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RESEARCH ARTICLE

Metal-Free C-X Functionalization in Solid-State via Photochemistry in Ball Mills

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Abstract: We report the first metal- and catalyst-free protocol for the facile cross-coupling of aryl halides towards C-B, C-P and C-S bonds under solid-state ball milling conditions via UV light irradiation. The reactions can be performed in the absence of bulk solvents at room temperature in a mixer mill, yielding up to 99% and being tolerant towards various functionalized aryl halides (X = I or Br). Furthermore, we developed a novel photoreactor design increasing the light intensity. With this we could demonstrate that our protocol surpasses classical solvent based as well as purely mechanochemical approaches in terms of green metrics and energy efficiency.

Introduction

The C-X functionalization of aryl halides is among the most reliable transformations in synthetic organic chemistry[1] and of high relevance in catalysis,[2] material science,[3] agriculture[4] and medicinal chemistry.[5] Next to the well-known Grignard reaction using trialkyl borates[6] or phosphonates,[7] cross-coupling routes using transition metal catalysts[8] like palladium,[9] nickel,[10] copper[11] and iron[12] to form carbon-boron, carbon-phosphorous or carbon-sulphur bonds can overcome the problem of moisture- and air-sensitive intermediates. Nonetheless, due to the high amount of metal residue in the final product and the costs of these catalysts, metal-free alternatives utilizing light have emerged. Besides photochemical C-X coupling reactions using photocatalysts,[13,14,15] especially metal- and catalyst-free photochemical routes convince in atom economy and efficiency. Here, transformations of aryl halides towards C-B,[16,17] C-P,[15,18] and C-S bonds[14,19] driven by ultra-violet (UV) light were described and investigated

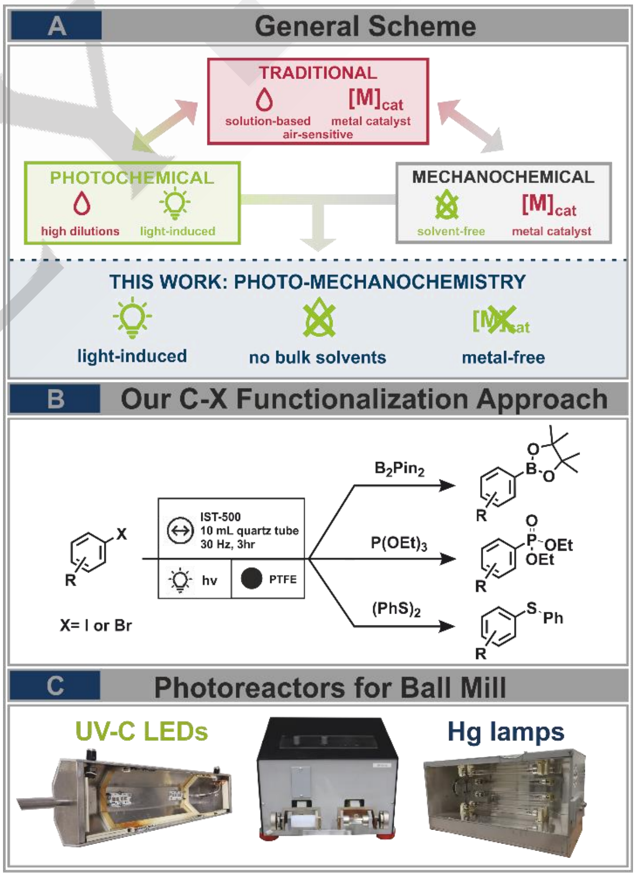

Figure 1. A: Traditional pathways towards C-X functionalization including solution-based, photochemical and mechanochemical approaches. B: Our photochemical solid-state functionalization approach of aryl halides with bis(pinacolato)diboron, triethyl phosphite, and diphenyl disulfide forming carbon-boron, carbon-phosphorous and carbon-sulfide bonds. C: Comparison of two different photoreactors (left: UV-C LEDs; right: Hg-lamps) for IST 500 ball mill (middle).

