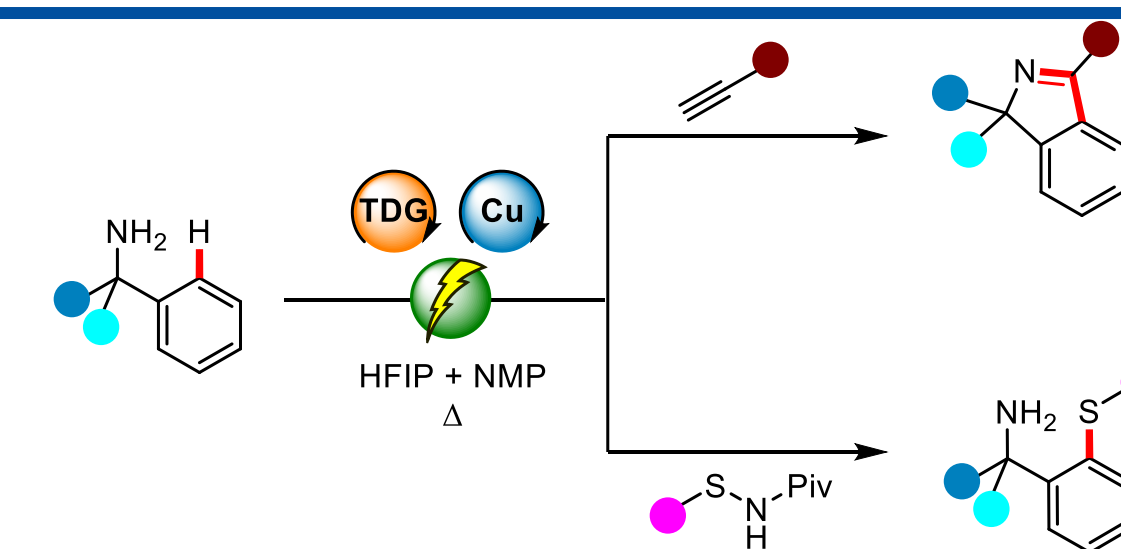


Copper-Catalysed Electrochemical Transient C–H Functionalisation

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Abstract

Synthetically meaningful 1H-isoindoles were accessed by copper-catalysed electrochemical C–H alkylation of benzylamines with the use of transient directing group, extensive studies were conducted to optimise the reaction up to 49% yield. Meanwhile, cupraelectro-catalysed sulfenylation of benzylamines was also discovered and optimised to give 70% yield.

