

University of Groningen

Light-driven benzylic azolation

Wei, Ning; Beil, Sebastian B.

Published in:
Trends in Chemistry

DOI:
[10.1016/j.trechm.2023.04.006](https://doi.org/10.1016/j.trechm.2023.04.006)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Version created as part of publication process; publisher's layout; not normally made publicly available

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Wei, N., & Beil, S. B. (2023). Light-driven benzylic azolation. *Trends in Chemistry*, 5(9), 711-712.
<https://doi.org/10.1016/j.trechm.2023.04.006>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

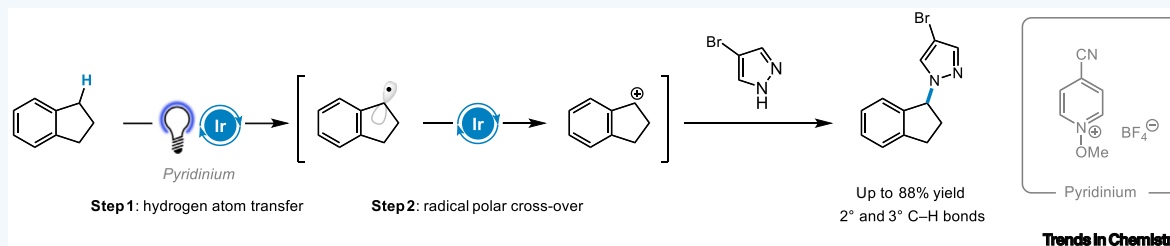
The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Light-driven benzylic azolation

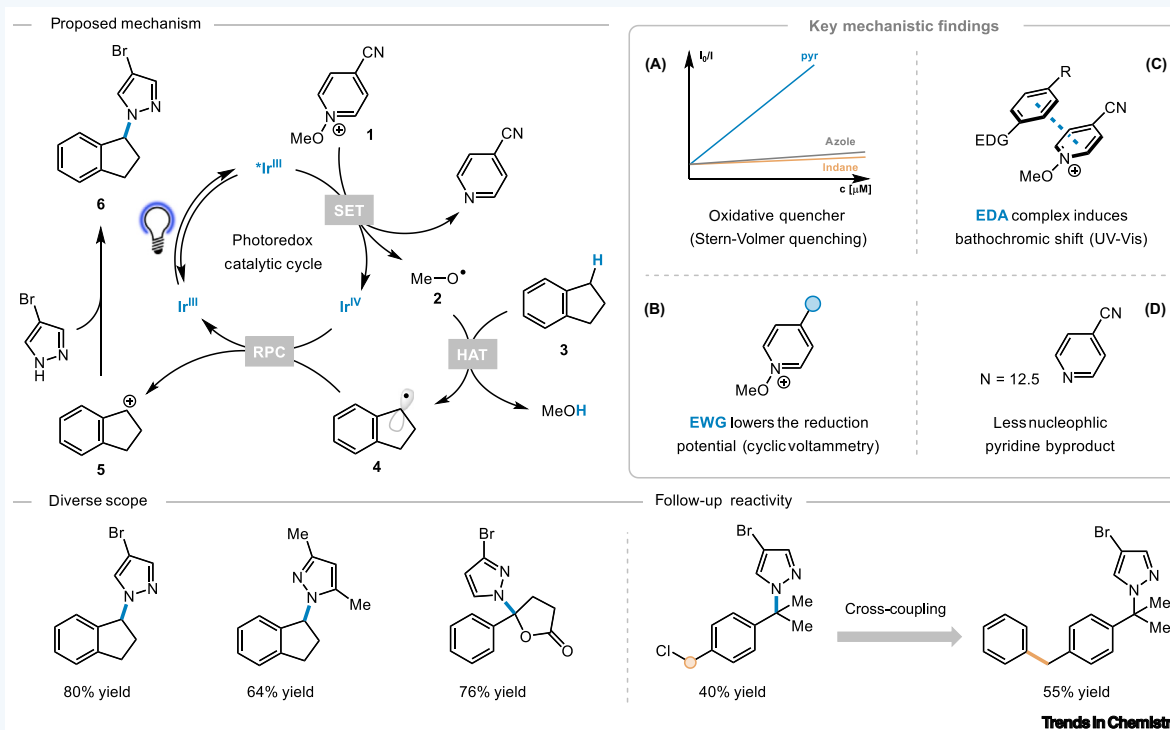
Ning Wei¹ and Sebastian B. Beil^{1,*}¹Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 7, 9747AG Groningen, The Netherlands

ORIGIN

Selective activation of C(sp³)-H bonds has been reported by Musacchio *et al.*, who developed a photoredox-catalyzed coupling between benzylic positions and azoles to afford *N*-benzylated products. Critically, *N*-alkoxy pyridinium salts are used for enabling C(sp³)-H azolation via a combination of hydrogen atom transfer (HAT) and oxidative radical polar crossover (RPC). This platform has been demonstrated with a broad series of heterocycles and various benzylic coupling partners.

