Mechanistic Insight into the Photoredox-Nickel-HAT Triple Catalyzed Arylation and Alkylation of α -Amino C_{sp3}-H Bonds

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ABSTRACT: We report here a comprehensive computational analysis of the mechanisms of the photoredox-nickel-HAT (HAT: hydrogen atom transfer) catalyzed arylation and alkylation of α -amino C_{sp3}-H bonds developed by MacMillan and coworkers. Different alternatives for the three catalytic cycles were tested to identify unambiguously the operative reaction mechanism. Our analysis indicated that the Ir^{III} photoredox catalyst, upon irradiation with visible light, can be either reduced or oxidized by the HAT and nickel catalysts, respectively, indicating that both reductive and oxidative quenching catalytic cycles can be operative, although the reductive cycle is favored. Our analysis of the HAT cycle indicated that activation of a α -amino C_{sp3}-H bond of the substrate is facile and selective relative to activation of a β -amino C_{sp3}-H bond. Finally, our analysis of the nickel cycle indicated that both arylation and alkylation of α -amino C_{sp3}-H bonds occurs via the sequence of nickel oxidation states Ni^{II}-Ni^{III}-Ni^I-Ni^{III}, and of elementary steps: radical addition-SET-oxidative addition-reductive elimination.

1. INTRODUCTION

Formation of C–C bonds is a fundamental step in chemical synthesis, which explains the efforts devoted to develop robust, selective and convenient methodologies to control it. Today a number of protocols based on transition-metal catalysis, such as several cross-couplings schemes,¹ functionalization of C–H bonds,² and olefin-metathesis,³ are available for the formation of different types of C–C bonds.⁴⁻⁶ Despite these advances, methods for the convenient and selective formation of C–C bonds involving C_{sp3} centers remain scarcely effective.^{4, 7} This is particularly true if activation of one of the coupling partners requires the selective functionalization of a C_{sp3}–H bond, since it requires the capability to selectively activate one specific C_{sp3}–H bond within a complex molecular architecture.^{4, 8, 9}

An emerging strategy, based on the combination of photoredox and transition metal catalysis, has the potential to solve some of these challenges.¹⁰⁻¹⁵ This methodology relies on the absorption of visible light exciting a transition-metal complex, the photocatalyst. On excitation, the photocatalyst can either act as redox agent by single electron transfer (SET), towards an organic substrate and/or another transition-metal complex, the organometallic catalyst, or it can excite the organometallic catalyst by energy transfer (EnT). The SET results in unusual oxidation states of the organometallic catalyst, which can trigger reactivity that is usually difficult to achieve under mild conditions. Similar reactivity can be achieved with the organometallic catalyst promoted to an electronic excited state by EnT. In this scenario, one of the most promising approaches is developing cooperative photoredox-transition metal catalysis using organometallic catalysts incorporating earth abundant first row transition metals, such as nickel.^{7, 10, 14, 15}

This combined photoredox-nickel dual catalysis has been proved to be an effective strategy for activating non-traditional cross-coupling nucleophiles.^{10, 11, 16} Among the most notable examples is the decarboxylative coupling of aliphatic carboxylic acids with aryl-bromides, where an alkyl radical – generated by decarboxylative SET between the carboxylic acid and the Ir-photocatalyst – is coupled with an aryl-bromide by the nickel complex.¹⁷⁻²⁰ Other notable studies expanded this methodology to use benzyl potassium trifluoroborate salts,²¹⁻²⁷ 4-alkyl-1,4-dihydropyridines,²⁸ or potassium alkylbis(catecholato) silicates as radical precursors,²⁹ and demonstrated broad functional group tolerance in the cross-coupling of different C(sp³)-radical precursors with aryl or vinyl halides.³⁰ These successful examples have shown that photoredox-

transition metal catalysis can be a winning methodology to solve some of the challenges related to functionalization of C_{sp3}–H bonds within C–C cross-coupling schemes.³¹⁻³⁴

Recently, a strategy for the functionalization of α -amino C_{sp3}–H bonds using photoredox catalysis, induced by visible-light in combination with a nickel and an organocatalyst, was reported by MacMillan and coworkers (Scheme 1).^{20, 35-37} In this protocol the organocatalyst acts as a hydrogen atom transfer, HAT, agent, generating an alkyl radical by selective activation of a α -amino C_{sp3}–H bond. This merger has culminated in the ability to cross-couple alkyl radicals with metal-activated electrophiles, such as aryl and alkyl bromides, to forge new C_{sp3}–C_{sp2} and C_{sp3}–C_{sp3} bonds.

Despite a large number of experimental papers in the field of photoredox-nickel dual catalysis, a comprehensive mechanistic picture of this chemistry is still missing. Focusing on theoretical studies, for C–N cross-coupling reaction it has been proposed that a Ni⁰ species, generated in situ, is the active coupling catalyst and the mechanism involves the modulation of the nickel oxidation state by SET from the photoredox catalyst, rather than by EnT.³⁸ In contrast, for C–O cross-coupling it has been proposed that a Ni^{II} species is the active coupling catalyst.³⁹ Different conclusions have been also proposed to explain formation of C–C bonds. In the case of the cross-coupling of aryl bromides with C-centered radicals derived from alkyltrifluoroborates it was proposed that a Ni⁰ species is the active coupling catalyst, with the Ni⁰–Ni^{II}–Ni^{III}–Ni^{II} sequence of oxidation states.^{24, 27, 40} Instead, for difunctionalization of alkynes to tri-substituted alkenes, an experimental and computational study indicated that Ni^{II} serves as the active catalyst.⁴¹

Scheme 1. Reactions and catalysts investigated in this work. The HAT catalyst **Q** is used for arylation reaction while **Q'** is used for alkylation reaction.