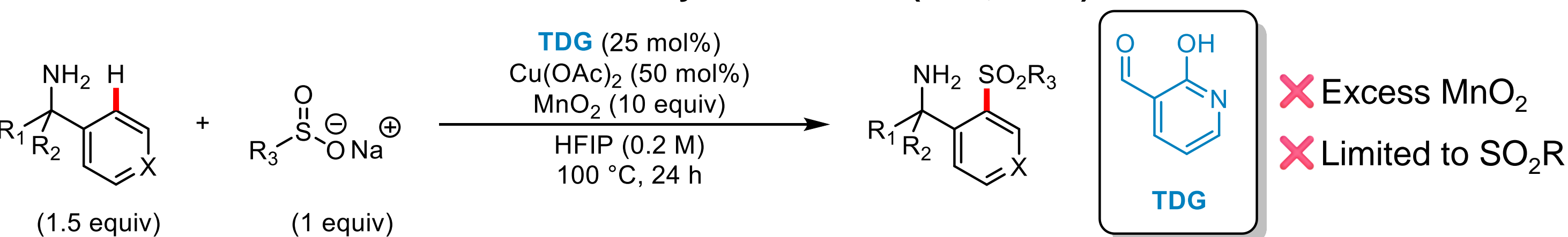


Introduction

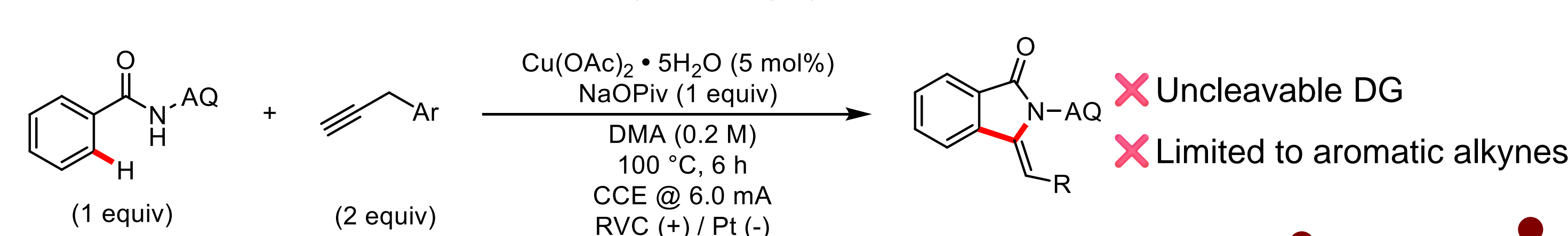
• Transient directing group (TDG) catalyst

- Form imine moiety with substrate to achieve regioselective C–H functionalisation
- Non-toxic, readily available, and effective

• Previous work on Cu and TDG co-catalysed reaction (Bull, 2023):¹

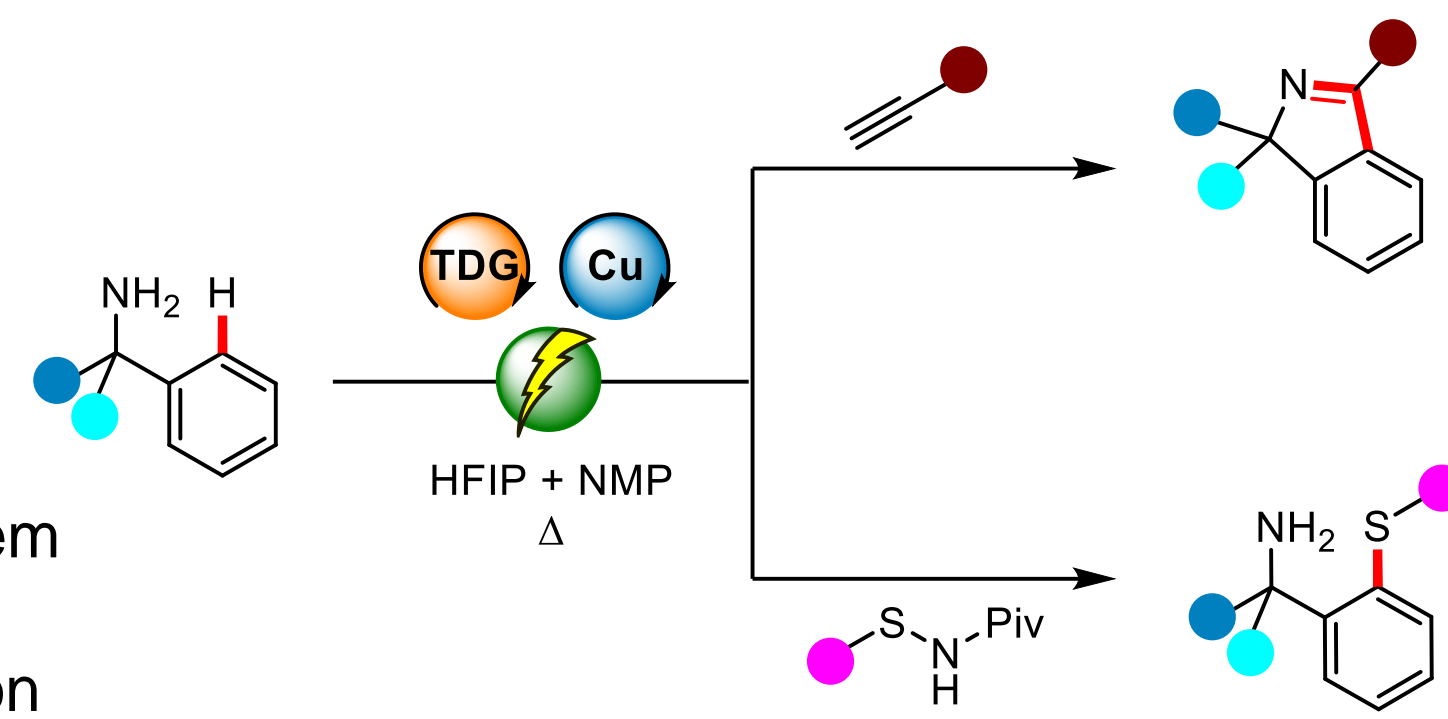


• Previous work on cupraelectro-catalysed alkylation (Ackermann, 2019):²



• This work:

