Site-selective arene C-H amination via photoredoxcatalysis

Nathan A. Romero, Kaila A. Margrey, Nicholas E. Tay, David A. Nicewicz*

Science, 2015, 349, Page 6254

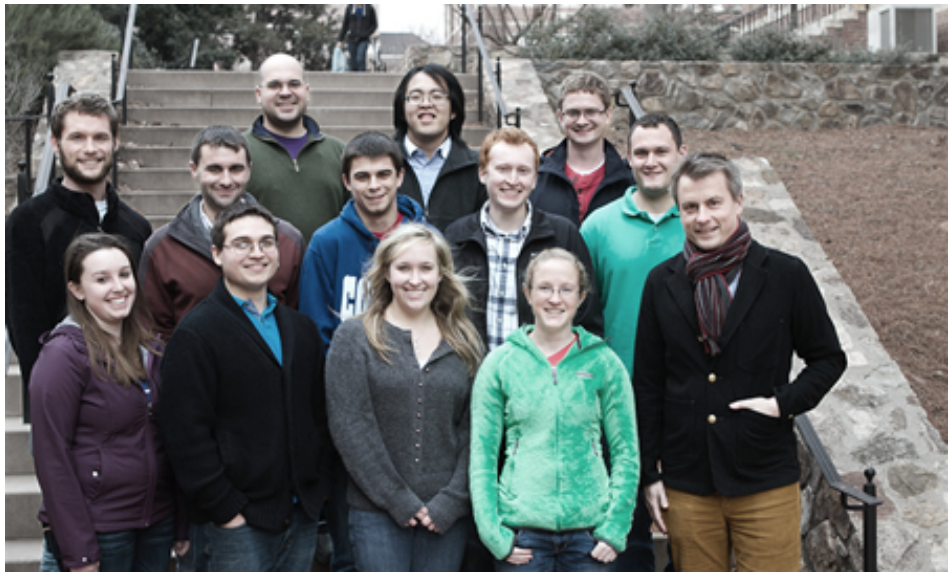
Presented by Alexander Chatterley

24th of October 2015

The Nicewicz Group

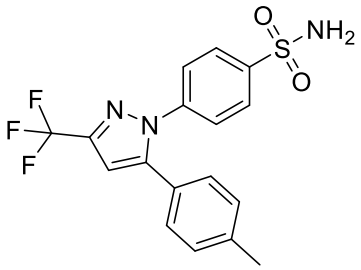
- David Nicewicz graduated from North Carolina University. Undertook at PhD at the same institution under J. Johnson. Went on to post doc with D. MacMillan at Princeton.

- Based at University of North Carolina
- Comprised of 12 members
- Research focuses include natural product synthesis and methodology.
- Specifically redox processes and enantioselective approaches.

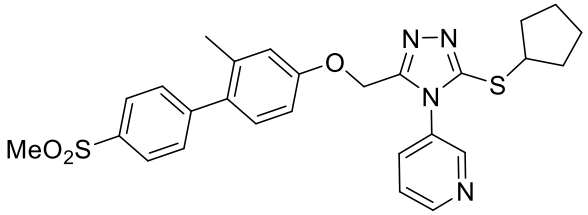


2

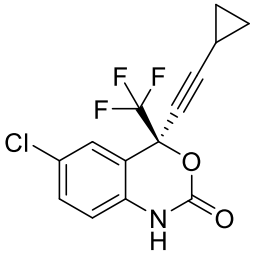
Why is Aryl Amination Important?



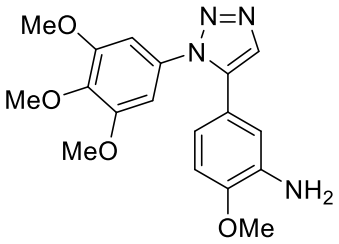
Celebrex
(Anti-inflamatory)



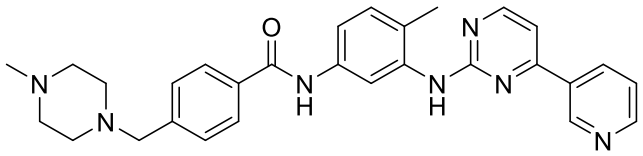
NMS-873
(Cancer)



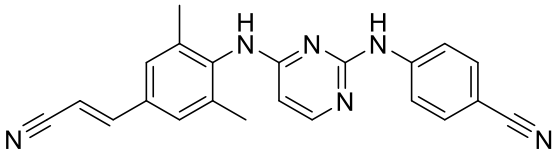
Efavirenz
(HIV)



Unnamed
(Cancer)



Imatinib
(Cancer)

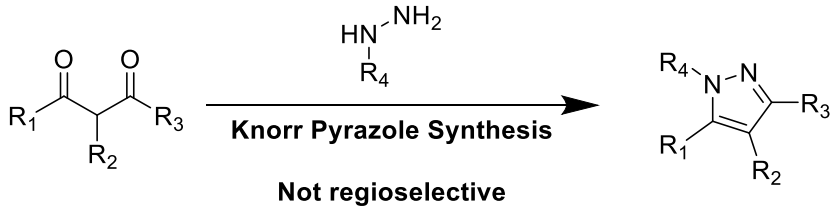


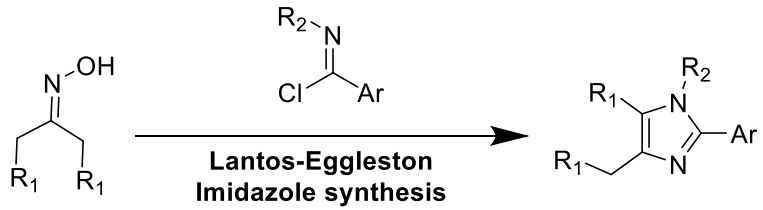
Rilpivirine
(Anti-viral)

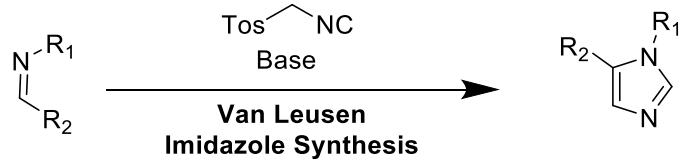
1) Top 200 Pharmaceutical Products by US Retail Sales in 2012, Najardarson et al. 2) J. Med Chem. 2013, 56, 437. 3) Bioorg. Med. Chem. 2008, 16, 4829.

What's different about this methodology?

Representative methodology of current methods to form aryl rings linked to nitrogen containing heterocycles.

