Asymmetric Photocatalytic C-H Functionalization of Toluene and Derivatives

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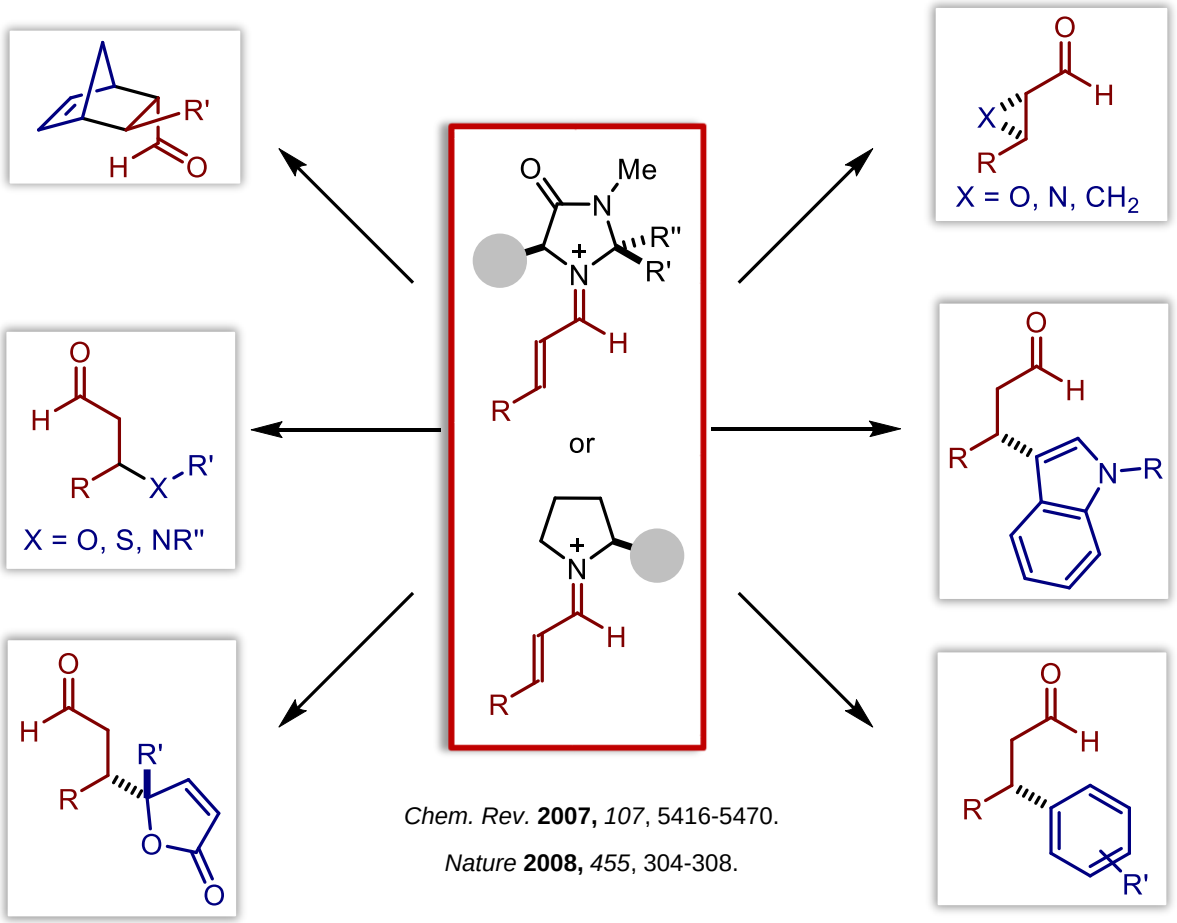
Poster OC5

project in collaboration with ***Daniele Mazzarella***

ICIQ – INTECAT School

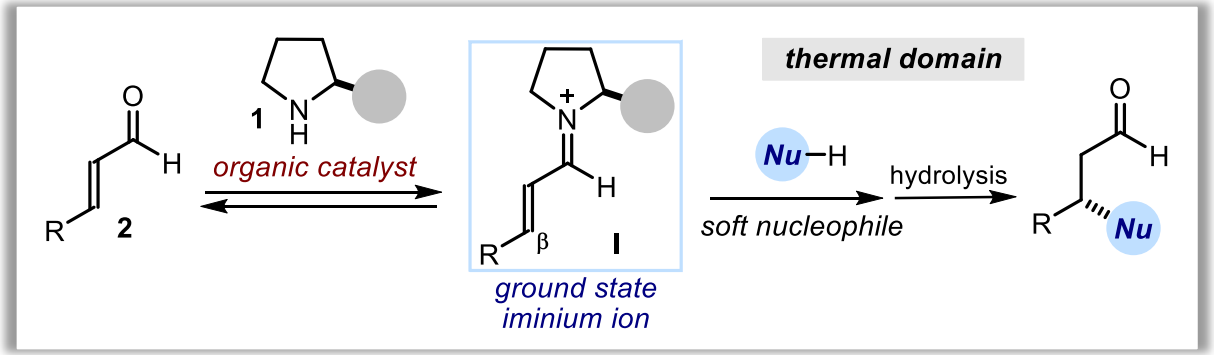
11th December 2018 – Montbrió del Camp

Iminium Ion Activation in Organocatalysis



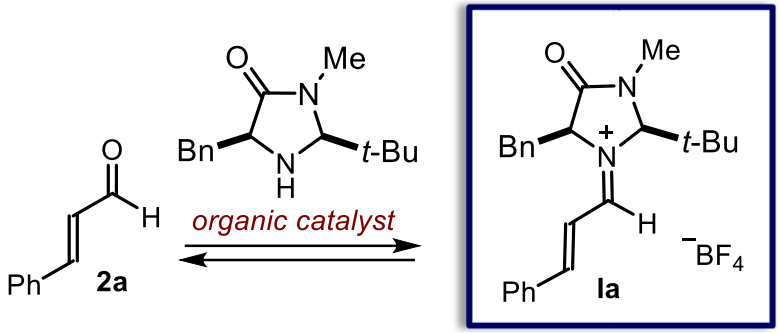
Chem. Rev. **2007,** *107*, 5416-5470.

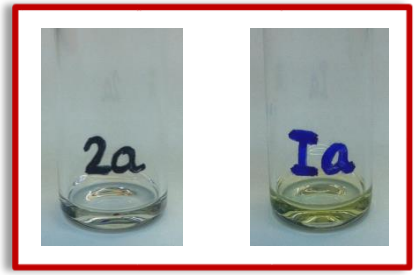
Nature **2008,** *455*, 304-308.