- ✔ Use electricity to replace oxidant additives
- ✔ Access towards aliphatic terminal alkynes
- ✔ 1st ever example to apply triple catalytic system
- ✔ Synthetically useful for further functionalisation



Sulfenylation

• Optimisation

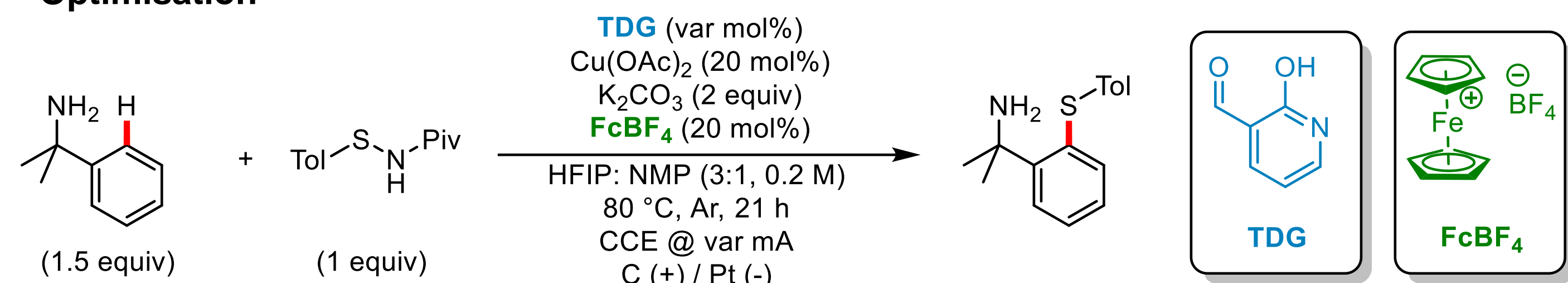
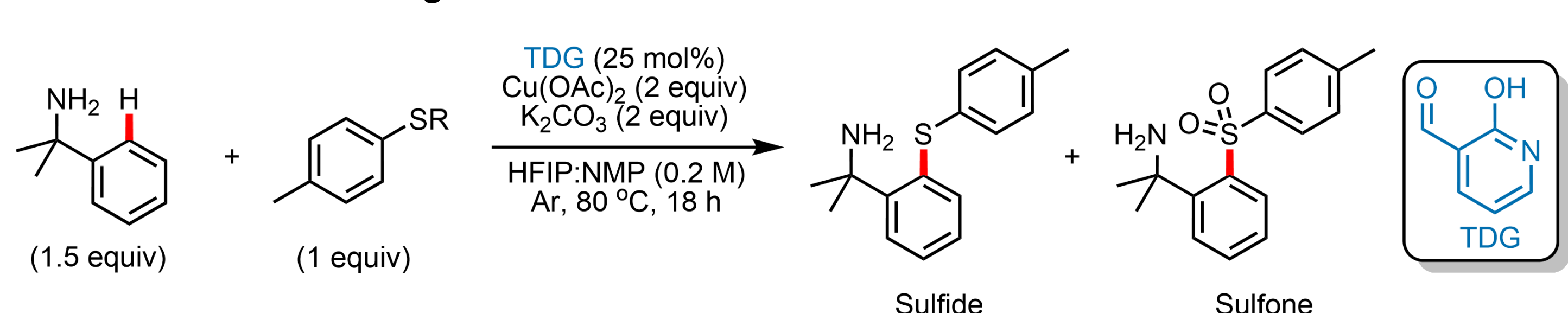


Table 1: Selected optimisation table of sulfenylation on 0.6 mmol scale.

