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Communication

Mechanochemically Activated Liebeskind–Srogl (L-S) Cross-Coupling Reaction: Green Synthesis of *meso*-Substituted BODIPYs

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Cite This: https://dx.doi.org/10.1021/acs.organomet.0c00037

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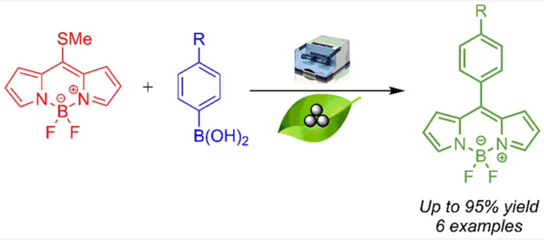
ABSTRACT: In the past decade mechanochemistry has become a highly versatile solvent-free methodology that fulfills several principles of so-called green chemistry. In this regard, we describe a mechanochemical activation protocol for the synthesis of several relevant *meso*-aryl-substituted BODIPYs via the Liebeskind–Srogl cross-coupling reaction with excellent yield and very short reaction times relative to alternative procedures in solution, thereby avoiding the use of bulk solvent. In contrast with previous assertions that the L-S reaction requires anaerobic conditions to avoid the oxidation of Cu(I) to Cu(II), our results seem to indicate that this paradigm may not be altogether accurate, since the L-S reactions studied here took place under aerobic conditions, possibly suggesting an alternative reaction mechanism.



meso-Substituted boron-dipyrromethenes (BODIPYs) are highly fluorescent compounds that constitute a valuable class of photodynamic therapy (PDT) agents,[1] with additional extensive applications in imaging,[2] in ion sensing,[3] or as components of organic solar cells.[4] Previously, *meso*-substituted BODIPYs were synthesized following the strategies described by Kreuzer[5a] and Biellmann[5b] (Figure 1). More recently, a significant number of substituted BODIPYs have been prepared through efficient strategies that employ the cross-coupling reaction known as the Liebeskind–Srogl (L-S) protocol.[6]

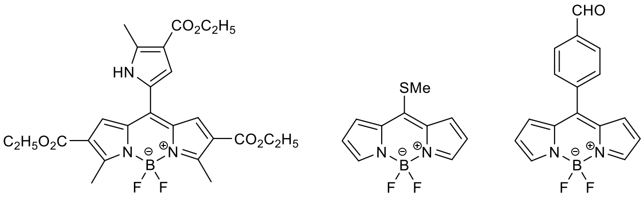


Figure 1. BODIPY serendipitously synthesized by Krauzer (**1**),[5a] Biellmann's BODIPY (**2**),[5b] and the iconic *para*-substituted phenyl BODIPY (**3a**).

The L-S cross-coupling reaction, i.e., the C–C bond formation between thioorganics and boronic acids or organostannanes,[7] is a process that takes place in the presence of a catalytic amount of Pd(0) and a stoichiometric amount of a Cu(I) carboxylate, under neutral conditions.[7,8] The remarkable results obtained when the L-S protocol is applied motivated the examination of alternative strategies such as the Suzuki–Miyaura, Stille, and Sonogashira coupling reactions in the synthesis of analogous *meso*-substituted BODIPYs.[9] Nevertheless, experimentally the L-S coupling reaction presently requires the use of an inert atmosphere and extremely dry conditions, restricting its synthetic application in coupling reactions in academic organic synthesis. Furthermore, those experimental conditions also result in increased cost in industrial settings. Finally, high-boiling-point and toxic solvents such as toluene are usually employed; thus, it is clear that a more environmentally benign protocol for the L-S coupling reaction is badly needed.[9]

In this context, in the last two decades synthetic organic chemistry has taken advantage of energetically more efficient strategies that employ nonconventional sources of energy.[10] Particularly noteworthy is the use of mechanical energy to synthesize organometallic complexes and catalysts.[11,12] Furthermore, advances in the still very young area of organometallic mechanosynthesis are enabling the development of mechanochemical metal-catalyzed processes in which the catalyst is efficiently generated by mechanochemical procedures.[12b]

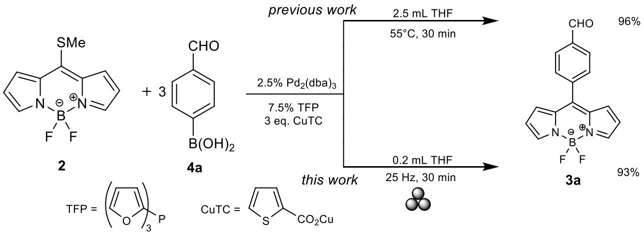
Bearing in mind the current need to develop more efficient and less polluting processes using nonconventional sources of energy[13] and the relevant application of the L-S protocol in organic synthesis,[14] we deemed it essential to explore the L-S cross-coupling reaction mediated by mechanical activation, eliminating the use of special reaction conditions and

Received: January 20, 2020

conducting a greener coupling strategy in line with the principles of green chemistry.