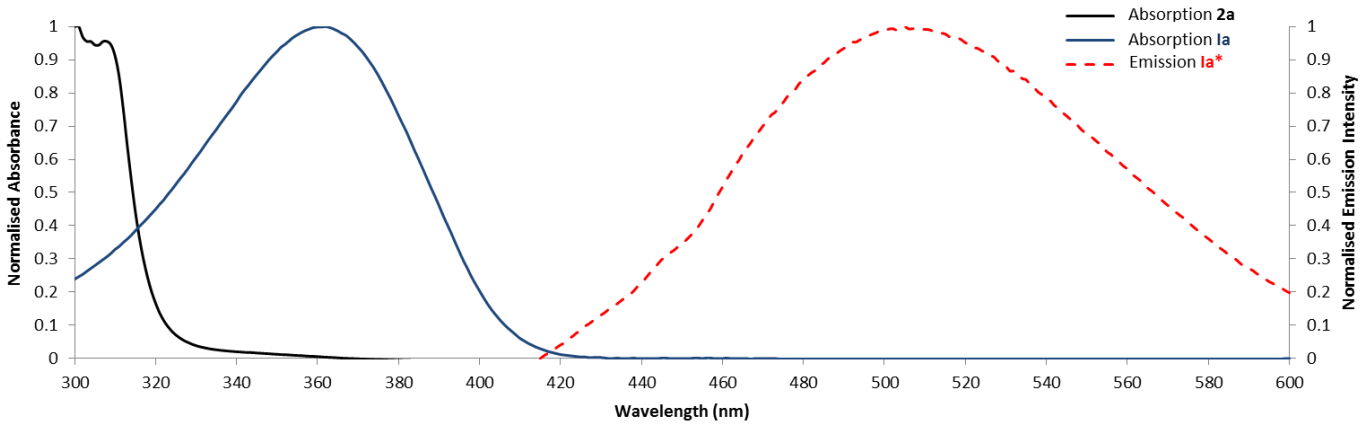


The Photochemistry of Iminium Ions

Experimental observation: *bathochromic shift upon condensation*







The primary event of vision

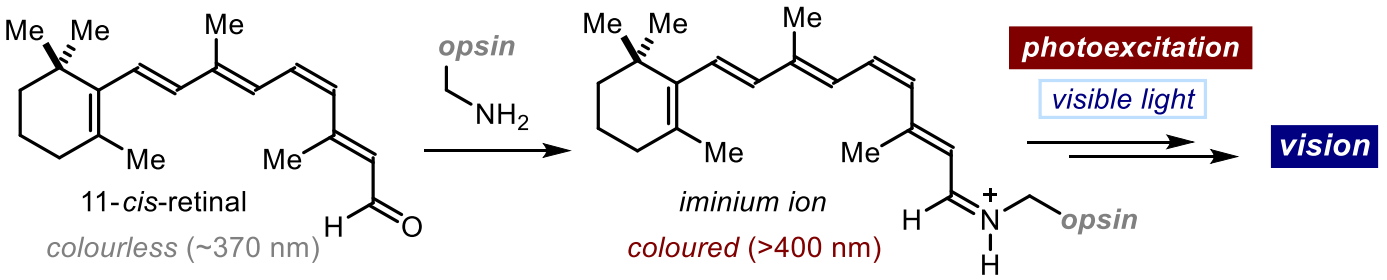
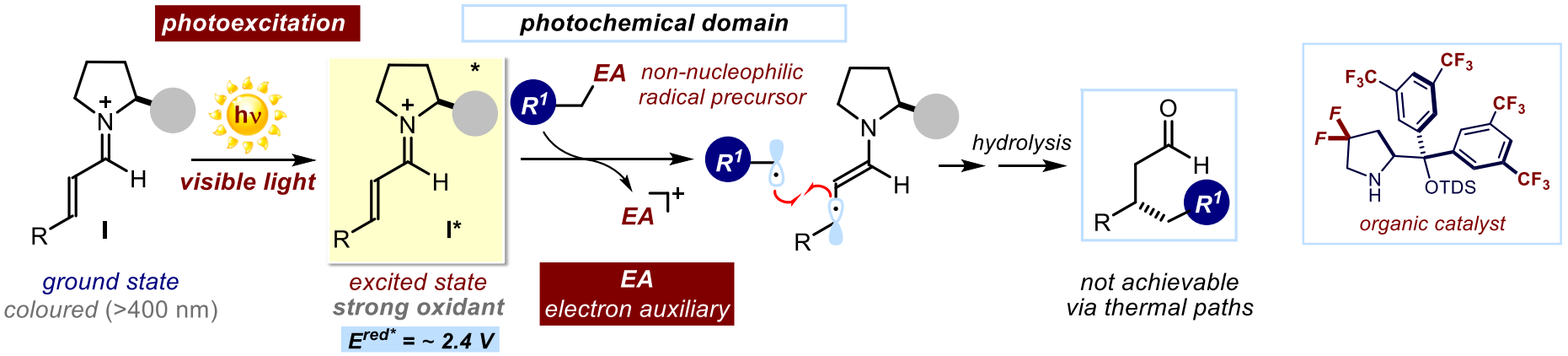
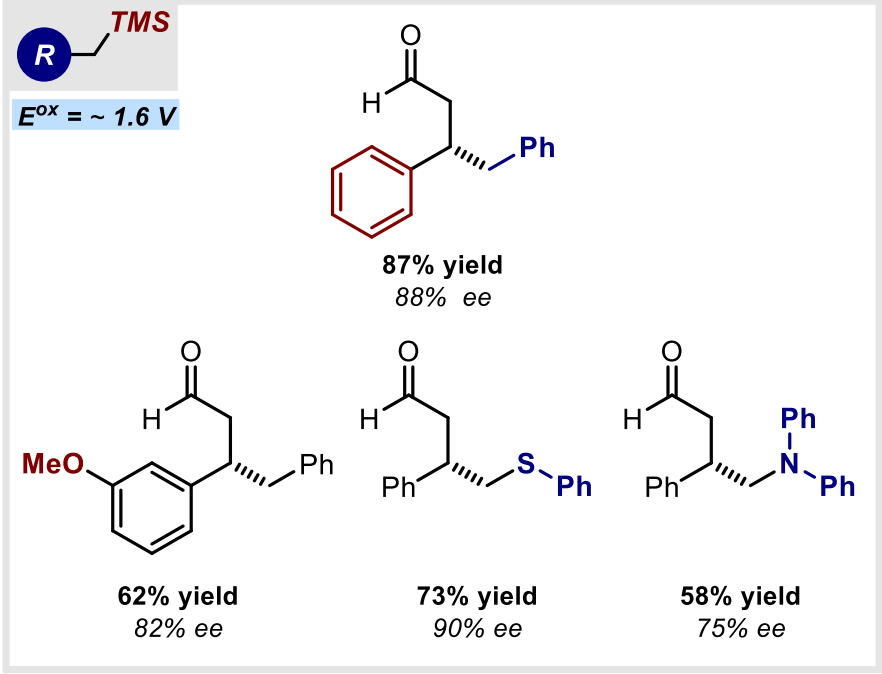
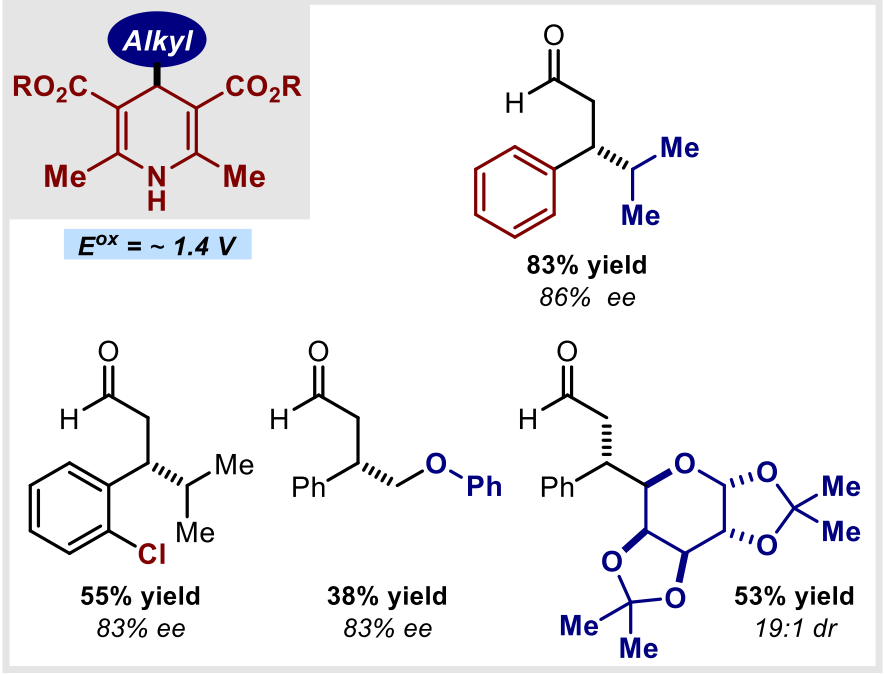


Photo-excited Iminium Ions in Organic Synthesis

Melchiorre (2017-2018)







Contributions by the Melchiorre group: (a) *Nat. Chem.* **2017**, *9*, 868. (b) *ACS Catal.* **2018**, *8*, 1062.