Considering that this catalysis still is in its infancy, we decided to embark in a systematic computational study aimed at providing a comprehensive mechanistic scenario of a prototype reaction in the field. Specifically, we choose to investigate the triple photoredox-HAT-nickel protocols for the arylation and the alkylation of α -amino C_{sp^3} -H bonds implemented by the MacMillan's group (Scheme 1).^{37, 42} The model substrates we considered are the pyrrolidine-Boc **A**, and the aryl and alkyl bromides PhBr and CyCH₂Br. The photoredox catalyst is the Ir[dF(CF₃)ppy]₂-(dtbbpy)⁺ species **1-IrIII**, the HAT catalyst is the quinuclidine species **Q**, and the nickel catalyst is the 4,7-dimethoxy-phenanthroline species **r1-NiII**. The triplet state **r1-NiII** was chosen for the nickel catalyst, as it is 7.4 kcal/mol more stable than the singlet state **1-NiII**. The neutral ion-pair consisting of the photoredox catalyst associated with the PF₆⁻ counter anion is less stable than the separated components both in the ground state, **1-IrIII**/PF₆, and in the excited state, ***1-IrIII**/PF₆, by 12.5 kcal/mol and 12.4 kcal/mol respectively (Figure S1 in SI). Therefore, PF₆⁻ was omitted in the following calculations.

The main aim of this work is address the following mechanistic aspects: i) providing details on the photoredox catalytic cycle, with identification of the nickel species active in the nickel catalyzed coupling cycle; ii) defining the reaction pathway within the HAT cycle; iii) defining the favored reaction pathway within the nickel catalytic cycle; iv) defining mechanistic differences between arylation versus alkylation of α -amino C_{sp^3} -H bonds; and v) exploring the cooperative nature between photoredox, HAT and nickel catalysts. We believe that the comprehensive mechanistic scenario set in this work can provide a basis for the rational design of improved photoredox-transition metal catalysts.

2. COMPUTATIONAL METHODS

All the calculations were performed with the Gaussian 09 program package.⁴³ For geometry optimization and frequency analysis we adopted the generalized gradient approximation (GGA) by using the exchange and correlation functional of Perdew, Burke and Ernzerhof, PBE.^{44, 45} During geometry optimization we used the split-valence plus one polarization basis set def2-SVP⁴⁶ for non-metal atoms and the triple-zeta basis set def2-TZVP⁴⁶ for nickel and iridium. The basis set combination of def2-SVP(non-metals)/def2-TZVP(Ni,Ir) is represented as BS1. In all cases, ultrafine integral grid was employed. To refine the computed energy, single point calculations were performed using the hybrid-meta-GGA M06 functional⁴⁷ with the def2-

TZVPP₄₆ basis set for all atoms, which is defined as BS2. The SMD solvent model₄₈ was used to simulate the implicit solvent effect. Unless specified otherwise, free energy values, ΔG , are used throughout the text. The ΔG value is obtained by augmenting the in solvent electronic energy, ΔE , calculated at the M06(SMD)/BS2 level, with the corresponding free energy corrections calculated at the PBE/BS1 level in gas phase. Since the thermal correction to the Gibbs free energy of each component depends on its concentration in solution, one can incorporate the concentration terms into calculations (details in the SI).⁴⁹⁻⁵¹ Activation barriers of single electron transfer (SET) steps involve in this work have been calculated using Marcus-Hush theory, and are denoted as $\Delta G_{\ddagger\text{MH}}$ (Table S2 in SI).⁵² Natural bond orbital (NBO) analysis were performed using the *NBO 6.0* package as implemented in Gaussian 09.⁴³

Choice of method: Our own screening, details in the SI (Table S1), indicates that for the photoredox catalyst considered in this work the M06(SMD)/BS2//PBE/BS1 method best reproduces 4 ground- and excited-state redox experimental redox potentials of Ir based photocatalysts, with a MAD = 0.23 V, and was then used throughout the whole project. Furthermore, a high level calculations were performed using DLPNO-CCSD(T) method. However, a larger MAD value (0.48) supports the reliability of the above DFT method.

Definition of the electronic state and of the molecularity of intermediates: As the electronic state and/or the molecularity of several of the species considered in this work is unclear,^{53, 54} we tested various possibilities in order to identify univocally the most stable structure. Specifically, for the starting Ni^{III} species we explored the singlet and triplet states (see Figure S2); for the Ni^{II} species we explored different ligand variations and the formation of dimeric Ni^{II}-Ni^{II} species (see Figure S3); for the Ni⁰ species we explored different ligand variations and electronic states (see Figure S4 and Figure S11). Only the most stable structures deriving from this analysis are considered for reactivity.

