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Organomagnesiates-Promoted Enantioselective Cascade Process: Straightforward Access to Chiral 3-Substituted Isobenzofuranones

Dr. Sabrina Touchet,^[a] Sai Shradha Reddy Kommidi,^[a] and Dr. Philippe C. Gros*^[a]

Abstract: The bimetallic organomagnesiates ate complex (*S*)-(BIPHEN)BuMgLi is reported here as a dual efficient halogen-metal exchange and chirality transfer agent in the reaction of ethyl-2-iodobenzoate with aldehydes leading to the formation of various chiral 3-substituted isobenzofuranones in good yields and enantiomeric ratios.

Introduction

Chiral 3-substituted isobenzofuranones are widespread in many natural compounds and have demonstrated their interest in medicinal chemistry^[1–5] (Figure 1). They are also very useful building blocks to create more sophisticated organic molecules.

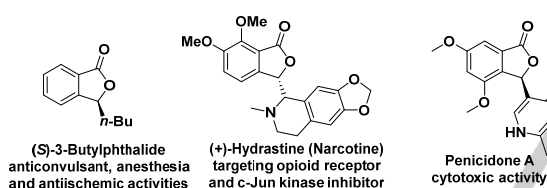
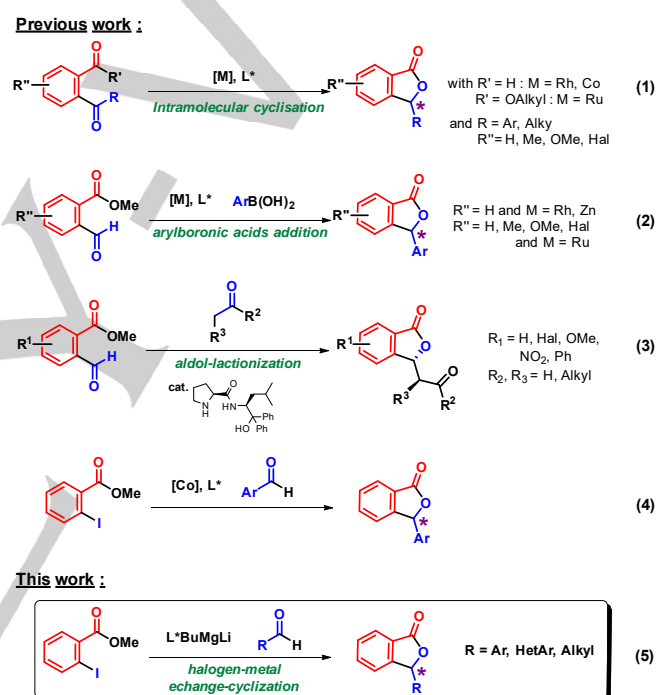


Figure 1. Examples of natural chiral 3-substituted phthalides with reports biological activities.

Few synthetic methodologies have been developed to access these key-compounds, mainly with the use of transition metal catalysts.

Intramolecular metal-catalyzed (Rh^[6], Co^[7] or Ru^[8]) cyclization leads to chiral 3-substituted isobenzofuranones with good yield and ee but suffer from the fact that the diversity is brought by the starting material that has to be prepared ahead (Scheme 1, Eq. (1)). Another efficient way is the enantioselective addition of arylboronic acids to methyl 2-formylbenzoates using a rhodium^[9], zinc^[10], or ruthenium^[11] transition metal catalyst (Scheme 1, Eq. (2)). An organocatalyzed aldol-lactonization reaction, to our knowledge, the only transition metal-free route, allowed the formation of 3-aliphatic substituted isobenzofuranones with good yield and ee (Scheme 1, Eq. (3)).^[12] Another promising route to furanones is the halogen-metal exchange-cyclisation, here catalyzed with cobalt (Scheme 1, Eq. (4)).^[13]

However, halogen-metal exchange (HME) can proceed in a stoichiometric process with polar metallation reagents, from the main group metals, as *i*PrMgCl^[14,15] or bimetallic Bu₃MgLi.^[16,17] To our knowledge, no asymmetric version of this latter reaction has been reported yet using this type of reagents.