…and Application to Cascade Reactions

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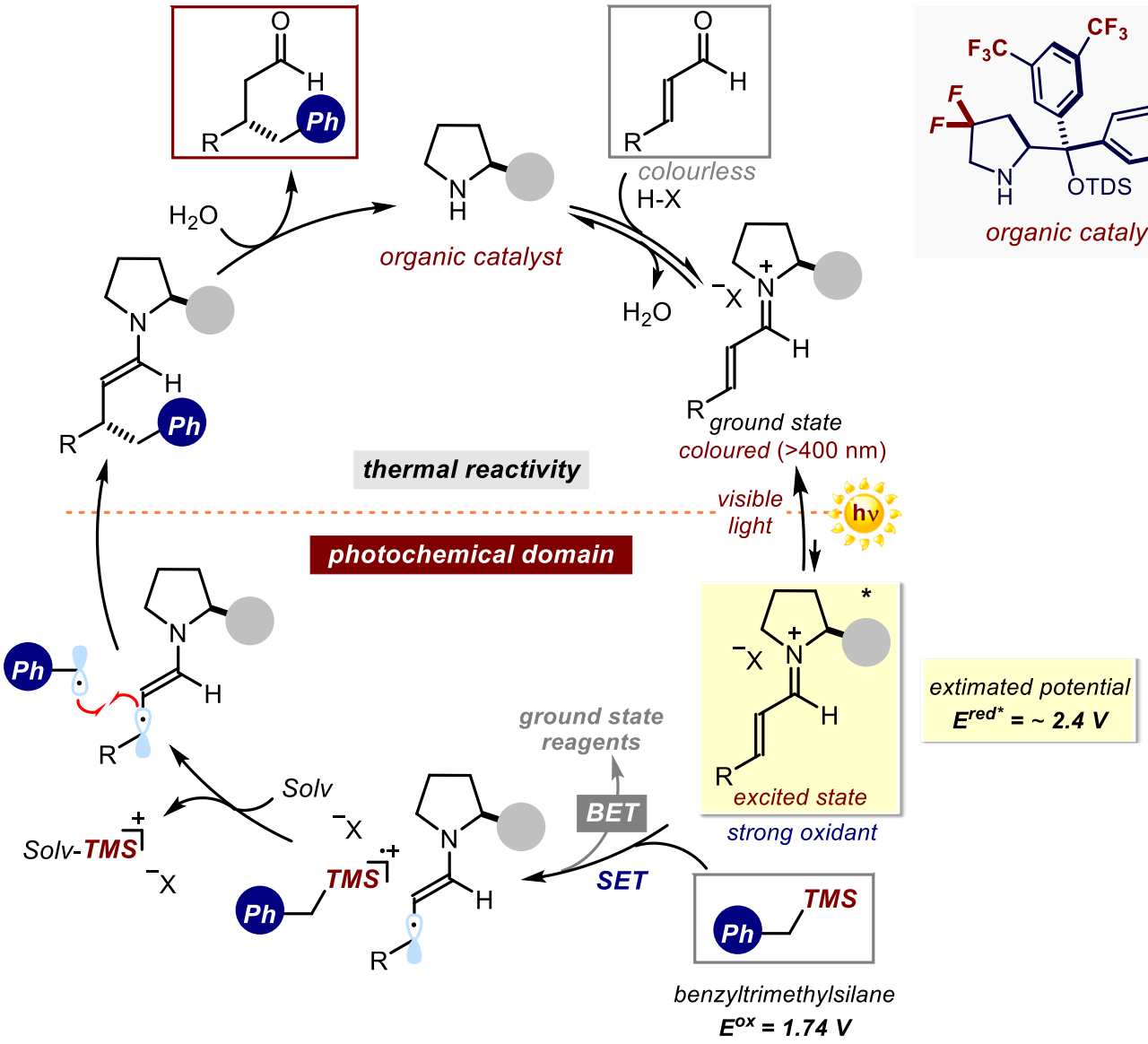
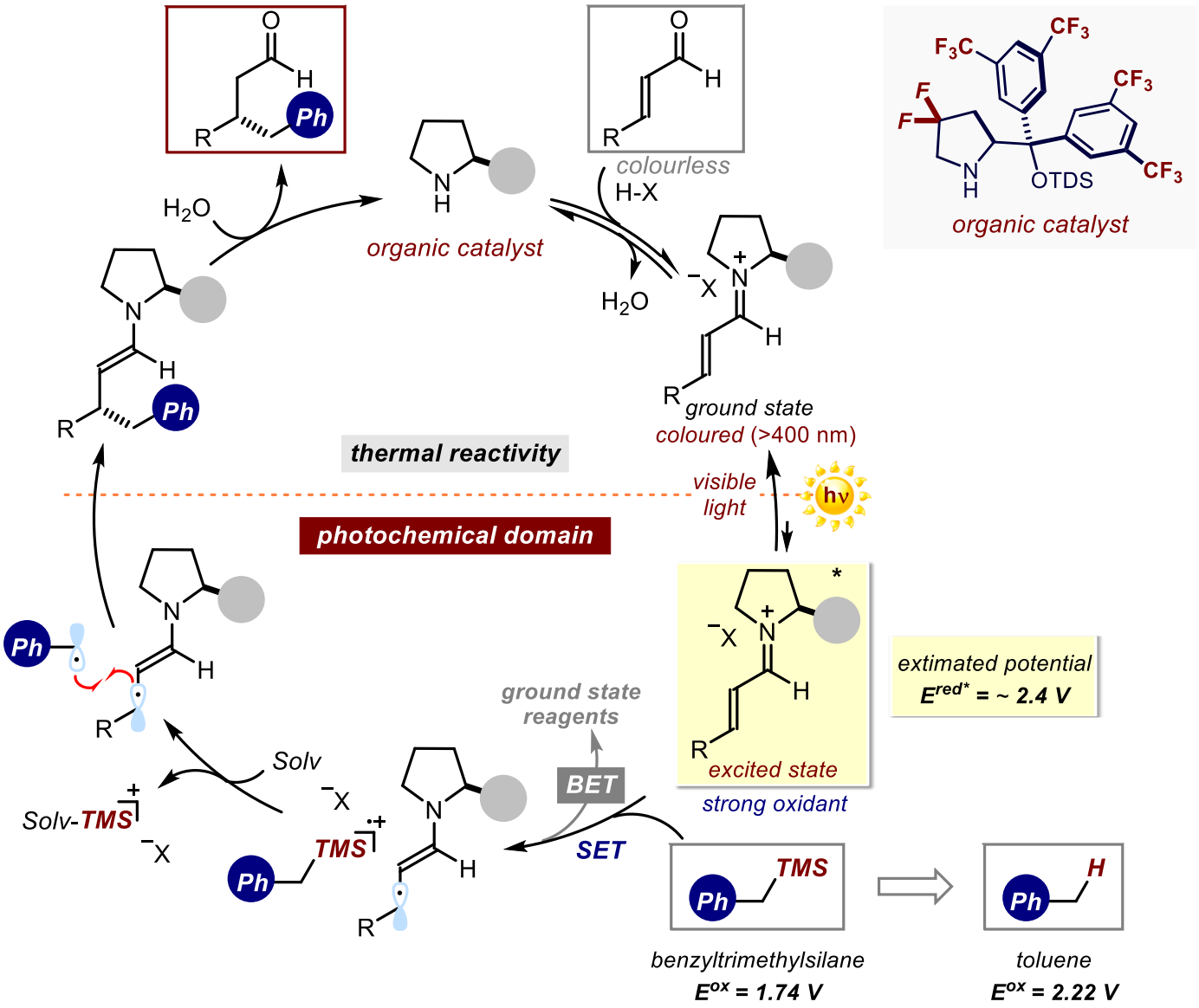
Contributions by the Melchiorre group: (a) *Angew. Chem. Int. Ed.* **2018**, *57*, 1068. (b) *Angew. Chem. Int. Ed.* **2018**, *57*, 12819.

