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New Photo-Induced Alkoxyarylation of 3-Methylene Isoindolinones Using Aryl Diazonium Salts

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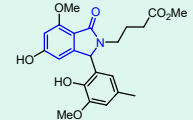
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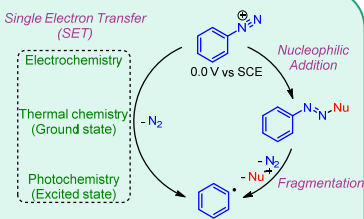
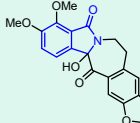
Introduction

Aryl diazonium salts are a versatile source of aryl radicals. Mechanically, two pathways are available to reduce these species to aryl radical. The first corresponds to a single electron transfer and can be operated via electrochemistry, thermal chemistry or photochemistry. The second one is an addition-fragmentation strategy.¹

Daldinan A
antioxidant
(*ascomyete Daldinia concentrica*)

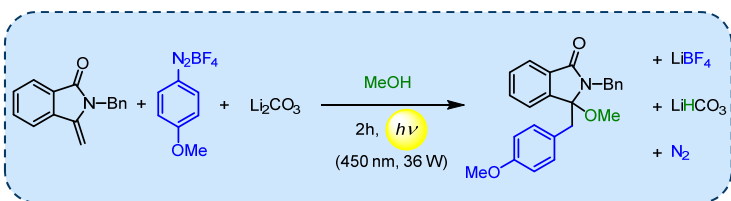


Chilenine
anti-cancer
(*Berberis empetrifolia*)



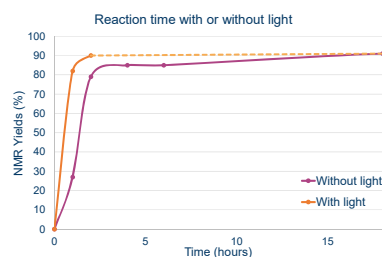
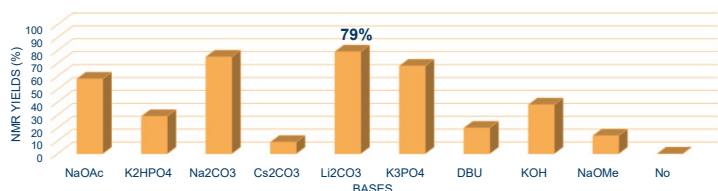
In parallel, **isoindolinones** are widely represented among natural products.² Moreover, many of these bio-sourced products have a biological activity. For example, Daldinan A³ is an antioxidant produced by the mushroom *ascomyete Daldinia concentrica*. A second example is Chilenine,⁴ which is used as an anticancer agent and is extracted from *berberis empetrifolia*.

