

CRITICAL LIGAND AND SALT EFFECTS IN ORGANOMAGNESIATE-PROMOTED 3,3'-DISUBSTITUTED PHTHALIDES SYNTHESIS

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Summary: Phthalides are prevalent in biologically active compounds and natural products.^[1,2] In addition, these heterocycles can serve as versatile building blocks for the synthesis of natural and pharmaceutically-important products. So, efforts have been dedicated to the development of new methodologies to prepare 3,3'-disubstituted phthalide derivatives. However, 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.^[2]

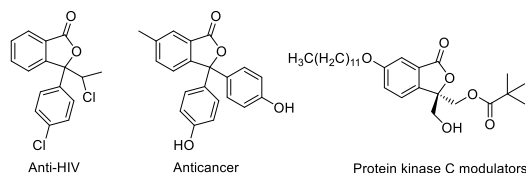


Fig. 1 Example of bioactive 3,3'-disubstituted Isobenzofuranones.

In the past few years, our laboratory has been focusing on developing chemistry using bimetallic ate complexes composed of a polar organometallic (e.g. an organolithium) and a “soft” organometallic (organomagnesium for example) in metal halogen exchange (MHE) reaction. Based on that expertise, we decided to start a research program with the aim of exploring the reactivity of organomagnesiate for the synthesis of substituted phthalides. Thereby, we showed that BIPHEN-based monobutylmagnesiate ((*rac*)-BIPHENBuMgLi where (*rac*)-BIPHEN is (*rac*)-5,5',6,6'-tetramethyl-3,3'-di-*t*-butyl-1,1'-biphenyl-2,2'-diol) can efficiently promote the MHE of easily available 2-iodobenzoate derivatives, followed by addition of a ketone which lead to an intramolecular cyclisation, and the formation of a series of new diversely 3,3'-disubstituted isobenzofuranones in good yield.^[2]

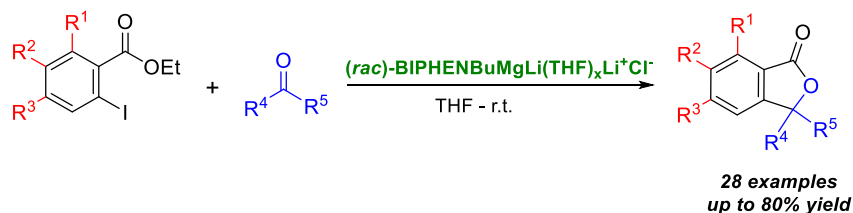
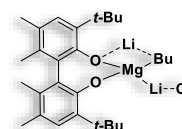


Fig. 2 Synthesis of unsymmetrical 3,3'-disubstituted phthalides.

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 ¹H, ⁷Li and ¹H DOSY NMR experiments.



References:

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2. Touchet, S.; Yearley, C.; O'Hara, C. T.; Gros, P. C., *Eur. J. Org. Chem.* **2021**, 4835-4845.