



HAL
open science

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

Sabrina Touchet, Callum Year-ley, Charles O'hara, Philippe Gros

► **To cite this version:**

Sabrina Touchet, Callum Year-ley, Charles O'hara, Philippe Gros. Critical ligand and salt effects in organomagnesi-ate-promoted 3,3-disubstituted phthalides synthesis from 2-iodobenzoate derivatives. *European Journal of Organic Chemistry*, 2021, 2021 (34), pp.4835-4845. 10.1002/ejoc.202100899 . hal-03325715v1

HAL Id: hal-03325715

<https://hal.science/hal-03325715v1>

Submitted on 1 Oct 2021 (v1), last revised 14 Jan 2022 (v2)

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Sabrina Touchet,^{*[a]} Callum Yeardley,^[b] Charles T. O'Hara,^[b] and Philippe C. Gros^[a]

[a] Dr S. Touchet, Dr. P. C. Gros
Université de Lorraine, CNRS, L2CM, F-54000, Nancy, France
E-mail: sabrina.touchet@univ-lorraine.fr

[b] Dr C. Yeardley, Dr C. T. O'Hara
WestCHEM, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK

Supporting information for this article is given via a link at the end of the document.

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 organomagnesiato 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 magnesiato has been found to play a prominent role in its reactivity. Therefore, the bimetallic magnesiato complex has been characterized by solution-state ¹H, ⁷Li and ¹H 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 A₂α inhibitor^[11] (Figure 1). They can also have an influence on the innate immune system^[12] or as vasodilators.^[13]

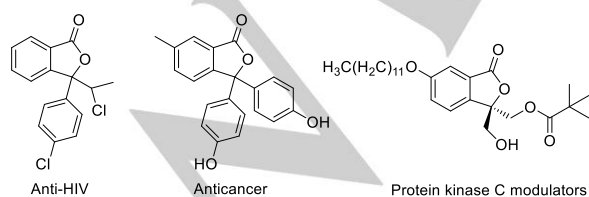
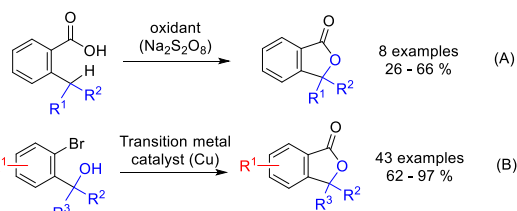


Figure 1. Bioactive 3,3-disubstituted Isobenzofuranones.

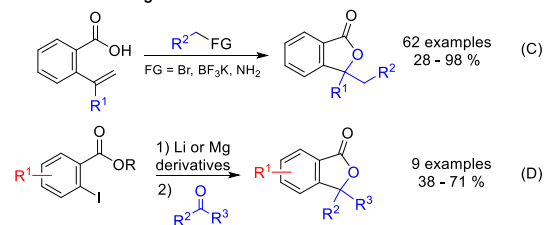
Given their important bioactivities, efforts have been dedicated to the development of new methodologies to prepare 3,3-

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 (Scheme 1C) can be classified as a convergent synthetic route as a part of the hydrocarbon chain (R²) of the product comes from a second reagent. However, R¹ of the product come from the starting material. This route used *ortho*-carboxy styrene as starting material *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]

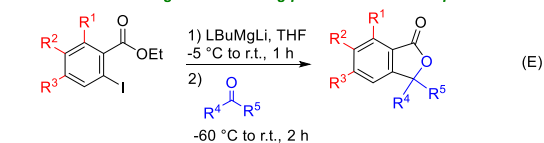
a. Current non-convergent routes



b. Current convergent routes



c. This work: convergent route using polar bimetallic complexes



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

The fourth methodology (Scheme 1E) is the only convergent route allowing the introduction of R² and R³ by the second reagent;

FULL PAPER

however, unlike the other 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]