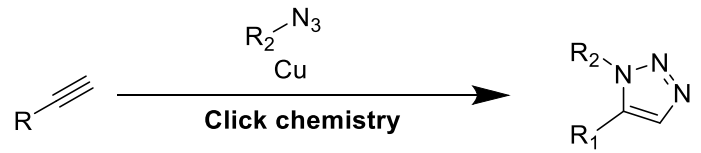




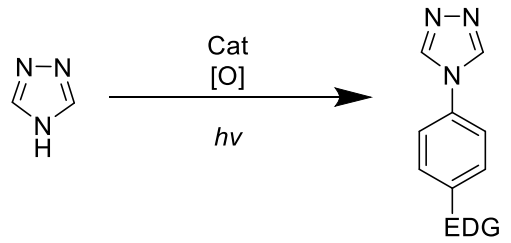


Whats different about this methodology cont.

Representative mythology of current methods to functionalise nitrogen containing heterocycles

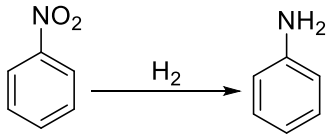


Other methodology exists such as SnAr and metal cross coupling reactions. In this publication aryl C-H amination is explored.

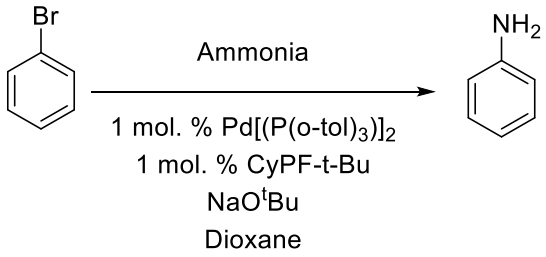


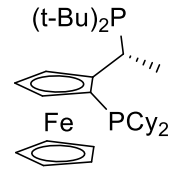
Existing aniline formation methodology

Reduction



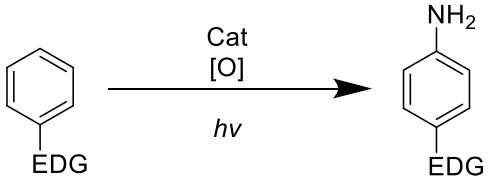
Buchwald coupling





CyPF-t-Bu

This paper:

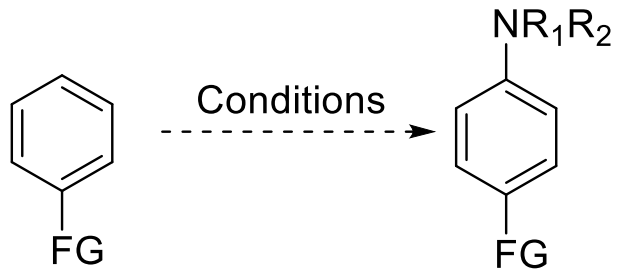


J. Am. Chem. Soc. 2009, 131, 11049

Aryl C-H amination

As seen most current strategies for aryl C-N bond construction revolve around multistep synthesis, transition metal cross couplings or harsh conditions.

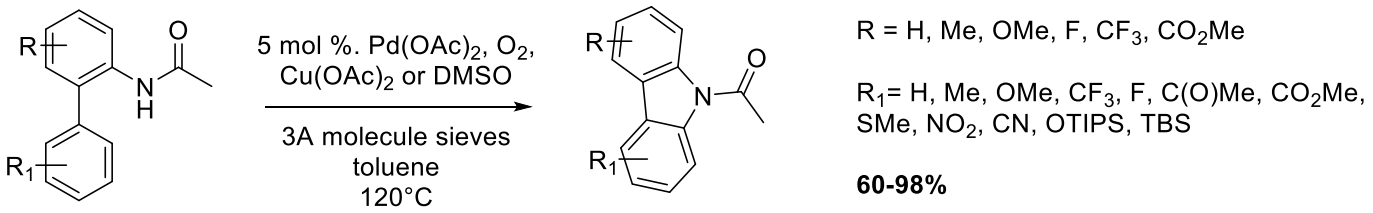
Direct aryl C-H amination offers a way around this as an appropriate C-H bond is the only requirement.



The drawbacks to this is selectivity is an intrinsic challenge, however, some progress has been made.

Aryl C-H amination examples

Initial forays into this area have been made by Buchwald using transition metal catalysis.



R = H, Me, OMe, F, CF_3, CO_2Me

R_1= H, Me, OMe, CF_3, F, C(O)Me, CO_2Me, SMe, NO_2, CN, OTIPS, TBS

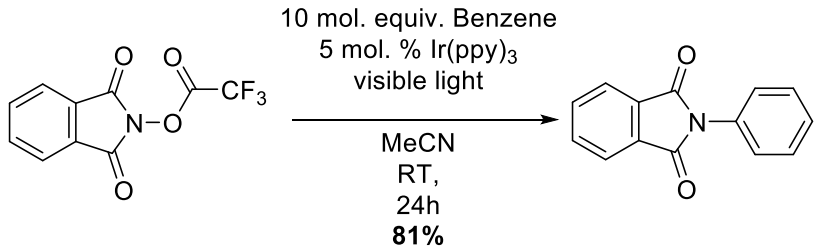
60-98%

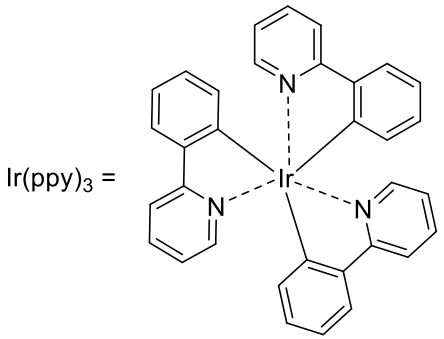
Others such as Daugulis, Shen and Nakamura have also achieved similar ortho-selectivity with transition metal catalysis.

1) J. Org. Chem. 2008, 73, 7603. 2) Angew. Chem. Int. Ed. 2013, 52, 6043. 3) J. Org. Chem. 2014, 79, 4414.
4) J. Am. Chem. Soc. 2014, 136, 646.

Intermolecular C-H amination

Sanford et al. have demonstrated intermolecular C-H amination under photocatalytic conditions.



