, the solution-state structure of the magnesiate complex (*rac*)-(BIPHEN)BuMgLi **A1** was investigated by ^{1}H, ^{7}Li and ^{1}H DOSY NMR spectroscopy in d_8-THF. For that, magnesiate complex was prepared as usual (Scheme 4), then solvents were removed under vacuum and the residue was dissolved in d_8-THF.



Scheme 4. Preparation of the magnesiate complex **A1** from 1 equiv. of (*rac*)-BIPHEN + 2 equiv. *n*BuLi + 1 equiv. *n*BuMgCl).

The formation of the magnesiate complex **A1**, described in Scheme 4, was clearly evidenced by solution ^{1}H and ^{7}Li NMR spectroscopy which were in agreement with previously reported data (Figure 2 and supporting information).[30] Indeed, the magnesiate complex **A1** showed two distinct singlets for aromatic protons of the ligand at 6.82 and 6.79 ppm, indicating two non-equivalent phenyl rings as expected (*i.e.*, one phenolic ring bridges between a Li and Mg center, while the other is terminally bound to only Mg). The hydrogen atoms on the carbon at α to the magnesium center (CH_2Mg), appear upfield as two multiplets at −0.77 and −0.98 ppm, displaying the diastereotopic nature of these protons.

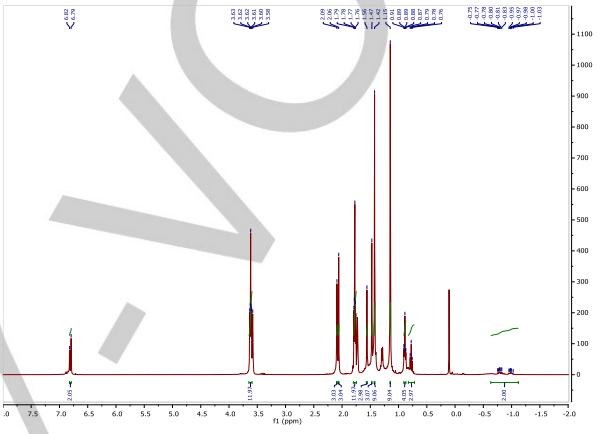
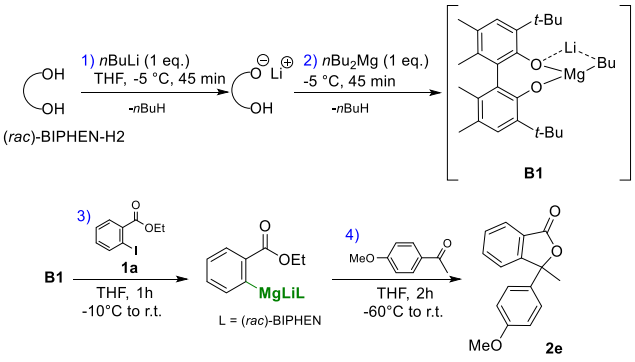


Figure 2. ^{1}H NMR spectrum (in d_8-THF) of magnesiate complex **A1** from 1 equiv. of (*rac*)-BIPHEN + 2 equiv. *n*BuLi + 1 equiv. *n*BuMgCl.

As shown in Scheme 4, the magnesiate synthetic route formally releases a molecule of LiCl. LiCl is well known to coordinate to organometallic species and often plays a pivotal role in the reactivity of these reagents. As such it is frequently not an innocent bystander.[31–37] In our case, it could be envisaged a direct association of a LiCl molecule to the magnesiate to yield a higher order species or its presence as a solvated $Li^{+}(THF)_xCl^{-}$ species. In an attempt to ascertain the solution behavior, we prepared the magnesiate complex (*rac*)-(BIPHEN)BuMgLi via a LiCl free route (Scheme 5 – **B1**) and then involved it in a metal-halogen-exchange reaction with substrate **1a**.



Scheme 5. Study of the magnesiation-lactonization reaction while using magnesiate complex **B1** from 1 equiv. of (*rac*)-BIPHEN + 1 equiv. *n*BuLi + 1 equiv. *n*Bu$_2$Mg.

However, under these conditions, MHE didn't occur at all and **1a** was fully recovered. In an attempt to understand this phenomenon, LiCl (as LiCl 0.5M in THF) has been added to the reaction at different stage: firstly, immediately after the addition of *n*BuLi (stage 1 - scheme 5); secondly, after *n*Bu_2Mg (stage 2 - scheme 5) or thirdly, after **1a** (stage 3 - scheme 5). Unfortunately, no MHE has been observed under any of those conditions.

Control reactions have been performed using optimized conditions previously determined (Table 1 – Entry 8). Firstly, 1 equivalent of LiCl has been added to the reaction mixture and no influence on the reaction was observed, lactone **2a** was obtained as previously. Secondly, because *n*Bu_2Mg is in heptane while *n*BuMgCl is in THF, heptane has been added and again no influence on the reaction was observed.

Collectively these data suggest that the route to synthesize the magnesiate is crucial and that LiCl is probably part of the magnesiate complex and has to come with the magnesium species (ie *n*BuMgCl).

In order to support this structural assumption ^{1}H DOSY NMR spectroscopy in d_8-THF has been performed on the magnesiate complex (*rac*)-(BIPHEN)BuMgLi **A1** (Figure 4).

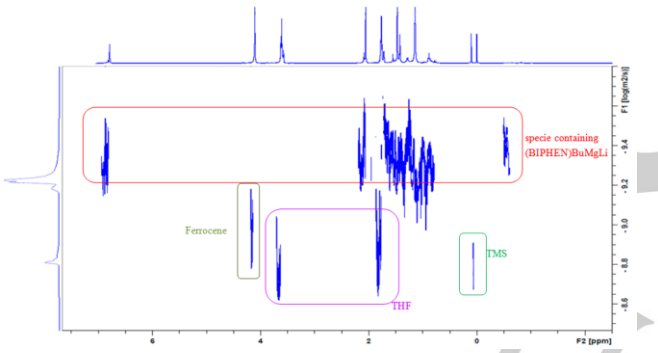


Figure 4. ^{1}H DOSY NMR spectrum of magnesiate complex **A1** and the standards tetramethylsilane (TMS) and ferrocene in d_8-THF at 25 °C.