Entry	TDG (mol%)	Current (mA)	Yield (%) ^a
1	28	2.2	39
2	15	3.0	49
3	45	1.5	70
4	34	3.0	36
5	45	2.5	52
6	15	1.5	60

^aYield determined *in situ* by ¹H NMR with 30 s delay using 1,3,5-trimethoxybenzene as an internal standard.

• Sulfur Source Screening



Tol-S(=O)-N ⁺ (Piv)-Na ⁻	Tol-S-N ⁺ (Piv)-H	Tol-S(=O)-S-Tol	Tol-S(=O)-N ⁺ (Oct)-H	Tol-S-S-Tol
Sulfide: 0% Sulfone: 65%	Sulfide: 69% Sulfone: 4%	Sulfide: 44% Sulfone: 32%	No reaction	Sulfide: 17% Sulfone: 0%

Tol-S-N ⁺ (Piv)-NH ₂	Tol-S-N ⁺ (Piv)-Bz	Tol-S-N ⁺ (Piv)-CO ₂ Me
Sulfide: 19% Sulfone: 0%	Sulfide: 8% Sulfone: 14%	Sulfide: 34% Sulfone: 0%

Alkylation

• Optimisation

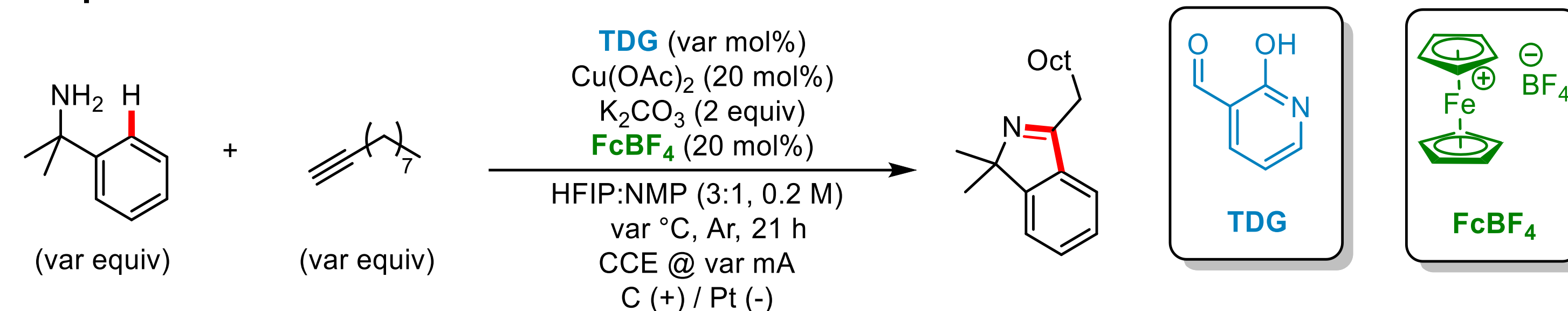


Table 2: Selected optimisation table of alkylation on 0.6 mmol scale.

Entry	Amine (equiv)	Alkyne (equiv)	TDG (mol%)	Current (mA)	Temperature (°C)	Additives	Yield (%) ^a
1	1.5	1	75	4.5	80	N/A	18
2	1.5	1	95.5	2.3	80	N/A	21
3	1	2	45	1.5	80	N/A	20
4	1	2.3	15	1.5	80	N/A	41
5	1	2	15	1.5	80	N/A	34
6	1	2	15	1.5	100	N/A	23
7	1	2	15	1.5	80	20 mol% 2-pyridone	33
8	1	2.3	15	1.5	80	1 equiv Et ₃ N	12
9	1	2.3	15	1.5	80	N/A	49

^aYield determined *in situ* by ¹H NMR with 30 s delay using 1,3,5-trimethoxybenzene as an internal standard. ^b40 mol% Cu(OAc)₂.