Enantioselective β-Benzylation of Enals



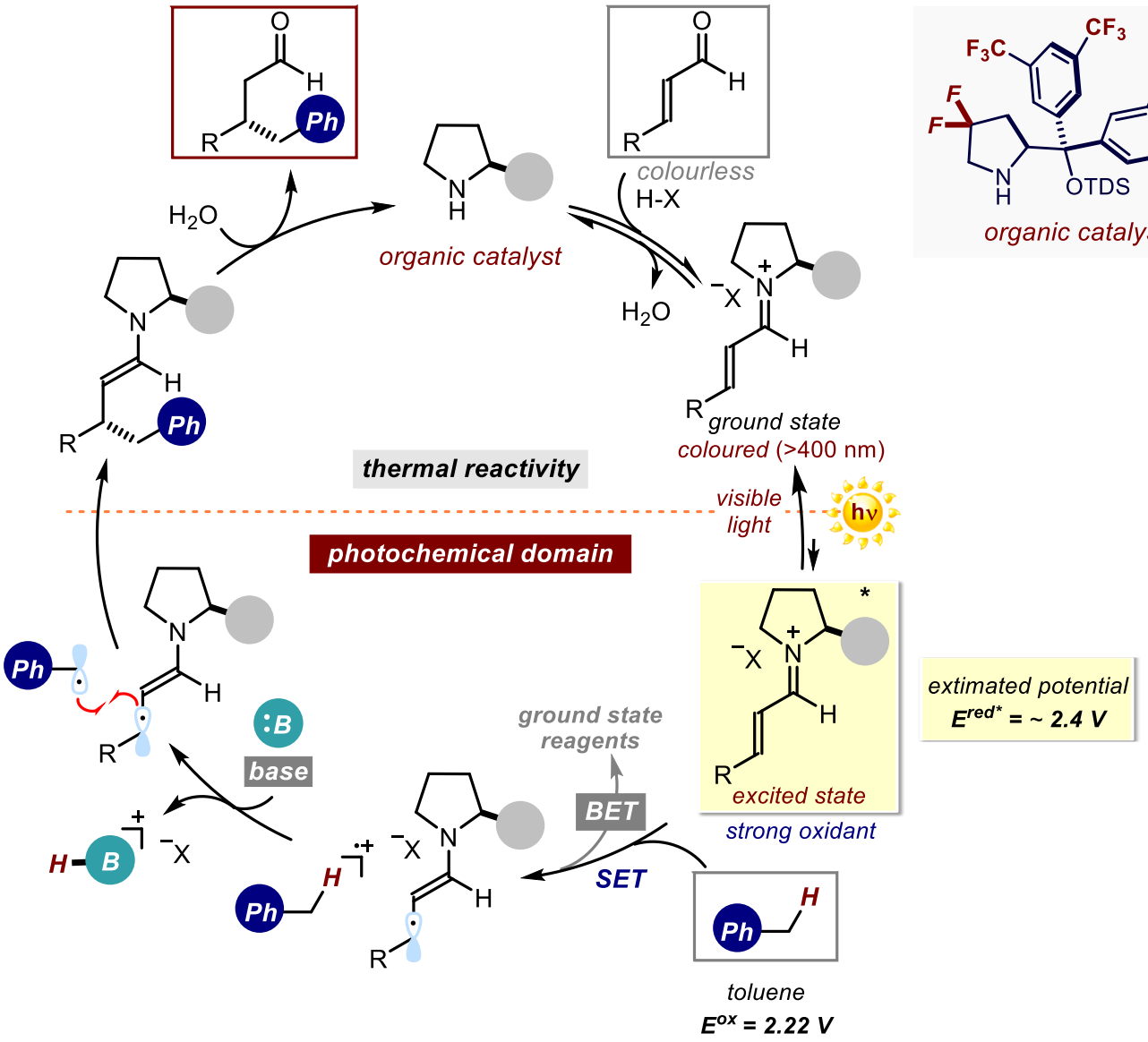
Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem.* **2017**, *9*, 868.

Enantioselective β-Benzylation of Enals

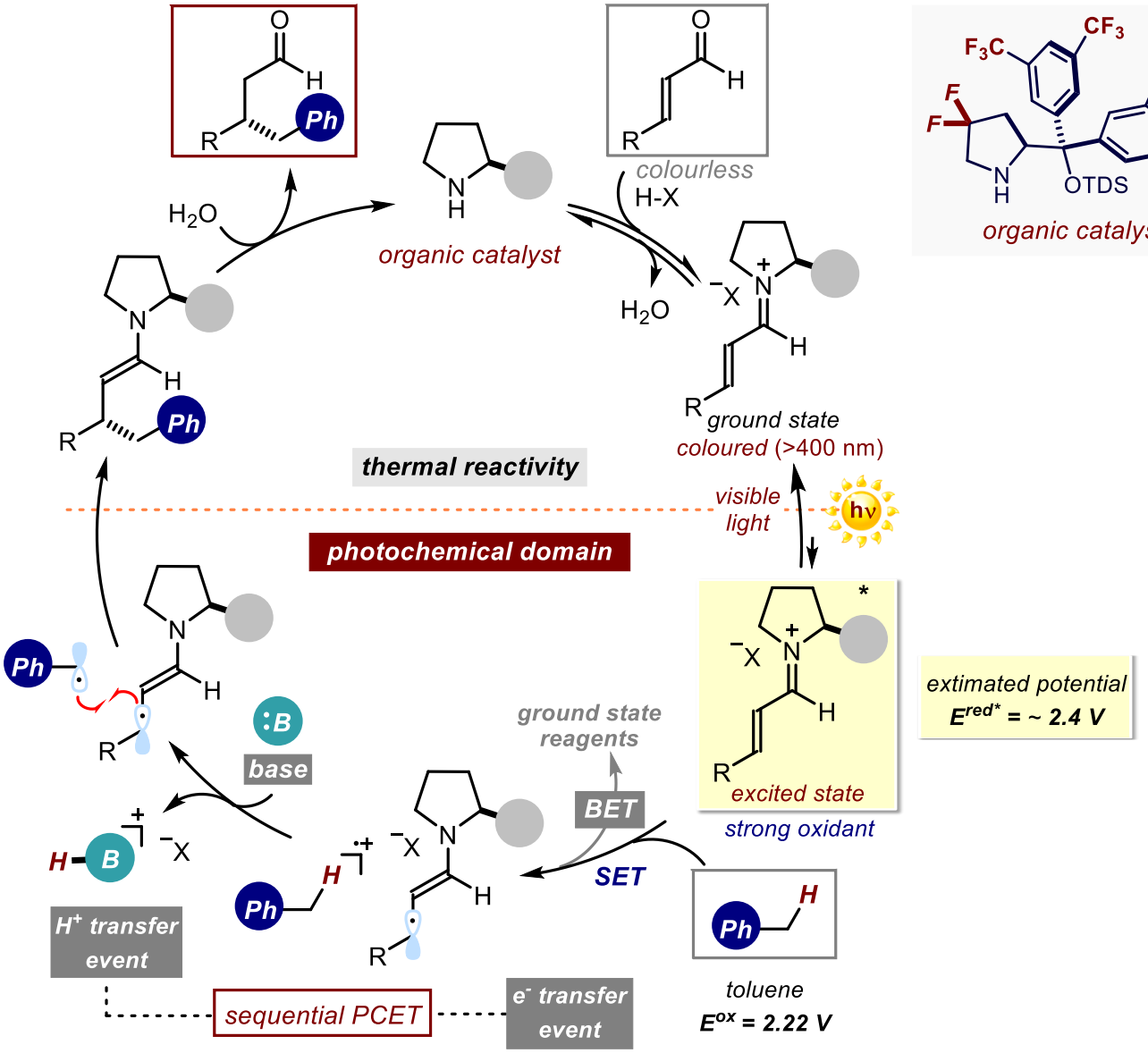


Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem.* **2017**, *9*, 868.