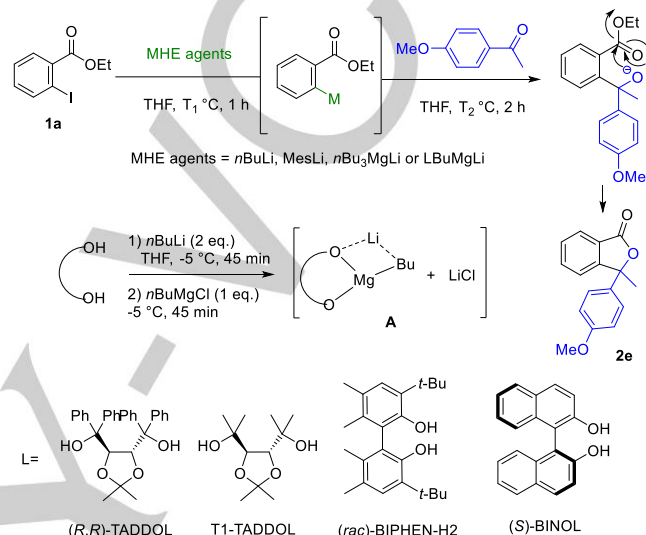
Herein we report our investigation on the synthesis of 3,3-disubstituted phthalides from enolizable ketones using organomagnesiates bearing dialkoxides ligands. We showed that the homoleptic alkyl bimetallic complex $n\text{Bu}_3\text{MgLi}$ is inefficient in such a reaction; however, when the heteroleptic (*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-ethylidobenzoate 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 quantitatively 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 $n\text{BuLi}$ 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 $n\text{Bu}_3\text{MgLi}$ reagent under Oshima's conditions at $-78\text{ }^\circ\text{C}$ (Entry 3 - Table 1)^[28] 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 magnesiation-lactonization reaction and preparation of reagents containing alkoxide.

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

Entry	MHEA (eq.)	T ₁ °C ^[b]	T ₁ °C	2e % ^[c]
1	<i>n</i> BuLi (1)	-78	-78 ^[d]	0
2	MesLi (1)	-78	-78 ^[e]	0
3	<i>n</i> Bu ₃ MgLi (1.2) ^[g]	-78	-78 ^[f]	0
4	<i>n</i> Bu ₃ MgLi (1.2) ^[g]	-10 to r.t.	-60 to r.t. ^[f]	0
5	(<i>rac</i>)-(BIPHEN)BuMgLi (2)	-10 to r.t.	-60 ^[d]	0
6	(<i>rac</i>)-(BIPHEN)BuMgLi (2)	-10 to r.t.	-40 ^[d]	7
7	(<i>rac</i>)-(BIPHEN)BuMgLi (2)	-10 to r.t.	-20 ^[d]	10
8	(<i>rac</i>)-(BIPHEN)BuMgLi (2)	-10 to r.t.	-60 to r.t. ^[d]	75
9	(<i>R,R</i>)-(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	(<i>S</i>)-(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 $-10\text{ }^\circ\text{C}$.