REACTION MECHANISM

In the mechanistic proposal, the photophysical properties of Ir(dFppy)₃ as a photocatalyst confirmed its strong photoreduction [$E_{1/2}^{ox}[Ir(III)/Ir(IV)] = -1.23$ V vs. Ag/AgCl in MeCN] and results in oxidative quenching via a single electron transfer (SET) with *N*-methoxy pyridinium **1** ($E_{1/2}^{red} = -0.44$ V vs. Ag/AgCl in MeCN). This process has been explored by cyclic voltammetry and Stern-Volmer fluorescence quenching studies **A**, which reveals efficient oxidative quenching of the excited state photocatalyst by electron withdrawing substituted pyridinium salt due to a preferable reduction potential **B**. The so obtained methoxy radical **2** is competent in an intermolecular HAT step with the benzylic proton of substrate **3** to form a carbon-centered radical intermediate **4** and simultaneously liberates pyridine, as low nucleophilic byproduct **D**. The initial formation of an electron donor-acceptor (EDA) complex with pyridinium and benzylic reagent via π - π stacking is plausible as observed by a bathochromic shift in the UV-Vis study **C**. Such an EDA complex could facilitate the reduction of **1**, therefore enhancing the release of radical **2**. Respectively, electron-rich substrate shows more competent stacking with electron-poor pyridinium salt. Subsequent SET oxidation of **4** with Ir(IV) results in an RPC to yield benzylic carbocation **5**, which enhances the azolation in a nucleophilic addition to yield the product **6**. This platform has been demonstrated for a series of *N*-heterocycles with diverse electronic properties, such as halides, cyano, ester, or phenyl substituents, which could couple with benzylic C(sp³)-H bonds. Gratifyingly, this methodology even tolerates benzylic chlorides, a modular functional group for follow-up derivatization.

*Correspondence: s.b.beil@rug.nl (S.B. Beil).

IMPORTANCE

This study reveals a combined photoredox-catalyzed HAT and RPC mechanism utilizing *N*-alkoxy-pyridinium salts for direct access to 2° and 3° benzylic carbocations. Enabling ubiquitous C(sp³)-H bonds in organic compounds is an advantage of this approach and this protocol tolerates common organic functional groups on the N-heterocycles and is even mild enough to leave benzylic electrophiles untouched, leading to potential late-stage functionalization of pharmaceutical targets.

Declaration of interests

No interests have been declared.

Literature

1. Musacchio, P.Z. *et al.* (2023) Azolation of benzylic C-H bonds via photoredox-catalyzed carbocation generation. *J. Am. Chem. Soc.* 145, 3861–3868
2. Kobayashi, R. *et al.* (2021) Decarboxylative N-alkylation of azoles through visible-light-mediated organophotoredox catalysis. *Org. Lett.* 23, 5415–5419
3. Liang, Y. *et al.* (2018) Decarboxylative sp³ C-N coupling via dual copper and photoredox catalysis. *Nature* 559, 83–88
4. Chen, S.J. *et al.* (2021) Copper-catalyzed cross-coupling of benzylic C-H bonds and azoles with controlled N-site selectivity. *J. Am. Chem. Soc.* 143, 14438–14444
5. Song, C. *et al.* (2018) DDQ-catalyzed direct C(sp³)-H amination of alkylheteroarenes: synthesis of biheteroarenes under aerobic and metal-free conditions. *ACS Catal.* 8, 2195–2199
6. Leibler, I.N.-M. *et al.* (2021) A general strategy for C(sp³)-H functionalization with nucleophiles using methyl radical as a hydrogen atom abstractor. *Nat. Commun.* 12, 6950
7. He, F.-S. *et al.* (2019) Recent advances in pyridinium salts as radical reservoirs in organic synthesis. *ACS Catal.* 9, 8943–8960
8. Sandfort, F. *et al.* (2018) Deaminative borylation of aliphatic amines enabled by visible light excitation of an electron donor-acceptor complex. *Chem. Eur. J.* 24, 17210–17214
9. Yang, M. *et al.* (2019) Visible-light-induced deaminative thioesterification of amino acid derived Katritzky salts via electron donor-acceptor complex formation. *Org. Lett.* 21, 8673–8678
10. Brotzel, F. *et al.* (2007) Nucleophilicities and carbon basicities of pyridines. *Chem. Eur. J.* 13, 336–345