This study suggested that the molecular weight for the species that contains the (*rac*)-(BIPHEN)BuMgLi is approximately 665 g mol^{-1} (External Calibration Curve ECC^{DSE} was used to determine molecular weight of the magnesiate complex in d_8-THF, the accuracy of the ECC^{DSE} is in the range ≤ ±9%) (see supporting information).[38,39]

Table 3. ECC^{DSE} was used to determine molecular weight of magnesiate complex in d_8-THF, the accuracy of the ECC^{DSE} is in the range ≤ ±9 %[38,39]

Complexes possibilities	Complex + 1 THF	Complex + 2 THF	Complex + 3 THF	Complex + 4 THF
MW_{det} (g.mol^{-1})	MW_{dif} (%)	MW_{dif} (%)	MW_{dif} (%)	MW_{dif} (%)
BiphenBuMgLi 440.88	-23	-12	-1	10
BiphenBuMgLi$_2$Cl 483.27	-16	-6	5	16

The molecular weight for a THF-free and LiCl-free framework should be 441 g mol^{-1} and for a THF-free with LiCl framework, 483 g mol^{-1}. Thus, it turns out that three complexes were possible: i) (BIPHEN)BuMgLi + 3 THF, ii) (BIPHEN)BuMgLi$_2$Cl + 2 THF or iii) (BIPHEN)BuMgLi$_2$Cl + 3 THF (Table 3). Mulvey's team showed that three THF molecules are incorporated in the structure of the turbo-Hauser reagent (THF)$_2$Li(μ-Cl)$_2$Mg(THF)(TMP).[37] Combining those results (Table 3) with the LiCl study (Scheme 5), it is suggested that two or three molecules of THF are coordinated to the magnesiate complex (*rac*)-(BIPHEN)BuMgLi plus one molecule of LiCl. So the DOSY data on its own does not allow us to conclude whether or not LiCl is associated to the magnesiate complex. However, coupled with the LiCl experiment described above (scheme 5) it can be tentatively suggested that LiCl is involved in the magnesiate suggesting an active species of the structure (*rac*)-(BIPHEN)BuMgLi(THF)$_x$ Li$^+$Cl$^-$.

Conclusion

In summary, a wide range of new functional 3,3′-disubstituted isobenzofuranones has been prepared in good yield applying a straightforward strategy using the magnesiate complex (*rac*)-(BIPHEN)BuMgLi (**A1**). Moreover various reactive functional substituents were tolerated which may be useful for subsequent transformations and allowed the preparation of a known biological active molecule, anti-HIV, **2o**. It is worthy of note that the BIPHEN-H2 was recovered safely after the reaction, recrystallized and reused with success. Studies of the synthetic pathway and salt effect on the magnesiate complex **A** as well as solution-state experiments (^{1}H, ^{7}Li and ^{1}H DOSY NMR in d_8-THF) suggest an active species of the structure (*rac*)-(BIPHEN)BuMgLi(THF)$_x$Li$^+$Cl$^-$ (with x = 2 or 3).

Experimental Section

General experimental methods: Tetrahydrofuran (THF) was dry and dispense using a MBRAUN Solvent Purification System (MB-SPS-800). All chemicals were used as received otherwise notice. *n*BuLi and *n*BuMgCl from sigma Aldrich were titrated prior to use with respectively Diphenylacetic acid or Diiode/Lithium chloride. All the NMR spectra were recorded on a Bruker Advance III 400. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded respectively at 400 MHz, 101 MHz and 376 MHz. ^{1}H and ^{13}C chemical shifts were reported in ppm and referenced to Me_4Si as internal reference. ^{19}F NMR chemical shifts were reported in ppm and referenced to external CFCl3 (0.0 ppm). Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d =doublet, t = triplet, q = quadruplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, m = multiplet,br = broad), coupling constant *J* (Hz) and integration. High-resolution mass spectra (HMRS) were recorded on a Bruker micrOTOF-Q spectrometer. Flash chromatography purifications were performed on a Grace Reveleris™ with Reveleris™ flash cartridges silica 40μM. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F254 plates. Preparative thin layer chromatography was performed on Merck Silica Gel 60 F254 Glass plates (layer

thickness 1 mm). Melting temperatures were recorded with a thermostatic oil bath device.

General procedure A for the synthesis of ethyl-2-iodobenzoates derivatives 1c-f: In a round-bottom flask under argon atmosphere, 2-iodobenzoic acid derivative (4 mmol, 1 eq.) was dissolved in DMF (10 mL) at r.t. Iodoethane (354 µL, 4.4 mmol, 1.1 eq.) and potassium carbonate (608 mg, 4.4 mmol, 1.1 eq.) was added dropwise and the mixture was stirred for 16 h r.t.. The reaction was diluted with addition of AcOEt (25 mL). The organic phase was washed with NH_4Cl (50 mL x 4) to remove the DMF, then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The desired ethyl-2-iodobenzoate derivatives was obtained pure and used without further purification.

General procedure B for the synthesis of 3,3-disubstituted-(3*H*)-isobenzofuran-1one 2a-o and 3a-n: In a flamed dried schlenk under argon atmosphere, (*rac*)-BIPHEN-H2 (177 mg, 0.50 mmol, 1 eq.) was dissolved in THF (3.5 mL) and cooled to -5°C. *n*-BuLi (1.0 mmol, 2 eq.) was added dropwise and the mixture was stirred for 45 min at -5°C. *n*-BuMgCl (0.50 mmol, 1eq.) was added dropwise and the mixture was stirred for 45 min at -5°C. Ethyl-2-iodobenzoate derivatives (0.25 mmol, 0.5 eq.) in 1 mL THF was added at -5°C and the resulting mixture was allowed to warn to RT and stir for 1h. The reaction was check by TLC to verify that metalation occurred and it's done. Then the reaction was cold down to -60°C and ketone (0.40 mmol, 0.8 eq.) in 1 mL THF was added slowly. The reaction mixture was allowed to warn to RT and stir for 2h. The reaction was quenched with addition of saturated NH_4Cl and AcOEt. The aqueous phase was extracted with AcOEt (10 mL x 3). Then acidified with HCl 0.4N (check with pH paper) and extracted one more time with AcOEt (10 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using silica cartridge to afford the desired product.

Ethyl-5-bromo-2-iodobenzoate (1b)[40]**:** Ethyl-5-bromo-2-iodobenzoate **1b** was prepared according to the literature method. To a stirred solution of ethyl-2-iodobenzoate (2g, 7.2 mmol, 1 eq.) and *N*-bromosuccinimide (1.5 g, 8.0 mmol, 1.1 eq.) in acetic acid (4 mL) was added concentrated H_2SO_4 (4 mL) dropwise while keeping the temperature at 20-40°C. The mixture was stirred at room temperature for 88 hours and then heated at 50°C for 4 hours. The mixture was cooled to 10°C then treated with 10 mL of ice water and extracted 2*15 mL of CH_2Cl_2. The combined organic phases were washed with 2*15 mL of 5% $NaHCO_3$, dried over $MgSO_4$ and concentrated under vacuum. The title compound was obtained after silica gel chromatography as a white solid. Yield 74% (1.90 g); R_f=0.71 (petroleum ether/EtOAc 90/10); m.p.: 41–43°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.83 (d, *J* = 2.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.33 (dd, *J* = 8.3, 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=165.2 (C), 142.6 (CH), 136.9 (C), 135.5 (CH), 133.8 (CH), 122.2 (C), 92.1 (C), 62.1 (CH_2), 14.2 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_9H_8BrIO_2Na$ $[M+Na]^+$: 376.8645 found 376.8632; Flash chromatography conditions: column 40 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 95/5.