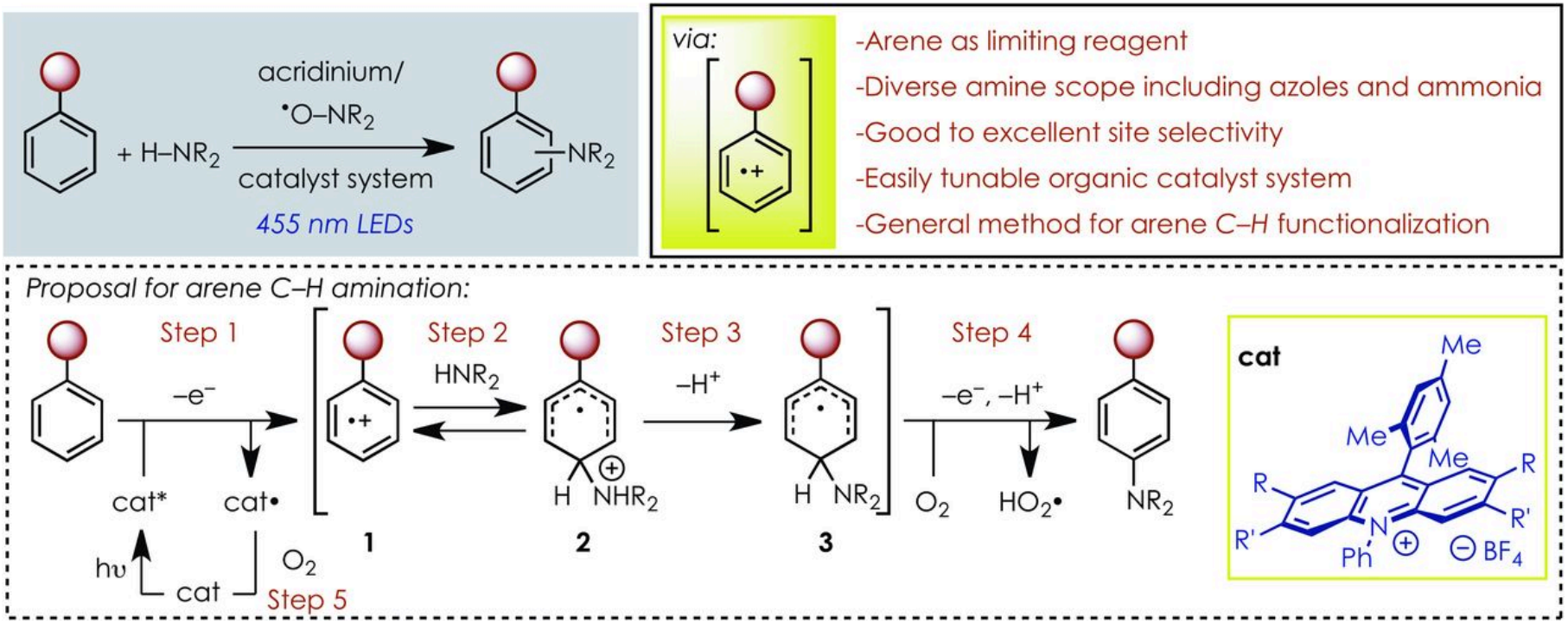


This methodology requires a small electron withdrawing group connected to the acetate carbonyl. This works on range of substrates, however, regio-selectivity is poor on unsymmetrical systems.

Advances have in this area have also been made by Chang and DeBoef.

1) J. Am. Chem. Soc. 2014, 136, 5607. 2) J. Am. Chem. Soc. 2011, 133, 19960. 3) J. Am. Chem. Soc. 2011, 133, 16382.

The Nicewicz Approach



They hypothesised that an amine could form a σ-adduct **2** with arene cation radical **1** generated upon a photo induced electron transfer.

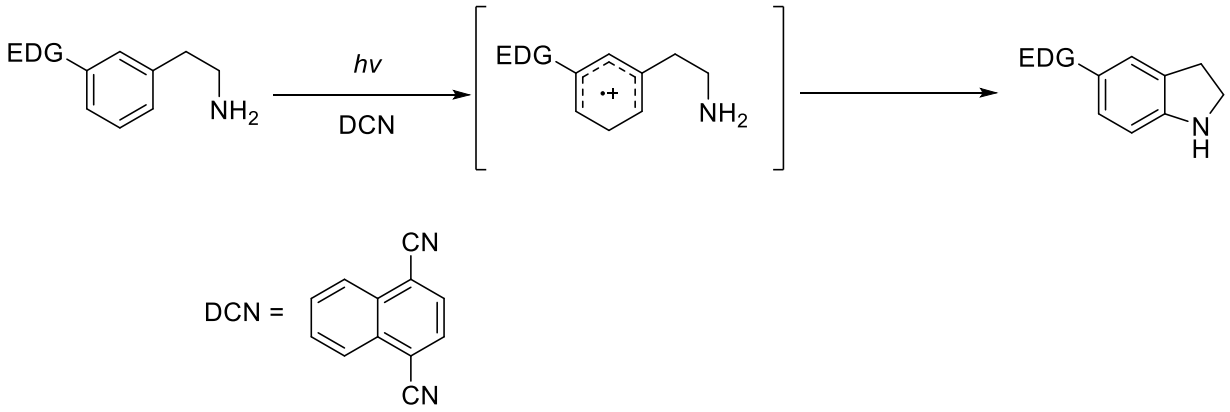
Subsequent deprotonation of distonic cation radical **2** followed by oxidative aromatisation of **3** would deliver the desired amine.

Chem. Rev. 2013, 113, 5322−5363

Supporting reactions

This hypothesis was supported by several previous publications.

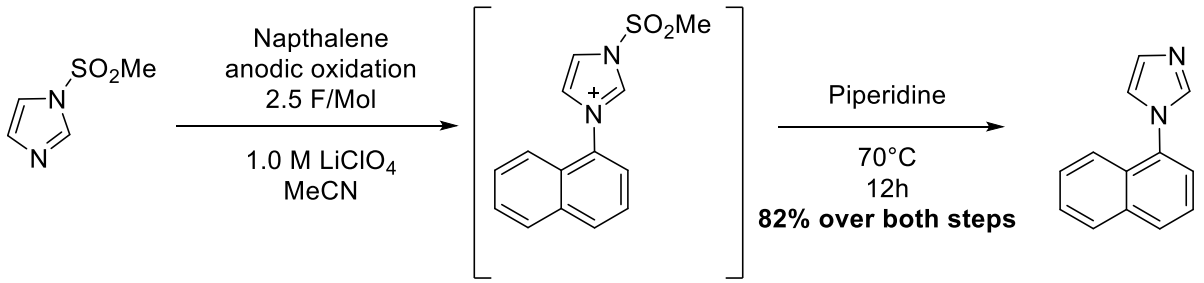
Pendy *et. al.* demonstrated an intra molecule cyclization initiated by a photo induced electron transfer



Tetrahedron Lett. 1990, 31, 5373.

Further support

Further evidence for the possibility of this transformation was garnered from Yoshia et al.



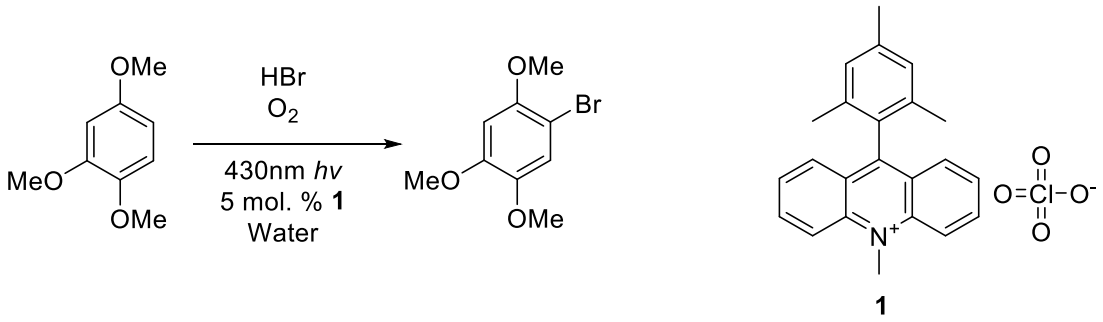
However, this method required a protective group on the second nitrogen or over oxidation was observed.

