# Boosting *N*-Heterocyclic Carbene Radical Organocatalysis with Nickel Chemistry: A Rational Mechanistic Study-based Approach.

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***ABSTRACT:*** A cooperative NHC/nickel catalytic methodology has been developed for the synthesis of ketones employing aromatic aldehydes and tertiary alkyl iodides. All key steps of the postulated catalytic cycle were validated with comprehensive stoichiometric and electrochemical studies, including reduction of $Ni^{II}$ by the deprotonated Breslow intermediate, $Ni^0$ promoted halogen-atom abstraction to generate transient tertiary alkyl radicals and coupling between the latter with the persistent acyl thiazolium radical intermediate. Such broadly proposed and accepted, yet elusive, acyl thiazolium radical intermediate has been isolated and studied by a single-crystal X-ray diffraction study.

*Keywords: Cooperative catalysis, N-Heterocyclic Carbenes, Nickel, Tertiary Alkyl Iodides, Radicals*

*N*-heterocyclic carbenes (NHC)[1] are long-known organocatalysts, which can promote the *umpolung* of aldehydes through the formation of enaminols **AH**, so-called Breslow intermediates.[2,3] Recently, the field witnessed an exciting revival with numerous reports of NHC-catalyzed radical transformations of aldehyde derivatives.[4] The key step of these processes usually involves the reductive activation of a substrate by single electron transfer (SET) from electron-rich enolates **A**$^-$,[5] which can feature reducing potentials as low as -2 V vs SCE (Figure 1a).[6] In line with this order of magnitude, the reductive activation of substrates through simple NHC-catalysis has culminated to date with iodoarenes ($E_{red(PhI)}$ ca. -2 V vs SCE[7]).[8-10] Very recently, primary and secondary unactivated alkyl iodides and bromides ($E_{red} <$ -2 V) have been acylated via NHC organocatalysis.[11,12] Note that in the case of these substrates, an $S_N2$ reaction with Breslow intermediates is also possible and it is likely that both ionic and radical pathways coexist. In any case, tertiary alkyl halides remain out of reach and therefore represent the new redox frontier for NHC-catalyzed radical activation of electrophiles.[13-15]

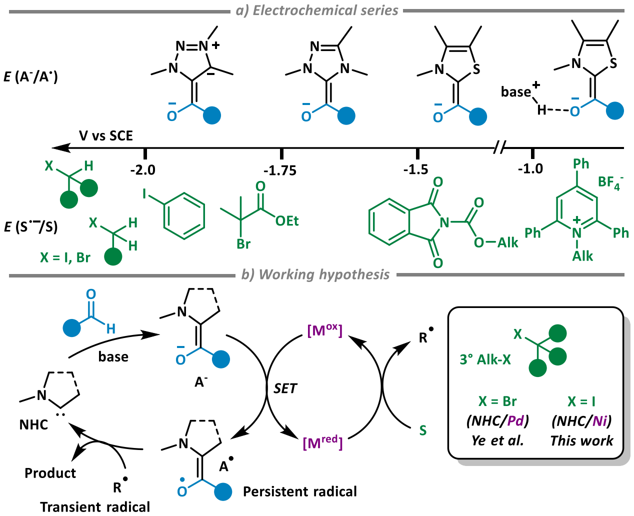


**Figure 1.** Electrochemical series in NHC radical catalysis and the working hypothesis of a cooperative NHC/M redox system.

We considered to run cooperative catalysis employing $Ni^0$ complexes[16] that can advantageously activate tertiary alkyl iodides to perform radical transformations.[17] In these cases, closure of the catalytic cycle requires the reduction of the oxidized Ni complex with a stoichiometric sacrificial electron donor.[18] Herein, we considered that the latter could be replaced by catalytically generated enolates **A**$^-$. In situ generated persistent radical **A**$^\bullet$ would then cross-couple with transient radical **R**$^\bullet$ (Figure 1b).[19] Metal cooperative catalysis have already been used to extend the scope of NHC organocatalysts, but most transformations involve either two-electron processes with metals,[20,21] or successive SET events.[22,23] Evidences for NHC-catalyzed SET from Breslow derivatives to metals that trigger pertinent radical formations are limited to few photocatalyzed transformations,[24-26] and the recent report of a cooperative NHC/Pd catalyzed alkylation of aldehydes with tertiary alkyl bromides.[27,28] We are not aware of any catalytic system for the direct formation of ketones from tertiary alkyl iodides and aldehydes.