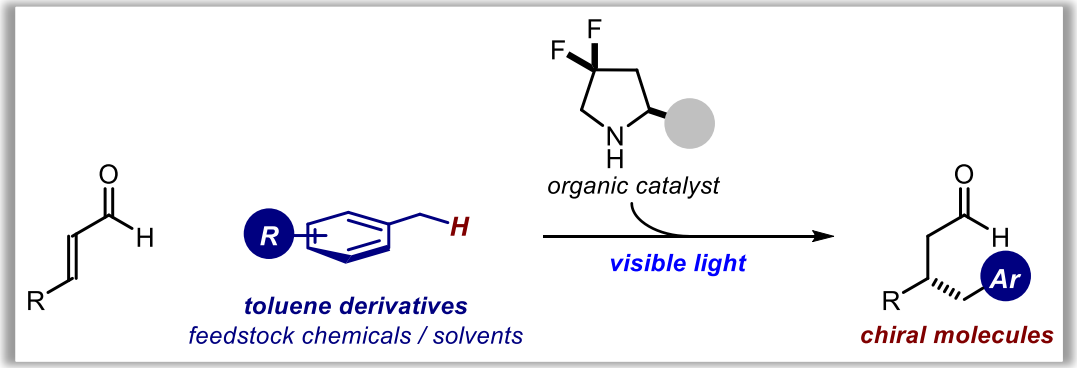
Proposed Approach to Asymmetric Functionalization of Toluene



Proposed Approach to Asymmetric Functionalization of Toluene

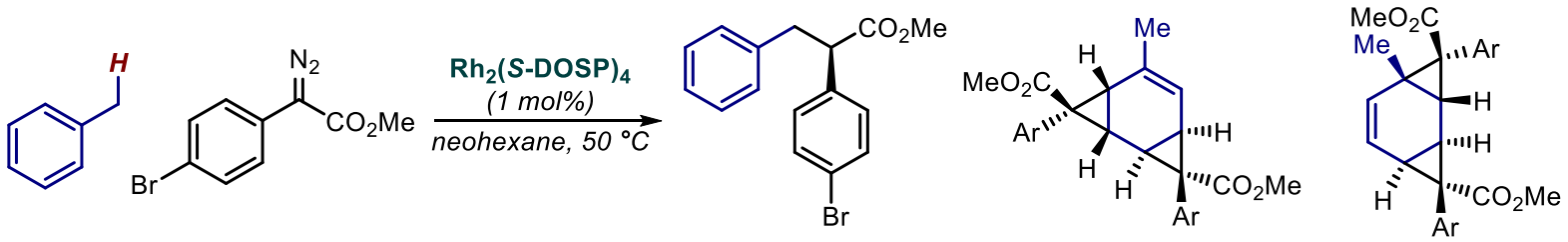


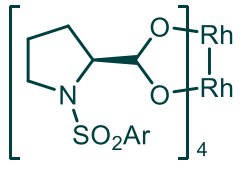
Asymmetric C-H Functionalization of Toluene Derivatives



- *Direct asymmetric C-H functionalization*
- *Use of highly available chemicals*
- *Mild conditions*
- *Use of toluene in enantioselective catalysis elusive*

Davies (2002): *Asymmetric C-H functionalization of toluene*



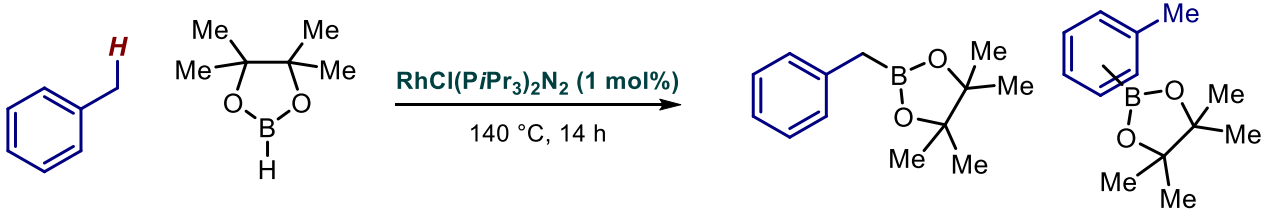


Ar = p-($C_{12}H_{25}$)C_6H_4
Rh_2(S-DOSP)

isolated as a 28 : 58 : 16 mixture of products
(50% overall yield, ee not provided)

Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Yu. *J. Org. Chem.* **2002**, *67*, 4165.

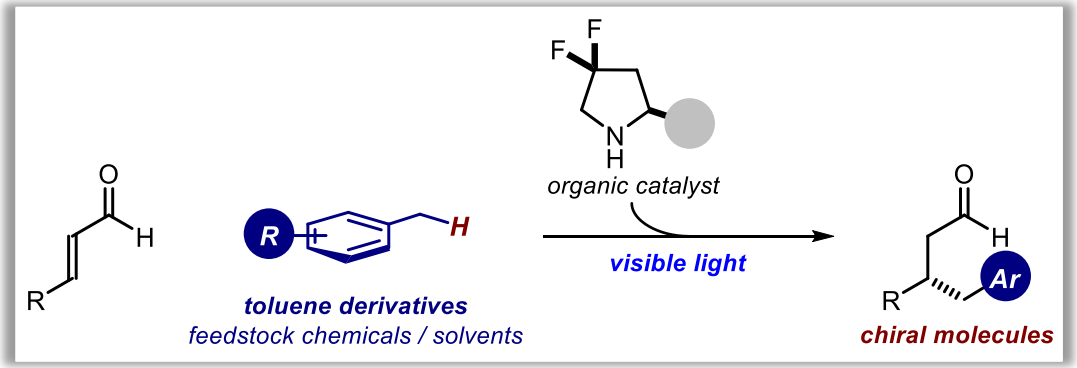
Marder (2001): *Formation of benzyl boronated esters*



isolated as a 83 : 17 mixture of products
(48% overall yield)

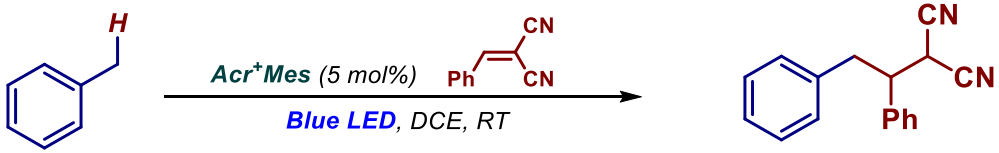
Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168.

Asymmetric C-H Functionalization of Toluene Derivatives

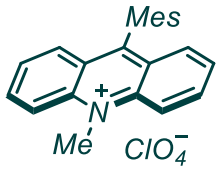


- *Direct asymmetric C-H functionalization*
- *Use of highly available chemicals*
- *Mild conditions*
- *Use of toluene in enantioselective catalysis elusive*

Wu (2017): *Photoredox activation of benzylic C(sp^3)-H bonds*



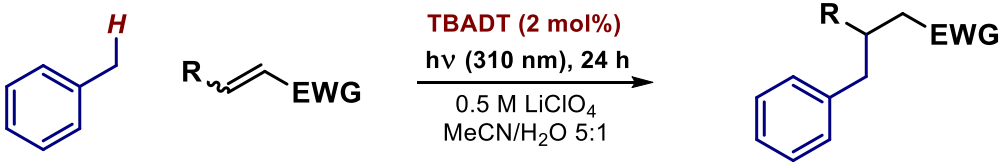
(46% yield)



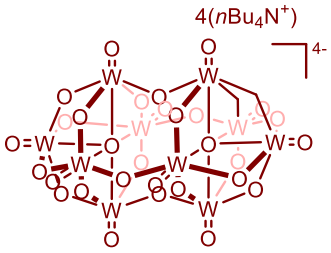
Acr⁺Mes
$E_{1/2}^{*}$ = 2.06 V

Zhuo, R.; Liu, H.; Tao, H.; Yu, X.; Wu, J. *Chem. Sci.* **2017**, *8*, 4654.