Ethyl-4,5-dimethyl-2-iodobenzoate (1c): Compound **1c** was prepared according to the general procedure **A** using 4,5-dimethyl-2-iodobenzoic acid (1.10 g, 4 mmol). The title compound was obtained without purification as a yellow oil; yield 95% (1.16 g); R_f=0.58 (petroleum ether/EtOAc 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.75 (s, 1H), 7.59 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.23 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=166.4 (C), 142.3 (C), 142.1 (CH), 136.7 (C), 132.3 (C), 132.1 (CH), 90.7 (C), 61.4 (CH_2), 19.3 (2*CH_3), 14.3 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{11}H_{14}IO_2$ $[M+H]^+$: 305.0033 found 305.0012 and for $C_{11}H_{13}IO_2Na$ $[M+Na]^+$: 326.9852 found 326.9881.

Ethyl-4-chloro-2-iodobenzoate (1d): Compound **1d** was prepared according to the general procedure **A** using 4-chloro-2-iodobenzoic acid (1.12 g, 4 mmol). The title compound was obtained without purification as a yellow solid; yield 95% (1.22 g); R_f=0.58 (petroleum ether/EtOAc 90/10); m.p.: 28–29°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.98 (d, *J* = 2.1 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.37 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=165.6 (C), 140.8 (CH), 138.0 (C), 133.5 (C), 131.7 (CH), 128.2 (CH), 94.4 (C), 61.9 (CH_2), 14.2 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_9H_8ClIO_2Na$ $[M+Na]^+$: 332.9150 found 332.9113.

Ethyl-5-fluoro-2-iodobenzoate (1e): Compound **1e** was prepared according to the general procedure **A** using 5-fluoro-2-iodobenzoic acid (1.06 g, 4 mmol). The title compound was obtained without purification as a yellow oil. Yield 90% (1.06 g); R_f =0.80 (petroleum ether/EtOAc 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.02 – 7.82 (m, 1H), 7.65 – 7.43 (m, 1H), 6.99 – 6.85 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ=165.3 (d, J_{C-F} = 2.4 Hz) (C), 162.4 (d, J_{C-F} = 249.3 Hz) (C), 142.6 (d, J_{C-F} = 7.2 Hz) (CH), 136.9 (d, *J* = 7.0 Hz) (C), 120.1 (d, J_{C-F} = 21.5 Hz) (CH), 118.3 (d, J_{C-F} = 24.1 Hz) (CH), 87.0 (d, J_{C-F} = 3.6 Hz) (C), 62.1 (CH_2), 14.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ=-113.4; HRMS (ESI positive) *m/z* calcd. for $C_9H_9FIO_2$ $[M+H]^+$: 294.9626 found 294.9608 and for $C_9H_8FIO_2Na$ $[M+Na]^+$: 316.9445 found 316.9410.

Ethyl-4-chloro-2-iodo-6-methylbenzoate (1f): Compound **1f** was prepared according to the general procedure **A** using 4-chloro-2-iodo-6-methylbenzoic acid (0.99 g, 3.7 mmol). The title compound was obtained after flash chromatography as a yellow oil; yield 95% (1.22 g); R_f=0.60 (petroleum ether/EtOAc 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.66 (s, 1H), 7.18 (s, 1H), 4.45 – 4.39 (m, 2H), 2.32 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=168.4 (C), 138.8 (C), 137.8 (C), 135.9 (CH), 135.3 (C), 129.9 (CH), 91.9 (C), 62.0 (CH_2), 19.9 (CH_3), 14.1 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{10}H_{11}ClIO_2$ $[M+H]^+$: 324.9487 found 324.9507 and for $C_{10}H_{10}ClIO_2Na$ $[M+Na]^+$: 346.9306 found 346.9274; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-Ethyl-3-phenyl-(3H)-isobenzofuran-1-one (2a): Compound **2a** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and propiophenone (54 mg, 0.40 mmol). The title compound was obtained after flash