Scheme 1. Way to access chiral 3-substituted isobenzofuranones.

In the past few years, our laboratory has been focusing on developing chemistry using bimetallic ate complexes from main group metals. Our group recently reported the preparation and use of chiral organomagnesiates for the asymmetric synthesis of pyridyl and pyrazyl carbinols.^[18–20] This was made possible by the ability of the central magnesium to easily accommodate chiral ligands such as (*R,R*)-TADDOL or (*R*)-BIPHEN H₂. The X-Ray and NMR characterization of the BIPHEN-based magnesiates and resulting azinylorganometallic intermediate revealed a perfectly controlled arrangement of the ligands around the central metal^[21] as a single compound, and therefore not as an aggregate, allowing for a high level of enantiocontrol along the reaction of azinylmagnesiates with aldehydes.

Based on these precedents, we initiated a research program with the aim of exploring the reactivity of chiral organomagnesiates for

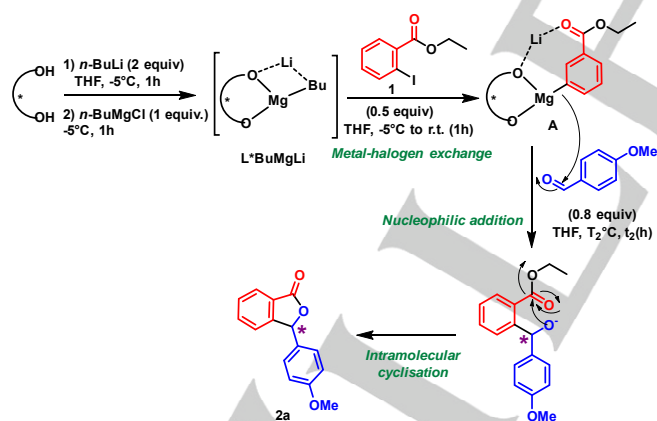
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the synthesis of chiral 3-various-substituted isobenzofuranones (Scheme 1, Eq. (5)). Herein we report that a BIPHEN-based chiral butylmagnesiates efficiently promotes the enantioselective magnesiation-lactonization of 2-halogenobenzoates, opening access to chiral 3-substituted Isobenzofuranones.

Results and Discussion

The reaction was first investigated starting from 2-Ethyl-iodobenzoate (**1**) and *p*-Anisaldehyde as a model substrate (Scheme 2). Various chiral ligands have been investigated focusing on bidentate ones (Figure 2).^[18] The chiral diol was first deprotonated using *n*-BuLi (2 equiv) in THF and the formed dialkoxide was reacted with *n*-BuMgCl (1 equiv) in order to get L*BuMgLi. Ethyl-2-iodobenzoate (**1**) was then reacted with the magnesiate and the mixture quenched with *p*-Anisaldehyde as shown in scheme 2. For the formation of L*Bu₂MgLi₂, another equivalent of *n*-BuLi is added after *n*-BuMgCl step.^[19] A prior optimization of the iodine-magnesium exchange step indicated the need of 2 equiv of L*BuMgLi for completion. This could be explained by the reaction of L*BuMgLi with the reactive iodobutane formed during the exchange process leading to the formation of a molecule of octane (see ESI for further information - schema 1).^[17] Indeed, we showed that 1 equiv of aldehyde (related to Ethyl-2-iodobenzoate) was found sufficient to trap the intermediate arylmagnesiates **A** quantitatively. This is only possible in the absence of free butyl magnesiate after the metal-halogen exchange step (see ESI for further information - schema 2).