Fagnoni (2013): *Benzylation of electron poor olefins*



(29%-90% yield)

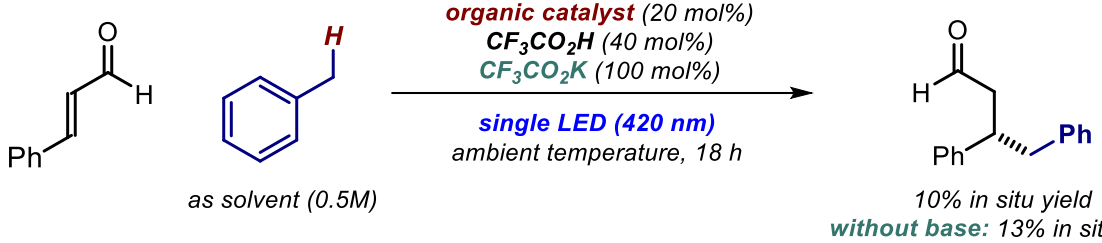


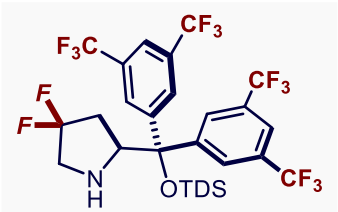
TBADT

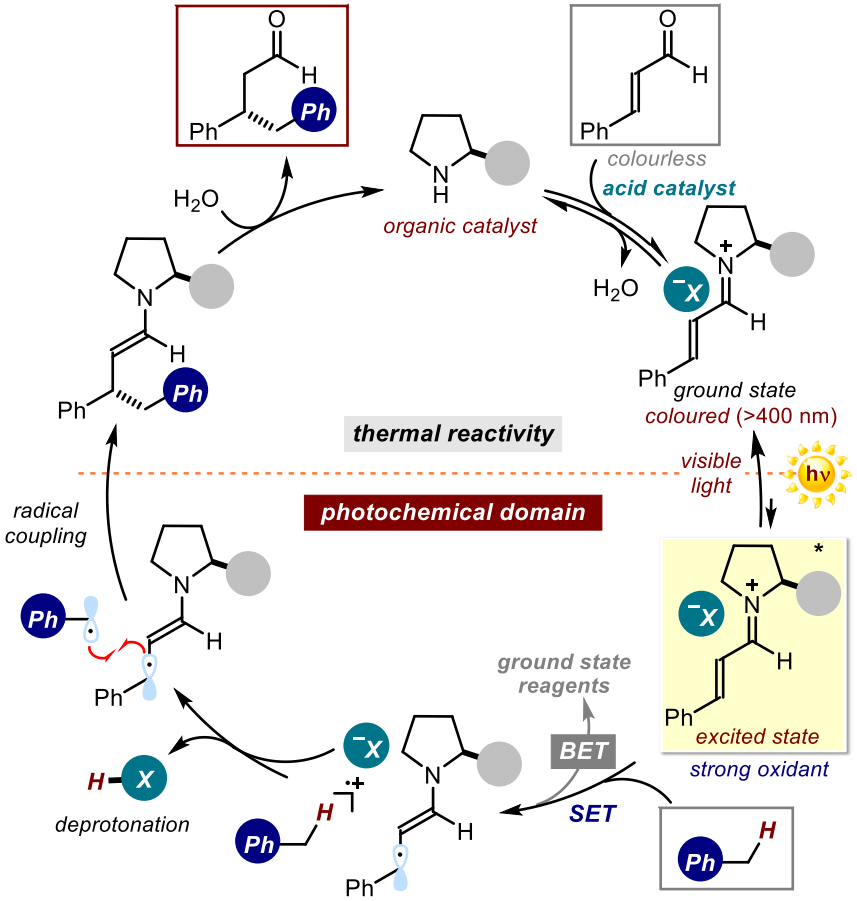
Qrareya, H.; Ravelli, D.;, Fagnoni M.; Albini, A. *Adv. Synth. Catal.* **2013**, *355*, 2891.

Reaction Optimization

Preliminary attempt

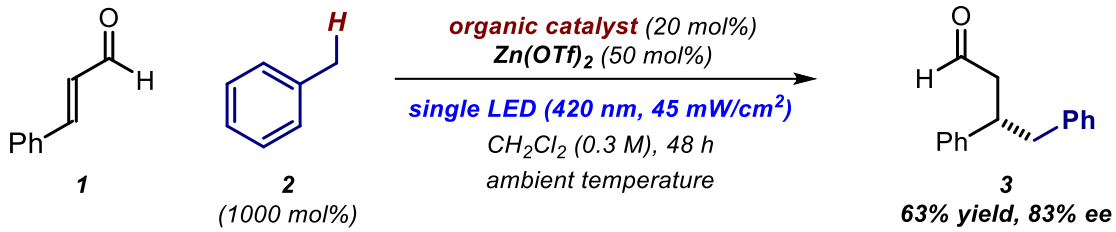




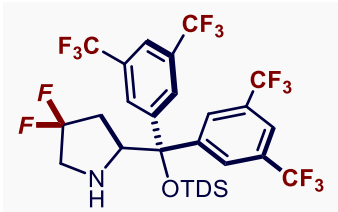


Reaction Optimization

Standard reaction conditions

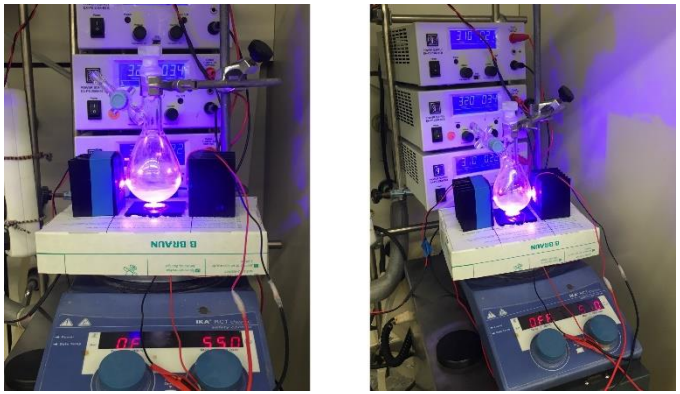


1 | **2** (1000 mol%) | **3** **63% yield, 83% ee**



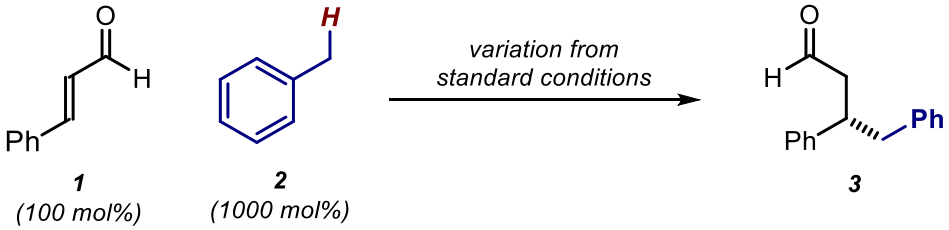
organic catalyst

Protocol scale-up *(1 mmol scale)*



*Product **3** afforded in **50% yield**, **83% ee***

Control Experiments



1 (100 mol%) | **2** (1000 mol%) | **3**

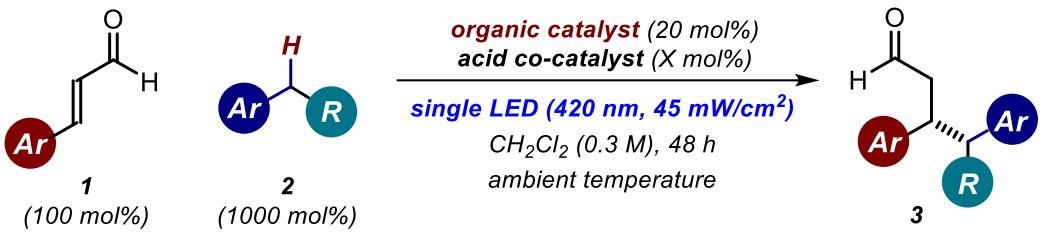
in the abscence of organic catalyst: *no reaction*

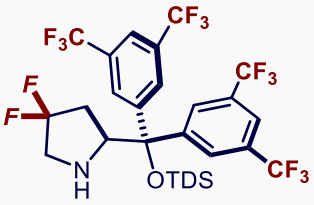
in the abscence of $Zn(OTf)_2$: *no reaction*

in the dark: *no reaction*

Mazzarella, D.; Crisenza, G. E. M.; Melchiorre P. *J. Am. Chem. Soc.* **2018**, *140*, 8439.