chromatography as yellow oil; yield 77% (46 mg); R_f=0.23 (petroleum ether/EtOAc 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.92 (d, *J* = 7.5 Hz, 1H), 7.68 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 7.56 – 7.51 (m, 4H), 7.39 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.33 (dd, *J* = 7.2, 7.2 Hz, 1H), 2.53 (dq, *J* = 14.6, 7.3 Hz, 1H), 2.29 (dq, *J* = 14.6, 7.3 Hz, 1H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=170.2 (C), 152.7 (C), 140.4 (C), 134.2 (CH), 129.1 (CH), 128.7 (2*CH), 128.1 (CH), 125.8 (CH), 125.7 (C), 125.0 (2*CH), 122.1 (CH), 90.5 (C), 33.3 (CH_2), 8.1 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{16}H_{15}O_2$ $[M+H]^+$: 239.1067 found 239.1118 and for $C_{16}H_{14}O_2Na$ $[M+Na]^+$: 261.0886 found 261.0942; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-Isopropyl-3-phenyl-(3H)-isobenzofuran-1-one (2b): Compound **2b** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and isobutyrophenone (56 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow oil; yield 78% (49 mg); R_f=0.21 (petroleum ether/EtOAc 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.86 (d, *J* = 7.6 Hz, 1H), 7.68 – 7.55 (m, 4H), 7.48 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H), 7.36 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 2.77 (p, *J* = 6.8 Hz, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=170.4 (C), 152.7 (C), 140.7 (C), 134.2 (CH), 128.9 (CH), 128.7 (2*CH), 127.8 (CH), 125.8 (CH), 125.6 (C), 124.8 (2*CH), 122.1 (CH), 92.8 (C), 36.9 (CH), 17.4 (CH_3), 16.4 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{17}H_{17}O_2$ $[M+H]^+$: 253.1223 found 253.1269; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-(tert-Butyl)-3-phenyl-(3H)-isobenzofuran-1-one (2c): Compound **2c** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 2,2-dimethylpropiophenone (65 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow oil; yield 80% (53 mg); R_f=0.55 (cyclohexane/EtOAc 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.91 (ddd, *J* = 7.9, 0.8, 0.8 Hz, 1H), 7.80 (ddd, *J* = 7.6, 1.2, 0.8 Hz, 1H), 7.67 – 7.62 (m, 3H), 7.45 (ddd, *J* = 7.5, 7.5, 0.8 Hz, 1H), 7.30 – 7.19 (m, 3H), 0.94 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.9 (C), 151.4 (C), 138.2 (C), 133.7 (CH), 129.2 (CH), 127.8 (CH), 127.7 (2*CH+C), 127.7 (2*CH+C), 126.1 (CH), 124.4 (CH), 94.7 (C), 25.7 (3*CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{18}H_{19}O_2$ $[M+H]^+$: 267.1380 found 267.1365 and for $C_{18}H_{18}O_2Na$ $[M+Na]^+$: 289.1199 found 289.1187; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-(1-Bromo)ethyl-3-phenyl-(3H)-isobenzofuran-1-one (2d): Compound **2d** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 2-bromopropiophenone (85 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow oil; yield 79% (62 mg); R_f=0.28 (cyclohexane/EtOAc 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.86 (d, *J* = 7.6 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.58 – 7.49 (m, 3H), 7.36 – 7.27 (m, 3H), 7.19 (s, 1H), 4.81 (q, *J* = 6.9 Hz, 1H), 1.52 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=168.9 (C), 149.0 (C), 138.1 (C), 134.1 (CH), 130.0 (CH), 128.8 (CH), 128.8 (2*CH), 126.8 (C), 126.3 (CH), 125.6 (2*CH), 123.1 (CH), 90.5 (C), 52.7 (CH), 20.6 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{16}H_{13}BrO_2Na$ $[M+Na]^+$: 339.9991 found 338.9969; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-(4-Methoxyphenyl)-3-methyl-(3H)-isobenzofuran-1-one (2e): Compound **2e** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 4'-methoxyacetophenone (60 mg, 0.40 mmol). The title compound was obtained after flash chromatography as colorless oil; yield 75% (48 mg); R_f=0.19 (petroleum ether/EtOAc 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.91 (ddd, *J* = 7.6, 0.9, 0.9 Hz, 1H), 7.65 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H), 7.52 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 7.42 (ddd, *J* = 7.7, 0.8, 0.8 Hz, 1H), 7.33 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=170.0 (C), 159.6 (C), 154.4 (C), 134.2 (CH), 132.6 (C), 129.0 (CH), 126.7 (2*CH), 125.9 (CH), 125.2 (C), 122.0 (CH), 114.0 (2*CH), 87.6 (C), 55.3 (CH_3), 29.7 (CH_3); HRMS (ESI positive) *m/z* calcd. for $C_{16}H_{15}O_3$ $[M+H]^+$: 255.1016 found 255.1054 and for $C_{16}H_{14}O_3Na$ $[M+Na]^+$: 277.0835 found 277.0859; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-(2-Methoxyphenyl)-3-methyl-(3H)-isobenzofuran-1-one (2f): Compound **2f** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 2'-methoxyacetophenone (60 mg, 0.40 mmol). The title compound was obtained after flash chromatography as white solid; yield 70% (43 mg); R_f=0.17 (petroleum ether/EtOAc 90/10); m.p.: 136 – 138°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.90 (d, *J* = 7.6 Hz, 1H), 7.62 – 7.55 (m, 3H), 7.51 – 7.47 (m, 1H), 7.35 – 7.30 (m, 1H), 6.98 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 3.73 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=170.5 (C), 157.2 (C), 154.8 (C), 133.8 (CH), 130.1 (CH), 128.7 (CH), 128.3 (C), 126.8 (CH), 126.0 (C), 125.2 (CH), 122.1 (CH), 120.6 (CH), 112.1 (CH), 87.2 (C), 55.3 (CH_3), 26.4 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{16}H_{15}O_3$ $[M+H]^+$: 255.1016 found 255.1019 and for $C_{16}H_{14}O_3Na$ $[M+Na]^+$: 277.0835 found 277.0835; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-(4-Chlorophenyl)-3-methyl-(3H)-isobenzofuran-1-one (2g): Compound **2g** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 4'-chloroacetophenone (62 mg, 0.40 mmol). The title compound was obtained after flash chromatography as colorless oil; yield 73% (47 mg); R_f=0.20 (cyclohexane/EtOAc 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.93 (ddd, *J* = 7.6, 0.9, 0.9 Hz, 1H), 7.69 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 7.56 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 7.46 (ddd, *J* = 7.7, 0.8, 0.8 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.6 (C), 153.7 (C), 139.3 (C), 134.5 (CH), 134.4 (C), 129.3 (CH), 128.9 129.3 (2*CH), 126.6 (2*CH), 126.0 (CH), 125.0 (C), 121.9 (CH), 87.0 (C), 27.3 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{15}H_{12}ClO_2$ $[M+H]^+$: 259.0520 found 259.0536 and for $C_{15}H_{11}ClO_2Na$ $[M+Na]^+$: 281.0340 found 281.0442; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-(4-Iodophenyl)-3-methyl-(3H)-isobenzofuran-1-one (2h): Compound **2h** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 4'-

iodoacetophenone (98 mg, 0.40 mmol). The title compound was obtained after flash chromatography as colorless oil; yield 76% (67 mg); R_f=0.33 (cyclohexane/EtOAc 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.91 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.65 (m, 3H), 7.53 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 2.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.6 (C), 153.6 (C), 140.6 (C), 137.8 (2*CH), 134.5 (CH), 129.4 (CH), 127.0 (2*CH), 126.0 (CH), 125.0 (C), 121.9 (CH), 94.2 (C), 87.0 (C), 27.2 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{15}H_{12}IO_2$ $[M+H]^+$: 350.9877 found 350.9856 and for $C_{15}H_{11}IO_2Na$ $[M+Na]^+$: 372.9696 found 372.9773; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-(2-Chlorophenyl)-3-(4-chlorophenyl)-(3H)-isobenzofuran-1-one (2i): Compound **2i** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 2,4'-dichlorobenzophenone (100 mg, 0.40 mmol). The title compound was obtained after flash chromatography as colorless oil; yield 73% (65 mg); R_f=0.36 (cyclohexane/EtOAc 80/20) and 0.53 (toluene/EtOAc 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.96 (d, *J* = 7.6 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.36 – 7.28 (m, 4H), 7.24 – 7.19 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.4 (C), 151.0 (C), 139.2 (C), 136.8 (C), 134.4 (C), 134.3 (CH+C), 132.4 (CH), 130.6 (CH), 129.8 (CH), 129.3 (CH), 128.9 (2*CH), 127.2 (2*CH), 126.6 (CH), 126.4 (CH), 125.6 (C), 124.7 (CH), 90.7 (C); HRMS (ESI positive): *m/z* calcd. for $C_{20}H_{12}Cl_2O_2Na$ $[M+Na]^+$: 377.0107 found 377.0210 and for $C_{20}H_{12}Cl_2O_2K$ $[M+K]^+$: 392.9846 found 392.9852; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10; Then preparative TLC toluene / EtOAc 95/5.