3. RESULTS AND DISCUSSION

Results are divided into three main sections corresponding to the three catalytic cycles shown in Scheme 1. We start discussing the photoredox catalytic, PC, cycle, since some of the intermediates within this cycle can react with intermediates within the organocatalytic, HAT, or nickel catalytic, NC, cycles. Then we discuss the HAT cycle, as it activates the amine substrate that is coupled with the aryl or alkyl halide in the NC cycle. In the third section we focused on

the NC cycle, we rationalize the details of the C–C coupling step between the activated amine and the aryl or alkyl halide.

Scheme 2. a) Alternative mechanisms for the photoredox catalytic cycle. b) Mechanism for the HAT catalytic cycle. c) Possible activation steps of the nickel pre-catalyst **1-Ni^{II}**. d) Energetics of SETs involved in the PC cycles. Energy values are in kcal/mol calculated at M06(DMSO-SMD)/BS2//PBE/BS1 level of theory. $\Delta G_{\ddagger\text{MH}}$ have been approximated using Marcus-Hush theory.

3.1. Photoredox catalytic (PC) cycle

It is known that the photoredox catalyst **1-Ir^{III}** undergoes metal to ligand charge transfer upon irradiation by visible light, followed by intersystem crossing to the triplet state, ***1-Ir^{III}**,⁵⁵ which

can acts as either strong reductant or strong oxidant.^{11, 14, 15, 55, 56} Therefore, two different PC cycles, both proposed to be operative in related reactions,^{38, 39} can be considered (Scheme 2a). The two cycles start with the same step, which is the photo induced excitation of **1-Ir^{III}** to ***1-Ir^{III}**, and they branch depending on the redox evolution of the ***1-Ir^{III}** intermediate. The main difference between the two PC cycles is in the sequence of the redox reactions starting from ***1-Ir^{III}**. Reduction-then-oxidation along the reductive quenching cycle, RPC, with the Ir^{III}-*Ir^{III}-Ir^{II} sequence of Ir oxidation states,³⁸ and oxidation-then-reduction in the oxidative quenching cycle, OPC, with the Ir^{III}-*Ir^{III}-Ir^{IV} sequence (Scheme 2a).³⁹ The calculated reduction potentials (against the saturated calomel electrode) of the most relevant species that can be involved in this reactivity are reported in Table 1.

Table 1. Calculated reduction potentials, $E_{1/2\text{red}}$ in V, of the most relevant species involved in the catalytic cycles shown in Scheme 2 for the arylation reaction (Scheme 1). The potentials are reported against the saturated calomel electrode (SCE).

Half reaction	$E_{1/2\text{red}}$	Half reaction	$E_{1/2\text{red}}$
3-Ir^{IV} + 1e⁻ → 1-Ir^{III}	1.25	τ1-Ni^{III} + QH⁺ + 1e⁻ → 2-Ni^{II} + QH⁺/Br⁻	-0.96
3-Ir^{IV} + 1e⁻ → *1-Ir^{III}	-1.46	τ1-Ni^{III} + QH⁺ + 2e⁻ → 3-Ni⁰ + QH⁺/Br⁻	-1.50
1-Ir^{III} + 1e⁻ → 2-Ir^{II}	-1.61	2-Ni^{II} + QH⁺ + 1e⁻ → 3-Ni⁰ + QH⁺/Br⁻	-2.04
*1-Ir^{III} + 1e⁻ → 2-Ir^{II}	1.10	Q^{•+} + 1e⁻ → Q	1.03

Along the RPC cycle ***1-Ir^{III}** is reduced to **2-Ir^{II}** by oxidation of **Q** to **Q^{•+}**, SET1. The calculated 1e reduction potential of the ***1-Ir^{III}/2-Ir^{II}** pair, $E_{1/2\text{red}} = 1.10$ V, is higher than that of the **Q^{•+}/Q** pair, $E_{1/2\text{red}} = 1.03$ V, indicating the thermodynamic feasibility of the ***1-Ir^{III} + Q → 2-Ir^{II} + Q^{•+}** redox process. The RPC cycle is closed by oxidation of **2-Ir^{II}** to **1-Ir^{III}** by the dibromide Ni^{III}-complex **τ1-Ni^{III}**, SET2, which is reduced to the Ni^{II} species **2-Ni^{II}** with release of a Br⁻ anion, which is stabilized by the organic **QH⁺** cation formed in the HAT cycle (see Scheme 2b). The calculated 1e reduction potential of the **1-Ir^{III}/2-Ir^{II}** pair, $E_{1/2\text{red}} = -1.61$ V, is lower than that of the **τ1-Ni^{III}/2-Ni^{II}** pair, $E_{1/2\text{red}} = -0.96$ V, indicating the thermodynamic feasibility of the **2-Ir^{II} + τ1-Ni^{III} + QH⁺ → 1-Ir^{III} + 2-Ni^{II} + QH⁺/Br⁻** redox process, and that the overall RPC cycle is characterized by two exergonic steps, SET1 and SET2 (Table 1, Scheme 2a).

Figure 1. Emission spectra of $^*1\text{-Ir}^{\text{III}}$ (0.01 mM) at different concentrations of a) Q and b) $\tau 1\text{-Ni}^{\text{II}}$; c) Stern-Volmer plot of $^*1\text{-Ir}^{\text{III}}$ (0.01 mM) at different concentrations of Q and $\tau 1\text{-Ni}^{\text{II}}$.

