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*sp*³ C–H Arylation and Alkylation Enabled by the Synergy of Triplet Excited Ketones and Nickel Catalysts

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ABSTRACT: Triplet ketone sensitizers are of central importance within the realm of photochemical transformations. Although the radical-type character of triplet excited states of diaryl ketones suggests the viability for triggering hydrogen-atom transfer (HAT) and single-electron transfer (SET) processes, among others, their use as multifaceted catalysts in C–C bond-formation via sp^3 C–H functionalization of alkane feedstocks still remains rather unexplored. Herein, we unlock a modular photochemical platform for forging $C(sp^3)-C(sp^2)$ and $C(sp^3)-C(sp^3)$ linkages from abundant alkane sp^3 C–H bonds as functional handles using the synergy between nickel catalysts and simple, cheap and modular diaryl ketones. This method is distinguished by its wide scope that is obtained from cheap catalysts and starting precursors, thus complementing existing inner-sphere C–H functionalization protocols or recent photoredox scenarios based on iridium polypyridyl complexes. Additionally, such a platform provides a new strategy for streamlining the synthesis of complex molecules with high levels of predictable site-selectivity and preparative utility. Mechanistic experiments suggest that sp^3 C–H abstraction occurs via HAT from the ketone triplet excited state. We believe this study will contribute to a more systematic utilization of triplet excited ketones as catalysts in metallaphotoredox scenarios.

INTRODUCTION

The photochemical behavior of diaryl ketones has undoubtedly played an important role for the foundation of modern molecular photochemistry.¹ Over the course of the last century, diaryl ketones have gained a prominent role as photosensitizers in material science, biology, organic synthesis and pharmacology.² Indeed, diaryl ketones have found immediate use in a wide number of phototherapeutic applications, for example as UV-blocking agents to prevent polymer photodegradation, or as sensitizers to transfer energy to DNA, among others.³ The favorable photochemical properties of diaryl ketones that allow such applications are commonly ascribed to a long-lived triplet state⁴ generated by the excitation of an electron from a non-bonding orbital at the C=O bond to a corresponding π^* orbital (n, π^*) followed by intersystem crossing (ISC).^{2,5} From a synthetic standpoint, the triplet excited state of diaryl ketones (I) holds considerable potential to provide opportunities to build up molecular complexity. In a formal sense, this triplet excited state behaves as a 1,2biradical, creating significant spin density on the oxygen atom. Consequently, the (n,π^*) triplet excited state possesses intriguing electrophilic and radical-type properties, making it particularly susceptible for radical addition, energy transfer (ET), single electron transfer (SET) or hydrogen atom transfer (HAT).¹

Scheme 1. Triplet Photoexcited Diaryl Ketones.



Convinced of the synthetic relevance of triplet excited ketones,^{1,5} we turned our attention to unravel their potential as catalysts for preparative purposes. A close look into the literature, however, indicated that this might not be as straightforward as initially anticipated. Indeed, stoichiometric amounts of diaryl ketones are frequently employed in photochemical processes, suggesting that catalytic turnover might be at risk.^{1,5} Additionally, high-energy UV irradiation is typically required when using diaryl ketones as photosensitizers.^{1,5} This observation is rather problematic due to the ability of a wide range of functional groups to absorb in the UV region, which may lead to deleterious side reactions arising from photoexcitation of the substrate. However, it is also reasonable to expect that facile tuning of the steric and electronic substituents of diaryl ketones might have a profound impact on its photochemical behaviour,⁷ changing the electronic configuration of the triplet excited states while shifting the maximum (n,π^*) absorption to longer wavelengths.8