J. Am. Chem. Soc. 2014, 136, 4496−4499

More inspiration

Fukuzumi and co-workers lent further support to the possibility of this transformation.

They observed the addition of anion halogens to cation radicals generated from photo induced electron transfer event via organic photoredox catalysis.

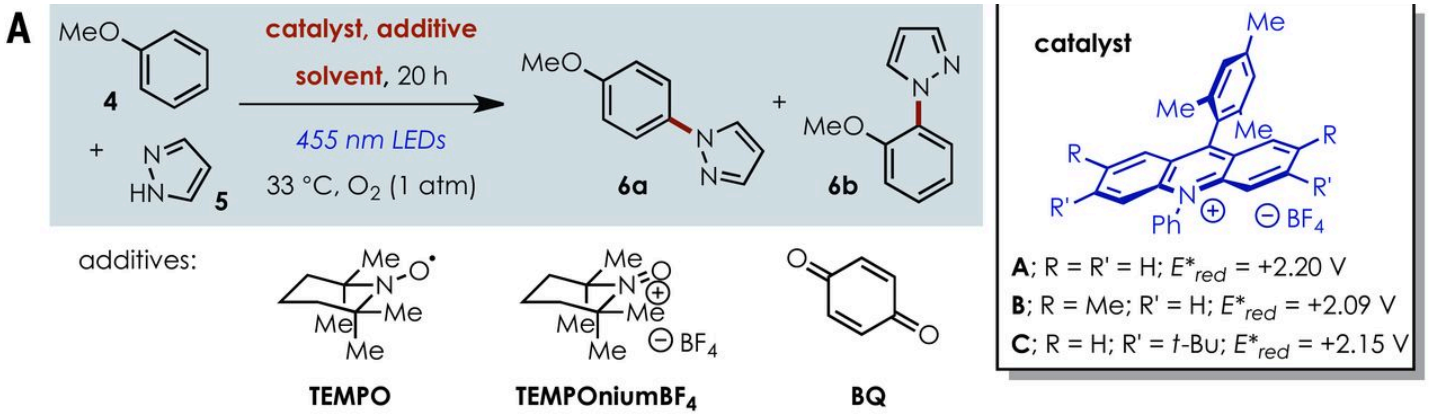


1

In this case oxygen served as the terminal oxidant and was believed to play a role in both regeneration of the catalyst.

Chem. Sci., 2011, 2, 715

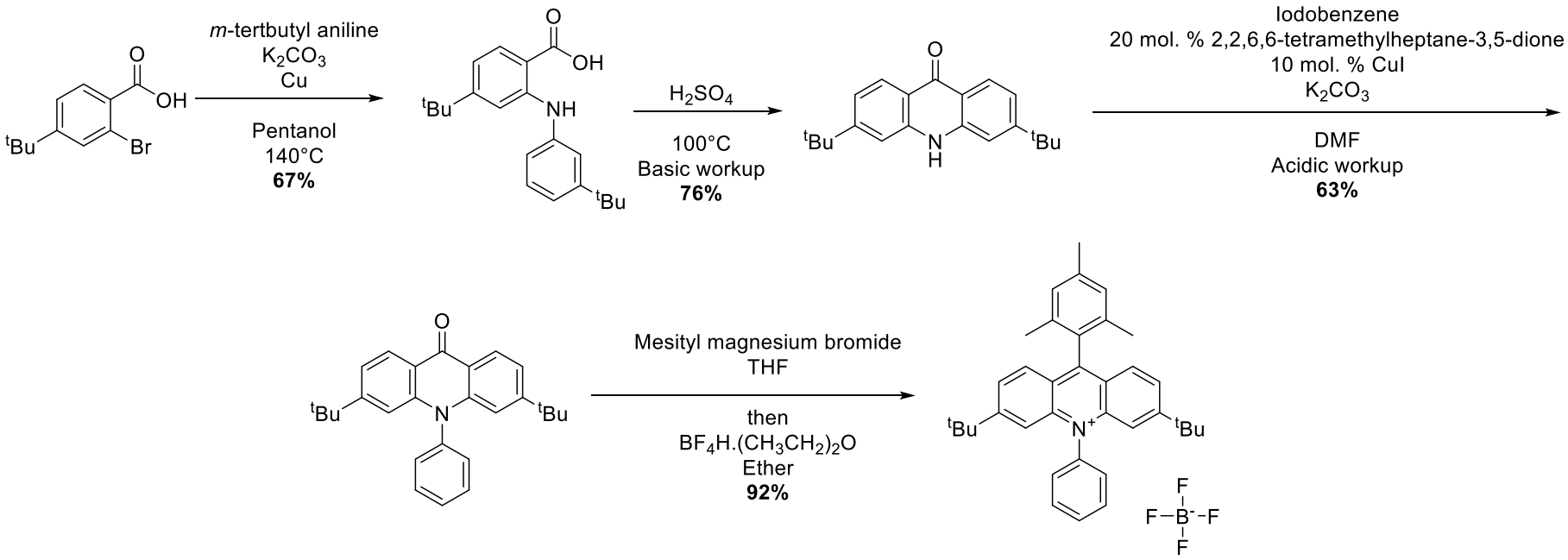
Trial Run and optimisation



- Acridinium catalyst chosen for high positive excited-state reduction potential and stability to nucleophiles.
- No reaction in the absence of oxygen, with oxygen initial yield of 47% (**6a:6b 6.7:1**).
- Initial optimization showed no gain in yield several possibilities were possible:
  - Products could be reducing the catalyst.
  - Phenyl formate observed as by-product indicating side reactions of arene were occurring.
  - Thirdly, it was not possible to recover the catalyst after the reaction, indicating it was not stable under these conditions. Both **4** and the catalyst are susceptible to degradation in the presence of oxygen centred radicals.

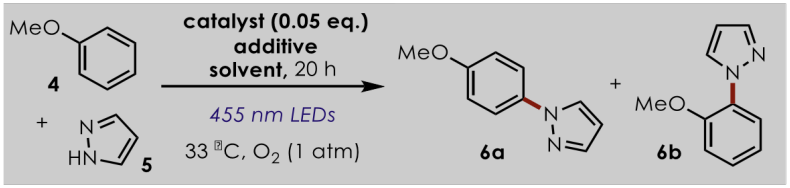
W. P. Hess, F. P. Tully, J. Phys. Chem. 1989, 93, 1944.