We first examined the ability of the ubiquitous [NiBr$_2$(dtbpy)] (dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) system[17] to activate *tert*-butyl iodide (**2a**). Cyclic voltammograms of the Ni complex featured intertwined reversible reductions between -1 and -1.5 V and a catalytic wave was observed in this range in presence of **2a** (Figure 2a). As the ligand plays a major role on the redox properties of nickel complexes,[29] we also considered a readily accessible phenyl substituted Xantphos ligand.[30,31] As shown in Figure 2b, the cyclic voltammogram of [NiBr$_2$(Xantphos)] showed two well-separated reversible reductions at $E_{\mathrm{Ni(I)/Ni(II)}}$ = -0.4 V vs SCE and $E_{\mathrm{Ni(0)/Ni(I)}}$ = -0.9 V, respectively. In the presence of *t*BuI a catalytic wave at the Ni$^0$/Ni$^\mathrm{I}$ reversible reduction wave was clearly observed. It is likely that a halogen-atom abstraction event proceeds with the release of *t*Bu$^\bullet$.[17,31,32] In any case, both systems showed promising catalytic activity (*vide infra*).

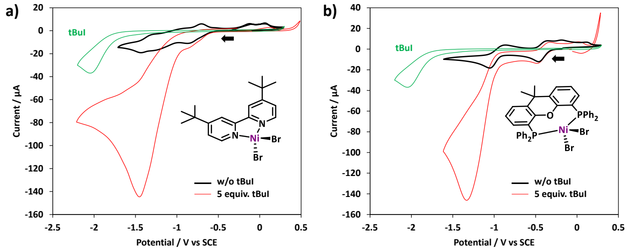
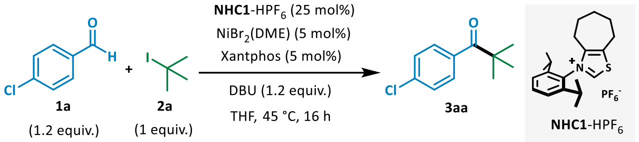


**Figure 2.** Cyclic voltammograms of (a) [NiBr$_2$(dtbpy)] and (b) [NiBr$_2$(Xantphos)] in the absence (in black) and in the presence (in red) of *tert*-butyl iodide. The CV of *t*BuI is shown in green. In all cases, 1 mM solution of [Ni] employing 0.1 M of *n*Bu$_4$NPF$_6$ in acetonitrile electrolyte; 100 mV/s rate.

We chose thiazol-2-ylidene **NHC1**, an efficient organocatalyst for a plethora of radical NHC-catalyzed transformations of aldehydes.[14,15] Indeed, we showed that it yields Breslow-type enolates with oxidation potentials ca. -1.4 V vs SCE,[6] a largely sufficient value for the reduction of the targeted Ni$^\mathrm{I}$ complex at $E_{\mathrm{Ni(0)/Ni(I)}}$ = -0.9 V. Thus, optimized reaction conditions for the coupling between 4-chlorobenzaldehyde (**1a**) and *t*BuI (**2a**) leading to **3aa** in 78% NMR yield were found employing 25 mol% of thiazol-2-ylidene precursor **NHC1**-HPF$_6$,[33] 5 mol% of in situ generated nickel Xantphos complex and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base in THF at 45 °C (Table 1, entry 1).