Along the OPC cycle $^*1\text{-Ir}^{\text{III}}$ is oxidized to 3-Ir^{IV} by the Ni^{II} -complex $\tau 1\text{-Ni}^{\text{II}}$, SET1', which is reduced to the Ni^{I} species 2-Ni^{I} with release of a Br^- anion, which is stabilized by the organic QH^+ cation formed in the HAT cycle (see Scheme 2b). The calculated 1e reduction potential of the $3\text{-Ir}^{\text{IV}}/^*1\text{-Ir}^{\text{III}}$ pair, $E_{1/2\text{red}} = -1.46$ V, is lower than that of the $\tau 1\text{-Ni}^{\text{II}}/2\text{-Ni}^{\text{I}}$ pair, $E_{1/2\text{red}} = -0.96$ V, indicating the thermodynamic feasibility of the $^*1\text{-Ir}^{\text{III}} + \tau 1\text{-Ni}^{\text{II}} + \text{QH}^+ \rightarrow 3\text{-Ir}^{\text{IV}} + 2\text{-Ni}^{\text{I}} + \text{QH}^+/\text{Br}^-$ redox process (Table 1). The OPC cycle is closed by reduction of 3-Ir^{IV} to 1-Ir^{III} by oxidation of the quinuclidine species Q, which is oxidized to the quinuclidinium radical cation $\text{Q}^{\bullet+}$, SET2'. The calculated 1e reduction potential of the $3\text{-Ir}^{\text{IV}}/1\text{-Ir}^{\text{III}}$ pair, $E_{1/2\text{red}} = 1.25$ V, is higher than that of the $\text{Q}^{\bullet+}/\text{Q}$ pair, $E_{1/2\text{red}} = 1.03$ V, indicating the thermodynamic feasibility of

the $3\text{-Ir}^{\text{IV}} + \text{Q} \rightarrow 1\text{-Ir}^{\text{III}} + \text{Q}^{\bullet+}$ redox process, and that the overall OPC cycle is also characterized by two exergonic steps, SET1' and SET2' (Table 1, Scheme 2a).

The above analysis indicates that both the RPC and OPC cycles are characterized by two exergonic SET steps with slightly lower activation energies within the OPC cycle. Considering the accuracy of Marcus-Hush theory activation barriers, we tried to support this conclusion by evaluating the experimental quenching rates of the $^*1\text{-Ir}^{\text{III}}$ emission, due to reduction of $^*1\text{-Ir}^{\text{III}}$ by **Q** or to its oxidation by $\tau 1\text{-Ni}^{\text{III}}$. The intensity of the $^*1\text{-Ir}^{\text{III}}$ emission at 482 nm is decreasing in presence of **Q** (Figure 1a), which indicates that $^*1\text{-Ir}^{\text{III}}$ is reduced by **Q**. Similarly, we found a quenching of the $^*1\text{-Ir}^{\text{III}}$ emission with increasing concentration of $\tau 1\text{-Ni}^{\text{III}}$ (Figure 1b). The most relevant molecular orbitals, MO, involved in the redox quenching are shown in Figure S5 (see SI). Consistently with the DFT calculations, the slopes of the Stern-Volmer plots (Figure 1c) indicate that the rate of quenching of the $^*1\text{-Ir}^{\text{III}}$ emission is approximately two times faster in presence of $\tau 1\text{-Ni}^{\text{III}}$ than in presence of **Q** at the same concentration. Considering that in the experimental conditions the concentration of **Q** is more than 100 times higher than that of $\tau 1\text{-Ni}^{\text{III}}$,⁴² quenching of $^*1\text{-Ir}^{\text{III}}$ by **Q** dominates.

In summary, the main message deriving from analysis of the PC cycle is that both the RPC and OPC cycles are possible but, under the reaction conditions used, the RPC cycle is favored.

3.2. HAT organocatalytic cycle

The HAT cycle starts with oxidation of **Q** by $^*1\text{-Ir}^{\text{III}}$ to generate $\text{Q}^{\bullet+}$ (SET1, Scheme 2b). This process corresponds to the first step of the RPC cycle and, as discussed above, it is thermodynamically possible and kinetically fast, with a $\Delta G = -1.7$ kcal/mol and a $\Delta G_{\ddagger\text{MH}} = 2.9$ kcal/mol (Scheme 2d, and Table S2). In the next step $\text{Q}^{\bullet+}$ selectively abstracts a α -amino hydrogen atom from the N-Boc-amine **A** to form the carbon centered radical **A** $\cdot$ and the cationic species **QH** $^+$, a step exergonic by 8.0 kcal/mol. A low free energy barrier ($\Delta G_{\ddagger} = 9.5$ kcal/mol) indicates a facile $\text{C}_{\text{sp}^3}\text{-H}$ activation, which is otherwise difficult to achieve in traditional catalysis. The α -amino alkyl radical **A** $\cdot$ generated in the HAT cycle is trapped in the nickel catalytic cycle (*vide infra*), modulating the oxidation state of nickel. The HAT cycle is closed by deprotonation of **QH** $^+$ by Br^- to regenerate **QH** $^+$ / Br^- . The Br^- anion can be generated in the activation of the nickel dibromide complex $\tau 1\text{-Ni}^{\text{III}}$ or in the activation of the aryl and alkyl bromide substrates within the NC cycle. For the sake of completeness, we also calculated

