Direct Asymmetric C–H Functionalization of Toluene Derivatives *via* Excited Iminium Ions Catalysis

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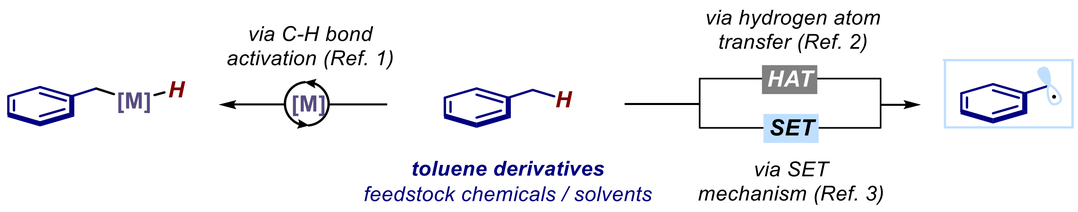
C(sp³)-H Functionalization of Toluene and Derivatives

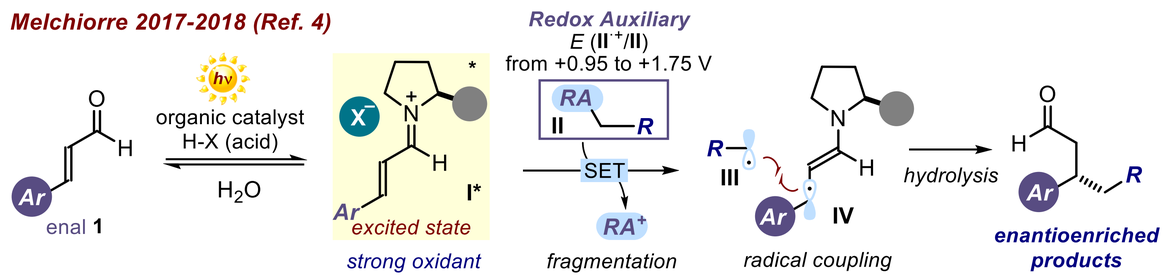
- Previous Strategies:



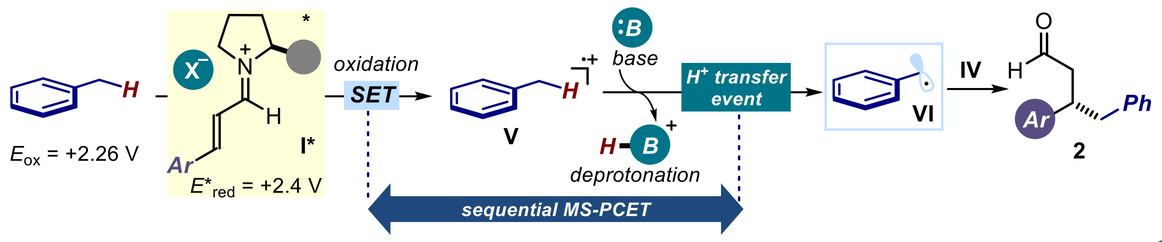
- *Direct functionalization of highly available feedstock chemicals*
- *Few examples of insertion into benzylic C(sp³)-H bonds (selectivity issues)*
- *Mainly achieved through radical pathways (HAT, SET)*
- *Use of toluene in enantioselective catalysis: elusive*

- Our Strategy:

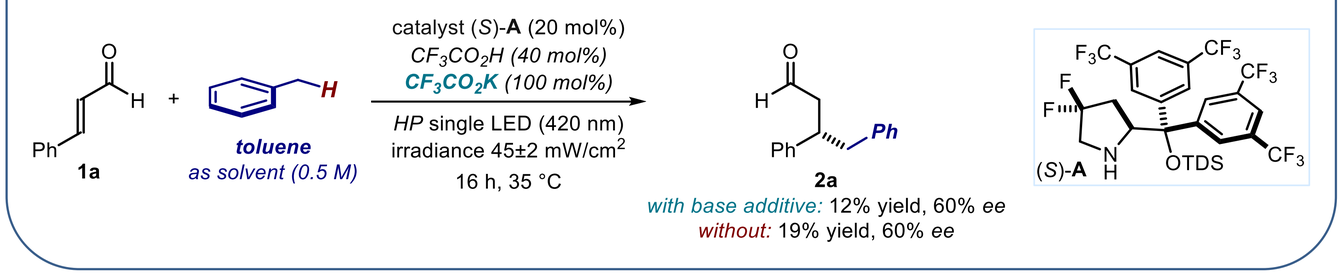
Melchiorre 2017-2018 (Ref. 4)