FULL PAPER

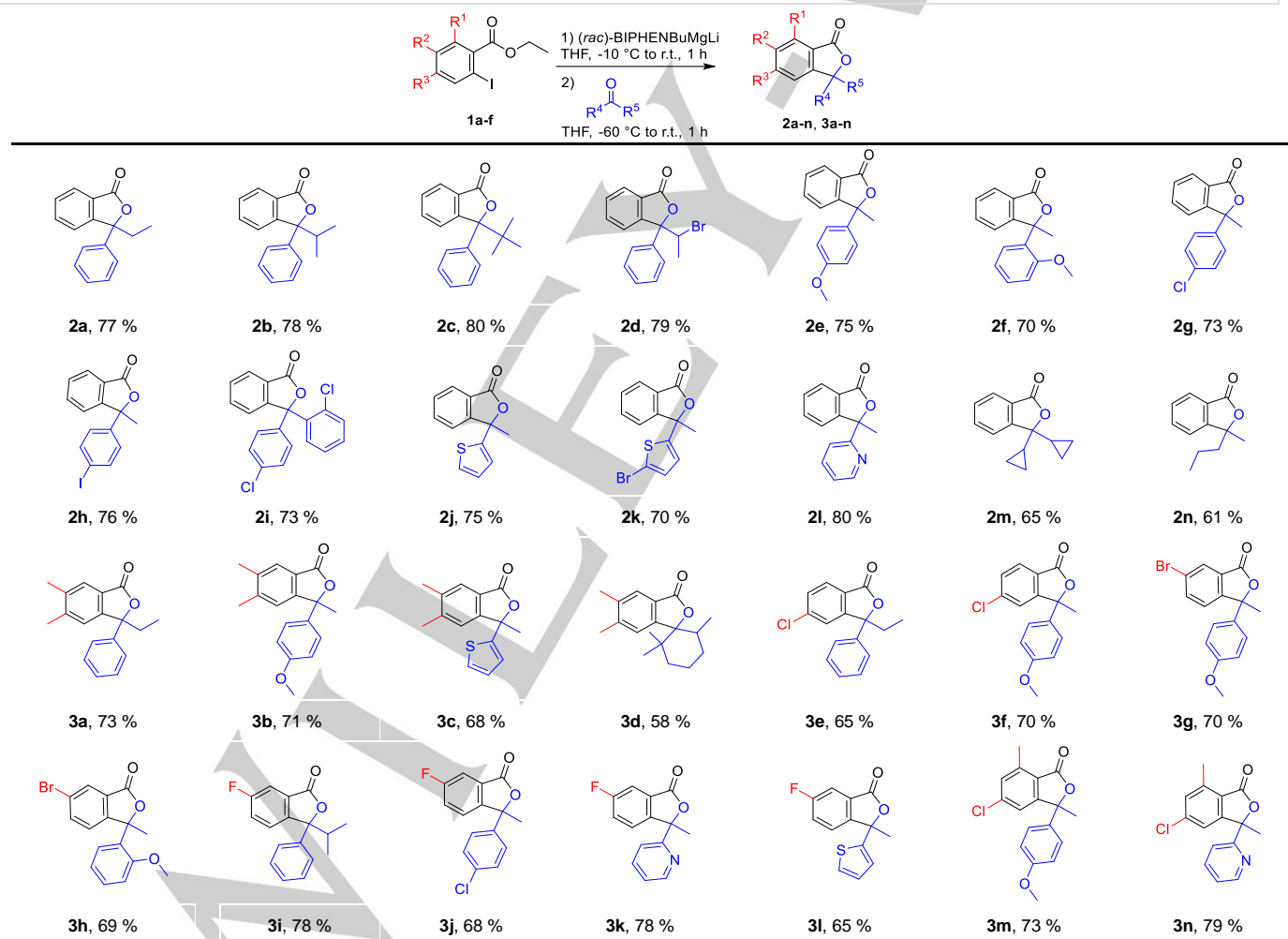
We then considered the introduction of alkoxide ligands, which were expected to favor the release of the aromatic intermediate via a modification of the metal coordination sphere and to have a better tolerance of sensitive functional groups. Thus, we examined the reactivity of magnesiate complex LBUmgLi A [$\text{L} = (\text{rac})\text{-BIPHEN}$, $(R,R)\text{-TADDOL}$, T1-TADDOL or $(S)\text{-BINOL}$] reagents. The reagents were obtained by reacting the doubly lithiated dialkoxide with $n\text{BuMgCl}$ (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.^[27] 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 $(\text{rac})\text{-BIPHEN}$ 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 $(\text{rac})\text{-BIPHEN}$ (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), $(\text{rac})\text{-BIPHEN}$ (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**

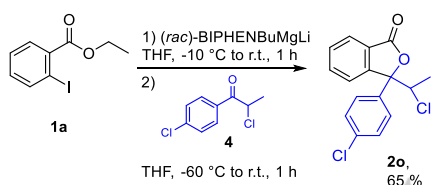
was obtained in a 61 % yield from the highly enolizable aliphatic 2-pentanone. This indicated a high nucleophilicity versus basicity of the organometallic aryl intermediate. Moreover, various reactive functional substituents, which may be useful for

FULL PAPER

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 bond 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.

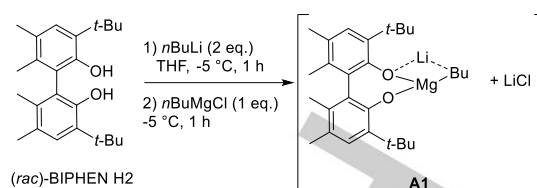
This methodology was successfully applied to the synthesis of an anti-HIV molecule **2o**^[6] (Figure 1 and Scheme 3) with 65 % yield using commercially available **1a** and enolizable chloro-ketone **4** easily synthesized in one step by α -chlorination^[29] of the commercially available 4'-chloropropiophenone 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 ¹H, ⁷Li and ¹H DOSY NMR spectroscopy in d₈-THF. For that, magnesiate complex was prepared as usual (Scheme 4), then solvents were removed under vacuum and the residue was dissolved in d₈-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 ¹H and ⁷Li 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 (CH₂Mg), appear upfield as two multiplets at -0.77 and -0.98 ppm, displaying the diastereotopic nature of these protons.