thermodynamics and kinetics of abstraction of a β -amino hydrogen atom from **A**, a step exergonic by 2.8 kcal/mol and with an activation barrier of 17.9 kcal/mol (Figure S6a in SI). This indicates that, consistently with the experimental evidence, α -amino hydrogen abstraction, with a $\Delta G^\ddagger = 9.5$ kcal/mol, is favored relative to β -amino hydrogen abstraction by a $\Delta\Delta G^\ddagger = 8.4$ kcal/mol. The extra stability of **A** $\cdot$ compared to **A β** $\cdot$, 5.2 kcal/mol, originates from comparticipation of the unpaired electron from the C $_{\alpha}$ center with the p MOs of the adjacent N–Boc group, as highlighted from the Mulliken spin density plot (Figure S6c in SI), and the reduced N–C $_{\alpha}$ bond length (1.392/1.464 Å in **A** $\cdot$ /**A β** $\cdot$).

In summary, the main message deriving from analysis of the HAT catalytic cycle is that, consistently with the experimental evidence, activation of a α -amino C $_{sp^3}$ –H bond of the substrate is a facile and selective process. Thus, we only considered the α -amino alkyl radical **A** $\cdot$ in the nickel catalytic cycle.

3.3. Ni-catalytic (NC) cycle: Arylation of α -amino C $_{sp^3}$ –H bonds

As discussed before, both the photocatalytic RPC and OPC cycles are feasible, and reduction of precatalyst **1**–Ni $_{III}$ to **2**–Ni $_{II}$ by either **2**–Ir $_{III}$ or ***1**–Ir $_{III}$ is possible, while further reduction of **2**–Ni $_{II}$ to **3**–Ni $_{I0}$ by ***1**–Ir $_{III}$ or **2**–Ir $_{III}$ is thermodynamically unfavored (Scheme 2 and Figure 2). Therefore, we investigated variants of the NC cycle starting from **2**–Ni $_{II}$ as the active catalyst, having in mind that the overall transformation can be considered to be composed by four elementary steps, corresponding to: i) 1e electron transfer from ***1**–Ir $_{III}$ to a Ni species (SET); ii) Radical addition of **A** $\cdot$ to a Ni species (RA); iii) Oxidative addition of PhBr to a Ni species (OA); iv) Reductive elimination of the product from a Ni species (RE). Different mechanistic possibilities can be imagined, by changing the sequence of the four elementary steps indicated above, with the condition that the RE step is the last, as it is the product release step.

Excluding sequences that would involve formation of Ni $_{IV}$ intermediates (see Scheme S3 in SI), four possibilities remain. Two of them, SET-OA-RA-RE and SET-RA-OA-RE, start with reduction of Ni $_{II}$ to Ni $_{I0}$, and correspond to the sequences of Ni oxidation states Ni $_{II}$ –Ni $_{I0}$ –Ni $_{III}$ –Ni $_{III}$ (mechanism **M1**) and Ni $_{II}$ –Ni $_{I0}$ –Ni $_{II}$ –Ni $_{III}$ (mechanism **M2**), proposed by Zuo²⁰ and Kozłowski,²⁴ respectively. The two others possibilities, OA-SET-RA-RE and RA-SET-OA-RE, correspond to the sequences Ni $_{II}$ –Ni $_{III}$ –Ni $_{III}$ –Ni $_{III}$ (mechanism **M3**) and Ni $_{II}$ –Ni $_{III}$ –Ni $_{II}$ –Ni $_{III}$ (mechanism **M4**), and

have been proposed by Johannes^{57, 58} and Rueping.⁴¹ The four catalytic cycles corresponding to mechanisms **M1-M4** are shown in Scheme S1 (see SI).

Figure 2. Free energy profiles of mechanisms **M1-M4** for the arylation of α -amino C_{sp3}-H bonds. Free energy values are at M06(SMD-DMSO)/BS2//PBE/BS1 level of theory. The energetics of the SET step is calculated assuming that the RPC cycle is operative, see the discussion in the PC cycle section. For the sake of completeness, the energetics of the SET step, assuming that the OPC cycle is operative, is also reported, see the insets.

Mechanisms M1 and M2: Mechanisms **M1** and **M2** (Figure 2 and Scheme S1) start both with reduction of **2-Ni^I** to **3-Ni⁰**, with binding of PhBr to nickel. Considering the redox potential of the species involved (Table 1), and the energetics of PhBr binding, the process is endergonic by 9.9 kcal/mol within the RPC cycle (SET4, Figure 2). The frontier MOs associated to SET4 are shown in Figure S7. Intermediate **3-Ni⁰** is the branching point separating reaction pathways **M1** and **M2**. Along reaction pathway **M1** the reaction continues with the oxidative addition of

PhBr to the Ni atom of **3-Ni⁰** via transition state **[3-4]‡** and an energy barrier of 12.1 kcal/mol, leading to **4-Ni^{III}**. The low activation barrier along with high exothermicity (33.5 kcal/mol) indicates that this oxidative addition step is facile.^{59, 60} The reaction continues with the binding of the α -amino alkyl radical **A•**, generated in the HAT catalytic cycle, to the Ni^{III}-complex **4-Ni^{III}** via transition state **[4-5]‡** and a free energy barrier of 5.1 kcal/mol, leading to the Ni^{III}-complex **5-Ni^{III}**. Pathway **M1** is completed by facile reductive elimination of the product from **5-Ni^{III}** via the C–C bond forming transition state **[5-2]‡** and an activation barrier of 7.8 kcal/mol, regenerating intermediate **2-Ni^I** with liberation of product **P**.