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mechanistically.[20] Yet, conventional solution-based photochemical reactions are lacking in sustainability since they are performed in highly diluted solutions leading to immense amounts of produced waste.[21] Due to the global incentives towards environmentally friendly synthesis alternatives, research on solvent free pathways is increasing. Mechanochemistry is such an alternative synthesis strategy capable to overcome these disadvantages as it is commonly performed in the solid state, avoiding bulk organic solvents. Mechanochemical synthesis describes the performance of chemical reactions under the impact of mechanical energy by ball milling [22] providing greener and more efficient reactions,[23] and also opening the pathways towards otherwise inaccessible products.[24] Recently, protocols in ball mills using Pd catalysts emerged to obtain organoboronic esters,[25] and aromatic thioethers [26], but similar to solution-based transition-metal synthesis these protocols are lacking in terms of metal contamination (**Figure 1A**). Other publications avoided metal catalysts by using highly reactive diazonium salts which are potentially explosive.[27,28]

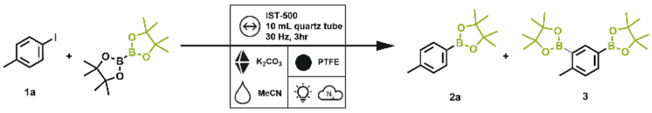
Therefore, it would be a significant step in development if one could marry mechanochemistry and its advantages of solvent-free chemistry with photochemistry and its advantages of metal-free chemistry.[29] Yet, the limited availability of suitable transparent milling vessels has hindered developments.[30,31] Existing vessels, primarily made from opaque materials, restrict the application of photochemical procedures and poly(methyl methacrylate) (PMMA) vessels used in previous attempts, e.g. for a visible light mediated borylation of aryldiazonium salts, are not resistant against organic chemicals.[30] Recently, Millward *et al.* proposed the usage of round-bottomed glass vials encapsuled inside PMMA vessels. Thus, while possible damage during the mechanophotocatalytic approaches could be avoided, sufficient light penetration, especially for UV light, is hindered by an additional layer of material.[32] Our working group has recently addressed this challenge and designed quartz glass milling vials transparent to UV light, opening up the opportunities for photochemical reactions with higher energy light.[33] This innovation has overcome a major hurdle enabling efficient photochemical organic transformations without metal catalysts and bulk solvents.

In this work, we propose a novel, robust and facile C-X functionalization of aryl halides towards organoboron compounds, phosphonates, and aryl thioethers by irradiation with UV-C light inside a ball mill in the absence of bulk solvents and transition-metal or organic catalysts (**Figure 1B**). To enable more illumination power, we also developed a new photoreactor design based on low-pressure Hg fluorescence tubes providing a six times higher light efficiency, leading to significant acceleration of the reaction (**Figure 1C**). This protocol avoids metal contamination and benefits from a better atom economy and superior Eco-scale as compared to literature-known protocols.

Results and Discussion

Reaction Development

Table 1: Evaluation of optimal reaction conditions of borylation reaction.



Entry	Evaluated Parameter	Yield[a] (%)	
		2a	**3**
1	Standard[b]	23	0
2	Under N_2	39	0
3	1 eq. K_2CO_3	30	4
	Amount of bis(pinacolato)diboron[c]		
4	0.5 eq. B_2Pin_2	23	4
5	1.5 eq. B_2Pin_2	26	7
6	3 eq. B_2Pin_2	37	10
	Bulk material		
7	Celite 545[d]	56	15
8	$BaSO_4$	39	8
9	Al_2O_3 acidic	57	11
10	K_2CO_3	66	15
	Ball size and material		
11	PTFE (5mm)	76[e]	19
12	ZrO_2 (2mm)	68	11
	Reference experiments under optimized conditions		
13	MeCN (η=0)	6	0
14	No light	0	0
15	No milling	54	12
16	No shaking	41	7
	Comparison of photoreactors for ball mills, 1h reaction time		
17	LED	19	4
18	Hg lamps	98	2

[a] determined by ^{1}H-NMR spectroscopy. [b] Reaction conditions if not stated otherwise: 0.46 mmol **1a**, 1 eq. bis(pinacolato)diboron, 1 g SiO_2 (bulk) and MeCN (η=0.15) were filled inside a quartz glass tube with PFA closures and 2 PTFE balls (d= 10 mm) and milled at 30 Hz for 3 h under irradiation of 12 LEDs (λ=272 nm, L=22.5 W*m^{-2}). [c] equimolar amount of K_2CO_3 in comparison to B_2Pin_2. [d] 0.5 g were used as bulk material due to the powder density [e] isolated yield by flash chromatography: 41%.