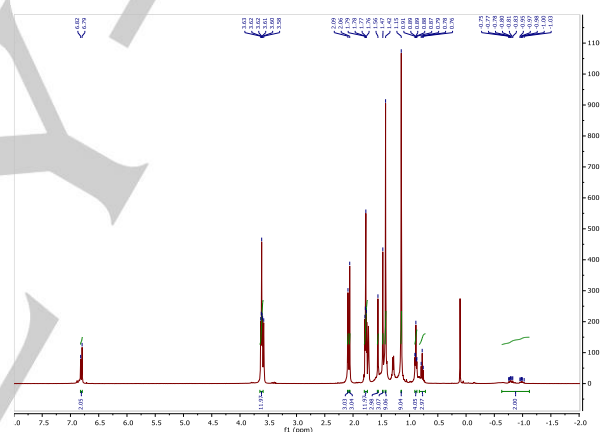
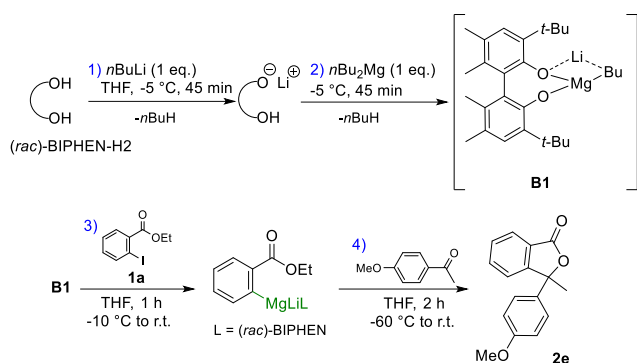


Figure 2. ¹H NMR spectrum (in d₈-THF) of magnesiate complex **A1** from 1 equiv. of (*rac*)-BIPHEN + 2 equiv. *n*BuLi + 1 equiv. *n*BuMgCl.

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 magnesian-lactonization reaction while using magnesiates complex **B1** from 1 equiv. of (*rac*)-BIPHEN + 1 equiv. *n*Bu₂Mg.

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*Bu₂Mg (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*Bu₂Mg 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 magnesiates is crucial and that LiCl is probably part of the magnesiates complex and has to come with the magnesium species (ie *n*BuMgCl).

In order to support this structural assumption ¹H DOSY NMR spectroscopy in d₈-THF has been performed on the magnesiates complex (*rac*)-(BIPHEN)BuMgLi **A1** (Figure 3).

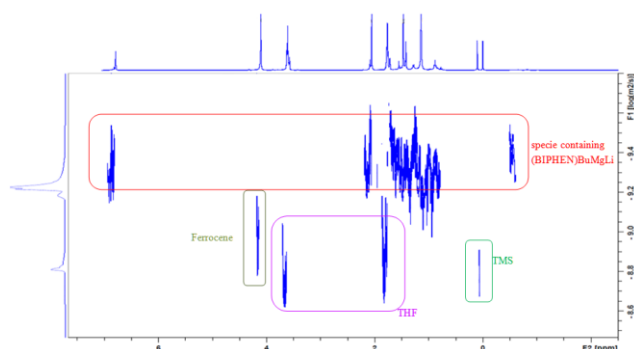


Figure 3. ¹H DOSY NMR spectrum of magnesiates complex **A1** and the standards tetramethylsilane (TMS) and ferrocene in d₈-THF at 25 °C.

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 magnesiates complex in d₈-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 magnesiates complex in d₈-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 _{diff} (%)	MW _{diff} (%)	MW _{diff} (%)
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)BuMgLi₂Cl + 2 THF or iii) (BIPHEN)BuMgLi₂Cl + 3 THF (Table 3). Mulvey's team showed that three THF molecules are incorporated in the structure of the turbo-Hauser reagent (THF)₂Li(μ-Cl)₂Mg(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 magnesiates 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 magnesiates complex. However, coupled with the LiCl experiment described above (scheme 5) it can be tentatively suggested that LiCl is involved in the magnesiates suggesting an active species of the structure (*rac*)-(BIPHEN)BuMgLi(THF)_xLi⁺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 magnesiates 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 magnesiates complex **A** as well as solution-state experiments (¹H, ⁷Li and ¹H DOSY NMR in d₈-THF) suggest an active species of the structure (*rac*)-(BIPHEN)BuMgLi(THF)_xLi⁺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 Diiodo/Lithium chloride. All the NMR spectra were recorded on a Bruker Advance III 400. ¹H, ¹³C, and ¹⁹F NMR spectra were recorded respectively at 400 MHz, 101 MHz and 376 MHz. ¹H and ¹³C chemical shifts were