**Table 1. Optimization of the reaction conditions.**[a]

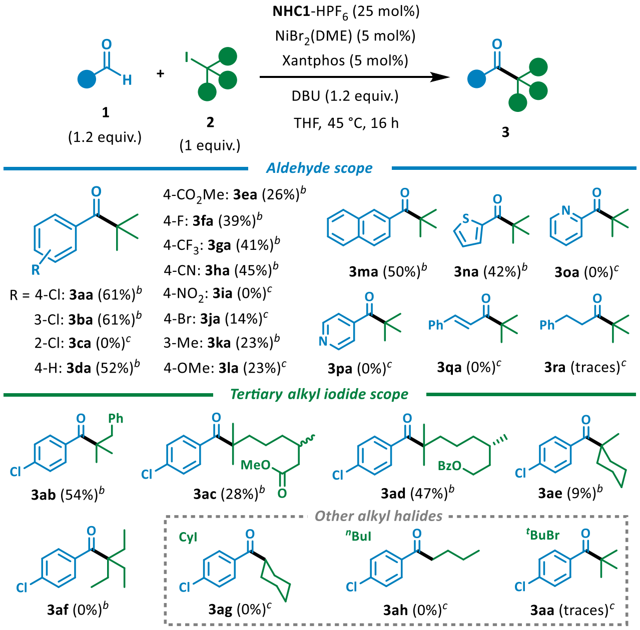


| Entry | Variation from the standard conditions[b] | Yield[c] |
|---|---|---|
| 1 | None | 78% |
| 2 | Table S1: 15 mol% **NHC1**, 30 °C | 57% |
| 3 | Table S1: 15 mol% **NHC1**, 30 °C, solvents | 3-36% |
| 4 | Table S1: 15 mol% **NHC1** | 52% |
| 5 | Table S2: In the absence of **NHC1** or Ni | 0% |
| 6 | Table S3: 15 mol% **NHC1**, N- or P- ligands | 13-56% |
| 7 | Table S4: Different ratios of reagents | 24-71% |
| 8 | Table S5: Carbenes **NHC2-8** I/O **NHC1** | 0-50% |
| 9 | Table S6: Different [Ni] I/O NiBr$_2$(DME) | 34-70% |
| 10 | Table S7: Different bases I/O DBU | 0-65% |

[a]Standard reaction conditions: **1a** (0.3 mmol), **2a** (0.25 mmol), **NHC1**-HPF$_6$ (0.0625 mmol), NiBr$_2$(DME) (0.0125 mmol), Xantphos (0.0125 mmol) and DBU (0.3 mmol) in 1 mL of dry THF under argon atmosphere for 16 h at 45 °C. [b]See Table S1-S7 in SI. [c]NMR yields for **3aa** are given employing 1,3,5-trimethoxybenzene (TMB) as internal standard.

The screening of the reaction conditions started employing 15 mol% of **NHC1** at 30 °C with an encouraging NMR yield of 57% of the desired ketone **3aa** (entry 2 and SI for further details). The use of other solvents such as dichloromethane, acetonitrile, 1,4-dioxane or dimethylsulfoxide did not lead to higher yields (entry 3). Rising the temperature to 45 °C gave a similar NMR yield (entry 4: 52 vs 57%); however, the formation of other side products (such as benzoin and/or benzil) was avoided (see SI). As expected, both the NHC and the nickel complex are required to obtain the desired ketone (entry 5). Working at 45 °C the screening of different N- and P-donor ligands was accomplished (entry 6). 2,2'-Bipyridine-based ligands (including dtbpy) are less efficient than phosphine ligands, Xantphos being optimal. The ratio between reagents **1a** and **2a** was also studied with an optimal ratio of 1.2/1 (entry 1 vs 7). An increase of the NHC loading to 25 mol% had a significant impact in the yield, in contrast to [Ni] loading, suggesting that the formation of the enolate is a limiting step. Among the different NHCs tested the most efficient is **NHC1**, a thiazol-2-ylidene which possesses a seven-member ring in the backbone and 2,6-diisopropylphenyl (Dipp) *N*-substitution (entry 1 vs 8). Several nickel sources were also tested (entry 9). The *in situ* formation of the precatalyst remained superior to the isolated one (60%) and a Ni$^0$ source such as Ni(COD)$_2$ was also fairly active[34] as expected from cyclic voltammetry. We also found that cesium and potassium carbonates afford 63-65% yields, while almost no reaction was observed with the sodium or lithium salts (entry 10). This is in line with previous studies, which indicated that the oxidation potential of Breslow enolates increases with the hardness of the counter-cation.[6,35] Note that, DBU which was found optimal for our reaction, leads to H-bond stabilized enolates with $E_{ox}$ ca. -1 V vs SCE, a value that still matches with the reduction of Ni$^I$ species at -0.9 V.

**Table 2. Scope of the reaction.**[a]

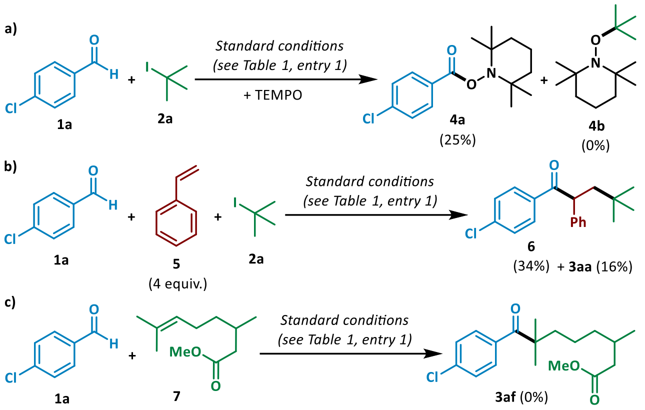


[a]Standard reaction conditions: **1a** (1.2 mmol), **2a** (1 mmol), **NHC1**-HPF$_6$ (0.25 mmol), NiBr$_2$(DME) (0.05 mmol), Xantphos (0.05 mmol) and DBU (1.2 mmol) in 4 mL of dry THF under argon atmosphere for 16 h at 45 °C. [b]Isolated yield. [c]NMR yields are given employing TMB as internal standard; in these cases, the scale was 0.25 mmol for **2a**.