We started our investigation by optimizing the reaction parameter for the photochemical borylation reaction under solid-state conditions. Therefore, 4-iodotoluene (**1a**, 0.46 mmol), bis(pinacolato)diboron (B_2Pin_2, 1 eq.), and silica (1 g as the bulk material) were mixed inside a quartz glass tube enclosed by two perfluoroalkoxy alkane (PFA) lids with two PTFE milling balls (d = 10 mm). Together with MeCN (η=0.15, as LAG additive) the solids were milled under ambient conditions in a vibratory ball mill (IST500, InSolido

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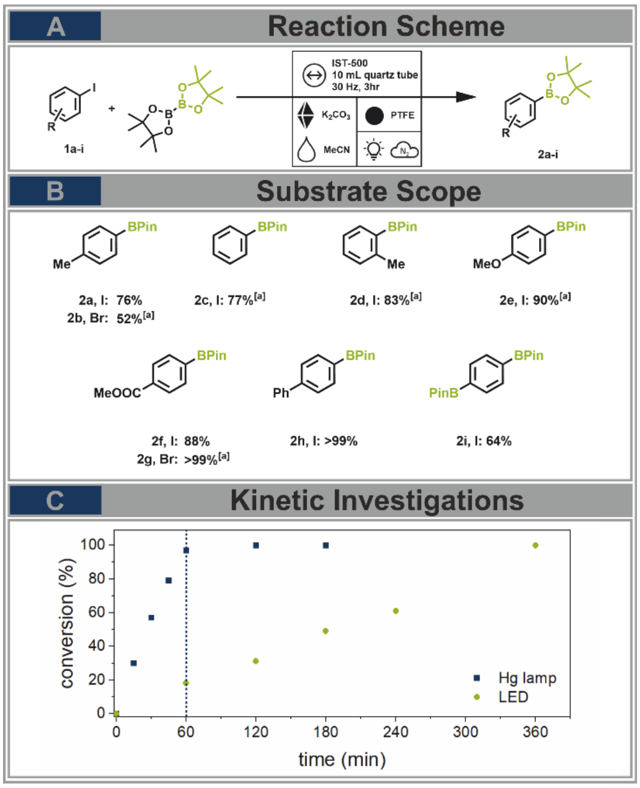

Figure 2: A: Photochemical solid-state borylation reaction of aryl halide and $B_2(Pin)_2$. B: Investigated substrates during the substrate scope with corresponding yields according to ^{1}H-NMR spectroscopy. Reaction conditions as follows: 100 mg aryl halide, 3 eq. $B_2(Pin)_2$, 1.19 g K_2CO_3, MeCN (η=0.15), inside a quartz glass tube with PFA closures with 18 PTFE balls (d=5 mm) milled at 30 Hz for 3 h under N_2. [a] reaction time: 8 h. C: Comparison of kinetic performance of the reaction while using different photoreactors based either on LED (green) or on low-pressure Hg lamps (blue). Reactions were performed independently for adjusted periods with reaction conditions as follows: 0.46 mmol 4-iodotoluene, 3 eq. $B_2(Pin)_2$, 1.19 g K_2CO_3, MeCN (η=0.15) inside a quartz glass tube with PFA closures with 18 PTFE balls (d=5 mm) milled at 30 Hz. prepared under N_2.