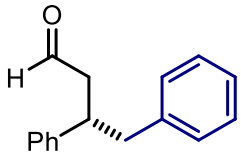
Scope Evaluation



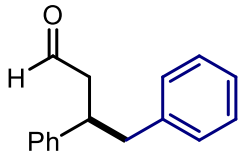


organic catalyst

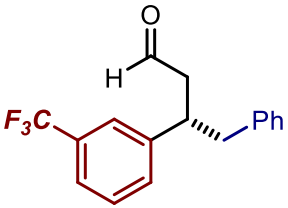
Selected Examples



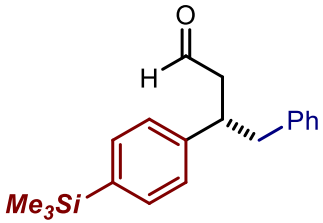
63% yield, 83% ee



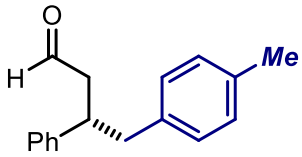
63% yield, 82% ee
with (R)-organic catalyst



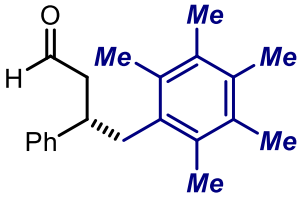
33% yield, 84% ee



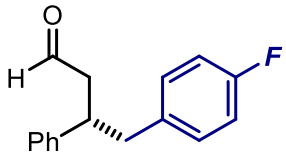
51% yield, 70% ee



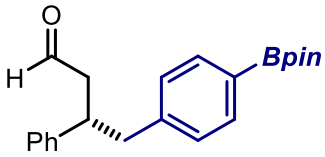
63% yield, 83% ee



75% yield, 82% ee



67% yield, 80% ee



54% yield, 81% ee

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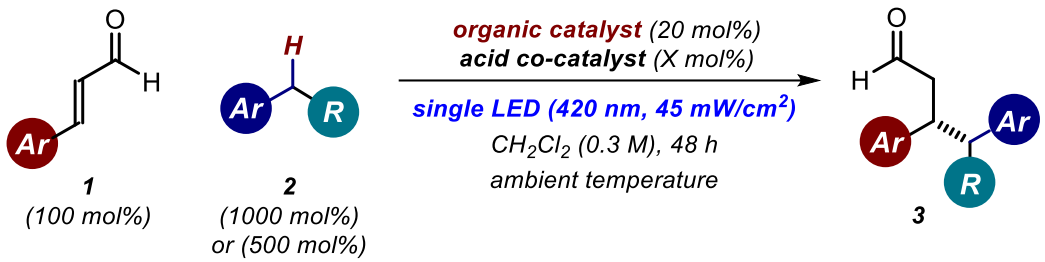
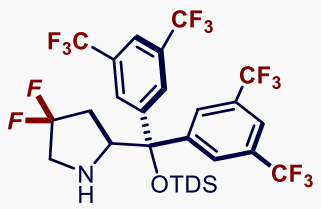
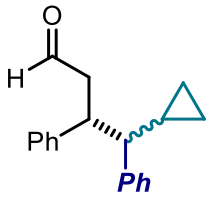
Scope Evaluation

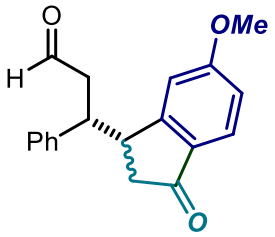




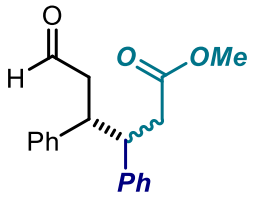
Selected Examples



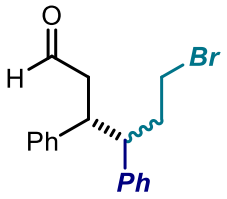
***39% yield**, 1:1 d.r.*
82% ee_A/85% ee_B



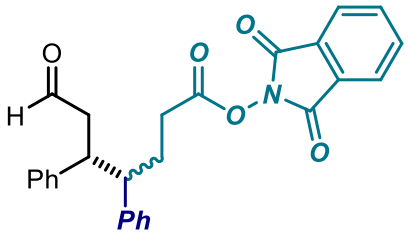
***58% yield**, 1.9:1 d.r.*
91% ee_{major}/86% ee_{minor}



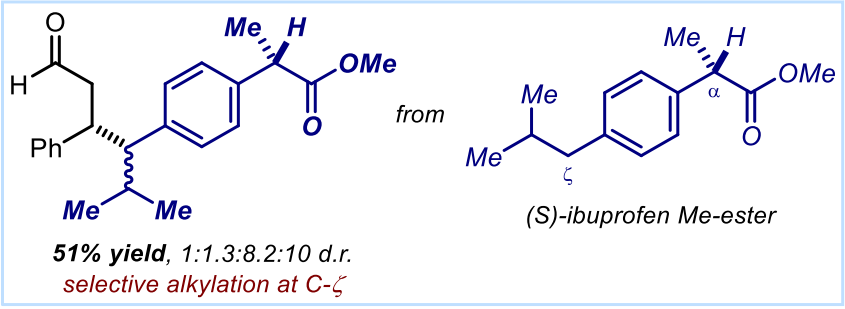
***45% yield**, 1.1:1 d.r.*
82% ee_{major}/82% ee_{minor}



***41% yield**, 1.5:1 d.r.*
80% ee_{major}/74% ee_{minor}



***51% yield**, 1.5:1 d.r.*
80% ee_{major}/83% ee_{minor}

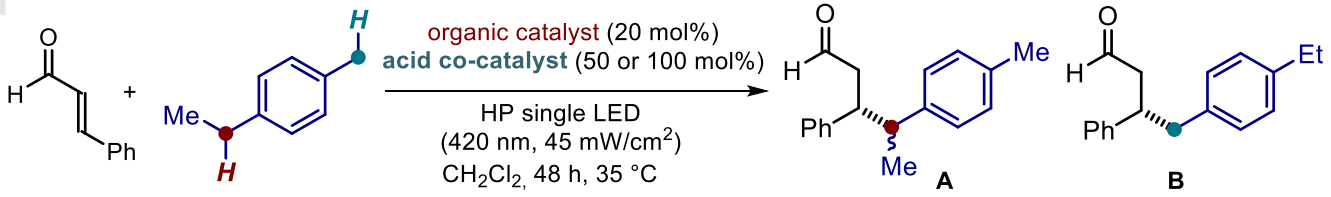


***51% yield**, 1:1.3:8.2:10 d.r.*
selective alkylation at C-ζ

Mazzarella, D.; Crisenza, G. E. M.; Melchiorre P. *J. Am. Chem. Soc.* **2018**, *140*, 8439.