Scheme 2. Preparation of L*BuMgLi and reaction mechanism

The first reactions were performed with (*R,R*)-TADDOL and some of its derivatives. While the halogen-metal exchange (HME) was complete with the parent ligand and **T1**, it was not the case when moving to substitution of the phenyl group (**T2**) or replacement by naphthyls (**T3**). These last results could be explained by a too hindered resulting structure. Same results were obtained when using BINOL-based reagent ((*S*) or (*R*)): the halogen-metal

exchange was quantitative but no formation of the target lactone **2a** was observed (see ESI for more details - Table 1). We were only able to observe the formation of Ethylbenzoate, resulting from hydrolysis of the arylmagnesiates intermediate **A**. This could be the result of the poor nucleophilicity of the intermediate arylmagnesiates. It is worthy of note that the magnesiate fully tolerates the ester function which is rare for this type of polar reagent.

Far better results were obtained using (*S*)-BIPHEN H2 as the ligand, leading to the formation of the desired lactone **2a** with very good yield (83%). In order to increase the reactivity of the magnesiate,^[19] we made the corresponding L*Bu₂MgLi₂ reagent (see ESI for more details - Table 1). However, this didn't improve the formation of the target lactone **2a**.

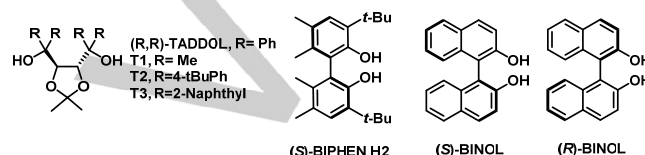


Figure 2. Chiral ligands used in the optimization of the reaction

As the best result was obtained with (*S*)-BIPHEN-BuMgLi, the influence of the reaction conditions in term of temperature (T_2) and time (t_2) has been investigated (Table 1). It can be seen that whatever the conditions, (*S*)-BIPHEN-BuMgLi promoted the formation of the enantioenriched targeted 3-substituted isobenzofuranones **2a**.

Table 1. Optimization of the reaction conditions: effects of the temperature and time on enantioccontrol during trapping-cyclization sequence using (*S*)-BIPHEN-BuMgLi.^[a]

Entry	T_2 (°C)	t_2 (h)	Yield ^[b]	e.r. ^[c]
1	-80 then r.t. ^[d]	4	67	71:29
2	-60 then r.t. ^[d]	4	83	77:23
3	-60 to r.t. ^[e]	4	64	82:12
4	-40 then r.t. ^[d]	4	76	75:25
5	-20 then r.t. ^[d]	4	69	79:23
6	-60 then -20 ^[f]	4	50	72:28
7	-60	4	63	82:18
8	-40	4	65	80:20
9	-20	4	75	78:22
10	-60	0.3	38	81:19
11	-60	1	61	85:15
12	-60	4	63	83:17
13 ^[e]	-60 ^[g]	1	84	89:11 (<i>S</i>)
14 ^[f]	-60 ^[h]	1	77	88:12

[a] Reaction conditions: (*S*)-BIPHEN-BuMgLi (1 equiv), Ethyl-2-iodobenzoate (0.5 equiv), *p*-Anisaldehyde (0.8 equiv), THF (3.5 mL). [b] Isolated yield. [c] e.r.: enantiomeric ratio determined by HPLC analysis using chiral column (Phenomenex Lux® series). [d] *p*-Anisaldehyde was added at -80°C and then the reaction was warmed to RT. [e] Cooling bath removed in every case except here. [f] *p*-Anisaldehyde was added at -80°C and then the reaction was warmed to -20°C. [g] Performed with recovered and

recrystallized ligand. [h] Performed with ligand obtained after resolution of racemic BIPHEN H2.^[22]

Good yields were generally obtained with e.r. ranging from 71:29 to 89:11. After a temperature effect investigation (Entries 1 to 9), the optimal enantiocontrol was obtained when maintaining the temperature at -60°C (Entry 7). Warming from -60°C to room temperature (removing of cooling bath) notably decreased the enantiomeric ratio (Entries 2 and 6).