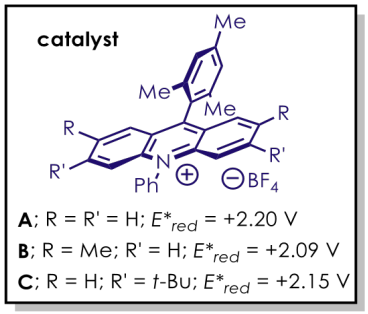
Catalyst modifications



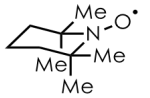
Additionally modifications were made to the catalyst to improve its stability toward nucleophiles.

Table S1. Initial Optimization

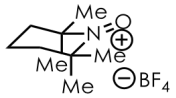




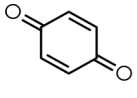
additives:



TEMPO

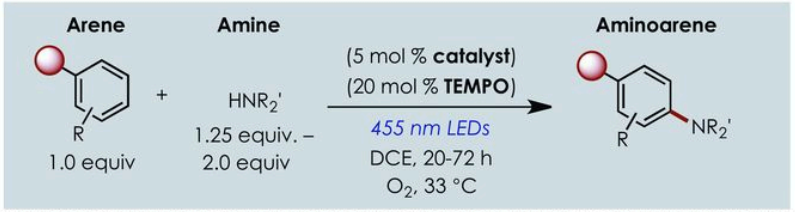


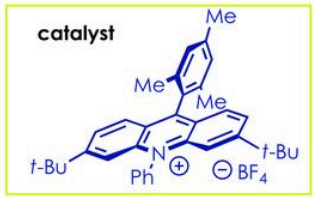
TEMPOniumBF$_4$



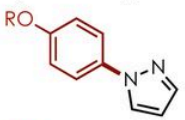
BQ

entry	additive	catalyst	solvent [M]	yield	*p*:*o*
1	no O_2	A	DCM [0.25]	2%	–
2	none	A	DCE [0.25]	47%	6.7:1
3	none	A	MeCN [0.25]	6%	2.0:1
4	none	A	MeOH [0.25]	4%	1:2.9
5	none	A	TFE[0.25]	9%	1:25
6	none	B	DCE [0.25]	37%	3.6:1
7	$PhI(OAc)_2$ (1.0 eq.)	B	DCE [0.25]	20%	4.1:1
8	**BQ** (1.0 eq.)	B	DCE [0.25]	18%	6.9:1
9	$K_2S_2O_8$ (1.0 eq.)	B	DCE [0.25]	14%	1.8:1
10	**TEMPO** (0.1 eq.)	B	DCM[0.25]	65%	6.7:1
11	**TEMPO** (0.2 eq.)	B	DCM[0.25]	74%	6.2:1
12	**TEMPO** (0.5 eq.)	B	DCM[0.25]	45%	6.3:1
13	**TEMPOniumBF$_4$** (0.2 eq.)	B	DCM[0.25]	69%	6.5:1
14	**TEMPO** (0.2 eq.)	A	DCM[0.1]	61%	6.8:1
15	**TEMPO** (0.2 eq.)	B	DCM[0.1]	79%	6.7:1
16	**TEMPO** (0.2 eq.)	C	DCM[0.1]	88%	6.9:1
17	**TEMPO** (0.2 eq.) (air)*	C	DCM[0.1]	97%	7.5:1
18	polymer-TEMPO (0.2 eq.)	C	DCM[0.1]	65%	6.7:1





Arenes | Amine = pyrazole



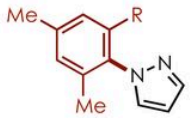
6; R = –OMe; 88% yield; 8.8:1 *p:o*

12; R = –OMOM; 52% yield; 7.8:1 *p:o*

13; R = –OTBS; 74% yield; 9.3:1 *p:o*

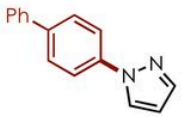
14; R = –O*t*-Bu; 63% yield; 6:1 *p:o*

15; R = –OPh; 86% yield; 11:1 *p:o*

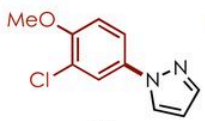


16 (R = –Me)
82% yield*

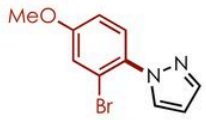
17 (R = –H)
36% yield*



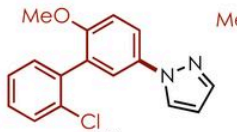
18
56% yield; 7.9:1 *p:o*



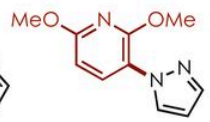
19
70% yield
single regioisomer



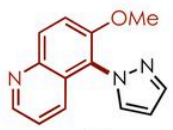
20
54% yield
single regioisomer



21
75% yield
single regioisomer



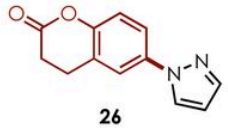
22
45% yield
single regioisomer



23
60% yield
single regioisomer

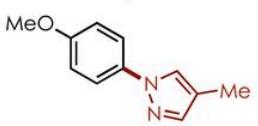
24
43% yield
>15:1 regioselectivity

25
43% yield
single regioisomer



26
30% yield
single regioisomer

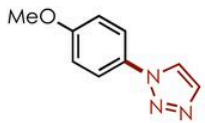
Amines | Arene = anisole



27
68% yield
8:1 *p:o*

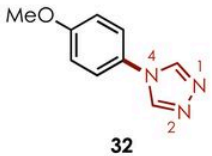
28 (R = –Me)
85% yield; 7.5:1 *p:o*

29 (R = –H)
73% yield; 3.6:1 N1 (6:1):N2 (8:1)

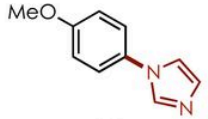


30
71% yield
3.5:1 *p:o*

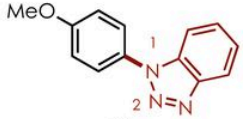
31
53% yield
1.5:1 N1 (10:1): N2 (10:1)



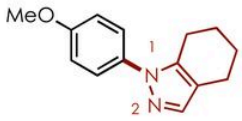
32
76% yield
1.1:1 N4 (4:1): N1 (4.5:1)



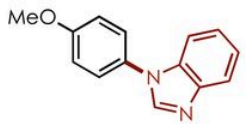
33
55% yield
4:1 *p:o*



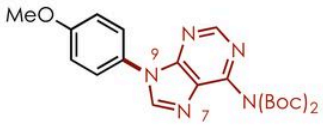
34
57% yield
3:1 *p:o*



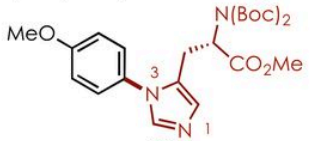
35
51% yield
1:1 N1 (10:1):N2 (>20:1)