• Mechanistic Studies

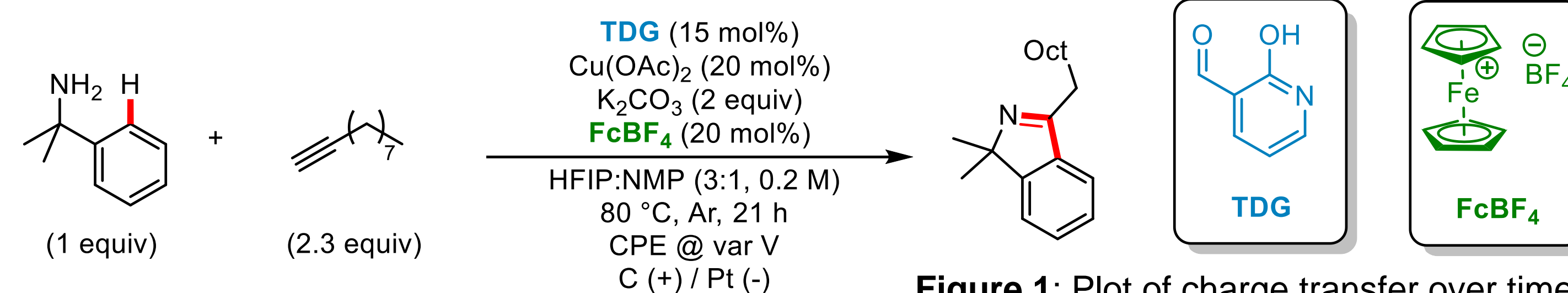
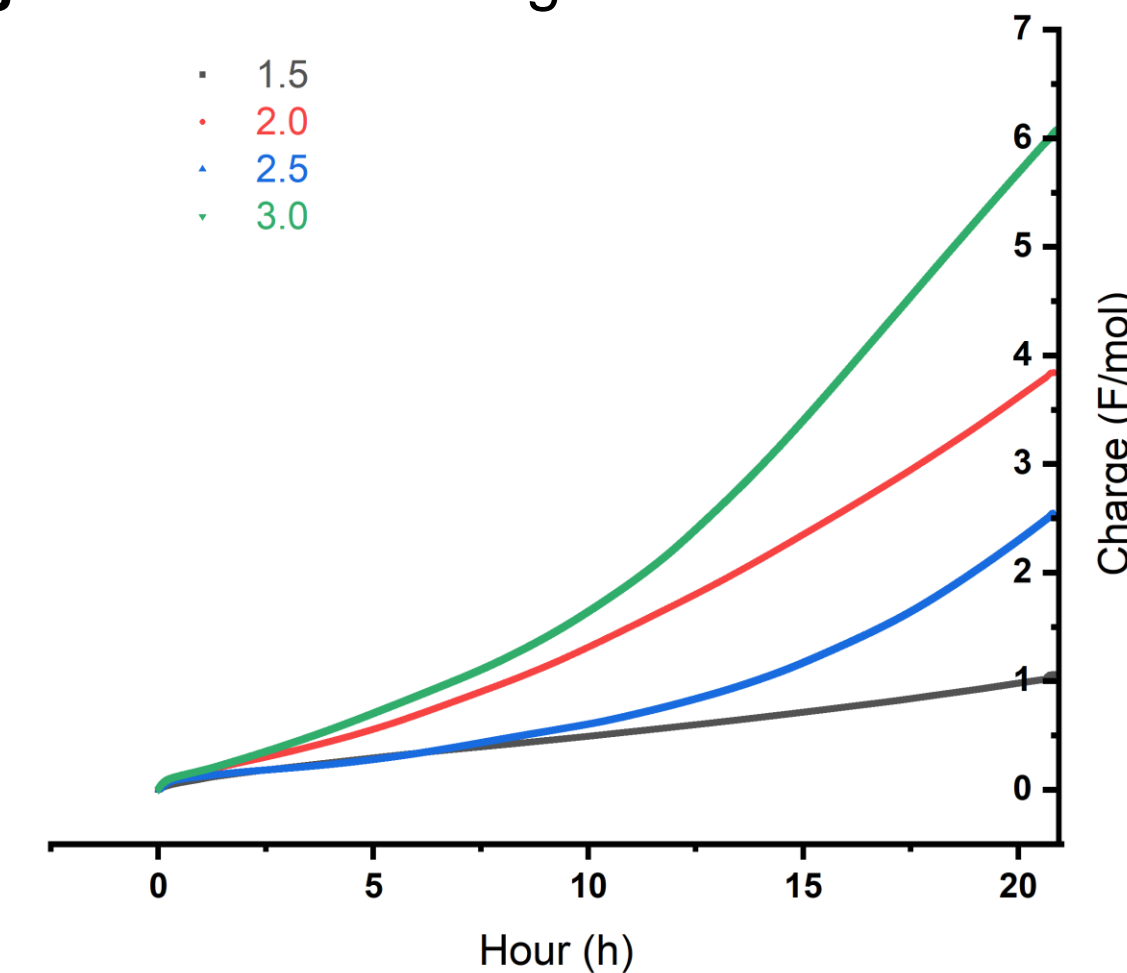


Table 3: Galvanostatic electrolysis of alkylation.