Under these optimized conditions, aromatic aldehydes led to a variety of ketones in moderate yields (Table 2). *Ortho*-substitution is detrimental in comparison to *meta* and *para* positions (**3ca** vs **3aa** & **3ba**) likely due to steric effects. Electron withdrawing groups increase the electrophilicity of the aldehydes and the nucleophilic attack of the NHC is aided. Thus, ester, fluoro, trifluoromethyl and cyano containing substrates reacted smoothly leaving little starting material unreacted (**3ea-ha**). Exceptions were the nitro group (**3ia**) and bromo (**3ja**), probably due to incompatibility with nickel catalysis. As expected, electron donating groups such as methyl (**3ka**) or methoxy (**3la**) gave lower yields. 2-Naphthyl (**3ma**) and thiophenyl (**3na**) are compatible, while pyridyl (**3oa** and **3pa**) derivatives are not due probably to nickel poisoning (note that they are predilect substrates in NHC/Pd catalysis).[26] Cinnamaldehyde (**3qa**) and aliphatic (**3ra**) aldehydes did not lead to ketones. Then, tertiary alkyl iodides were screened. Relatively low hindered dimethyl substituted alkyl iodides led in moderate yields to the corresponding ketones **3ab-ad**. In the case of **2c** and **2d**, their respective elimination olefin products were observed during $^1$H NMR analysis, suggesting a competing decomposition reaction of tertiary alkyl iodides which is a clear limitation of this methodology. In order to discard a putative mechanism via olefin intermediates we confirmed that methyl citronellate (**7**) did not lead to ketone **3af** under standard conditions (Scheme 1c, *vide infra*). Indeed, more sterically encumbered substrates such as **2e** and **2f** gave poor results (9% **3ae** and 0% **3af**, respectively). Also, iodocyclohexane and 1-iodobutane were tested. In both cases, they were consumed leading to complex mixtures where the corresponding ketones **3ag** and **3ah** were not present. In fact, the CVs of [NiBr$_2$(Xantphos)] in their presence showed catalytic waves followed by EC processes (see SI), suggesting further transformations and avoiding cooperative catalysis. Finally, *tert*-butyl bromide gave only traces of **3aa** even if *t*BuBr is not activated by Ni$^0$ as observed by CV.

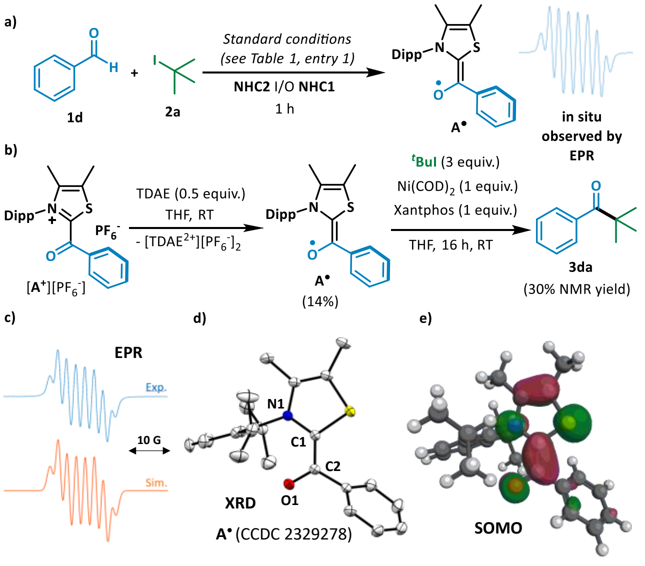
To shed light on the mechanism, we run a couple experiments to proof the generation of transient radicals. Addition of TEMPO led to the formation of **4a**, but trapping of transient $t$Bu$^{\bullet}$ leading to **4b** did not take place (Scheme 1a). The reduction of TEMPO by enolate **A**$^-$[36] is probably faster than the reduction of nickel avoiding its cycle to turn. In contrast, addition of styrene (**5**) led to the corresponding radical relay product **6** which was isolated in moderate yield, supporting the generation of $t$Bu$^{\bullet}$ (Scheme 1b).[15b]