3-Methyl-3-(thiophen-2-yl)-(3H)-isobenzofuran-1-one (2j): Compound **2j** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 2-acetylthiophene (51 mg, 0.40 mmol). The title compound was obtained after flash chromatography as brown oil; yield 75% (43 mg); R_f=0.30 (cyclohexane/EtOAc 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.92 (d, *J* = 7.6 Hz, 1H), 7.70 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 5.0 Hz, 1H), 7.00 (d, *J* = 3.6 Hz, 1H), 6.98 – 6.93 (m, 1H), 2.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.2 (C), 153.3 (C), 144.4 (C), 134.4 (CH), 129.5 (CH), 126.9 (CH), 126.2 (CH), 125.9 (CH), 125.3 (CH), 125.2 (CH), 122.1 (CH), 85.3 (C), 28.2 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{13}H_{11}O_2S$ $[M+H]^+$: 231.0474 found 231.0490 and for $C_{13}H_{10}O_2SNa$ $[M+Na]^+$: 253.0294 found 253.0316 and for $C_{13}H_{10}O_2SK$ $[M+K]^+$: 269.0033 found 269.0050; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 95/5.

3-(5-Bromothiophen-2-yl)-3-methyl-(3H)-isobenzofuran-1-one (2k): Compound **2k** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 2-acetyl-5-bromothiophene (82 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow oil; yield 70% (54 mg); R_f=0.33 (cyclohexane/EtOAc 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.85 (ddd, *J* = 7.6, 1.0, 1.0 Hz, 1H), 7.64 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 7.51 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 7.41 (ddd, *J* = 7.7, 0.8, 0.8 Hz, 1H), 7.19 (s, 1H), 6.84 (d, *J* = 3.9 Hz, 1H), 6.70 (d, *J* = 3.9 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.0 (C), 152.7 (C), 146.0 (C), 134.7 (CH), 130.0 (CH), 129.9 (CH), 126.2 (CH), 125.7 (CH), 125.3 (C), 122.1 (CH), 113.5 (C), 85.0 (C), 27.9 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{13}H_{10}BrO_2S$ $[M+H]^+$: 308.9579 found 308.9562 and for $C_{13}H_9BrO_2S$ Na $[M+Na]^+$: 330.9399 found 330.9388; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-Methyl-3-(2-Pyridyl)-(3H)-isobenzofuran-1-one (2l): Compound **2l** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 2-acetylpyridine (49 mg, 0.40 mmol). The title compound was obtained after flash chromatography as white solid; yield 80% (45 mg); R_f=0.22 (petroleum ether/EtOAc 90/10); m.p.: 82 – 84°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.61 (d, *J* = 4.7 Hz, 2H), 7.87 (dd, *J* = 7.9, 7.9 Hz, 2H), 7.64 (d, *J* = 7.6, 7.6 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.21 – 7.17 (m, 1H), 2.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=170.1 (C), 160.1 (C), 153.5 (C), 149.2 (CH), 137.0 (CH), 134.3 (CH), 129.2 (CH), 125.4 (CH), 124.4 (C), 123.4 (CH), 122.8 (CH), 118.6 (CH), 88.0 (C), 27.3 (CH_3); HRMS (ESI positive) *m/z* calcd. for $C_{14}H_{12}NO_2$ $[M+H]^+$: 226.0863 found 226.0904 and for $C_{14}H_{11}NO_2Na$ $[M+Na]^+$: 248.0682 found 248.0725; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, cyclohexane/EtOAc 100/0 to 90/10.

3,3-Dicyclopropyl-(3H)-isobenzofuran-1-one (2m): Compound **2m** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and dicyclopropylketone (44 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow oil; yield 65% (35 mg); R_f=0.42 (petroleum ether/EtOAc 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.83 (d, *J* = 7.6 Hz, 1H), 7.64 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H), 7.50 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 1.41 – 1.34 (m, 2H), 0.61 – 0.52 (m, 2H), 0.47 – 0.35 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=170.1 (C), 152.3 (C), 133.8 (CH), 129.0 (CH), 126.2 (C), 125.6 (CH), 121.7 (CH), 88.0 (C), 18.0 (2*CH), 1.6 (2*CH_2), 0.6 (2*CH_2); HRMS (ESI positive): *m/z* calcd. for $C_{14}H_{15}O_2$ $[M+H]^+$: 215.1067 found 215.1079 and for $C_{14}H_{14}O_2Na$ $[M+Na]^+$: 237.0886 found 237.0928; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, cyclohexane/EtOAc 100/0 to 90/10.

3-Methyl-3-propyl-(3H)-isobenzofuran-1-one (2n)[14]: Compound **2n** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 2-pentanone (35 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow oil. Yield 61% (29 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.79 (d, *J* = 7.7 Hz, 1H), 7.57 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.43 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.32 – 7.27 (m, 1H), 1.99 – 1.89 (m, 1H), 1.82 – 1.70 (m, 1H), 1.56 (s, 3H), 1.43 – 1.1 (m, 1H), 1.00 – 0.88 (m, 1H), 0.78 (t, *J* = 7.3 Hz, 3H); HRMS (ESI positive): *m/z* calcd. for $C_{12}H_{14}O_2Na$ $[M+Na]^+$: 213.0886 found 213.0880; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, cyclohexane/EtOAc 100/0 to 90/10.

3-(1-Chloro)ethyl-3-(4-chlorophenyl)-(3H)-isobenzofuran-1-one (2o)[6]: Compound **2o** was prepared according to the general procedure **B** using ethyl-2-iodobenzoate **1a** (69 mg, 0.25 mmol) and 2-chloro-1-(4-chlorophenyl)propan-1-one (81

mg, 0.40 mmol). The title compound was obtained after flash chromatography as a white solid. Yield 65% (80 mg); m.p.: 119 – 121°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.93 (d, *J* = 7.6 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.62 – 7.58 (m, 3H), 7.37 (d, *J* = 8.6 Hz, 2H), 4.67 (q, *J* = 6.7 Hz, 1H), 1.43 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=168.9 (C), 149.1 (C), 136.1 (C), 135.1 (C), 134.5 (CH), 130.3 (CH), 129.0 (2*CH), 127.5 (2*CH), 126.5 (CH), 126.4 (C), 123.5 (C), 90.1 (CH), 61.1 (CH_3), 19.82; HRMS (ESI positive): *m/z* calcd. for $C_{16}H_{13}Cl_2O_2$ $[M+H]^+$: 307.0287 found 307.0312 and for $C_{16}H_{12}Cl_2O_2K$ $[M+K]^+$: 344.9846 found 344.9843; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, cyclohexane/EtOAc 100/0 to 90/10.