Technology) at 30 Hz for 3 h under constant irradiation of 12 UV-light emitting diodes (LEDs) (**Figure S2**). Under these conditions, we obtained 23% of the desired borylation product 4,4,5,5-tetramethyl-2-(p-tolyl)-1,3,2-dioxaborolane (**2a**) (**Table 1**, Entry 1) according to ^{1}H-nuclear magnetic resonance (NMR) spectroscopy. To prevent possible side reactions with oxygen,[34] we performed the same reaction under inert conditions (**Table 1**, Entry 2) and observed 39% yield. Interestingly iodine radicals are generated during the reaction, which is clearly indicated by the pink colour of the NMR solution. To capture these radicals and thus simplifying the work-up, we added K_2CO_3 to the reaction leading to a successful capturing as KI, but a reduced yield of 30% according to ^{1}H-NMR spectroscopy (**Table 1**, Entry 3) (**Figure S9**). In literature, K_2CO_3 is further used to stabilize the B-B bond cleavage by forming a nucleophilic sp^2-sp^3 Lewis base diboron adduct.[35] Please note that up to this point, however, we still observe small amounts of a side product, the 1,3-diborylation adduct 2,2'-(4-methyl-1,3-phenylene) bis[4,4,5,5-tetramethyl-1,3,2 dioxaborolane] (**3**). This observation hints at a possible radical pathway of the reaction similar to the observations in previous publications.[28,36] To improve the product formation, we performed reactions with 0.5, 1.5, and 3 equivalents of B_2Pin_2 to determine the optimal amount of the borylating agent (**Table 1**, Entries 4-6). Surprisingly, only the latter reaction showed an increased yield of 37% according to ^{1}H-NMR spectroscopy, while the prior reactions remained unchanged. We continued our investigations using 3 eq. of B_2Pin_2 in all further reactions. Although silica is beneficial as a bulking material in terms of the rheology of the reaction mixture, we observed low isolated yields, which can be explained by the decomposition of organoboronic acids and esters by silica dioxide.[37] Therefore, we screened different materials as milling auxiliaries, including Celite, barium sulphate ($BaSO_4$), aluminium oxide (Al_2O_3), and an excess of K_2CO_3 (**Table 1**, Entry 7-10). As K_2CO_3 performed best, giving 66% of **2a** and was present for iodine radical capture anyway, we used it from hereon as bulk material. However, changes of the bulk material impact the reaction rheology greatly, i.e. from a fine powder towards a paste-like reaction mixture causing agglomeration of the substrates inside the PFA lids. We decided to screen different milling ball sizes to improve the distribution of the solids. Therefore, we decreased the milling ball size using 5 mm PTFE balls (qty=18), observing 76% yield (**Table 1**, Entry 11). A further decrease to 2 mm ZrO2 milling balls (9 g) gave 68% (**Table 1**, Entry 12), while in this case the decreased size and weight again led to accumulation of the reaction mixture. We continued our investigations using 18 PTFE balls with a diameter of 5 mm and examined the influence of the liquid additive. Neat grinding of **1a** with B_2Pin_2 and K_2CO_3 resulted in an accumulation of solids inside the PFA lids and only 6% yield due to the lack of efficient irradiation of the reaction mixture (**Table 1**, Entry 13). The optimized conditions defined in **Table 1**, Entry 11, were used to examine the mechanochemical and photochemical influences of the setup on the reaction. We observed no formation of **2a** or **3** when milling was conducted without light. This confirms the exclusively photochemical-driven nature of the reaction (**Table 1**, Entry 14). The absence of milling balls while mixing the reaction mixture at a frequency of 30 Hz decreased the yield to 54% compared with the optimized conditions (**Table 1**, Entry 15). Furthermore, we observed only 41% yield when the reaction mixture was irradiated in the absence of shaking (**Table 1**, Entry 16). As the reference reaction has demonstrated, the mechanical energy is not the driving-force for the reaction, but it is increasing mixing of the reaction mixture. This process ensures a constant renewal of the outer layer of the solid powder, thereby facilitating the exposure of unreacted substrates to the UV light- a common problem in solid-state photochemistry. To demonstrate the applicability of our protocol, we tested a variety of aryl halides (X= I or Br) bearing different functional groups (**Figure 2B**). While we observed excellent yields for electron-rich aryl halides under the previously optimized conditions, the functionalization of electron-poor substrates required elongated reaction times to achieve product formation up to >99% (for detailed information on the purification see ESI).

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We were able to further optimize the photochemical influence by designing a novel photoreactor based on low-pressure Hg-lamps, in which the number of emitted photons was increased by a factor of five due to the higher light intensity (see calculation of number of photons in SI, Chapter 1.2.5). We tracked our model reaction of **2a** under optimized conditions at different reaction times by ex-situ ^{1}H-NMR spectroscopy (**Figure 2C**, blue) and compared the kinetic behaviour to our previous investigations (**Figure 2C**, green). Using the Hg lamp photoreactor dramatically increased the reaction rate: the reaction was completed after 1 h of milling and lamp irradiation, while the UV-LED photoreactor showed only 20 % yield after the same time and a total conversion after 6 h (**Table 1**, Entries 17-18). Under these optimized parameters, we observed that the reaction performs just as efficiently under ambient conditions due to the increased reaction rate, eliminating the need for an inert atmosphere and a glovebox. Further information, emission spectra, and a detailed comparison of the photoreactors can be found in the supporting information.

