Photocatalytic and Photoinduced Phosphonylation of Aryl Halides: A Batch and Flow Study.

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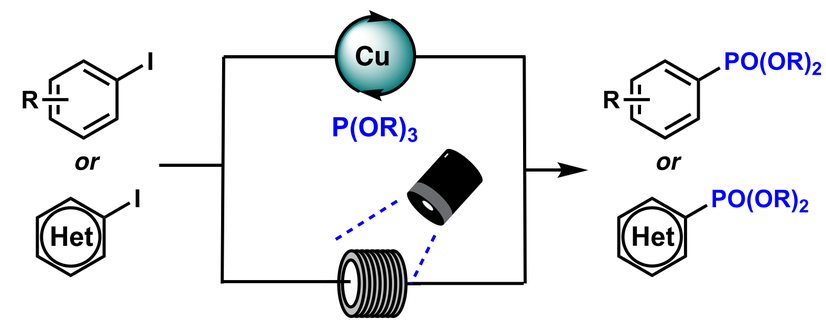
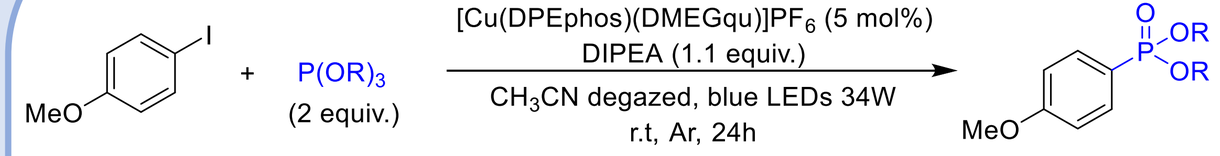
Context and aim of this work. In a society where the **environment protection** is a central concern, processes using the solar energy has a key role. Resulting from the discoveries made over the last fifty years[1,2], **photochemistry** is now considered as a promising alternative to usual chemical process, commonly used in industry. In this context, there is a growing interest for the development of original methodologies that can reduce 1/ the impact on the environmental footprint and 2/ the energy demand. There is no doubt that the use of reactions mediated or initiated by photons (light) as one of the simplest reagent in chemical transformations is becoming a crucial tool in **drugs development** in a close future.

This study discloses the **synthesis of aryl phosphonates** either using photocatalytic conditions in **batch** or photoinduced process in **continuous flow**. The **absence of noble metals**[3,4,5,6] in these methodologies enhances their interests for industrial application, leaded by the possibility to scale up the reaction without any impact on the reaction yield.



- ✓ Batch and continuous flow.
- ✓ 24 exemples.
- ✓ Up to 50 mmol scale.

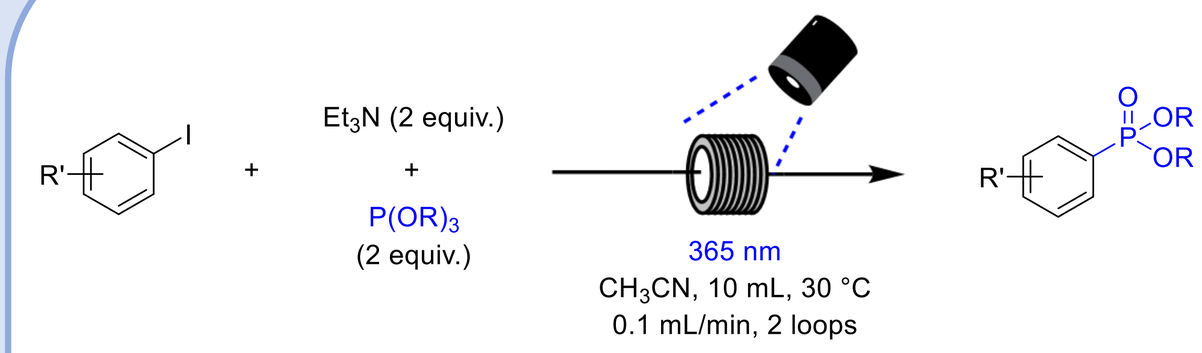
Batch Conditions



Variation from standard conditions	Yield (%)[a]
None	52
DMA, acetone, DCM, toluene, or HFIP	<15
Air atmosphere or non-degazed solvent	N.R.
Other bases (Et_3N, TMEDA, DABCO, nBu_3N, Cy_2NiBu)	<37
[Cu(Xantphos)(DMEGqu)]PF_6	24
[Cu(XantphosTEPD)(bcp)]PF_6	27
[Cu(XantphosTEPD)(phen)]PF_6	0
[Cu(N-Xantphos)(bcp)]PF_6	28

a: determined by ^1H NMR

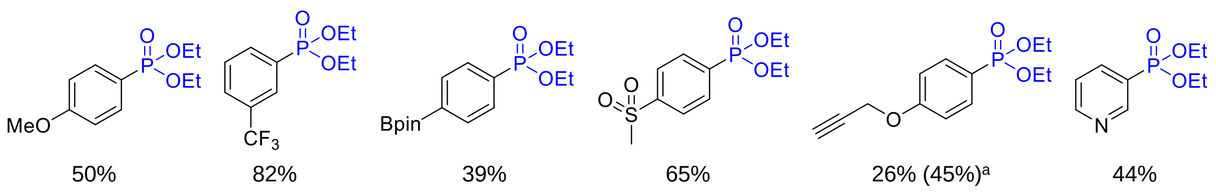
Continuous Flow Conditions



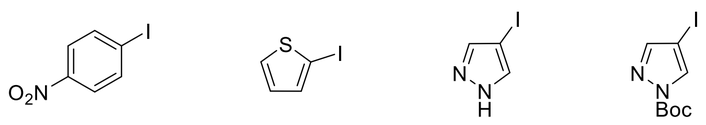
[Cu] (mol%)	Base (2 equiv.)	Yield (%)[a]
/	NEt_3	70
2.5	NEt_3	49
/	DIPEA	0
2.5	DIPEA	30