3-Ethyl-5,6-dimethyl-3-phenyl-(3H)-isobenzofuran-1-one (3a): Compound **3a** was prepared according to the general procedure **B** using ethyl-4,5-dimethyl-2-iodobenzoate **1c** (76 mg, 0.25 mmol) and propiophenone (54 mg, 0.40 mmol). The title compound was obtained after flash chromatography as beige solid; yield 73% (49 mg); R_f=0.40 (petroleum ether/EtOAc 90/10); m.p.: 65 – 67°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.63 (s, 1H), 7.52 – 7.48 (m, 2H), 7.38 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.24 (s, 1H), 2.47 (dq, *J* = 14.6, 7.3 Hz, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 2.23 (dq, *J* = 14.5, 7.3 Hz, 1H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=170.5 (C), 150.9 (C), 144.3 (C), 140.8 (C), 138.2 (C), 128.6 (2*CH), 127.9 (CH), 126.0 (CH), 125.0 (2*CH), 123.6 (C), 122.8 (CH), 90.0 (C), 33.2 (CH_2), 20.9 (CH_3), 19.9 (CH_3), 8.1 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{18}H_{19}O_2$ $[M+H]^+$: 267.1380 found 267.1354 and for $C_{18}H_{18}O_2Na$ $[M+Na]^+$: 289.1199 found 289.1218; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3-(4-Methoxyphenyl)-3,5,6-trimethyl-(3H)-isobenzofuran-1-one (3b): Compound **3b** was prepared according to the general procedure **B** using ethyl-4,5-dimethyl-2-iodobenzoate **1c** (76 mg, 0.25 mmol) and 4'-methoxyacetophenone (60 mg, 0.40 mmol). The title compound was obtained after flash chromatography as white solid; yield 71% (50 mg); R_f=0.20 (petroleum ether/EtOAc 90/10); m.p.: 151 – 153°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.64 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.15 (s, 1H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.78 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=170.3 (C), 159.4 (C), 152.7 (C), 144.4 (C), 138.2 (C), 133.0 (C), 126.6 (2*CH), 126.0 (CH), 123.1 (C), 122.7 (CH), 113.9 (2*CH), 87.1 (C), 55.3 (CH_3), 27.2 (CH_3), 20.8 (CH_3), 19.9 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{18}H_{19}O_3$ $[M+H]^+$: 283.1329 found 283.1302 and for $C_{18}H_{18}O_3Na$ $[M+Na]^+$: 305.1148 found 305.1132; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

3,5,6-Trimethyl-3-(thiophen-2-yl)-(3H)-isobenzofuran-1-one (3c): Compound **3c** was prepared according to the general procedure **B** using ethyl-4,5-dimethyl-2-iodobenzoate **1c** (76 mg, 0.25 mmol) and 2-acetylthiophene (51 mg, 0.40 mmol). The title compound was obtained after flash chromatography as white solid; yield 68% (44 mg); R_f=0.18 (petroleum ether/EtOAc 90/10); m.p.: 92 – 94°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.65 (s, 1H), 7.27 (d, *J* = 1.2 Hz, 1H), 7.23 (s, 1H), 7.00 (dd, *J* = 3.6, 1.3 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.38 (s, 3H), 2.37 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.7 (C), 151.8 (C), 145.1 (C), 144.7 (C), 138.9 (C), 127.0 (CH), 126.24 (CH), 126.16 (CH), 125.3 (CH), 123.1 (C), 122.9 (CH), 85.1 (C), 28.3 (CH_3), 21.0 (CH_3), 20.1 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{15}H_{15}O_2S$ $[M+H]^+$: 259.0787 found 259.0805 and for $C_{15}H_{14}O_2SNa$ $[M+Na]^+$: 281.0607 found 281.0659; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

2,2,5',6,6'-pentamethyl-spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-3'-one (3d): Compound **3d** was prepared according to the general procedure **B** using ethyl-4,5-dimethyl-2-iodobenzoate **1c** (76 mg, 0.25 mmol) and 2,2,6-trimethylcyclohexanone (56 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow sticky oil; yield 58% (40 mg); R_f=0.57 (petroleum ether/EtOAc 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.61 (s, 1H), 7.12 (s, 1H), 2.40 (s, 3H), 2.36 (s, 3H), 2.34 – 2.31 (m, 1H), 1.97 – 1.90 (m, 1H), 1.74 – 1.61 (m, 4H), 1.39 – 1.35 (m, 1H), 1.28 (s, 3H), 0.56 (s, 3H), 0.42 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=171.2 (C), 149.0 (C), 143.1 (C), 137.6 (C), 125.8 (C), 125.7 (CH), 123.6 (CH), 94.0 (C), 38.3 (C), 37.2 (CH_2), 34.5 (CH), 30.9 (CH_2), 24.8 (CH_3), 23.4 (CH_3), 21.4 (CH_2), 20.9 (CH_3), 19.8 (CH_3), 15.6 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{18}H_{25}O_2$ $[M+H]^+$: 273.1849 found 273.1891 and for $C_{18}H_{24}O_2Na$ $[M+Na]^+$: 295.1669 found 295.1759; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

5-Chloro-3-ethyl-3-phenyl-(3H)-isobenzofuran-1-one (3e): Compound **3e** was prepared according to the general procedure **B** using ethyl-4-chloro-2-iodobenzoate **1d** (78 mg, 0.25 mmol) and propiophenone (54 mg, 0.40 mmol). The title compound was obtained after flash chromatography as white solid; yield 65% (44 mg); R_f=0.46 (petroleum ether/EtOAc 90/10); m.p.: 120 – 122°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.81 (d, *J* = 8. 5 Hz, 1H), 7.50 – 7.45 (m, 4H), 7.41 – 7.36 (m, 2H), 7.35 – 7.30 (m, 1H), 2.50 (dq, *J* = 14.6, 7.3 Hz, 1H), 2.25 (dq, *J* = 14.5, 7.3 Hz, 1H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.0 (C), 154.5 (C), 140.9 (C), 139.7 (C), 129.9 (CH), 128.9 (2*CH), 128.4 (CH), 127.0 (CH), 124.9 (2*CH), 124.1 (C), 122.6 (CH), 90.0 (C), 33.1 (CH_2), 8.0 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{16}H_{14}ClO_2$ $[M+H]^+$: 273.0677 found 273.0605 and for $C_{16}H_{13}ClO_2Na$ $[M+Na]^+$: 295.0496 found 295.0433; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

5-Chloro-3-(4-methoxyphenyl)-3-methyl-(3H)-isobenzofuran-1-one (3f): Compound **3f** was prepared according to the general procedure **B** using ethyl-4-chloro-2-iodobenzoate **1d** (78 mg, 0.25 mmol) and 4'-methoxyacetophenone (60 mg, 0.40 mmol). The title compound was obtained after flash chromatography as white solid; yield 70% (51 mg); R_f=0.45 (toluene / EtOAc 95/5); m.p.: 106 – 108°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.83 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.38 (dd, *J* = 1.7, 0.5 Hz, 1H), 7.31 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=168.8 (C), 159.8 (C), 156.1 (C), 140.9 (C), 131.8 (C), 129.8 (CH), 127.1 (CH), 126.6 (2*CH), 123.7 (C), 122.5 (CH), 114.1 (2*CH), 87.1 (C), 55.3 (CH_3), 27.0 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{16}H_{14}ClO_3$ $[M+H]^+$: 289.0626 found 289.0668 and for $C_{16}H_{13}ClO_3Na$ $[M+Na]^+$: 311.0445 found 311.0486 and for $C_{16}H_{13}ClO_3K$ $[M+K]^+$: 327.0185 found 327.0185; Flash

chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10; Then preparative TLC toluene/EtOAc 95/5.