It was gratifying to obtain good yields even at such a low temperature indicating that the sterically hindered liganded arylmagnesiates intermediate remained sufficiently nucleophilic to react with the carbonyl of the aldehyde.[§] Modifying the reaction time (Entries 10, 11 and 12) showed that 1h was the optimal duration. Importantly, entry 13 clearly demonstrated that the chiral ligand could be recovered safely, recrystallized and reused with success in the reaction leading to even better yield and e.r. (84% - 89:11). Of interest was also the result obtained with a sample of (S)-BIPHEN H2 resulting from the kinetic resolution of the racemic parent compound.^[22] Finally the best condition obtained for the trapping-cyclization sequence were -60°C for 1h with recycled (S)-BIPHEN H2 (Entry 13). By comparison with the literature data (see ESI), 3-(4-Methoxyphenyl)-(3*H*)-isobenzofuran-1-one **2a** was obtained as the (S) enriched enantiomer.

From these first promising results, we examined the reaction scope and limitation with a set of variously substituted aldehydes (Table 2).

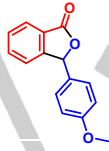
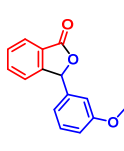
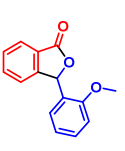
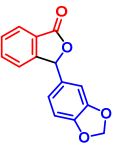
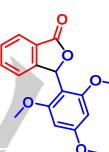
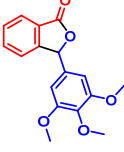
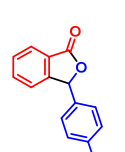
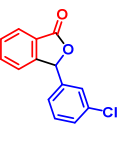
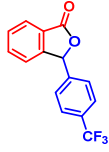
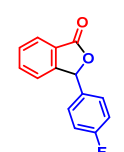
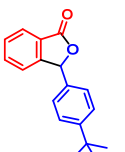
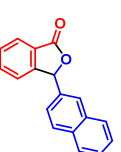
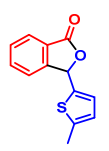
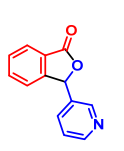
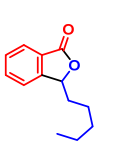
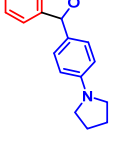
As a general trend the reaction was found efficient producing the expected enantioenriched lactones in good to excellent yields. However, the enantiomeric ratios were found dependent on the nature of the aldehyde substitution. As far as the reaction of methoxybenzaldehydes is concerned, when the methoxy group was moved from the *para* to the *ortho* position (product **2c**) the e.r. was nicely increased up to 96:4. However, the introduction of the methoxy group at the *meta* position (product **2b**), decreased the e.r. to 76:24. A similar e.r. (80:20) was obtained using 2,4,6-Trimethoxybenzaldehyde (product **2e**). Finally, when the methoxy groups were placed far from the carbonyl like in 3,4,5-Trimethoxybenzaldehyde (product **2f**) the e.r. dramatically dropped (58:42). The same situation (e.r. 59:41) can be observed when piperonal was reacting (product **2d**).

A positive effect is obtained with electron-withdrawing halogen substituents. Switching from methoxy to chloro and trifluoromethyl at the *para* position considerably raised the e.r. up to respectively 93:7 and 95:5 (products **2g** and **2i**). Changing to fluoro in *para* position lead to a e.r. similar to the -OMe substitution (88:12, product **2j**). However, when *m*-chlorobenzaldehyde was reacted, a significant decrease of e.r. (54:46) was observed (product **2h**).