Reaction

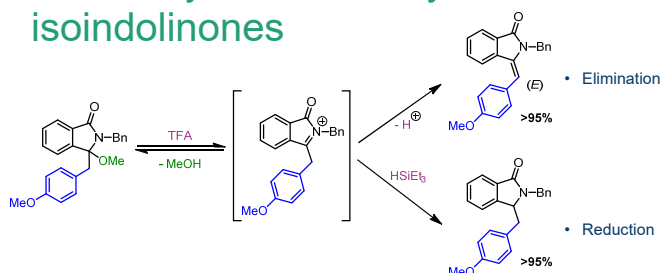


Optimization

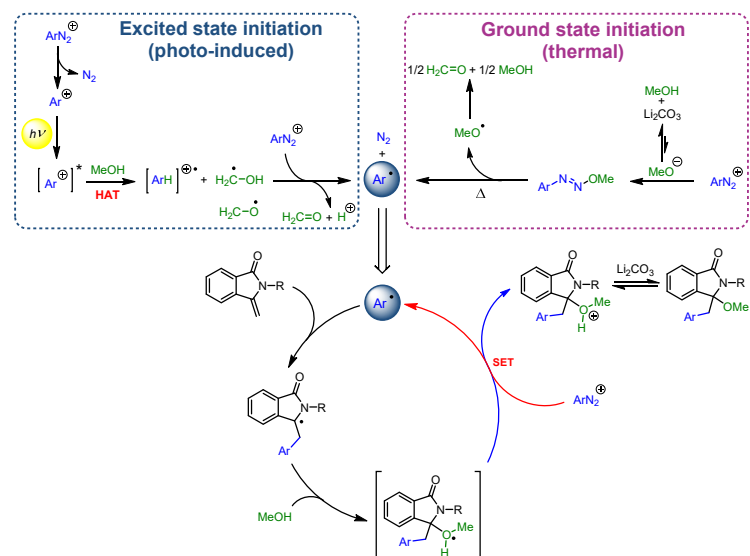
Yields / bases



Reactivity of 3-methoxy isoindolinones

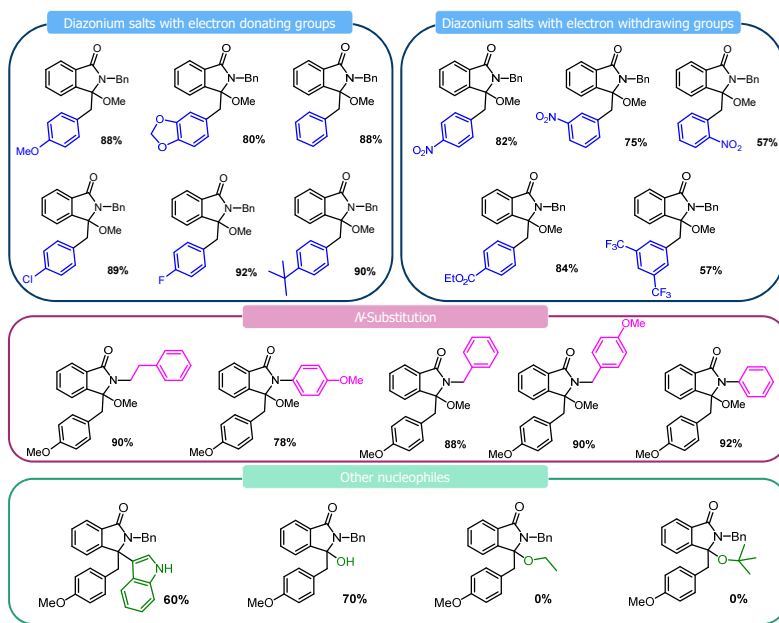


Proposed mechanisms

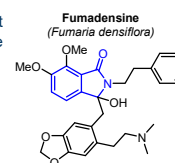


Proposed mechanism⁵ of the alkoxyarylation with two complementary initiations steps (excited state⁶ and ground state⁷)

Scope



Example of a natural isoindolinone that could be obtained via the synthetic route presented in this work.



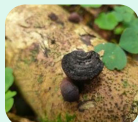
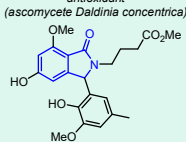
References

- [1] Tatumashvili, E.; Chan, B.; Nashar, P.E.; McErlane, C.S.P. *Org. Biomol. Chem.* **2020**, *18*, 1812 – 1819.
- [2] Sharma, M. and coll., *Fitoterapia.* **2020**, *146*, 104722 – 104745.
- [3] Yun, B.-S. and coll. *J. Antibiot.* **2012**, *65*, 95 – 97.
- [4] Moody, C. J.; Warrellow, G. J. *Tetrahedron Lett.* **1987**, *28*, 6089 – 6092.
- [5] Govindarajan, R. and coll., *J. Org. Chem.* **2019**, *84*, 13490 – 13502.
- [6] Galli, C. *Chem. Rev.* **1988**, *88*, 765 – 792.
- [7] Witzel, S. and coll., *Cell. Rep. Phy. Sci.* **2021**, *2*, 100325 – 100339.

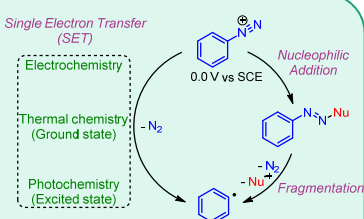
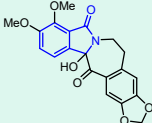
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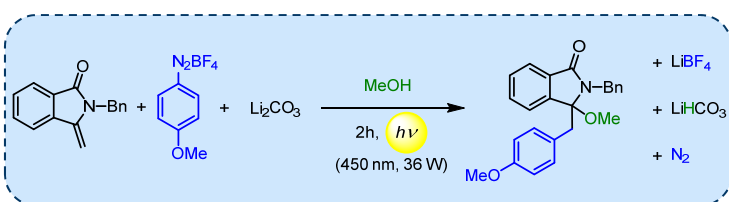


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anti-cancer
(*Berberis empetrifolia*)



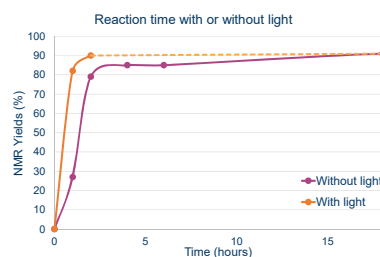
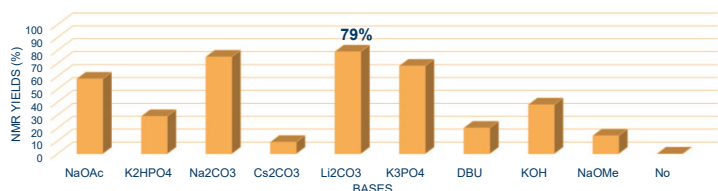
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Reaction