reported in ppm and referenced to Me₄Si as internal reference. ¹⁹F NMR chemical shifts were reported in ppm and referenced to external CFC13 (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 NH₄Cl (50 mL x 4) to remove the DMF, then dried over anhydrous MgSO₄, 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-(3H)-isobenzofuran-1-one 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, 1 eq.) 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 warm to RT and stir for 1 h. The reaction was checked by TLC to verify that metalation occurred and it's done. Then the reaction was cooled 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 warm to RT and stir for 2 h. The reaction was quenched with addition of saturated NH₄Cl 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 MgSO₄, 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 H₂SO₄ (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 CH₂Cl₂. The combined

organic phases were washed with 2*15 mL of 5 % NaHCO₃, dried over MgSO₄ 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ=165.2 (C), 142.6 (CH), 136.9 (C), 135.5 (CH), 133.8 (CH), 122.2 (C), 92.1 (C), 62.1 (CH₂), 14.2 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₉H₈BrIO₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ=166.4 (C), 142.3 (C), 142.1 (CH), 136.7 (C), 132.3 (C), 132.1 (CH), 90.7 (C), 61.4 (CH₂), 19.3 (2*CH₃), 14.3 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₁H₁₄O₂ [M+H]⁺: 305.0033 found 305.0012 and for C₁₁H₁₃O₂Na [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ=165.6 (C), 140.8 (CH), 138.0 (C), 133.5 (C), 131.7 (CH), 128.2 (CH), 94.4 (C), 61.9 (CH₂), 14.2 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₉H₈ClIO₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₂), 14.2 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ=-113.4; HRMS (ESI positive) *m/z* calcd. for C₉H₈FIO₂ [M+H]⁺: 294.9626 found 294.9608 and for C₉H₈FIO₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ=168.4 (C), 138.8 (C), 137.8 (C), 135.9 (CH), 135.3

(C), 129.9 (CH), 91.9 (C), 62.0 (CH₂), 19.9 (CH₃), 14.1 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₀H₁₁ClIO₂ [M+H]⁺: 324.9487 found 324.9507 and for C₁₀H₁₀ClIO₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₂), 8.1 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₆H₁₅O₂ [M+H]⁺: 239.1067 found 239.1118 and for C₁₆H₁₄O₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃), 16.4 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₇H₁₇O₂ [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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*CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₈H₁₉O₂ [M+H]⁺: 267.1380 found 267.1365 and for C₁₈H₁₈O₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₆H₁₃BrO₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃), 29.7 (CH₃); HRMS (ESI positive) *m/z* calcd. for C₁₆H₁₅O₃ [M+H]⁺: 255.1016 found 255.1054 and for C₁₆H₁₄O₃Na [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃), 26.4 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₆H₁₅O₃ [M+H]⁺: 255.1016 found 255.1019 and for C₁₆H₁₄O₃Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ=169.6 (C), 153.7 (C), 139.3 (C), 134.5 (CH), 134.4 (C), 129.3 (CH), 128.9