6-Bromo-3-(4-methoxyphenyl)-3-methyl-(3H)-isobenzofuran-1-one (3g): Compound **3g** was prepared according to the general procedure **B** using ethyl-5-bromo-2-iodobenzoate **1b** (89 mg, 0.25 mmol) and 4'-methoxyacetophenone (60 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow oil; yield 70% (58 mg); R_f=0.36 (toluene/EtOAc 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.02 (d, *J* = 2.2 Hz, 1H), 7.76 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.30 – 7.26 (m, 3H), 6.86 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=168.3 (C), 159.7 (C), 153.1 (C), 137.3 (CH), 131.9 (C), 128.8 (CH), 127.3 (C), 126.6 (2*CH), 123.7 (CH), 123.0 (C), 114.1 (2*CH), 87.7 (C), 55.3 (CH_3), 27.0 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{16}H_{14}BrO_3$ $[M+H]^+$: 333.0121 found 333.0103 and for $C_{16}H_{13}BrO_3Na$ $[M+Na]^+$: 354.9940 found 355.0003; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10; Then preparative TLC toluene/EtOAc 95/5.

6-Bromo-3-(2-methoxyphenyl)-3-methyl-(3H)-isobenzofuran-1-one (3h): Compound **3h** was prepared according to the general procedure **B** using ethyl-5-bromo-2-iodobenzoate **1b** (89 mg, 0.25 mmol) and 2'-methoxyacetophenone (60 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow solid; yield 69% (57 mg); R_f=0.33 (petroleum ether/EtOAc 90/10); m.p.: 122 – 124°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.01 (d, *J* = 1.8 Hz, 1H), 7.70 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.34 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H), 6.99 (ddd, *J* = 7.7, 7.7 1.1 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 3.72 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=168.9 (C), 157.1 (C), 153.4 (C), 136.8 (CH), 130.4 (CH), 128.2 (C), 128.1 (CH), 127.5 (C), 126.7 (CH), 123.7 (CH), 122.5 (H), 120.7 (CH), 112.1 (CH), 87.2 (C), 55.4 (CH_3), 26.3 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{16}H_{10}BrO_3$ $[M+H]^+$: 333.0121 found 333.0151 and for $C_{16}H_{13}BrO_3Na$ $[M+Na]^+$: 354.9940 found 354.9968; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

6-Fluoro-3-isopropyl-3-phenyl-(3H)-isobenzofuran-1-one (3i): Compound **3i** was prepared according to the general procedure **B** using ethyl-5-fluoro-2-iodobenzoate **1e** (74 mg, 0.25 mmol) and isobutyrophenone (56 mg, 0.40 mmol). The title compound was obtained after flash chromatography as colorless oil; yield 78% (53 mg); R_f=0.29 (cyclohexane/EtOAc 80/20) and 0.39 (petroleum ether/dichloromethane 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.60 – 7.47 (m, 4H), 7.39 – 7.27 (m, 4H), 2.77 (dq, *J* = 13.6, 6.8 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.1 (d, J_{C-F} = 3.9 Hz) (C), 163.0 (d, J_{C-F} = 249.7 Hz) (C), 148.2 (d, J_{C-F} = 2.4 Hz) (C), 140.3 (C), 128.8 (CH), 128.0 (CH), 127.7 (d, J_{C-F} = 8.8 Hz) (C), 124.7 (CH), 123.8 (d, J_{C-F} = 8.4 Hz) (CH), 122.1 (d, J_{C-F} = 23.8 Hz) (CH), 112.1 (d, J_{C-F} = 23.5 Hz) (CH), 92.8 (C), 36.9 (CH), 17.3 (CH_3), 16.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ=-111.8; HRMS (ESI positive): *m/z* calcd. for $C_{17}H_{15}FO_2Na$ $[M+Na]^+$: 293.0948 found 293.1079; Flash chromatography conditions: Petroleum ether/EtOAc 100/0 to 90/10; Then preparative TLC petroleum ether / dichloromethane 50/50.

3-(4-Chlorophenyl)-6-fluoro-3-methyl-(3H)-isobenzofuran-1-one (3j): Compound **3j** was prepared according to the general procedure **B** using ethyl-5-fluoro-2-iodobenzoate **1e** (74 mg, 0.25 mmol) and 4'-chloroacetophenone (62 mg, 0.40 mmol). The title compound was obtained after flash chromatography as colorless oil; yield 68% (47 mg); R_f =0.30 (cyclohexane/EtOAc 80/20) and 0.48 (petroleum ether/dichloromethane 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.48 (ddd, *J* = 7.1, 2.2, 0.7 Hz, 1H), 7.35 – 7.25 (m, 6H), 1.95 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ=168.3 (d, J_{C-F} = 3.8 Hz) (C), 163.2 (d, J_{C-F} = 250.4 Hz) (C), 149.3 (d, J_{C-F} = 2.3 Hz) (C), 138.9 (C), 134.6 (C), 129.0 (CH), 127.2 (d, J_{C-F} = 9.0 Hz) (C), 126.5 (CH), 123.7 (d, J_{C-F} = 8.5 Hz) (CH), 122.4 (d, J_{C-F} = 24.1 Hz) (CH), 112.3 (d, J_{C-F} = 23.7 Hz) (CH), 87.0 (C), 27.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ=-111.1; HRMS (ESI positive): *m/z* calcd. for $C_{15}H_{10}ClFO_2Na$ $[M+Na]^+$: 299.0246 found 299.0338; Flash chromatography conditions: Petroleum ether/EtOAc 100/0 to 90/10; Then preparative TLC petroleum ether/dichloromethane 50/50.