Moving to mechanism **M2**,²⁴ it corresponds to an interchange of the sequence of the RA/OA steps, occurring in reaction pathway **M1**, to the OA/RA sequence. Thus, intermediate **3-Ni⁰**, formed from **2-Ni^I** via SET4, undergoes radical addition with **A•** prior to oxidative addition of PhBr. Binding of **A•** to **3-Ni⁰** is exergonic by 14.4 kcal/mol and generates the Ni^I-alkyl intermediate **6-Ni^I**. Despite several efforts we were not able to locate a transition state for this process because the one dimensional potential energy surface forming the Ni–C bond as reaction coordinate is downhill. This is consistent with the negligible energy barrier of 1.5 kcal/mol reported for benzyl radical²⁴ and barrierless for tBu radical addition to Ni⁰-complex.²⁷ The next step is the oxidative addition of PhBr to the Ni^I center of **6-Ni^I** via formation of complex **7-Ni^I**, 11.0 kcal/mol above **6-Ni^I**. This step occurs via transition state **[7-5]‡** and a free energy barrier of 17.9 kcal/mol from **6-Ni^I**, leading to the Ni^{III} complex **5-Ni^{III}**, and merging reaction pathways **M1** and **M2**. Facile reductive elimination of the product from **5-Ni^{III}**, already discussed within reaction pathway **M1**, completes the **M2** reaction pathway.

Mechanisms M3 and M4: Reaction pathways **M3** and **M4** (Figure 2, Scheme S1) occur with an interplay between Ni^I, Ni^{III} and Ni^{III} complexes, with the Ni^I-complex **2-Ni^I** again considered as the starting species. The main difference between reaction pathways **M3** and **M4** is in the sequence of the elementary steps, which is OA-SET-RA along reaction pathway **M3**, and RA-SET-OA along reaction pathway **M4**.

Pathway **M3** starts with oxidative addition of PhBr to **2-Ni^I**, via coordination intermediate **8-Ni^I**, 11.3 kcal/mol above **2-Ni^I**, followed by transition state **[8-9]‡** (for geometry see Figure 4), for an overall free energy barrier of 17.8 kcal/mol. The resulting Ni^{III}-intermediate **9-Ni^{III}**, 12.6 kcal/mol above **2-Ni^I**, undergoes exergonic 1e reduction by **2-Ir^{II}** to generate the Ni^{II}-intermediate **4-Ni^{II}**, SET5 in Figure 2. The redox potential of Table 1 indicates that SET5 is a

highly exergonic process, with a ΔG of -36.2 kcal/mol. The frontier MOs associated to SET5 are shown in Figure S7 (see SI). Radical addition of **A•** to **4-Ni^{III}**, via transition state **[4-5]‡** and an energy barrier of 5.1 kcal/mol, leads to the common Ni^{III} intermediate **5-Ni^{III}**, from which facile reductive elimination of the product completes the reaction pathway.

As anticipated, the only difference between mechanisms **M3** and **M4** (Figure 2) is in the sequence of the first three elementary steps, which is RA-SET-OA along reaction pathway **M4**. Addition of **A•** to **2-Ni^I**, consisting in the coupling of two radical doublet species to form the closed shell Ni^{III} complex **10-Ni^{III}** is, as typical for radical couplings, a barrier less process. The subsequent reduction of **10-Ni^{III}** by **2-Ir^{II}** to form **6-Ni^I**, SET6 in Figure 2, is endergonic by 3.0 kcal/mol (frontier MOs in Figure S7). The following oxidative addition step starts with coordination of PhBr to **6-Ni^I** to form intermediate **7-Ni^I**, followed by transition state **[7-5]‡** (geometry in Figure 4), for an overall energy barrier of 17.9 kcal/mol from **6-Ni^I**. Facile reductive elimination from **5-Ni^{III}**, common to the four reaction pathways considered, liberates the product and regenerates **2-Ni^I**.

To have an experimental support helping us to decipher the complex mechanistic scenario of Figure 2, we performed control experiments where (4,7-dMeO-phen)Ni^{III}(*o*-Tol)Br, as a model of **4-Ni^{III}**, and thus we labeled it as **mod-4-Ni^{III}**, was taken as starting complex (Scheme 3a-d). The detailed results and discussion of stoichiometric reactions is in the supporting information. In reaction 3a both (4,7-dMeO-phen)Ni^{III}Br₂ and the aryl bromide are missing. Only 9% product is formed, although ~1.5 eq. of **A** was consumed in a reaction involving oxidation of **Q** and reduction of **mod-4-Ni^{III}**, as in the photoredox cycle. This indicates that **mod-4-Ni^{III}** does not react rapidly enough with the alkyl radical **A•** to form a Ni^{III} intermediate, analogous of **5-Ni^{III}**, from which the product is released. We thus performed reaction 3b, where (4,7-dMeO-phen)Ni^{III}Br₂ is added (1 mol%) as oxidizing Ni agent active in the oxidation of **Q**, leaving **mod-4-Ni^{III}** the possibility of reacting with **A•**. Also in this case only a small amount of product was observed, 8%, confirming the weak capability of **mod-4-Ni^{III}** to trap **A•**. In a separate experiment (reaction 3c), where more oxidizing agent (4,7-dMeO-phen)Ni^{III}Br₂ (1 eq.) is used, the yield is reduced to 1%, indicating that the tendency of **mod-4-Ni^{III}** to trap **A•** is minimized. This indicates that **A•** preferentially binds with the reduced (4,7-dMeO-phen)Ni^IBr complex **2-Ni^I**, a barrierless step, rather than binding with **mod-4-Ni^{III}**, an indication that pathway **M4** is operative. Finally, in reaction 3d we added the aryl bromide, and also minimal amount of product was observed