FULL PAPER

129.3 (2*CH), 126.6 (2*CH), 126.0 (CH), 125.0 (C), 121.9 (CH), 87.0 (C), 27.3 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₅H₁₂ClO₂ [M+H]⁺: 259.0520 found 259.0536 and for C₁₅H₁₁ClO₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₅H₁₂O₂ [M+H]⁺: 350.9877 found 350.9856 and for C₁₅H₁₁O₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₀H₁₂Cl₂O₂Na [M+Na]⁺: 377.0107 found 377.0210 and for C₂₀H₁₂Cl₂O₂K [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₃H₁₁O₂S [M+H]⁺: 231.0474 found 231.0490 and for C₁₃H₁₀O₂SNa [M+Na]⁺: 253.0294 found 253.0316 and for C₁₃H₁₀O₂SK [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃); HRMS (ESI positive): *m/z* calcd. for C₁₃H₁₀BrO₂S [M+H]⁺: 308.9579 found 308.9562 and for C₁₃H₉BrO₂S 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃); HRMS (ESI positive) *m/z* calcd. for C₁₄H₁₂NO₂ [M+H]⁺: 226.0863 found 226.0904 and for C₁₄H₁₁NO₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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*CH₂), 0.6 (2*CH₂); HRMS (ESI positive): *m/z* calcd. for C₁₄H₁₅O₂ [M+H]⁺: 215.1067 found 215.1079 and for C₁₄H₁₄O₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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)⁶¹: 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃), 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₂), 20.9 (CH₃), 19.9 (CH₃), 8.1 (CH₃); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃), 27.2 (CH₃), 20.8 (CH₃), 19.9 (CH₃); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃), 21.0 (CH₃), 20.1 (CH₃); 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₂), 34.5 (CH), 30.9 (CH₂), 24.8 (CH₃), 23.4 (CH₃), 21.4 (CH₂), 20.9 (CH₃), 19.8 (CH₃), 15.6 (CH₃); 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; ¹H NMR (400 MHz, CDCl₃) 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), 7.50 (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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₂), 8.0 (CH₃); 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; ¹H NMR (400 MHz, CDCl₃) 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 (CH₃), 27.0 (CH₃); HRMS (ESI positive): m/z calcd. for $\text{C}_{16}\text{H}_{14}\text{ClO}_3$ [M+H]⁺: 289.0626 found 289.0668 and for $\text{C}_{16}\text{H}_{13}\text{ClO}_3\text{Na}$ [M+Na]⁺: 311.0445 found 311.0486 and for $\text{C}_{16}\text{H}_{13}\text{ClO}_3\text{K}$ [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); ^1H 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 (CH₃), 27.0 (CH₃); HRMS (ESI positive): m/z calcd. for $\text{C}_{16}\text{H}_{14}\text{BrO}_3$ [M+H]⁺: 333.0121 found 333.0103 and for $\text{C}_{16}\text{H}_{13}\text{BrO}_3\text{Na}$ [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; ^1H 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 (CH₃), 26.3 (CH₃); HRMS (ESI positive): m/z calcd. for $\text{C}_{16}\text{H}_{10}\text{BrO}_3$ [M+H]⁺: 333.0121 found 333.0151 and for $\text{C}_{16}\text{H}_{13}\text{BrO}_3\text{Na}$ [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); ^1H 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, $J_{\text{C-F}}$ = 3.9 Hz) (C), 163.0 (d, $J_{\text{C-F}}$ = 249.7 Hz) (C), 148.2 (d, $J_{\text{C-F}}$ = 2.4 Hz) (C), 140.3 (C), 128.8 (CH), 128.0 (CH), 127.7 (d, $J_{\text{C-F}}$ = 8.8 Hz) (C), 124.7 (CH), 123.8 (d, $J_{\text{C-F}}$ = 8.4 Hz) (CH), 122.1 (d, $J_{\text{C-F}}$ = 23.8 Hz) (CH), 112.1 (d, $J_{\text{C-F}}$ = 23.5 Hz) (CH), 92.8 (C), 36.9 (CH), 17.3 (CH₃),

16.4 (CH₃); ^{19}F NMR (376 MHz, CDCl_3) δ =-111.8; HRMS (ESI positive): m/z calcd. for $\text{C}_{17}\text{H}_{15}\text{FO}_2\text{Na}$ [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); ^1H 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, $J_{\text{C-F}}$ = 3.8 Hz) (C), 163.2 (d, $J_{\text{C-F}}$ = 250.4 Hz) (C), 149.3 (d, $J_{\text{C-F}}$ = 2.3 Hz) (C), 138.9 (C), 134.6 (C), 129.0 (CH), 127.2 (d, $J_{\text{C-F}}$ = 9.0 Hz) (C), 126.5 (CH), 123.7 (d, $J_{\text{C-F}}$ = 8.5 Hz) (CH), 122.4 (d, $J_{\text{C-F}}$ = 24.1 Hz) (CH), 112.3 (d, $J_{\text{C-F}}$ = 23.7 Hz) (CH), 87.0 (C), 27.3 (CH₃); ^{19}F NMR (376 MHz, CDCl_3) δ =-111.1; HRMS (ESI positive): m/z calcd. for $\text{C}_{15}\text{H}_{10}\text{ClFO}_2\text{Na}$ [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); ^1H 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, $J_{\text{C-F}}$ = 4.0 Hz) (C), 163.27 (d, $J_{\text{C-F}}$ = 249.4 Hz) (C), 159.83 (C), 149.27 (CH), 149.07 (d, $J_{\text{C-F}}$ = 2.3 Hz) (C), 137.10 (CH), 126.47 (d, $J_{\text{C-F}}$ = 9.1 Hz) (C), 125.38 (d, $J_{\text{C-F}}$ = 8.4 Hz) (CH), 122.87 (CH), 122.18 (d, $J_{\text{C-F}}$ = 23.8 Hz) (CH), 118.51 (CH), 111.53 (d, $J_{\text{C-F}}$ = 23.6 Hz) (CH), 87.94 (C), 27.59 (CH₃); ^{19}F NMR (376 MHz, CDCl_3) δ =-111.8; HRMS (ESI positive): m/z calcd. for $\text{C}_{14}\text{H}_{11}\text{FNO}_2$ [M+H]⁺: 244.0768 found 244.0694 and for $\text{C}_{14}\text{H}_{10}\text{FNO}_2\text{Na}$ [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); ^1H 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, $J_{\text{C-F}}$ = 3.9 Hz) (C), 163.33 (d, $J_{\text{C-F}}$ = 250.5 Hz) (C), 148.93 (d, $J_{\text{C-F}}$ = 2.4 Hz) (C), 144.0 (C), 127.40 (d, $J_{\text{C-F}}$ = 8.9 Hz) (C), 127.0 (CH), 126.4 (CH), 125.5 (CH), 123.88 (d, $J_{\text{C-F}}$ = 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 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ = -110.8; HRMS (ESI positive): m/z calcd. for C₁₃H₁₀FSO₂ [M+H]⁺: 249.0380 found 249.0380 and for C₁₃H₉FSO₂Na [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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃), 27.1 (CH₃), 17.3 (CH₃); HRMS (ESI positive): m/z calcd. for C₁₇H₁₆ClO₃ [M+H]⁺: 303.0782 found 303.0812 and for C₁₇H₁₅ClO₃Na [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 (CH₃), 17.3 (CH₃); HRMS (ESI positive): m/z calcd. for C₁₅H₁₃ClNO₂ [M+H]⁺: 274.0629 found 274.0658 and for C₁₅H₁₂ClNO₂Na [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.