Mechanistic Insights

Selectivity Study

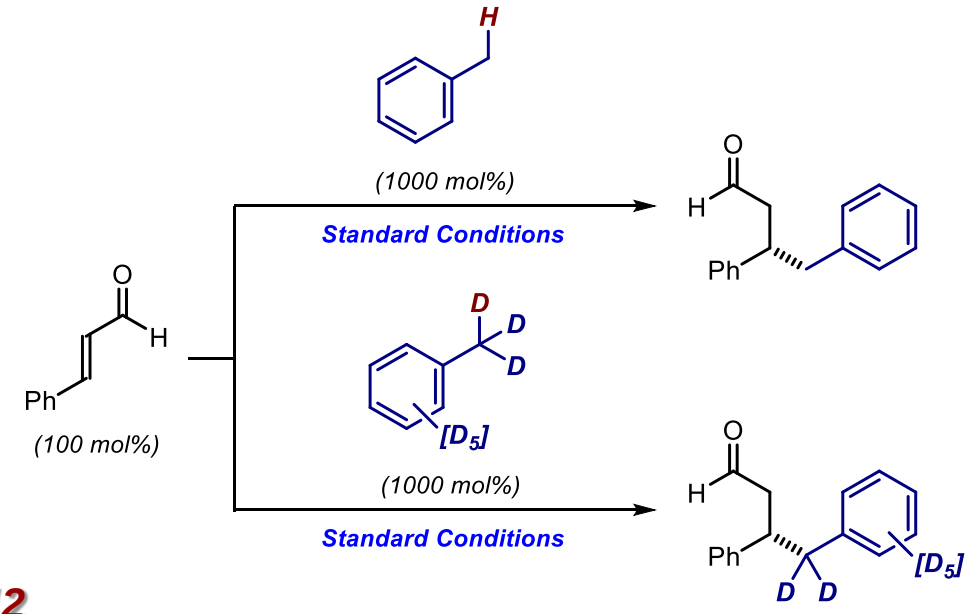


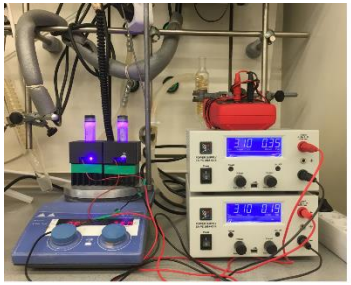
strength of the conjugate base

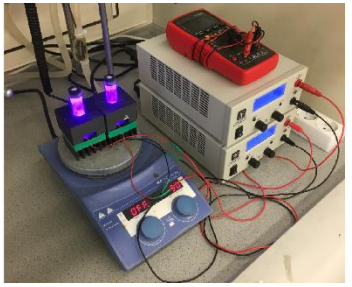
	CH_2ClCO_2H	$CHCl_2CO_2H$	CCl_3CO_2H	CF_3CO_2H	$Zn(OTf)_2$
acid co-catalyst	(100 mol%) *pKa = 2.86*	(100 mol%) *pKa = 1.35*	(100 mol%) *pKa = 0.66*	(100 mol%) *pKa = 0.23*	(50 mol%) *pKa (TfOH) = -14.7*
overall yield	**no reaction**	**50% yield**	**62% yield**	**65% yield**	**63% yield**
regioisomeric ratio (A:B)	**---**	**2.6 : 1**	**3 : 1**	**3.3 : 1**	**6 : 1**

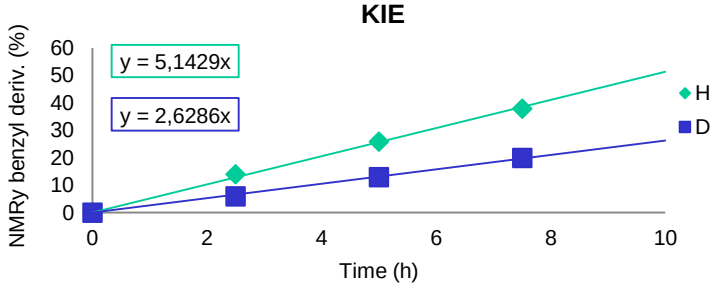
regioselectivity

Kinetic studies (parallel experiments) *(KIE = 1.95)*

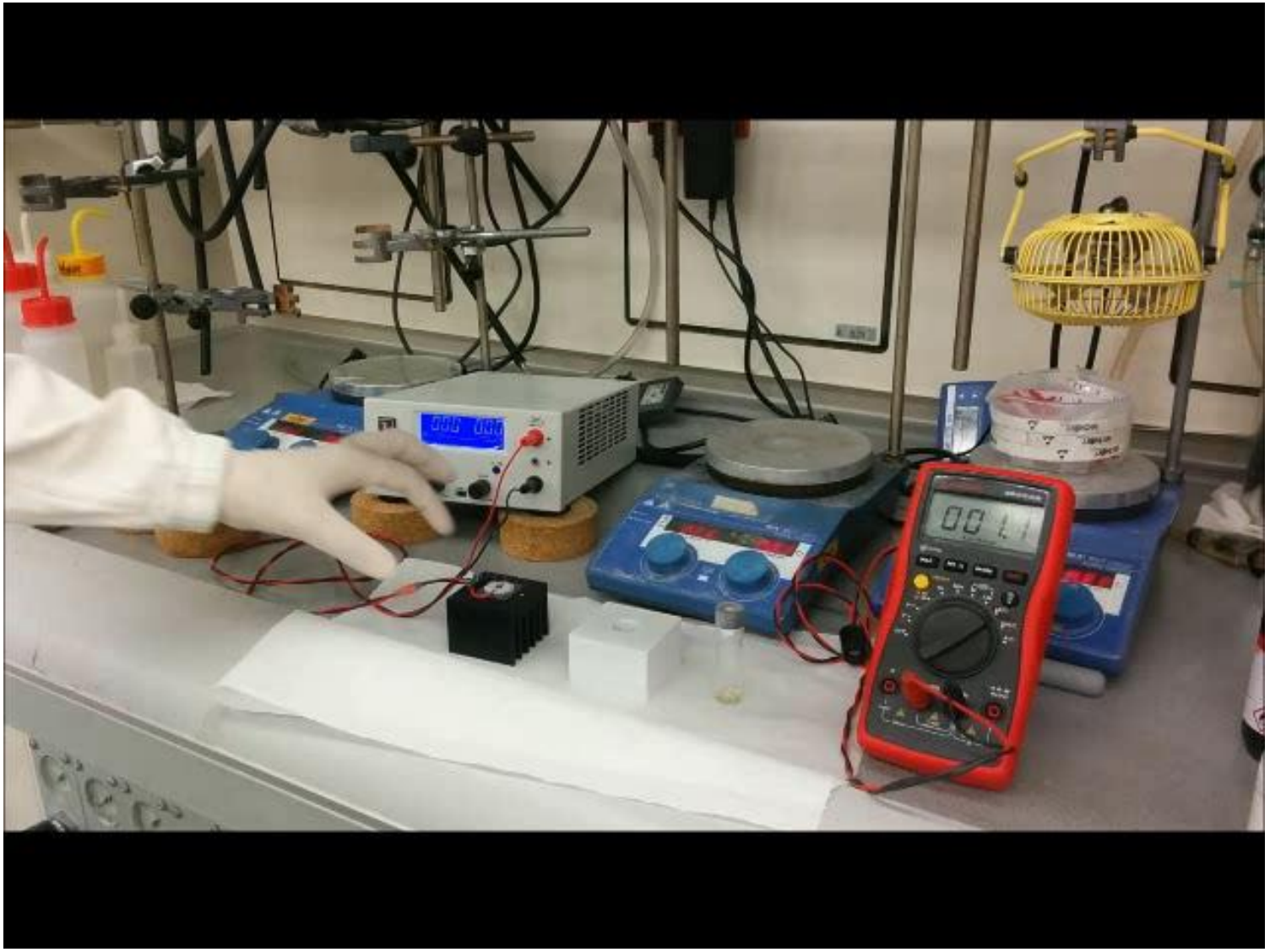








Standard Reaction Set-Up

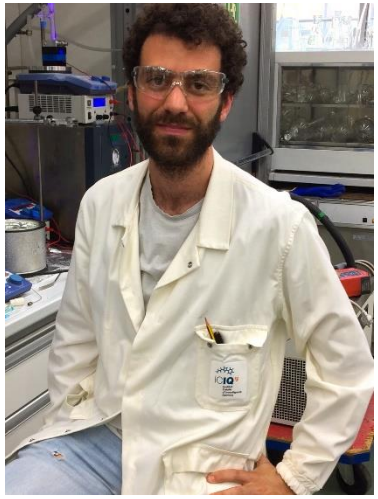


Buzzetti, L.; Crisenza, G. E. M.; Melchiorre P. *Angew. Chem. Int. Ed.* **2018**, DOI:10.1002/anie.201809984.

Thank you for your attention

Poster P33

Poster P26



Poster P12

This work is supported by PHOTO ORGANO-Ir CAT project that received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 795793.