Among various conceivable scenarios, the ability of triplet excited ketones I to trigger a HAT process is particularly noteworthy.^{1,5} During this elementary step, a persistent ketyl radical II and a transient nucleophilic radical III are formed. While the former is inherently predisposed to SET with appropriate electron acceptors, the latter is prone to C-C bondformation in the presence of radical acceptors (Scheme 2). As part of our ongoing interest in Ni and photoredox catalysis⁹ and prompted by the seminal studies of Chow and Murakami on the photoreduction of $Ni(acac)_2$ by triplet benzophenones¹⁰ and on the propensity of ketyl radicals to undergo SET processes,¹¹ we envisioned that nickel complexes could act both as the electron and radical acceptors in Scheme 2, thus setting the basis for turnover of the triplet ketone catalyst. If successful, a generic platform aimed at interfacing triplet excited ketones and Ni catalysis might provide an enabling C-C bondforming redox-neutral strategy from simple hydrocarbon feedstocks by using sp^3 C–H bonds as functional handles without the need for sacrificial electron-donors or electron-acceptors.¹² We recognized that this scenario might offer new reactivity within the field of triplet ketone catalysis while complementing existing inner-sphere sp³ C-H functionalization techniques¹³ and recent *outer-sphere* metallaphotoredox processes reported by MacMillan,¹⁴ Molander¹⁵ and Doyle¹⁶ based on Ir polypyridyl sensitizers. Unlike Ir photocatalysts that are used as either SET or ET catalysts,^{17,18} however, the utilization of simple and easily-accessible diaryl ketones as photocatalysts offers the added value of activating sp^3 C–H bonds¹⁹ via HAT processes, thus expanding the boundaries of metallaphotoredox processes.²⁰ Herein, we describe our efforts towards this goal, which have resulted in a practical, modular and exceedingly tolerant platform for C-C bond construction that streamlines synthetic sequences from native sp^3 C–H bonds, even in the context of late-stage functionalization. Control experiments and mechanistic studies suggest a mode of action that might have relevance in other photocatalytic bond-forming reactions.

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Scheme 2. Triplet Ketones as HAT & SET Catalysts.



RESULTS AND DISCUSSION

Mechanistic hypothesis. Under the premise that suitable diaryl ketones might qualify as HAT & SET catalysts, we initially focused our attention on the suitability of an integrated photocatalytic platform that enables C–C bond-formation via the outer-*sphere sp*³ C–H functionalization of saturated hydrocarbons in the absence of Ir polypyridyl complexes.^{21,22} Specifically, we hypothesized that an electron-rich carbon-centered radical III would be generated upon HAT from long-

lived triplet excited I (τ [Ph₂CO] = 6.5 µs) along with the formation of a ketyl radical II (Scheme 3).²³ Concurrently, oxidative addition of an organic halide to low-valent Ni(0)L_n would give rise to an electrophilic Ni(II) entity (IV). Radical recombination with III might generate discrete Ni(III) V species, which would set the stage for C–C bond-forming reductive elimination to deliver the targeted C–H functionalization product and Ni(I) intermediate VI. It is expected that the two catalytic cycles could be interfaced under basic conditions²⁴ by a final SET from II (E_{1/2}^{red} (Ph₂CO) = -2.20 V *vs* Ag/AgNO₃ in MeCN)²⁵ to VI (E_{red} [Ni¹/Ni⁰] \approx -1.13V *vs* Ag/AgNO₃ in DMF)²⁶, thus recovering both the propagating diaryl ketone and Ni(0)L_n catalysts.

Scheme 3. Mechanistic Hypothesis.