Accordingly, in this communication, we report the effective application of the L-S cross-coupling reaction under mechanical conditions. Considering the rather good results obtained when this coupling reaction was applied in the synthesis of *meso*-substituted BODIPYs under traditional solution conditions,[6] we proceeded to evaluate the mechanochemically activated process by adequate modification of the previously reported protocol (Scheme 1).

Scheme 1. L-S Cross-Coupling Reaction under Traditional Reaction Conditions (Upper Reaction) and under Mechanochemical Activation (Lower Reaction)[a]



[a]The three balls on the arrow represent the mechanochemical method.[16]

Initially, the L-S cross-coupling reaction was carried out under the reported conditions using a dry and deoxygenated solvent (tetrahydrofuran (THF), 2.5 mL) and under an argon atmosphere (Scheme 1; see also the Supporting Information). Gratifyingly, after 1 h of continuous stirring at 55 °C BODIPY **3a** was obtained in very high yield (96% yield of crude product), although it was contaminated with traces of several byproducts. Surprisingly, when the mechanochemical L-S coupling reaction was conducted without special precautions (i.e., reagent-grade solvent that had been exposed to air before use and not under hermetically closed conditions) analytically clean BODIPY **3a** was synthesized in 93% yield. All reagents were placed in an agate milling jar charged with one agate ball, in the presence of 0.2 mL of THF as adjuvant to improve the solubility of the reagents (liquid-assisted grinding, LAG[15]). The resulting mixture was milled for 90 min at 25 Hz of frequency (see also the Supporting Information) (Scheme 1).

As can be appreciated from Scheme 1, the rather similar results obtained when the L-S coupling reaction is activated mechanically clearly demonstrates the applicability of the mechanochemical protocol, with the additional advantage that a minimal amount of solvent is required in this case.

With the aim to optimize the mechanochemically activated L-S reaction, this reaction was subjected to different milling times and vibration frequencies. Additionally, the constituting material of the milling jar and balls was evaluated, and the nature of LAG additives was examined in the mechanochemical procedure. In this regard, the reaction progress was followed by thin-layer chromatography, confirming that the reaction was complete after 30 min of milling. At this point, the desired BODIPYs could be isolated in high yield (ca. 90%). Nevertheless, additional mechanical activation (i.e., more than 30 min of milling) promotes the production of undesirable byproducts. Mechanical energy directly associated with the milling frequency is a determining parameter for the appropriate conduction of the coupling process.[17] Hence, lower frequencies considerably reduce the reaction yield (see the Supporting Information). Therefore, a 25 Hz frequency was used for subsequent reactions.

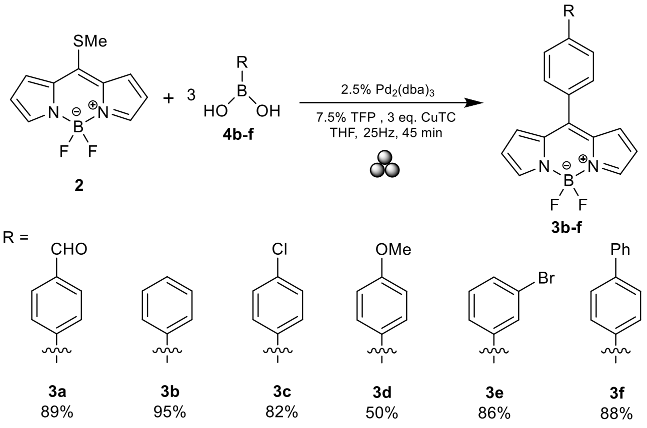
As has been demonstrated, the nature of the milling jar and balls plays a crucial role in the efficiency of the mechanochemical process.[17] In the present work, stainless steel (SS), agate, and Teflon (PTFE) components were compared in the L-S coupling reaction. It was found that the mechanochemical process proceeds in a cleaner way when an SS milling jar and balls are used. In contrast, with Teflon components a lower yield was obtained (see the Supporting Information). This effect seems to correlate with the hardness of the vial and ball materials, reaching the best results when a denser and harder material, in this case SS (ca. 7.67 g cm^{-3} and Rockwell C60, respectively)[17a] was used. Additional advantages encountered in the use of SS components are convenient scale-up processes and easier cleaning up of the reaction vessel, in addition to greater compatibility with the reagents needed for the coupling process. Therefore, we decided to use a metallic milling jar and balls during the optimization process.

As was already mentioned, when the L-S cross-coupling reaction is performed under mechanochemical conditions, it is not essential to use a dry and deoxygenated solvent. This practical observation facilitated the evaluation of a great variety of LAG additives as assistants in the mechanochemical protocol, providing mobility inside the milling jar in moderate quantities.[15] Surprisingly, polar solvents such as 1,4-dioxane and *tert*-butyl methyl ether significantly decrease the reaction yield (67% and 43%, respectively; see also the Supporting Information). Lower yields of the desired BODIPYs were also observed when a nonpolar solvent such as toluene was used (see the Supporting Information). The observed reduction in reaction yield in polar media could be associated with excessive stabilization of the metallic complexes by the LAG additive.[18,19] Notwithstanding, given the minimal amount of additive used, a direct association of the LAG effect with the observed yield is not clear at this moment. In this context, the optimum loads of boronic acid, palladium catalyst, phosphine adjuvant, and copper carboxylate were also determined in the mechanically activated L-S reaction. As it turned out, the original amounts of reagents employed in the solution reactions were also the most convenient for the mechanochemical procedure (see the Supporting Information).