36
72% yield
5:1 *p:o*

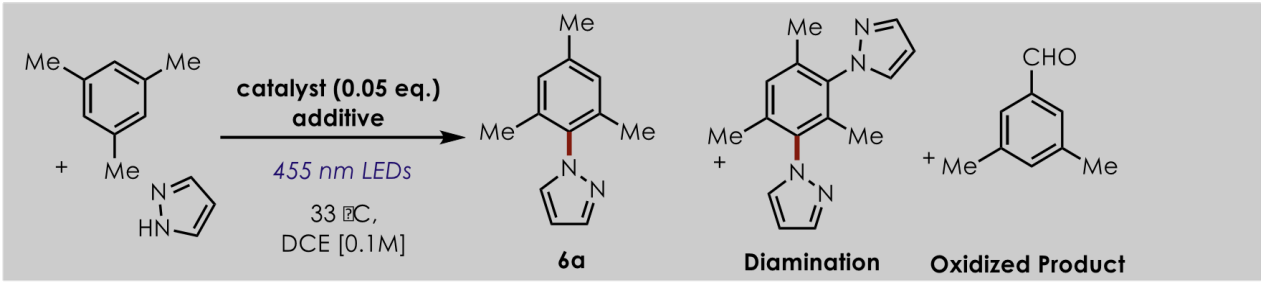


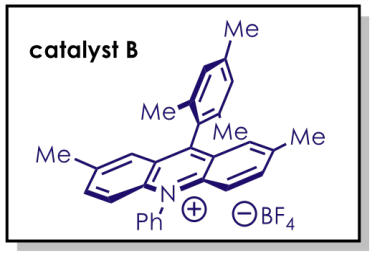
37
99% yield
1.1:1 N7 (4:1):N9 (3:1)



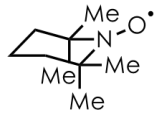
38
52% yield†
1.2:1 N3 (5:1):N1 (8:1)

Mesyitl optimisation



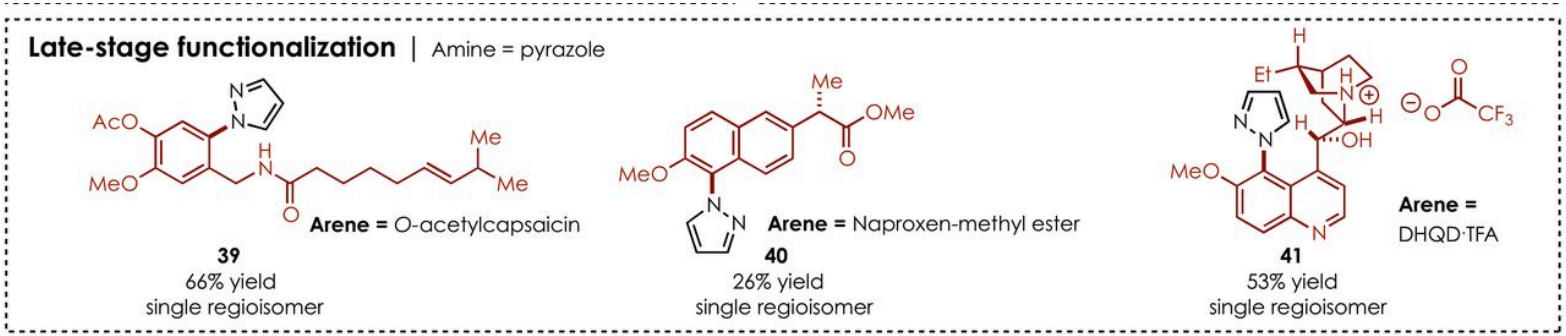


additives:



entry	Atmosphere	Arene:Amine	TEMPO	Time	Yield **6a**	Yield **Diamination**	Yield **Oxidized**
1	O_2	1:2	None	24 hours	39%	16%	10%
2	O_2	1:2	0.2 equiv.	24 hours	40%	49%	5%
3	O_2	2:1	0.2 equiv.	24 hours	78%	12%	20%
4	O_2	2:1	0.2 equiv.	48 hours	80%	11%	22%
5	N_2	1:2	0.2 equiv.	24 hours	20%	3%	0%
6	N_2	1:2	1.0 equiv.	24 hours	52%	3%	0%
7	N_2	2:1	1.0 equiv.	24 hours	70%	2%	0%
8	N_2	2:1	1.0 equiv.	48 hours	86%	3%	0%
9	N_2	1:2	None	24 hours	11%	1%	0%