6-Fluoro-3-methyl-3-(2-Pyridyl)-(3H)-isobenzofuran-1-one (3k): Compound **3k** was prepared according to the general procedure **B** using ethyl-5-fluoro-2-iodobenzoate **1e** (74 mg, 0.25 mmol) and 2-acetylpyridine (49 mg, 0.40 mmol). The title compound was obtained after flash chromatography as colorless oil; yield 78% (47 mg); R_f=0.20 (cyclohexane/EtOAc 80/20) and 0.32 (toluene/EtOAc 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.60 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.89 (dd, *J* = 8.5, 4.4 Hz, 1H), 7.66 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.56 (ddd, *J* = 8.0, 1.1, 1.1 Hz, 1H), 7.49 (ddd, *J* = 7.2, 2.4, 0.5 Hz, 1H), 7.35 (dd, *J* = 8.6, 8.6, 2.4 Hz, 1H), 7.21 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=168.77 (d, J_{C-F} = 4.0 Hz) (C), 163.27 (d, J_{C-F} = 249.4 Hz) (C), 159.83 (C), 149.27 (CH), 149.07 (d, J_{C-F} = 2.3 Hz) (C), 137.10 (CH), 126.47 (d, J_{C-F} = 9.1 Hz) (C), 125.38 (d, J_{C-F} = 8.4 Hz) (CH), 122.87 (CH), 122.18 (d, J_{C-F} = 23.8 Hz) (CH), 118.51 (CH), 111.53 (d, J_{C-F} = 23.6 Hz) (CH), 87.94 (C), 27.59 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ=-111.8; HRMS (ESI positive): *m/z* calcd. for $C_{14}H_{11}FNO_2$ $[M+H]^+$: 244.0768 found 244.0694 and for $C_{14}H_{10}FNO_2Na$ $[M+Na]^+$: 266.0588 found 266.0512**;** Flash chromatography conditions: Petroleum ether/EtOAc 100/0 to 90/10; Then preparative TLC toluene/EtOAc 95/5.

6-Fluoro-3-methyl-3-(thiophen-2-yl)-(3H)-isobenzofuran-1-one (3l): Compound **3l** was prepared according to the general procedure **B** using ethyl-5-fluoro-2-iodobenzoate **1e** (74 mg, 0.25 mmol) and 2-acetylthiophene (51 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow oil; yield 65% (40 mg); R_f=0.20 (Cyclohexane/EtOAc 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.56 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.47 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.40 (td, *J* = 8.5, 2.4 Hz, 1H), 7.30 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.00 (dd, *J* = 3.7, 1.3 Hz, 1H), 6.96 (dd, *J* = 5.0, 3.6 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=167.9(d, J_{C-F} = 3.9 Hz) (C), 163.33 (d, J_{C-F} = 250.5 Hz) (C), 148.93 (d, J_{C-F} = 2.4 Hz) (C), 144.0 (C), 127.40 (d, J_{C-F} = 8.9 Hz) (C), 127.0 (CH), 126.4 (CH), 125.5 (CH), 123.88 (d, J_{C-F} = 8.6 Hz) (CH), 122.28 (d, J_{C-F} = 24.1 Hz) (CH), 112.16 (d, J_{C-F} = 23.7 Hz) (CH), 85.3 (C), 28.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ=-110.8; HRMS (ESI positive): *m/z* calcd. for $C_{13}H_{10}FSO_2$ $[M+H]^+$: 249.0380 found 249.0380 and for $C_{13}H_9FSO_2Na$ $[M+Na]^+$:

271.0199 found 271.0242; Flash chromatography conditions: Petroleum ether/EtOAc 100/0 to 90/10.

5-Chloro-3,7-dimethyl-3-(4-methoxyphenyl)-(3H)-isobenzofuran-1-one (3m): Compound **3m** was prepared according to the general procedure **B** using ethyl-4-chloro-2-iodo-6-methylbenzoate **1f** (85 mg, 0.25 mmol) and 4'-methoxyacetophenone (60 mg, 0.40 mmol). The title compound was obtained after flash chromatography as yellow oil; yield 73% (55 mg); R_f=0.36 (petroleum ether/EtOAc 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.31 (d, *J* = 8.9 Hz, 2H), 7.25 (s, 1H), 7.17 (s, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 2.69 (s, 3H), 1.99 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.1 (C), 159.7 (C), 156.6 (C), 141.5 (C), 140.2 (C), 132.3 (C), 131.0 (CH), 126.6 (2*CH), 121.2 (C), 119.8 (CH), 114.1 (2*CH), 86.0 (C), 55.3 (CH_3), 27.1 (CH_3), 17.3 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{17}H_{16}ClO_3$ $[M+H]^+$: 303.0782 found 303.0812 and for $C_{17}H_{15}ClO_3Na$ $[M+Na]^+$: 325.0602 found 325.0634; Flash chromatography conditions: column 24 g, flow rate = 20 mL/min, petroleum ether/EtOAc 100/0 to 90/10.

5-Chloro-3,7-dimethyl-3-(2-Pyridyl)-(3H)-isobenzofuran-1-one (3n): Compound **3n** was prepared according to the general procedure **B** using ethyl-4-chloro-2-iodo-6-methylbenzoate **1f** (85 mg, 0.25 mmol) and 2-acetylpyridine (49 mg, 0.40 mmol). The title compound was obtained after flash chromatography as white solid; yield 79% (54 mg); R_f=0.42 (petroleum ether/EtOAc 90/10); m.p.: 153 – 155°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.61 (d, *J* = 4.8 Hz, 1H), 7.69 (s, 1H), 7.65 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.17 (m, 2H), 2.65 (s, 3H), 2.02 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ=169.1 (C), 159.8 (C), 155.5 (C), 149.4 (CH), 141.0 (C), 140.3 (C), 137.0 (CH), 131.1 (CH), 122.9 (CH), 121.2 (CH), 120.5 (C), 118.6 (CH), 86.5 (C), 27.5 (CH_3), 17.3 (CH_3); HRMS (ESI positive): *m/z* calcd. for $C_{15}H_{13}ClNO_2$ $[M+H]^+$: 274.0629 found 274.0658 and for $C_{15}H_{12}ClNO_2Na$ $[M+Na]^+$: 296.0449 found 296.0430; Flash chromatography conditions: column 12 g, flow rate = 20 mL/min, cyclohexane/EtOAc 100/0 to 90/10.

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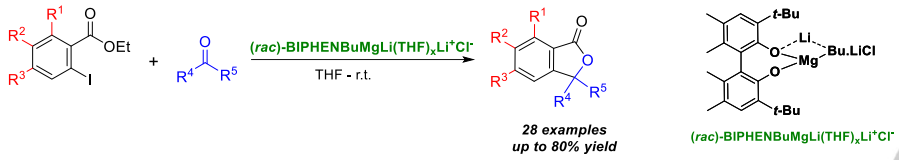

Surprisingly (*rac*)-(BIPHEN)BuMgLi(THF)$_x$Li$^+$Cl$^-$. Metal halogen exchange, using the bimetallic organomagnesiate ate complex (*rac*)-(BIPHEN)BuMgLi, of easily available 2-iodobenzoates derivatives followed by addition of (enolizable) ketones and intramolecular cyclisation lead to the formation of a panel of new diversely 3,3′-disubstituted phthalides in good yield. The magnesiate (*rac*)-(BIPHEN)BuMgLi was the only MHE agent we tested which allowed this transformation and it has been characterized by solution-state ^{1}H, ^{7}Li and ^{1}H DOSY NMR experiments and used for the synthesis of known biological active molecule.

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