(16%). Taken together, these stoichiometric experiments indicate that reduction of **mod-4-Ni** most likely evolves to (4,7-dMeO-phen)Ni(*o*-Tol) via SET, which causes the lack of reactivity towards **A•**. Indeed, our calculated reduction potentials indicate that reduction of **4-Ni** ($E_{1/2\text{red}} = -1.65$ V) is thermodynamically easier than reduction of **2-Ni** to **3-Ni** ($E_{1/2\text{red}} = -2.04$ V) or reduction of **10-Ni** to **6-Ni** ($E_{1/2\text{red}} = -1.74$ V). These observations indicate that reactivity does not proceed through **4-Ni**, thus excluding pathways **M1** and **M3**.

Scheme 3. Stoichiometric experiments with (4,7-dMeO-phen)Ni(*o*-Tol)Br, **mod-4-Ni**.

As for a comparison between **M2** and **M4**, which converge at intermediate **6-NiI**, **M4** starts with barrier less addition of **A•** to **2-NiI**, followed by the slightly endergonic SET6 converting **10-NiII** to **6-NiI**. Differently, **M2** starts with endergonic SET4 of **2-NiI**, followed by barrier less addition of **A•**, converting **3-Ni0** to **6-NiI**. Both processes are kinetically viable, although the potential energy profiles of Figure 2 suggest that **M4** should be preferred.

In summary, the main conclusion regarding the arylation of α -amino C_{sp^3} -H bonds is that both the pathways **M2** and **M4** are feasible. Nevertheless, the smoother free energy profile corresponds to **M4**, which assumes the sequence of nickel oxidation states NiI-NiII-NiI-NiIII, and of elementary steps RA-SET-OA-RE.

Figure 3. Free energy profiles of mechanisms **M1-M4** for alkylation of α -amino C_{sp^3} -H bonds. Free energy values are at M06(SMD-MeCN)/BS2//PBE/BS1 level of theory. For other conventions refer Figure 2.

3.4. Ni-catalytic (NC) cycle: Alkylation of α -amino C_{sp^3} -H bonds

In this section we use knowledge developed in the previous sections to discuss alkylation of α -amino C_{sp^3} -H bonds using the photoredox-nickel-HAT catalytic protocol, reported by MacMillan (Scheme 1).³⁷ To achieve alkylation of α -amino C_{sp^3} -H bonds slightly different reaction conditions, specifically a different solvent, MeCN, and an inorganic base, K_2CO_3 , were used. Consistently, for the modeling of alkylation reaction mechanism we used MeCN as implicit solvent, we included K_2CO_3 in the reactants pool, we selected cyclohexylmethyl bromide (CyCH₂Br) as alkylating agent and the quinuclidine **Q'** (R=H, refer Scheme 1) as the HAT catalyst (Scheme S4 in SI). As for the mechanistic framework, we considered the four cycles we investigated for arylation of α -amino C_{sp^3} -H bonds (Figure 3 and Scheme S1).

Pathways **M1** and **M2** start with the slightly endergonic reduction of **2-Ni^{II}** to the triplet ground state of **τ 3b'-Ni⁰** (SET7 in Figure 4, $\Delta G = 3.2$ kcal/mol), which is the most stable Ni⁰-complex over all other possibilities in the current reaction condition (see Figure S11 in SI). **τ 3b'-Ni⁰** is the structure from which pathways **M1** and **M2** bifurcate. Along **M1** the reaction proceeds with the oxidative addition of CyCH₂Br via transition state **τ [3'-4']_‡** and an energy barrier of 13.3 kcal/mol, leading to the tightly associated doublet species **2b'-Ni^{II}** and CyCH₂•, which barrier less recombine into **4'-Ni^{III}**. The following addition of **A•** to **4'-Ni^{III}** leads to **5'-Ni^{III}** via transition state **[4'-5']_‡** and a relatively low energy barrier, $\Delta G_{‡}^{\ddagger} = 3.6$ kcal/mol. Pathway **M1** is completed by facile reductive elimination of product **P'** from **5'-Ni^{III}** via transition state **[5'-2']_‡** and an activation barrier of 12.3 kcal/mol, regenerating intermediate **2-Ni^{II}**. Along pathway **M2**, intermediate **τ 3b'-Ni⁰** undergoes radical addition of **A•** to generate the Ni^{II}-alkyl intermediate **6'-Ni^{II}** with the removal of MeCN, a step exergonic by 16.9 kcal/mol. The following oxidative addition of CyCH₂Br to **6'-Ni^{II}** via transition state **[7'-5']_‡** and a $\Delta G_{‡}^{\ddagger} = 24.2$ kcal/mol from **6'-Ni^{II}**, leads to complex **5'-Ni^{III}**, thus merging reaction pathways **M1** and **M2**.