Optimization of the reaction conditions. We began our investigations by studying the sp^3 C-H arylation of 4trifluoromethyl bromobenzene with tetrahydrofuran as both C-H precursor and solvent under household compact fluorescent lamp (CFL) irradiation for 18 h (Table 1). We anticipated that the electronic effects on the arene backbone of the diaryl ketone might have a non-negligible influence on reactivity,^{7,8} (1) enhancing and shifting the (n,π^*) absorption into the visible light region, (2) tuning the rate of decay of the triplet excited state I, and/or (3) stabilizing the ketyl radical II that results from the HAT process;²⁷ the latter is particularly important, as this putative reaction intermediate is critical for turnover of the triplet ketone catalyst and nickel catalyst by a final SET (Scheme 3). Therefore, we decided to investigate the behaviour of a representative set of diaryl ketone catalysts bearing different electronic effects.²⁸ Under a catalytic regime based on Ni(acac)₂/L1 in tetrahydrofuran, it was quickly apparent that electronic effects on the diaryl ketone were critical for success. Among all diaryl ketones analysed, we found that bench-stable A1 ($E_{1/2}^{red} = -2.05 \text{ V} \text{ vs Ag/AgNO}_3 \text{ in MeCN}$)²⁵ possessing a "push-pull" structure provided promising results en route to 1 (Table 1, entry 1). Interestingly, the utilization of push A2 or pull A3 as catalysts resulted in a markedly lower reactivity, thus arguing against a direct correlation between

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reaction rate and the Hammett parameter of the *para*substituent (entries 2 and 3).²⁹ Similarly, lower yields were obtained with benzophenone (A4) (entry 4). Interestingly, A1-A4 have similar absorption spectra; however, we found that A1 possesses the maximum (n,π^*) absorption at longer wavelengths.²⁸ Putting everything into perspective, the higher photochemical reactivity of A1 can tentatively be interpreted on the basis of a higher molar absorption coefficient in the visible light region and the stability of the corresponding ketyl radicals with CF₃-substituted analogues.^{27,1}

Table 1. Electronic Effects on the Diaryl Ketone.



^{*a*} Reaction conditions: aryl bromide (0.30 mmol), Ni(acac)₂ (10 mol%), 5,5'-dimethyl-2,2'-bipyridine (L1, 10 mol%), A (10 mol%), Na₂CO₃ (0.30 mmol), THF (0.075M), CFL (32W) at rt for 18 h. ^{*b*} GC yields using decane as internal standard.

Systematic evaluation of all other reaction parameters indicated that a cocktail consisting of Ni(acac)₂, L1 (5,5'dimethyl-2,2'-bipyridine), Na₂CO₃ and A1 under CFL irradiation was particularly suited for our purposes, obtaining 1 in 95% isolated yield after 60 h (Table 2, entry 1).³⁰ As expected, the nature of the ligand had a non-negligible effect on reactivity.²⁸ Indeed, the utilization of otherwise related neocuproine (L2), 2,2'-bipyridine (L3) or even 4,4'-ditertbutyl-2,2'bipyridine (L4), a ligand commonly employed in the metallaphotoredox arena, resulted in lower yields of 1 (entries 2-4). As shown in entries 5-7, Ni(COD)₂ and Ni(II) salts other than Ni(acac)₂ could also be employed as precatalysts, hence suggesting that acac does not play a critical role on the reaction outcome (vide infra). Next, we turned our attention to study the influence of the light source. The results are particularly illustrative: (a) irradiation by a dark lamp ($\lambda_{max} = 365$ nm) or dark LED (390 nm) resulted in an enhanced rate acceleration but with lower chemoselectivity profile (entry 8 and 10) to that observed under CFL irradiation, and (b) 1 was selectively observed under 34 W Kessil Blue-LEDs, albeit in lower yields (entry 9). These results are particularly noteworthy, suggesting that residual UV emission on fluorescent light bulbs cannot be exclusively responsible for the observed selectivity and reactivity in the sp^3 C–H arylation of tetrahydrofuran. Importantly, 87% yield of 1 was obtained under air (entry 11), thus constituting an additional bonus from a practical standpoint while complementing existing iridium polypyridyl photochemical scenarios that commonly require exclusion of oxygen atmospheres.³¹ As expected, control experiments showed that all of the parameters were crucial for the reaction to occur (entries 12-14). Note, however, that the absence of L1 gave rise to 1 in 35% yield, albeit with considerable amounts of homocoupling product (entry 14).

Table 2. Optimization of the Reaction Conditions.