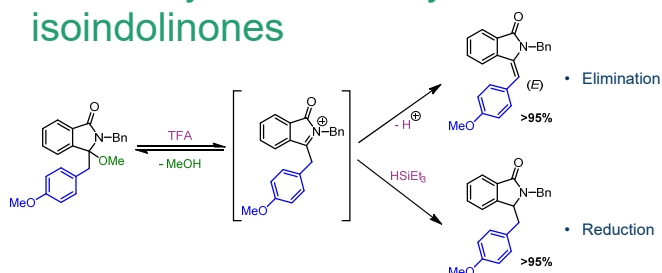
Optimization

Yields / bases

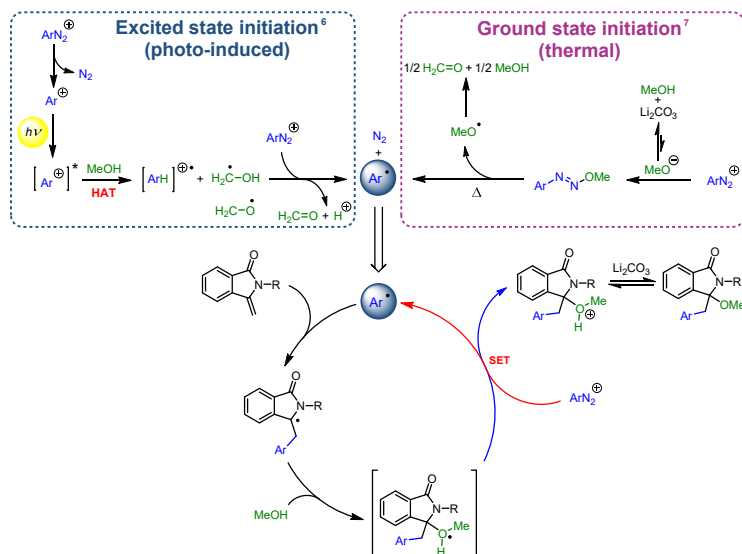


The reaction times were compared with and without irradiation under standard conditions. The reaction peaks at around 90% yield after 16h without irradiation. The same phenomenon is observed under irradiation in only 2h.

Reactivity of 3-methoxy isoindolinones

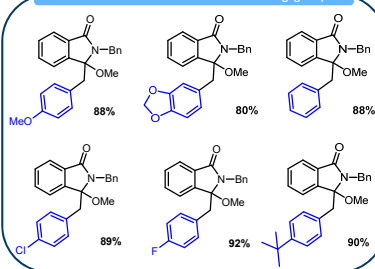


Proposed mechanism⁵

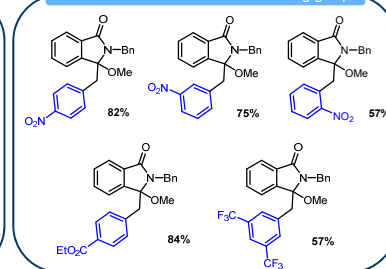


Scope

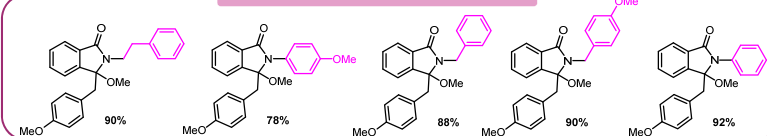
Diazonium salts with electron donating groups



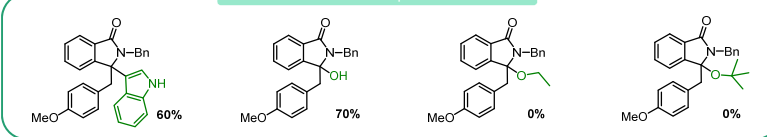
Diazonium salts with electron withdrawing groups



N-Substitution

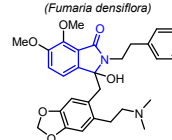


Other nucleophiles



Example of a natural isoindolinone that could be obtained via the synthetic route presented in this work.

Fumadensine
(*Fumaria densiflora*)



References

- [1] Tatumashvili, E.; Chan, B.; Nashar, P.E.; McErlan, C.S.P. *Org. Biomol. Chem.* **2020**, *18*, 1812 – 1819.
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