Comparison of Synthesis Protocols

Table 2: Calculation of the Eco-Scale under additional consideration of the reaction time and the specific energy consumption.

Penalty points	Solution/ Cu[38]	Solution/ UV[17]	Ball mill/ vis[30]	Ball mill/ UV[a]
Yield	0[b]	9.5[c]	3[c]	0.5[c]
Price[d]	5	5	5	5
Safety	20	5	10	0[e]
Technical setup	5	2	2	2
Temperature/time	1	1	1	0
workup	10	10	10	12
Total	41	32.5	31	19.5
Eco-Scale	59	67.5	69	80.5
Reaction time [h]	17	4	1.5	1
Specific Energy consumption [kWh/mmol]	234	13.6	0.68	0.36

[a] under optimized conditions using the photoreactor based on Hg-tubes. [b] determined by GC-MS spectrometry. [c] determined by ^{1}H-NMR spectroscopy. [d] Price of reaction components for 10 mmol of product. [e] Note: the calculation of the Eco Scale by van Aken overlooks the safety implications of using UV light.

To examine the ecological benefit of our model reaction towards aryl boronic esters, we compared traditional solution-based photochemical routes using either a copper catalyst or UV light, a mechanochemical approach using visible light under the addition of Eosin Y as the photocatalyst, and our reaction under consideration of the Eco-scale by van Aken *et al.* (**Table 2**).[39] The copper-catalysed borylation reaction in solution scored the lowest with an Eco-scale of 56, mainly due to the choice of hazardous solvents involved in the reaction scoring, 20 penalty points in the safety category. This reaction also required the longest reaction time of up to 22 h. The solution-based photochemical borylation reaction scored better (65.5 points) because safer solvents such as acetonitrile and water were used, and the reaction was performed within 4 h. The mechanochemical approach with visible light by Hernández *et al.* performs well in terms of efficiency (1.5 h) and yields. Still, it involves highly reactive diazonium salts as substrates, which may be explosive under impact and shearing forces, leading to an Eco-scale of 69. Our optimized photochemical approach starting from commercial aryl halides performs best in terms of safety scoring 80.5 points on the Eco-scale. But also, in the context of energy consumption, the approach presented here is advantageous, with 0.36 kWh/mmol being twice as efficient as the organocatalytic-mechanochemical approach and 1-3 orders of magnitude better than both solution-based alternatives.