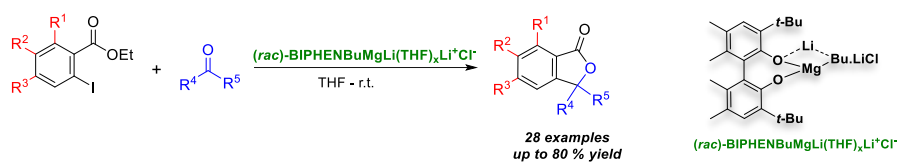
Acknowledgements

The authors would like to thank François Dupire (UMR 7053 – L2CM) and Fabien Lachaud (UMR 7053 – L2CM) for the HRMS and GC-MS experiments and related discussions. We gratefully acknowledge the support of the Royal Society (IEC\R2\170207) for the grant. They thank also the Université de Lorraine, the CNRS and the University of Strathclyde for their support.

Keywords: BIPHEN-H2 • Cyclization • Lactones • Magnesiate • Metal-halogen exchange

- [1] X. Z. Zhu, X.-Y. Li, J. Liu, *Eur. J. Pharmacol.* **2004**, *500*, 221–230.
- [2] Mo Jun Xiong, Zhong Hui Li, *Curr. Org. Chem.* **2007**, *11*, 833–844.
- [3] A. Díaz-Rodríguez, I. Lavandera, S. Kanbak-Aksu, R. A. Sheldon, V. Gotor, V. Gotor-Fernández, *Adv. Synth. Catal.* **2012**, *354*, 3405–3408.
- [4] A. Di Mola, L. Palombi, A. Massa, *Curr. Org. Chem.* **2012**, *16*, 2302–2320.
- [5] R. Karmakar, P. Pahari, D. Mal, *Chem. Rev.* **2014**, *114*, 6213–6284.