a: Isolated yield

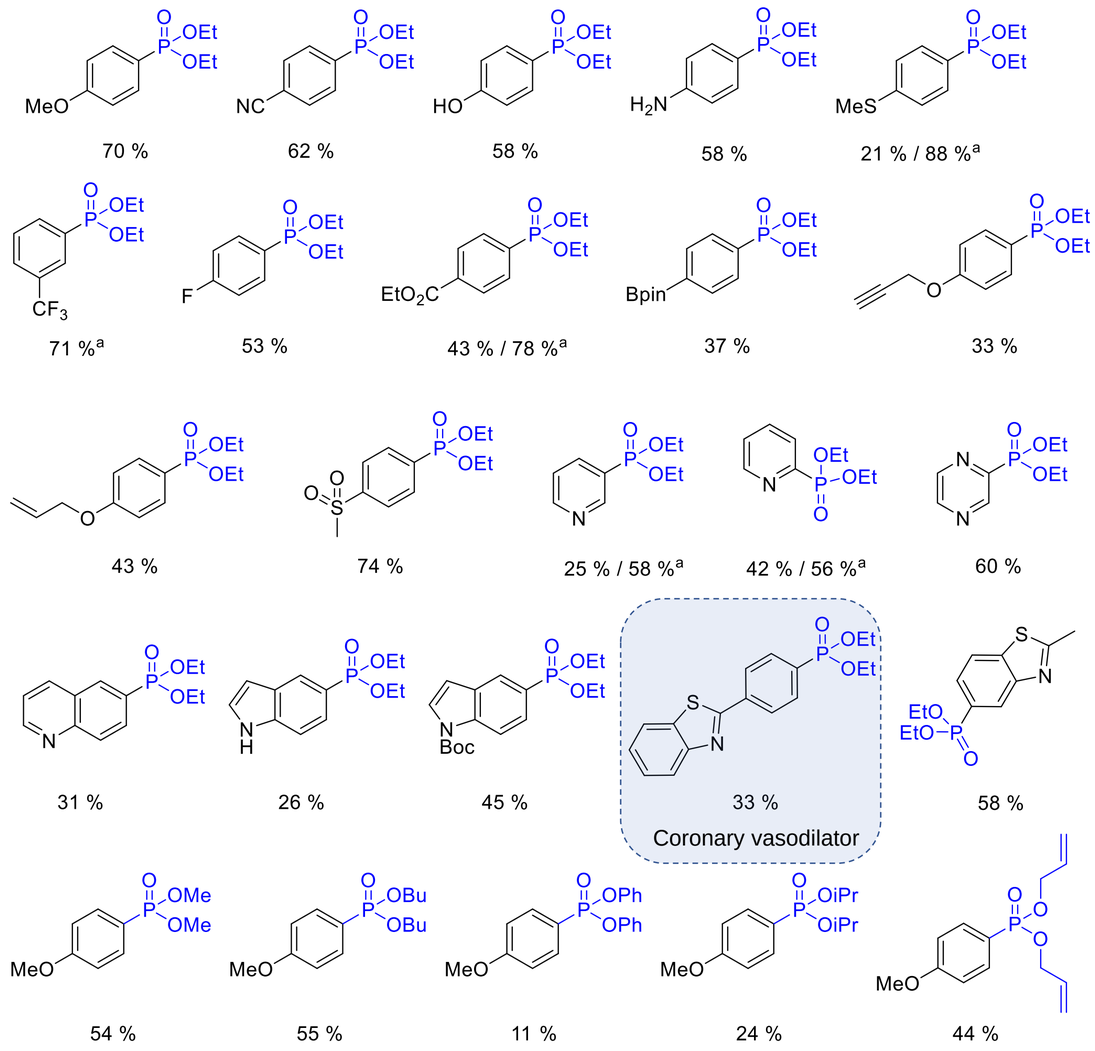
Scope Selected Exemples



Reluctant Substrats



Scope



a: 6 equiv. of phosphite.

Scale Up

- ✓ *Batch*: 3.0 g/L/h. On 50 mmol scale (0.5 L reactor).
- ✓ *Flow*: 17.8 g/L/h. On 4 mmol scale (20 mL reactor).
- ✓ Reaction yield between 71% - 78%.
- ✓ Hepatochem Company©

Conclusion. In summary, we explored the photocatalytic conversion of aryl and heteroaryl iodides using a copper photocatalyst. This reaction, developed in batch, gave moderate results and its extension to continuous flow was unfortunately inefficient. An alternative photoinduced phosphonylaton was developed under continuous flow, giving higher yields to the corresponding phosphonates. However, the low efficiency in terms of productivity, led us to investigate an alternative. A partnership with the Hepatochem Company© has showed the robustness of our methodology and has permitted to scale up the reaction in batch and in continuous flow without reduction of the yield. This scale up led to an increase of the reaction productivity.

References:

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