Optimal L-S cross-coupling reaction conditions (1 equiv of Biellmann's BODIPY **2**, 3 equiv of boronic acid **4**, 2.5% mol of $Pd_2(dba)_3$, 7.5% mol of TFP, 3 equiv of CuTC, 0.2 mL of THF, SS milling jar and balls, and 25 Hz frequency for 30 min in an MM200 Mixer Mill (Retsch)) were then used to synthesize a variety of *meso*-substituted aryl BODIPYs by using different arylboronic acids, as shown in Scheme 2 (see also the Supporting Information).

High reaction yields were obtained when unsubstituted **4b** or electron-deficient boronic acids **4c**,**e** were used, providing BODIPYs **3b**,**c**,**e** in 95%, 82% and 86% yield, respectively. In contrast, the electron-rich substituted arylboronic acid **4d** afforded BODIPY **3d** in a low 50% yield. Saliently, reaction yields of compounds **3b**,**e**,**f** were higher under mechanical activation relative to the same process in solution (see the Supporting Information). In this regard, the reaction time required for the preparation of compounds **3b**,**f** was significantly shorter (by 25% and more than 200%, respectively) relative to procedures under the traditional solution conditions (see the Supporting Information).

Scheme 2. Arylboronic Acid Scope for the Mechanochemical L-S Cross-Coupling Reaction[a]



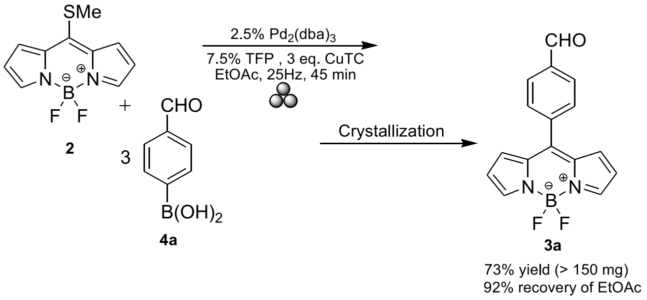
[a]An SS milling jar and balls were used.

As indicated in previous reports,[19] the nature of the copper(I) reagent is determining for the adequate outcome of the L-S reaction. Interestingly, mechanochemical cross-coupling reactions have been successfully carried out using a copper milling jar and balls.[12] Furthermore, several examples of mechanochemical transformations taking place by activation with copper reagent substitutes such as brass balls have been reported.[20] These precedents suggested the potential application of copper components in the ball mill as a convenient option in the application of mechanochemical synthetic strategies. Thus, aiming to eliminate the use of copper(I) thiophene-2-carboxylate (CuTC) in the mechanochemically activated L-S coupling reaction, we used copper balls. Unfortunately, the reaction proceeded in a very low yield (2%; see the Supporting Information for additional details).

Finally, aiming to increase the amount of BODIPY synthesized in the mechanochemical reaction, we carried out the reaction on a larger scale according to a slightly modified protocol. In particular, ethyl acetate, a green solvent, was employed successfully as an LAG additive in the cross-coupling reaction. At the end of the mechanochemical process, the product was extracted with fresh ethyl acetate and washed with basic aqueous solution. This ethyl acetate solvent was efficiently recovered by distillation and BODIPY **3** was readily crystallized to provide the pure product in 73% yield (Scheme 3).

In conclusion, a convenient L-S cross-coupling protocol activated by mechanical energy was developed for the preparation of several novel BODIPYs. This strategy avoids the use of special reaction conditions, such as inert atmosphere and dry solvents, and employs a minimal amount of liquid additive (LAG) in the coupling reaction. The optimal conditions found for the mechanochemical procedure were used to synthesize a family of *meso*-aryl-substituted BODIPYs (**3a−f**) with good results (50−95% yields) in a short time (45 min). Furthermore, sustainable techniques, such as the employment of recyclable copper, were successfully applied, confirming the adaptability of mechanochemical procedures in organometallic processes. In the same way, a greener strategy using ethyl acetate as an LAG additive in a larger-scale reaction allows for the isolation of the BODIPYs by simple crystallization. In contrast with previous assertions that the L-S requires anaerobic conditions to avoid the oxidation of Cu(I) to Cu(II), our results seem to indicate that this paradigm may not be altogether accurate, since the L-S reactions studied here took place under aerobic conditions, possibly suggesting an alternative reaction mechanism.

Scheme 3. Larger Scale Process for the Mechanochemical LS Cross-Coupling Reaction Using Ethyl Acetate (EA) for LAG additive



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00037.

Full experimental details, tables with all relevant results, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are indebted to the Consejo Nacional de Ciencia y Tecnología (CONACyT, project numbers A1-S-44097, 253623, and 123732) and SEP-CINVESTAV project No. 126. M.P.-V. thanks the CONACyT for Ph.D. scholarship No. 70766.

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