- [6] X. Han, H. Wu, C. Dong, P. Tien, W. Xie, S. Wu, H.-B. Zhou, *RSC Adv.* **2015**, *5*, 10005–10013.
- [7] X. Han, C. Dong, H.-B. Zhou, *Adv. Synth. Catal.* **2014**, *356*, 1275–1280.
- [8] X. Han, H. Shu, B. Tian, H. Wu, S. Wu, H. Zhou, *Benzo Lactone Compounds and Application Thereof in Preparation of Anti-Aids Medicines*, **2014**, CN103980238A.
- [9] Samuele Calò, D. Tondi, A. Venturelli, S. Ferrari, P. Pecorari, M. Rinaldi, S. Ghelli, P. M. Costi, *Arkivoc* **2004**, *2004*, 382.
- [10] G. Hirai, T. Shimizu, T. Watanabe, Y. Ogoshi, M. Ohkubo, M. Sodeoka, *ChemMedChem* **2007**, *2*, 1006–1009.
- [11] M. Hess, A. Schulze Elfringhoff, M. Lehr, *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 946–957.
- [12] A. Forsbach, G. B. Lipford, C. M. Zepp, *Small Molecule Toll-like Receptor (TLR) Antagonists*, **2005**, WO2005007672A2.
- [13] Y. Fukuda, K. Hori, T. Kitayama, Y. Nishizawa, *Vasodilator*, **1995**, JPH07206843A.
- [14] K. Nozawa-Kumada, S. Kurosu, M. Shigeno, Y. Kondo, *Asian J. Org. Chem.* **2019**, *8*, 1080–1083.
- [15] D. Parmar, M. S. Maji, M. Rueping, *Chem. - Eur. J.* **2014**, *20*, 83–86.
- [16] H. Egami, J. Asada, K. Sato, D. Hashizume, Y. Kawato, Y. Hamashima, *J. Am. Chem. Soc.* **2015**, *137*, 10132–10135.
- [17] L.-N. Guo, Y.-R. Gu, H. Yang, J. Hu, *Org. Biomol. Chem.* **2016**, *14*, 3098–3104.
- [18] L. Mahendar, G. Satyanarayana, *J. Org. Chem.* **2015**, *80*, 7089–7098.
- [19] J. P. Ariyaratna, F. Wu, S. K. Colombo, C. M. Hillary, W. Li, *Org. Lett.* **2018**, *20*, 6462–6466.
- [20] J. M. Shikora, C. Um, Z. M. Khoder, S. R. Chemler, *Chem. Sci.* **2019**, *10*, 9265–9269.
- [21] D. Felipe-Blanco, J. C. Gonzalez-Gomez, *Eur. J. Org. Chem.* **2019**, *2019*, 7735–7744.
- [22] Y. Kondo, M. Asai, T. Miura, M. Uchiyama, T. Sakamoto, *Org. Lett.* **2001**, *3*, 13–15.
- [23] Y. Nakamura, S. Yoshida, T. Hosoya, *Chem. Lett.* **2017**, *46*, 858–861.
- [24] D. Catel, F. Chevallier, F. Mongin, P. C. Gros, *Eur. J. Org. Chem.* **2012**, *2012*, 53–57.
- [25] D. Catel, O. Payen, F. Chevallier, F. Mongin, P. C. Gros, *Tetrahedron* **2012**, *68*, 4018–4028.
- [26] O. Payen, F. Chevallier, F. Mongin, P. C. Gros, *Tetrahedron: Asymmetry* **2012**, *23*, 1678–1682.
- [27] S. Touchet, S. S. R. Kommidi, P. C. Gros, *ChemistrySelect* **2018**, *3*, 3939–3942.
- [28] A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333–4339.
- [29] Lee, Jong Chan, Bae, Yong-Hun, Chang, Suk-Kyu, *Bull. Korean Chem. Soc.* **2003**, *24*, 407–408.
- [30] J. Francos, P. C. Gros, A. R. Kennedy, C. T. O'Hara, *Organometallics* **2015**, *34*, 2550–2557.
- [31] E. Hevia, R. E. Mulvey, *Angew. Chem., Int. Ed.* **2011**, *50*, 6448–6450.
- [32] B. Tchoubar, A. Loupy, in *Salt Effects in Organic and Organometallic Chemistry*, VCH, New York, **1992**, pp. 1–322.
- [33] D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624–1654.
- [34] Paul. Caubere, *Chem. Rev.* **1993**, *93*, 2317–2334.
- [35] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336.
- [36] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958–2961.
- [37] P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079–8081.
- [38] S. Bachmann, B. Gernert, D. Stalke, *Chem. Commun.* **2016**, *52*, 12861–12864.
- [39] R. Neufeld, D. Stalke, *Chem. Sci.* **2015**, *6*, 3354–3364.
- [40] R. J. Altenbach, L. A. Black, S.-J. Chang, M. D. Cowart, R. Faghhi, G. A. Gfesser, Y.-Y. Ku, H. Liu, K. A. Lukin, D. L. Nersesian, Y.-M. Pu, M. P. Curtis, US patent 20050256309A1, **2005**.



Surprisingly (rac)-(BIPHEN)BuMgLi(THF)_xLi⁺Cl⁻. Metal halogen exchange, using the bimetallic organomagnesiato 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 magnesiato (rac)-(BIPHEN)BuMgLi was the only MHE agent we tested which allowed this transformation and it has been characterized by solution-state ¹H, ⁷Li and ¹H DOSY NMR experiments and used for the synthesis of known biological active molecule.

@L2CM_UMR7053, @oharalab