C-X functionalization

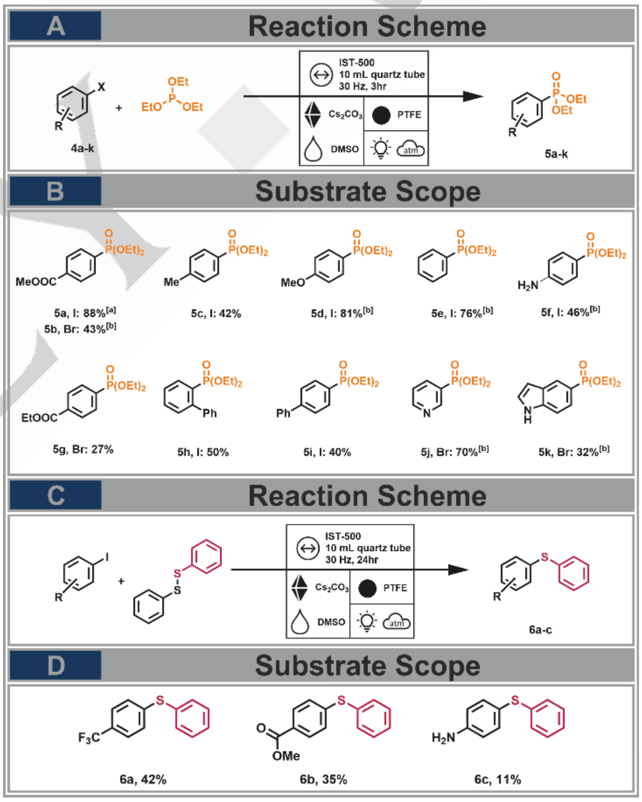

Figure 3: A: Photochemical phosphonation reaction of aryl halide and $P(OEt)_3$ in the ball mill. B: Investigated Substrates during the substrate scope with corresponding yields according to ^{1}H-NMR spectroscopy using dibromo methane as an internal standard. Reaction conditions as follows: 100 mg aryl halide, 3 eq. $P(OEt)_3$, 2 eq. Cs_2CO_3, 1 g silica, DMSO (η=0.15) inside a quartz glass tube with PFA closures with 18 PTFE balls (Ø=5 mm) milled at 30 Hz for 3 h. [a] isolated yield [b] reaction time: 8 h. C: Photochemical thiolation reaction of iodoarene and S_2Ph_2 in the ball mill. D: Investigated substrates during the substrate scope with corresponding yields according to ^{1}H-NMR spectroscopy using dibromo methane as an internal standard. Reaction conditions as follows: 100 mg aryl halide, 3 eq. S_2Ph_2, 2 eq. Cs_2CO_3, 1 g silica, DMSO (η=0.15) inside a quartz glass tube with PFA closures with 18 PTFE balls (Ø=5 mm) milled at 30 Hz for 24 h.

Apart from the photochemical borylation of aryl halides, we were successful in transferring our protocol to the facile formation of carbon-phosphorous as well as carbon-sulphur bonds under solid-state conditions by slightly adjusting the reaction parameters (**Figure 3**). Therefore, we continued our investigations on the photochemical solid-state phosphonation of 4-methyl iodobenzoate (**1f**) with triethyl phosphite ($P(OEt)_3$) as our model reaction by screening different bulk materials, various amounts of base as well as different solvents as LAG agents (for detailed representation of the parameter screening see supporting information **Table S3**). The optimal reaction parameters were established to 0.38 mmol 4-methyliodobenzoate, 3 eq. triethyl phosphite, 2 eq. caesium carbonate, 1 g silica as bulk material and DMSO (η=0.15) as LAG agent being milled in our standard quartz glass vessel at 30 Hz for 3 h under constant irradiation of 12 LEDs (λ=272 nm, L=22.5 W*m^{-2}) giving 88 % isolated yield. The reaction did not proceed in the absence of light. When mixing the reaction mixture under optimized conditions without milling media, 63% **4a** were observed, while only 11% of product formation could be observed in the absence of shaking according to ^{1}H-NMR spectroscopy (see **Table S2**, Entries 22-25). Other substrates operated in excellent to moderate yields under optimized conditions, including iodo- and bromo-substituted arenes as well as heterocycles (**Figure 3B**) (for detailed information on the purification see ESI).

Similarly, our protocol was also applicable to photochemical thiolation (**Figure 3C**). 4-Iodobenzyltrifluoride was converted successfully using diphenyl disulfide giving 42% of 1-(phenylthio) 4-(trifluoromethylbenzene (**6a**) after 24 h. The lower reactivity for this reaction type observed during the substrate scope (**Figure 3D**) is likely due to the unsuitable light source mediating the reaction. Similar to the previous functionalization protocols, a reference reaction in the absence of light resulted in no product formation at all.

To understand the mechanism of the reaction better, we performed a radical trapping experiment with 2,2,6,6-tetramethylpiperidinylnyloxyl (TEMPO) under our optimized conditions observing an inhibition of the product formation (**5a**) to 23%. The analysis by GC-MS revealed the formation of triethylphosphate, the oxidation product of $P(OEt)_3$, but no formation of TEMPO-adduct was detected. **Figure 4B** proposes a possible reaction mechanism via a radical pathway. The aryl halide is excited into the first excited state by irradiation (**I**), where the halide is detached by homolysis (**II**). The free iodine radical is trapped by a potassium carbonate moiety forming KI (see Figure S9). In the next step, the aryl radical forms (**III**) by intercepting with tri ethyl phosphite. Finally (**III**) dissociates into the desired product and an ethyl radical.