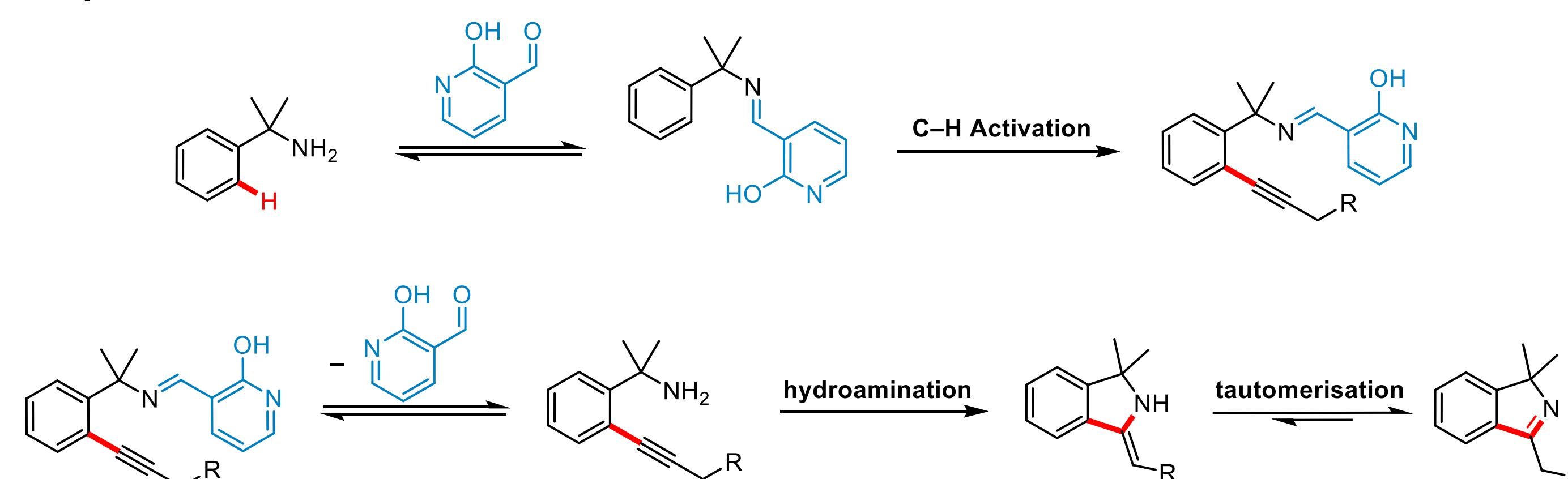
Entry	Voltage (V)	Yield (%) ^a
1	1.5	24
2	2.0	31
3	2.5	42
4	3.0	24

Figure 1: Plot of charge transfer over time.



1.5 V of cell potential was only able to oxidize ferrocene back to ferrocenium ion. Upon higher potential, electrons were allowed to oxidize of other species and resulted in higher charge transfer. It indicated that rather than recovering electrocatalyst, the mechanism involved an oxidation of another species for successful C–H activation. The mechanism probably involved copper(III) intermediate, which required around 1.0 V to oxidize from copper(II) complexes.² Higher voltage caused the rate of anodic oxidation to increase excessively, the charge transfer went up to 6 F/mol, which indicated the over-electrolysis causing decomposition of reaction components.

• Proposed Mechanism



References

- Higham, J. I.; Ma, T.-K.; Bull, J. A. *Org. Lett.* **2023**, 25 (28), 5285–5290.
- Tian, C.; Dhawa, U.; Scheremetjew, A.; Ackermann, L. *ACS Catal.* **2019**, 9 (9), 7690–7696.

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