As discussed before, pathway **M3** starts with the oxidative addition of CyCH₂Br to **2-Ni^{II}** via transition state **[8'-9']_‡**, (geometry in Figure 4) and $\Delta G_{‡}^{\ddagger} = 30.6$ kcal/mol. The resulting **9'-Ni^{III}** complex undergoes facile 1e reduction by **2-Ir^{III}**. The process is exergonic by 42.2 kcal/mol, and has a low energy barrier, $\Delta G_{‡}^{\ddagger}{}_{MH} = 15.2$ kcal/mol (SET8, Figure 3). The reaction continues with the addition of **A•**, giving **5'-Ni^{III}**, followed by reductive elimination of the product. Pathway **M4**, starts with the barrier less binding of **A•** to **2-Ni^{II}**, to form intermediate **10'-Ni^{III}** with release of 7.1 kcal/mol (Figure 3). In the next step **10'-Ni^{III}** undergoes 1e reduction to **6'-Ni^{II}** by **2-Ir^{III}** (SET9), for a $\Delta G = -6.6$ kcal/mol, and a relatively low energy barrier, $\Delta G_{‡}^{\ddagger}{}_{MH} = 0.9$ kcal/mol. The

next step is the oxidative addition of CyCH_2Br , leading to **5'-Ni^{III}**, merging pathway **M4** to pathways **M1-M3**.

Figure 4. Optimized geometries (at PBE/BS1 level) of transition states of oxidative addition of PhBr and CyCH_2Br to Ni^{II} and Ni^{I} complexes involved in the arylation and alkylation of α -amino $\text{C}_{\text{sp}^3}\text{-H}$ bonds. Key bond distances are in Å.

Comparison of the energy profiles of Figures 2 and 3 indicates quite similar energy profiles. Due to instability of **4'-Ni^{III}** we were unable to perform similar control experiments (Scheme 3) for the alkylation reaction. However, supported by the stoichiometric studies on the arylation reaction (Scheme 3), pathways **M1** and **M3** are considered to be less likely also in case of alkylation. As for pathways **M2** and **M4**, differences between them are reduced, compared to what we calculated for the arylation reaction in Figure 2, since the initial SET7 along **M2** is substantially thermoneutral in Figure 3, whereas it is endergonic by 9.9 kcal/mol in Figure 2. Further, SET9 is exergonic in Figure 3, whereas it is almost thermoneutral in Figure 2. In summary, as for the arylation reaction, pathways **M2** and **M4** are both viable, with a smoother free energy surface in case of **M4**.

Scheme 4. Nickel catalytic cycle for the arylation and alkylation of α -amino C_{sp^3} -H bond proposed by the current computational study.

4. CONCLUSIONS AND OUTLOOK

In conclusion, this work reports a DFT based mechanistic clarification of the interplay between the catalytic cycles in the photoredox-nickel-HAT triple catalyzed protocol for arylation and alkylation of α -amino C_{sp^3} -H bonds. Initial efforts were focused on identifying the most reliable computational approach to model this catalysis. The tuned protocol was used to achieve the following insights:

1) Regarding the photoredox catalytic cycle our results clearly indicate that both the reductive (RPC) and oxidative quenching cycles (OPC) are possible under the reaction conditions used. Within the RPC the visible light excited $^*Ir^{III}$ undergoes reduction to Ir^{II} first, then oxidation to Ir^{III} , while in the OPC it undergoes oxidation to Ir^{IV} first, then reduction to Ir^{III} . In both cases reduction of the Ir photocatalyst is promoted by the quinuclidine HAT catalyst, while oxidation is promoted by the $Ni^{III/IV}$ catalyst. However, RPC is favored considering much higher concentration of HAT than Ni^{III} catalyst.

2) Regarding the HAT catalytic cycle, our results clearly indicate that, consistently with the experimental evidence, activation of a α -amino C_{sp^3} -H bond of the substrate by the oxidized quinuclidine catalyst is facile and highly selective relative to activation of a β -amino C_{sp^3} -H bond.

3) Regarding the nickel catalytic cycle, our results clearly indicate that for both arylation and alkylation of α -amino C_{sp^3} -H bonds two mechanisms can be operative, via the sequence of nickel oxidation states Ni^{II} - Ni^{I0} - Ni^{II} - Ni^{III} with the sequence of elementary steps SET-RA-OA-RE; and Ni^{II} - Ni^{III} - Ni^{II} - Ni^{III} with the sequence RA-SET-OA-RE. The latter one (see Scheme 4) is energetically favored over the former.

4) Finally, our study highlights the central role played by the photoredox Ir^{III} catalyst, which promotes activity in the HAT cycle by oxidation of the quinuclidine catalyst to a quinuclidine radical cation, which is capable to activate the inert C_{sp^3} -H bond of the amino substrate, and promotes activity in the nickel cycle by reduction of the Ni^{III} catalyst to a Ni^{II} species, allowing to enter facile cross-coupling reactivity involving an interplay between the Ni^{II} , Ni^{III} and Ni^{III} oxidation states. We believe our findings can help experimental groups to identify new strategies for the selective activation of less reactive C-H bonds and/or new halide or pseudohalide partners.

ASSOCIATED CONTENT

Supporting Information

Computational and experimental details, coordinates

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Notes

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