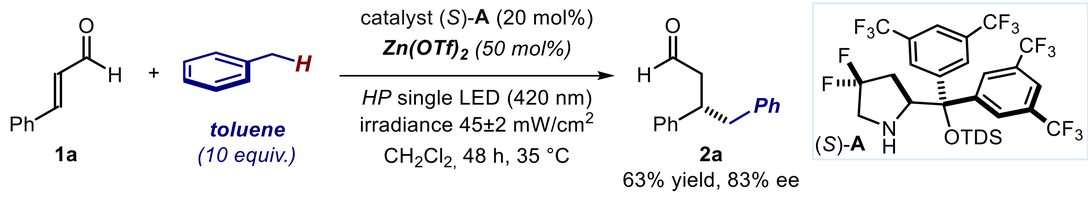
This Study: Use of Toluene in Enantioselective Catalysis



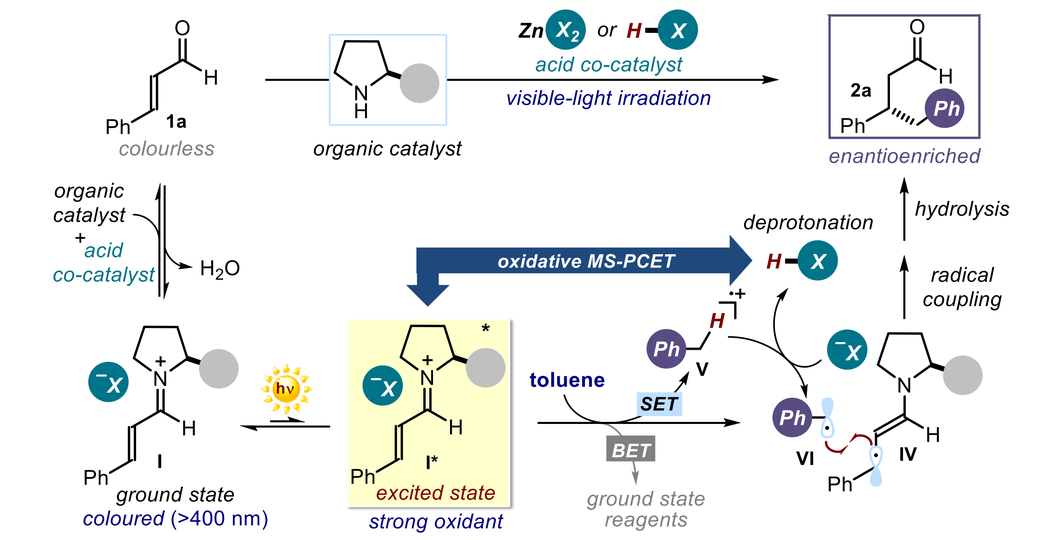
Preliminary Studies



Optimized Conditions

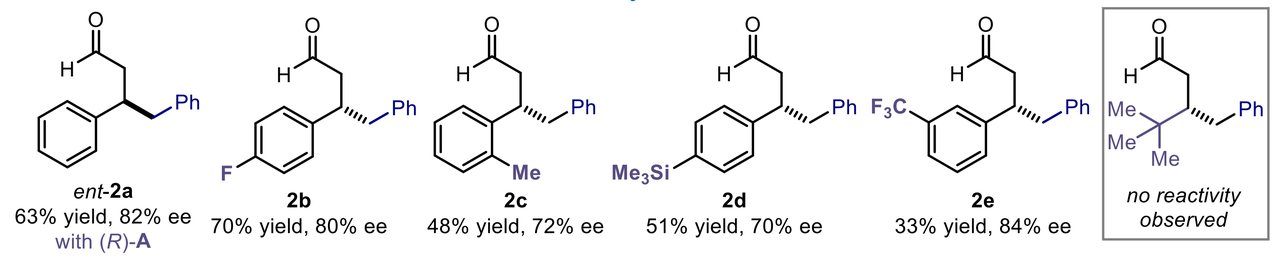


- Proposed Mechanism:

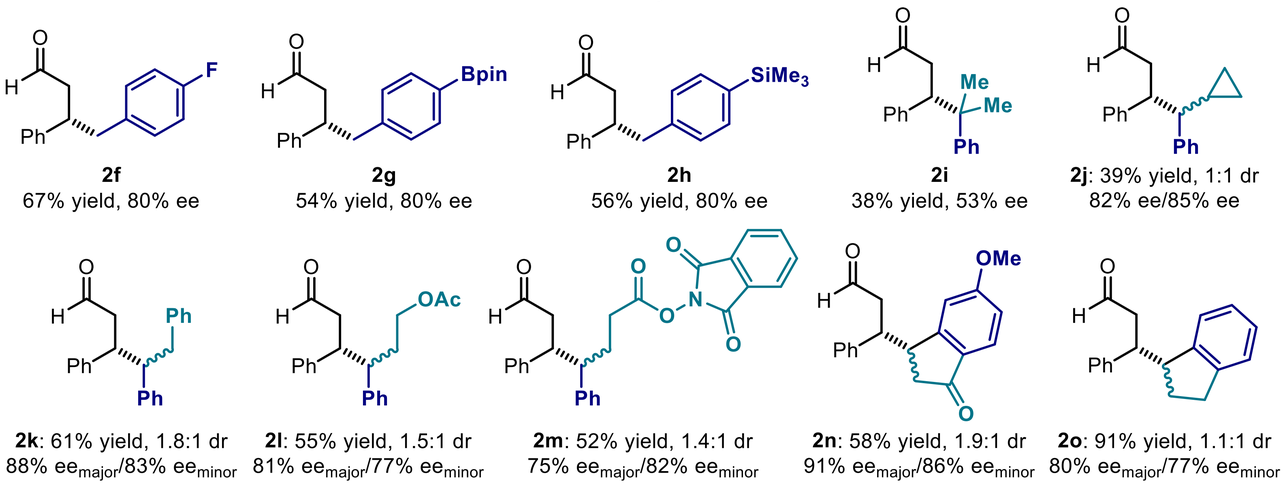


Substrate Scope

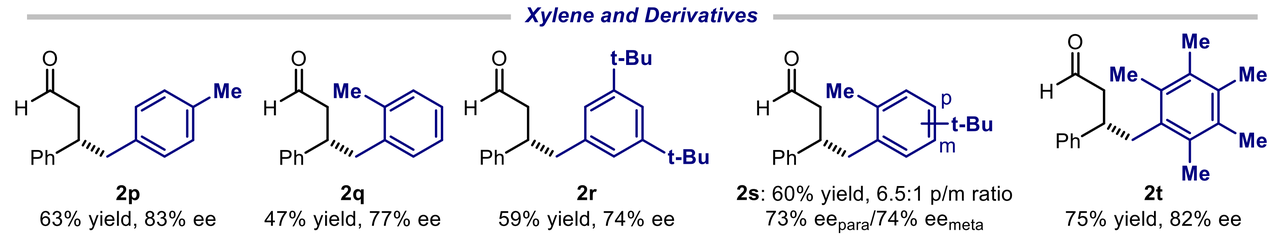
Cinnamaldehyde Derivatives



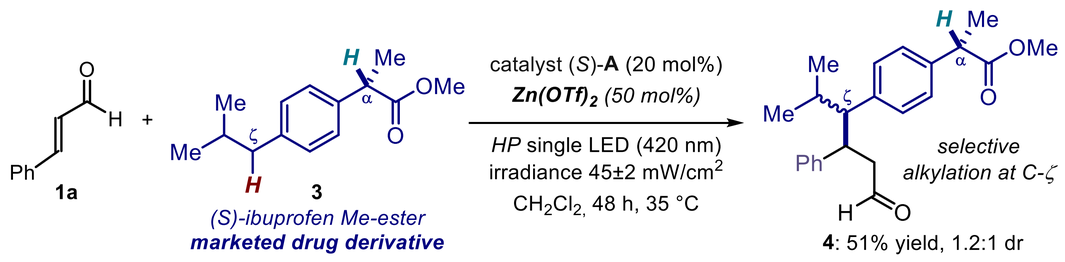
Toluene and Benzylic Derivatives



Xylene and Derivatives

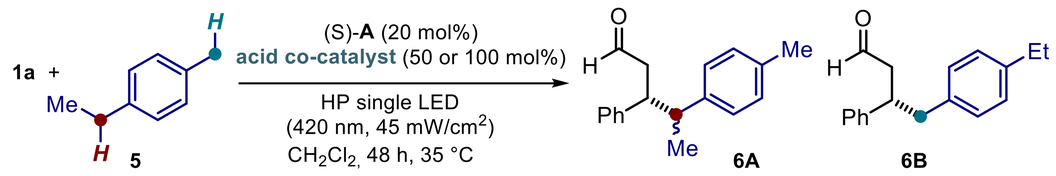


Selective Functionalization of Pharmaceuticals



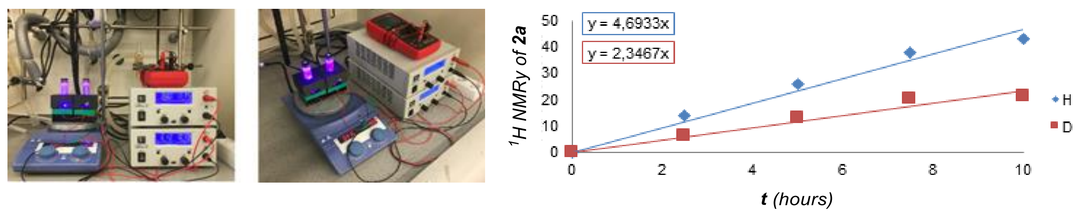
Mechanistic Insights

- Selectivity Study:

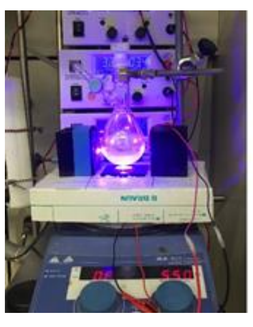


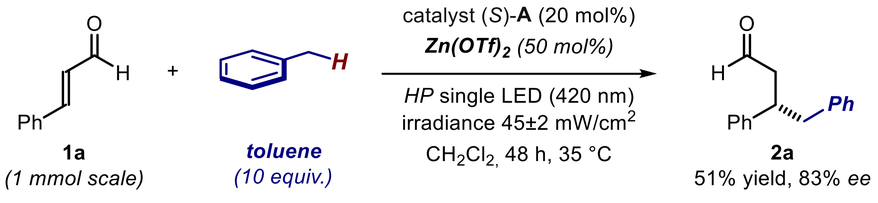
	CH_2ClCO_2H (100 mol%) *pKa = 2.86*	$CHCl_2CO_2H$ (100 mol%) *pKa = 1.35*	CCl_3CO_2H (100 mol%) *pKa = 0.66*	CF_3CO_2H (100 mol%) *pKa = 0.23*	$Zn(OTf)_2$ (50 mol%) *pKa (TfOH) = -14.7*
strength of the conjugate base →					
acid co-catalyst					
overall yield	**no reaction**	**50% yield**	**62% yield**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

- KIE Determination (2.00): *benchmark reactions between* **1a** *and either* ***toluene*** *or* ***toluene-d₈*** *under standard conditions*



Methodology Scale-up





References:
(1) a) *Org. Lett.* **2013,** *15*, 4098; b) *J. Org. Chem.* **2002**, *67*, 4165.
(2) a) *J. Am. Chem. Soc.* **2014**, *136*, 15509; b) *Adv. Synth. Catal.* **2013**, *355*, 2891.
(3) a) *Chem. Sci.* **2017**, *39*, 3845-3879; b) *Chem. Commun.* **2010**, *46*, 601.
(4) a) *ACS Catal.* **2018**, *8*, 1062; b) *Angew. Chem., Int. Ed.* **2018**, *57*, 1068;
c) *Nat. Chem.* **2017**, *9*, 868.

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