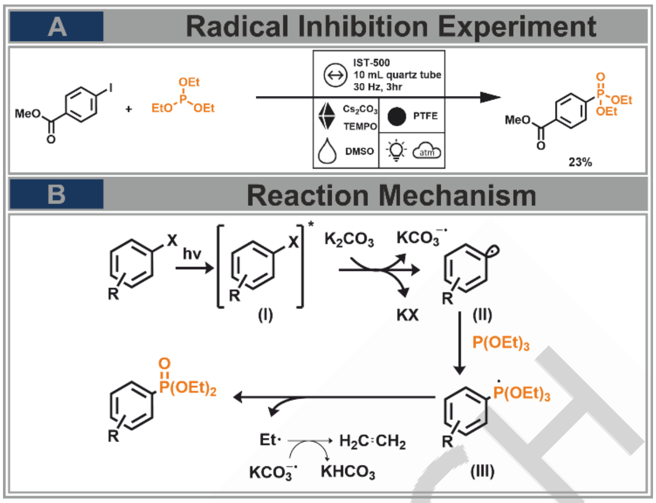

Figure 4: A: Radical inhibition experiment of the photochemical phosphonation reaction of 4-iodomethyl benzoate using 1.2 eq. TEMPO. B: Proposed reaction mechanism following a radical pathway.

Conclusion

In summary, we have reported a facile, rapid, and robust protocol for the borylation reaction of aryl halides by irradiation with UV-light under solid-state conditions without the need of catalysts or bulk solvents on the example of 4,4,5,5-tetramethyl-2-(p-tolyl)-1,3,2-dioxaborolane (**2a**). After investigating the optimal reaction parameters, we applied the method to a versatile range of commercially available substrates bearing various functional groups. We observed yields up to 99%, demonstrating its robustness and avoiding the need for highly reactive aryldiazonium salts as in previous publications. Further, we increase the reaction rate by a factor of six by presenting a novel ball mill photo reactor design based on low-pressure mercury lamps. The calculation of the green metrics compared to solution-based and mechanochemical borylation reactions revealed the ecological benefit of the method regarding safety and sustainability. Furthermore, the presented protocol using UV-C light irradiation opened a new horizon to study the reactivity of various molecules under ball mill conditions, avoiding the need for bulk solvents or metal- and photocatalysts. Here, we showed the transferability of the unique and powerful method towards C-P and C-S bond formation. The photochemical phosphonation performed in yields up to 88 % within 3 h under ambient air conditions. The related thiolation yielded 42 % of product after 24 h of irradiation. With this work, we present an innovative approach enhancing the overall sustainability and efficiency by combining photo- and mechanochemistry and enable the application of well-studied solution-based pathways in the solid-state in a ball mill under catalyst free conditions.

Supporting Information Summary

The authors have cited additional references within the Supporting Information.[40] The Supporting Information includes the experimental section with detailed information on the photoreactors, measurements, purification and characterisation. Further, it includes additional information on parameter screenings as well as detailed calculations for the Eco Scale and the specific energy consumption.

Acknowledgements

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Keywords: C-X functionalization • photochemistry• sustainable chemistry • mechanochemistry • photoreactor

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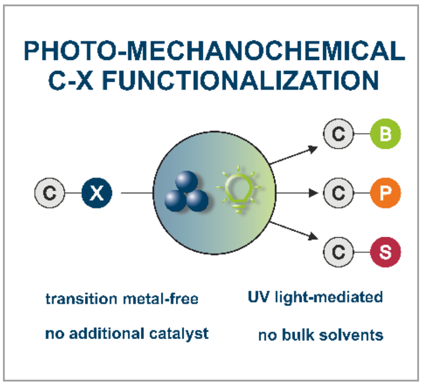

Our research introduces the first metal- and catalyst-free aryl halides cross-coupling under mechanochemical conditions via ultraviolet (UV) light irradiation towards C-B, C-P, and C-S bonds. With up to 99% yields and tolerance to diverse substrates, our approach boasts eco-friendliness and cost-effectiveness, pushing the boundaries of green chemistry. We also introduce an innovative photoreactor design, amplifying light intensity, and assess the green metrics, establishing a sustainable approach to chemical synthesis.

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