Electron-releasing *tert*-butyl group allowed obtaining 80:20 e.r. (product **2k**). In contrast, the strongly donating pyrrolidine (product **2p**) was found to be deleterious leading to the racemic lactone. In this case, a competitive coordination of metallic species by the nitrogen atom could perturb the stability of the

chiral coordination complex. 2-Naphthyl aldehyde was also reacted leading to the corresponding lactone in good yield and e.r. (product **2l**). The reaction of various heteroaromatic aldehydes was next examined in order to expand the scope to the synthesis of thienyl (product **2m**) and pyridyl (product **2n**) lactones. The products were obtained in moderate to good yields with a e.r. respectively of 80:20 and 72:28. Finally enolizable 1-Hexanal was reacted leading to the corresponding alkyl lactone (product **2o**) in 51% yield and 78:22 e.r. indicating the low basicity of the intermediate magnesiate, opening new route for the synthesis of naturally occurring 3-substituted alkyl isobenzofuranones.^[23]

Table 2. Synthesis of chiral 3-substituted isobenzofuranones from various aldehydes.^[a]

			
(S)- 2a , 84%, e.r.: 89:11	(S)- 2b , 95%, e.r.: 76:24	(S)- 2c , 92%, e.r.: 96:4	(-)- 2d , 68%, e.r.: 59:41
			
(+)- 2e , 65%, e.r.: 80:20	(+)- 2f , 68%, e.r.: 58:42	(S)- 2g , 50%, e.r.: 93:7	(S)- 2h , 82%, e.r.: 54:46
			
(S)- 2i , 65%, e.r.: 95:5	(S)- 2j , 80%, e.r.: 88:12	(S)- 2k , 50%, e.r.: 80:20	(S)- 2l , 81%, e.r.: 81:19
			
(-)- 2m , 86%, e.r.: 80:20	(+)- 2n , 44%, e.r.: 72:28	(+)- 2o , 55%, e.r.: 78:22	2p , 56%, rac

[a] *Reaction conditions:* (S)-BIPHEN-BuMgLi (1 equiv), Ethyl-2-iodobenzoate (0.5 equiv), *p*-Anisaldehyde (0.8 equiv), THF (3.5 mL). [b] Isolated yield. [c] e.r.: enantiomeric ratio determined by HPLC analysis using chiral column (Phenomenex Lux® series).

Conclusions

Chiral (BIPHEN)BuMgLi organomagnesiates have been prepared from deprotonated (S)-BIPHEN H₂ and *n*-BuMgCl and used for the synthesis of chiral 3-substituted isobenzofuranones via a cascade process. This smooth reagent promoted the quantitative iodo-metal exchange of 2-iodobenzoate while fully tolerating the ester function. This allowed the reaction of the formed arylmagnesiates with several aldehydes leading to chiral lactones in good to excellent e.r. via an efficient intramolecular trapping of the intermediate chiral alkoxides. Chirality and diversity are provided in one single reaction directly from commercial available compounds. Moreover, (S)-BIPHEN H₂ has been found recyclable and reusable without any loss in yields and enantiocontrol.

Supporting Information Summary

Details of the synthesis, characterization, copies of HPLC chromatograms and NMR spectra of the compounds **2a-2p** are described. In addition, complementary information on the influence of the nature of the magnesiates and mechanism of the reaction are described.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cascade reaction • Enantiocontrol • Halogen-Metal-Exchange • Isobenzofuranone • Organomagnesiates

§ Previous studies in the group showed that lowering temperature increased e.r. but decreased yield.^[18,20]

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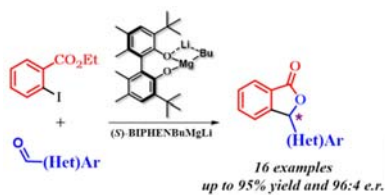
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Layout 1:

FULL PAPER

Here we report the synthesis of chiral 3-substituted isobenzofuranones using a enantioselective cascade reaction (halogen-metal exchange-cyclisation) using a polar metalation reagents (S)-(BIPHEN)BuMgLi starting from commercially available Ethyl-2-iodobenzoates and aldehydes. Chiral 3-substituted isobenzofuranones have been successfully accessed in good yields and enantiomeric ratios.

**Enantioselective cascade**

*Dr. Sabrina Touchet, Sai Shradha Reddy Kommidi, and Dr. Philippe C. Gros**

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Organomagnesium-Promoted**Enantioselective Cascade Process:****Straightforward Access to Chiral 3-****Substituted Isobenzofuranones**