**Scheme 1. Indirect investigations on transient radicals.**



In situ EPR analysis of a catalytic run proved the accumulation of persistent radical **A**$^{\bullet}$ in the medium (Scheme 2a). Its experimental X-band EPR spectrum matches well with the one found after bulk electrolysis in our previous work.[6] Encouraged by its persistency, [**A**$^{+}$][$PF_6^{-}$] was reduced employing half equiv. of TDAE and radical **A**$^{\bullet}$ was isolated as a dark red powder and characterized by EPR (Schemes 2b-c). We obtained suitable single-crystals of radical **A**$^{\bullet}$ for an X-ray diffraction study (Scheme 2d). N1, C1, C2, and O1 atoms are coplanar (dihedral angle of 3.8°). Besides, the relatively short C1-C2 (1.424(2) Å), long N1-C1 (1.380(1) Å) and C2-O1 (1.251(1) Å) bonds suggest delocalization of the electron along the $\pi$-system, which is reminiscent of related analogues.[5,9,37,38] DFT calculations at the M06/6-311g++(d,p) level confirmed the planar structure and the SOMO along the $\pi$-system (Scheme 2e). With radical **A**$^{\bullet}$ in hands, we attempted the cross-coupling reaction of radicals. Satisfyingly, reaction of **A**$^{\bullet}$ with Ni(COD)$_2$/Xantphos[34] in the presence of **2a** led to **3da** in 30% yield (Scheme 2b).

**Scheme 2. Mechanistic studies with persistent radicals.**



Finally, we considered the missing pieces of the catalytic puzzle: the two SET events for the generation of Ni$^{0}$ from Ni$^{II}$ and Ni$^{I}$ complexes. Catalytically relevant enolate [DBUH$^{+}$][**A**$^{-}$] was prepared in the electrochemical cell via bulk electrolysis upon reducing [**A**$^{+}$][$PF_6^{-}$] and consecutive addition of [DBUH$^{+}$][$PF_6^{-}$].[6] [DBUH$^{+}$][**A**$^{-}$] has a characteristic absorption band at 390 nm (Figure 3, spectrum in blue). After addition of excess of [NiBr$_2$(Xantphos)] (Figure 3a) the UV-visible spectrum instantaneously changed showing three bands corresponding to radical **A**$^{\bullet}$ (575 nm), [Ni$^{I}$] complex (315 nm) and excess of [Ni$^{II}$] complex (410 nm). Addition of a sub-stoichiometric amount of [Ni$^{II}$] (Figure 3b) led to some unreacted [DBUH$^{+}$][**A**$^{-}$] (390 nm), **A**$^{\bullet}$ (575 nm) and formation of a light brown powder (tentatively a [Ni$^{0}$] complex).[39] These results suggest that two equivalents of [DBUH$^{+}$][**A**$^{-}$] ($E_{ox}$ = -1 V vs SCE)[6] are able to reduce Ni$^{II}$ to Ni$^{0}$ and generate two equiv. of **A**$^{\bullet}$.[40]

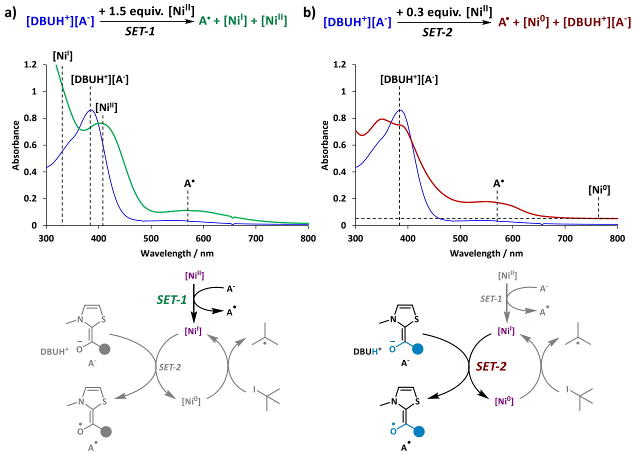


**Figure 3.** Spectroscopic studies for disclosing SET events.

In conclusion, a catalytic cooperative NHC/Ni radical strategy has been developed for the unprecedented coupling between aryl aldehydes and tertiary alkyl iodides leading directly to ketones. Importantly, the combination of reactivity (including the isolation of the omnipresent, yet elusive, Breslow-type radical), electrochemical and spectroscopic studies fully validated the conceptual mechanism and demonstrate that, indeed, NHC and nickel catalytic cycles merge via SET events. We plan to apply this rational approach to other cooperative strategies. On the basis of solid electrochemical data, on-going work is focusing on the activation of more challenging redox non-accessible substrates, beyond the intrinsic limitations of NHC radical catalysis.

## NOTES

The authors declare no competing financial interest.

CCDC 2329277-2329278 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/structures.

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