Late stage functionalisation

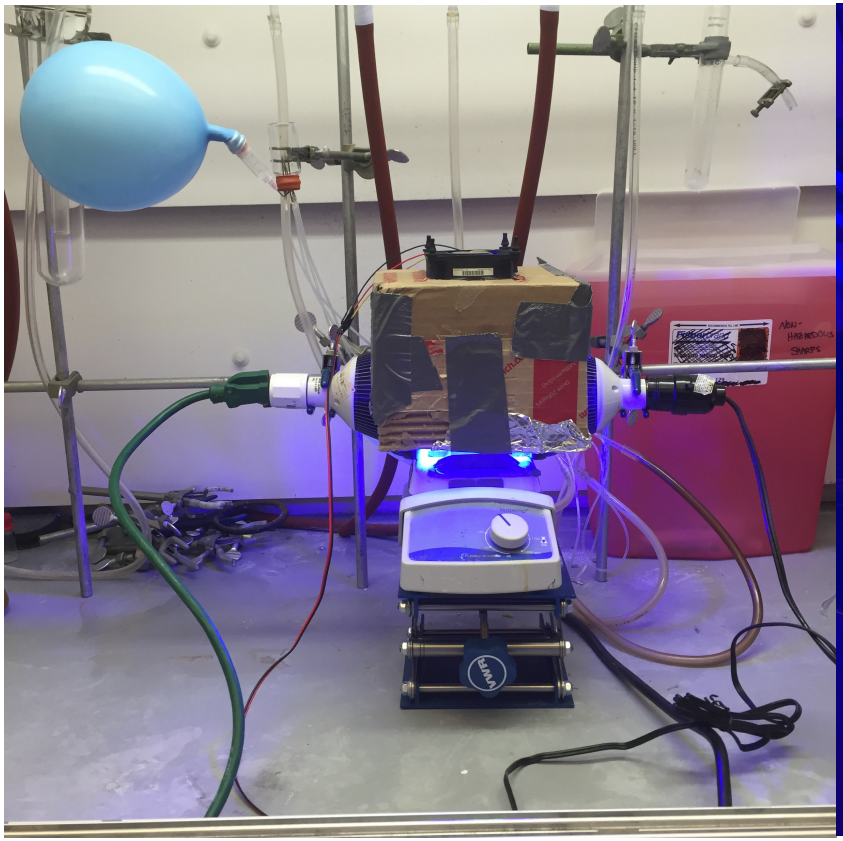


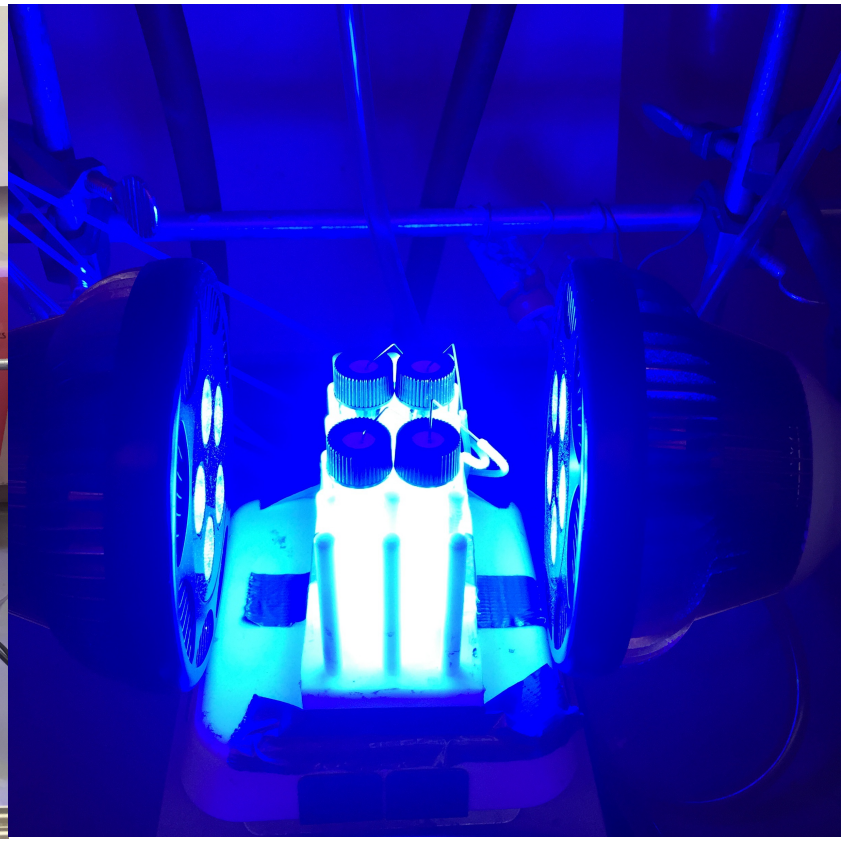
Nicewicz and his group have also demonstrated that it is possible to functionalise several late stage compounds using this methodology.

It is important to note that in each case no benzylic oxidation was observed.

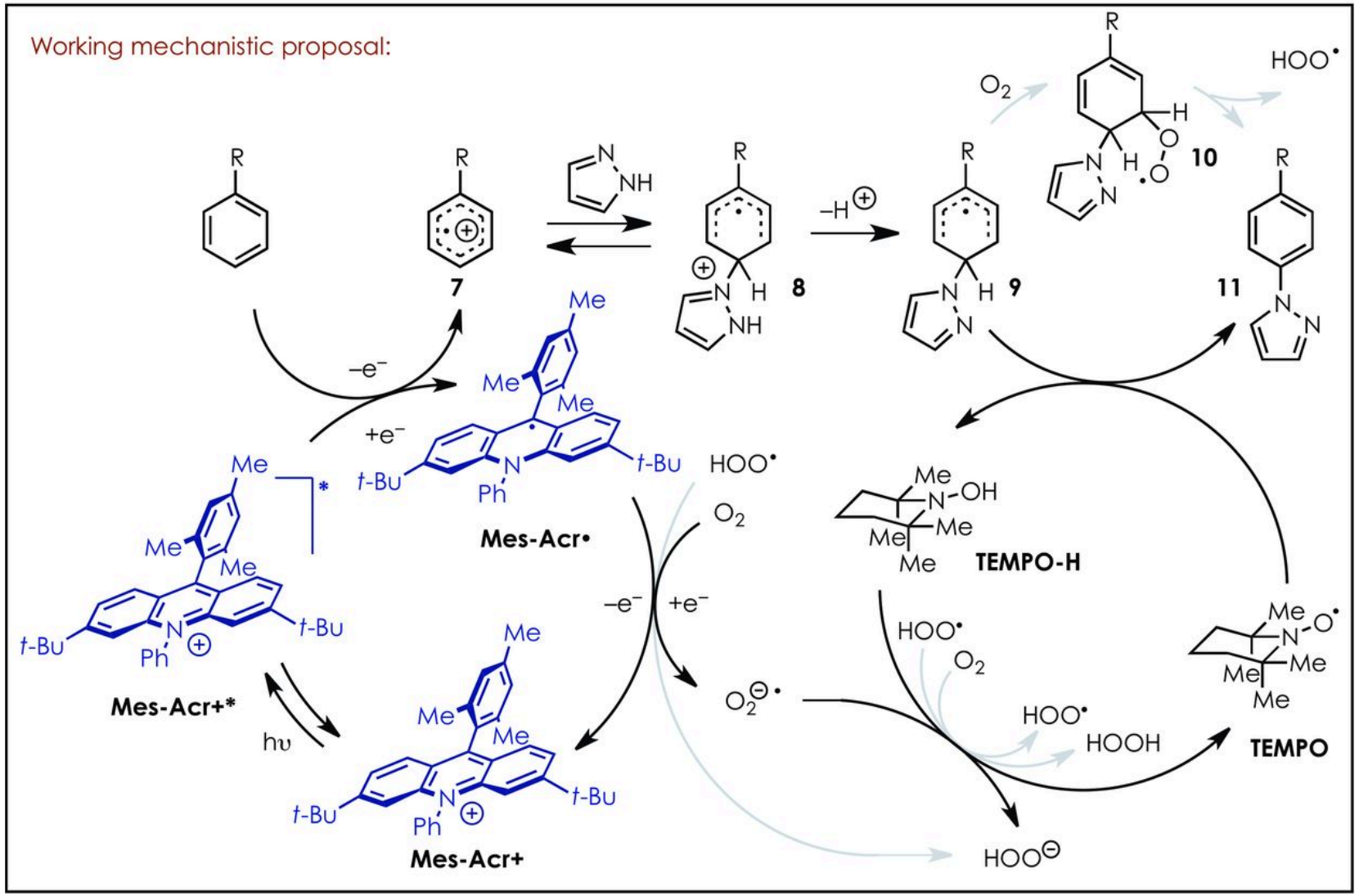
They believe site selectivity is due to a range of factors.

Photo-reactor setup



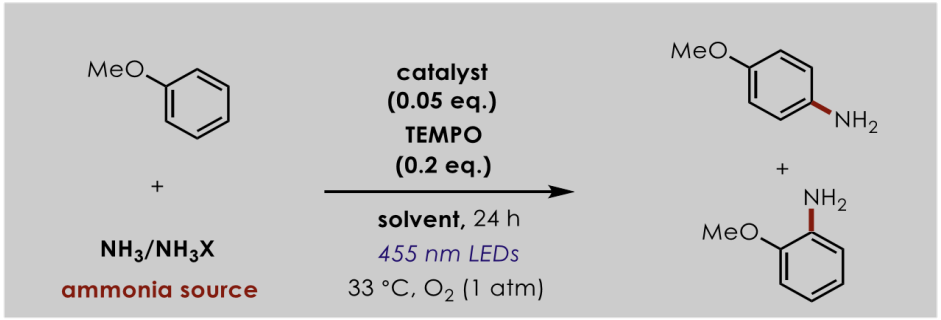


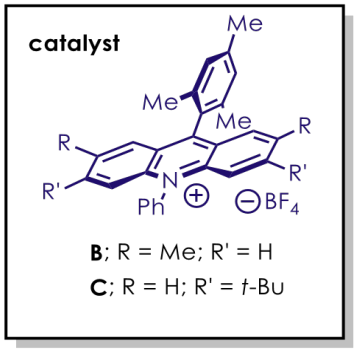
Proposed mechanism



1) J. Chem. Soc. Perkin Trans. 1933, 2, 289. 2) Chem. Sci. 2011 2, 715. 3) Anal. Chem. 1996, 68, 3815.

Aniline optimisation

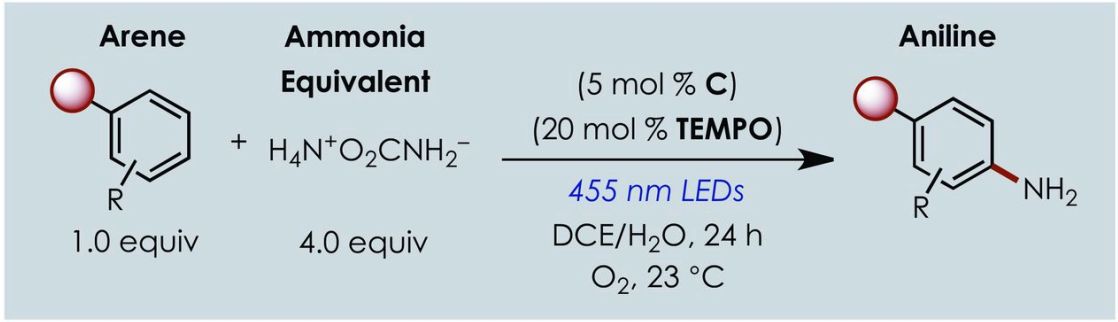


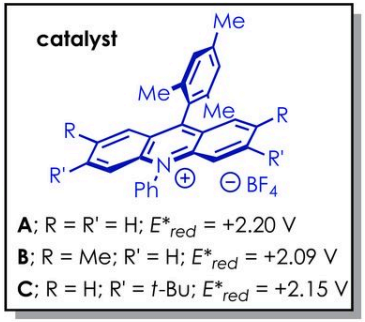


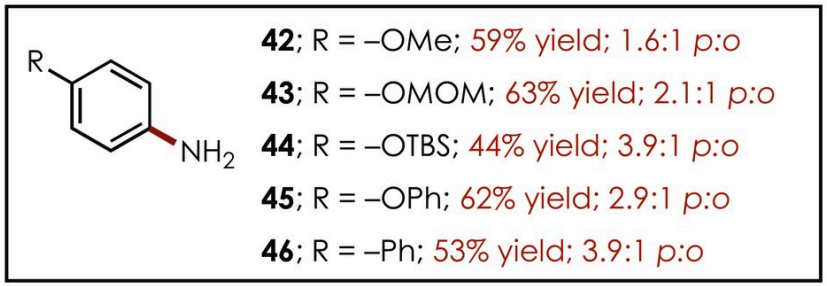
entry	ammonia source	catalyst	solvent [M]	yield†	para:ortho
1	NH_4OAc, 2 eq.	**B**	DCE [0.10]	15%	1:1
2	NH_4HCO_3, 2 eq.	**B**	DCE [0.10]	24%	1:1.5
3	$(NH_4)_2CO_3$, 2 eq.	**B**	DCE [0.10]	35%	1:1
4	$(NH_4)_2CO_3$, 2 eq.	**B**	MeCN[0.10]	24%	2:1
5	$(NH_4)_2SO_3$, 2 eq.	**B**	DCE [0.10]	0%	--
6	$(NH_4)_2CO_3$, 2 eq.	**B**	DCE:H_2O [0.10*]	43%	1.6:1
7	$(NH_4)_2CO_3$, 4 eq.	**C**	DCE:H_2O [0.10*]	40%	1.2:1
8	$NH_4O_2CNH_2$, 4 eq.	**C**	DCE:H_2O [0.10*]	58%	1.4:1
9	$NH_4O_2CNH_2$, 2 eq.	**C**	DCE:H_2O [0.10*]	45%	1.5:1
10	$NH_4O_2CNH_2$, 4 eq.	**B**	DCE:H_2O [0.10*]	47%	1.4:1
11	$NH_4O_2CNH_2$, 4 eq.	**C**	TFE [0.10]	7%	--
12	$NH_4O_2CNH_2$, 4 eq.	**C**	DCE:TFE [0.10*]	25%	1:1

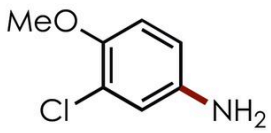
Reactions were performed using anisole (0.460 mmol), catalyst **B** or **C** (5 mol %), TEMPO (20 mol%)
*A 10:1 ratio of DCE:H_2O was utilized as the solvent system.
†Yields determined by GC analysis using 3-bromotoluene as the internal standard

Aniline formation









47

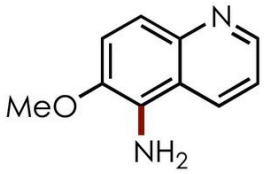
33% yield

single regioisomer

48

61% yield

>6:1 regioselectivity



49

36% yield

single regioisomer

Pros and Cons

Pros

- This methodology is very mild.
- High yielding in some cases.
- Late stage functionalisation and direct formation of anilines is possible in some cases.
- Avoids the need for multiple steps where applicable.
- Tolerant of most functional groups.

Cons

- Limited to electronic rich aromatic rings.
- Regio-selectivity can be poor.

Future work

- Improve substrate scope e.g. electro-neutral or slightly deficient aromatics
- Improve direct aniline formation methodology.
- Expand scope to other amines.
- Explore scability, reactions in this paper were conducted on 0.1 mmol.

Questions?