^{*a*} Reaction conditions: As Table 1, 60 h. ^{*b*} GC yields with dodecane as internal standard. ^{*c*} Isolated yield, average of two independent runs. ^{*d*} Mass balance accounts for reduced ArBr. ^{*e*} Mass balance accounts for homocoupling of ArBr. ^{*f*} 47 μ W/cm².

 sp^{3} C–H arylation of saturated hydrocarbons aided by triplet excited ketones and Ni catalysts. Encouraged by our initial findings, we next turned our attention to study the generality of our sp^3 C–H arylation. As evident from the results compiled in Table 3, a wide variety of aryl bromides bearing either electron-rich or electron-poor substituents underwent the targeted sp^{3} C–H arylation. Notably, our photochemical C– H arylation displayed an excellent chemoselectivity profile, and ketones (5), phenols (10, 14), primary alcohols (9), amides (8, 29), nitriles (2, 22, 24), esters (3, 6, 7, 17, 26-29), alkynes (7), alkenes (6, 18), anilines (11), acetals (16) and aldehydes (20) could perfectly be tolerated. Likewise, aryl boronates (12), organostannanes (13) or electrophilic sites that are susceptible to Ni-catalyzed cross-coupling reactions such as aryl chlorides (4, 14, 15) and aryl pivalates (15) were also accommodated, thus providing an additional handle for further functionalization.³² As shown for 25, the photochemical sp^3 C–H arylation could also be extended to vinyl bromides, albeit in lower yields. Precursors derived from the chiral pool, such as cholesterol (26), (L)-menthol (27), (D)-allofuranose (28) and (D)-phenylglycine (29) were also within reach, showcasing the preparative potential of this transformation. The ability to easily scale up the reaction without noticeable erosion in yield (3, 21, 37) constitute an additional bonus from a practical standpoint. Notably, our protocol allowed for the coupling of a wide variety of electron-poor nitrogen-containing heterocycles, including pyridines (30-32), pyrimidines (33), and quinolines (36). Similarly, electron-rich heterocycles such as (benzo)thiophenes (34, 35) and free indole do not interfere (37). This finding showcases the complementarity of our photochemical technique with classical metallaphotoredox reactions based on iridium polypyridyl complexes that typically result in low yields when using electron-rich heterocycles as substrates processes.14-16,20 SET due to competitive



^{*a*} Reaction conditions: as Table 2 (entry 1). ^{*b*} Isolated yields, average of at least two independent runs. ^{*c*} 10 mmol scale. ^{*d*} 4-Br-C₆H₄N(TMS)₂ (0.30 mmol) was used as masked aniline. ^{*e*} 20 mol% of A1.

With the results of Table 3 in hand, we wondered whether our photochemical arylation could be extended to C–H precursors other than tetrahydrofuran. Gratifyingly, this was indeed the case and a variety of cyclic ethers (**38-40**) and acyclic ether analogues (**41-44**) could be employed as sp^3 C–H functional handles with equal ease (Table 4).³³ Particularly noteworthy is the coupling of 1,3-dioxolane as C–H precursor (**39**), thus representing a mild and complementary approach to introduce the formyl group into arenes after routine hydrolytic workup.^{22d,34} The ability to access **40** as a single diastereoisomer possessing a tetrasubstituted carbon center is equally relevant; to the best of our knowledge, this example constitutes the first nickel-catalyzed cross-coupling reaction via functionalization of sterically-encumbered tertiary sp^3 C–H bonds possessing an α -heteroatom.³⁵ As shown for **45** and **46**,³⁶ our protocol was not limited to ether motifs and the targeted sp^3 C–H arylation could also be conducted with methyl-

substituted benzene backbones, furnishing the corresponding diarylmethanes in good yields.

Table 4. Scope of Alkane sp³ C–H Precursors.^{*a,b*}



^{*a*} Reaction conditions: as Table 2 (entry 1). ^{*b*} Isolated yields, average of at least two independent runs. ^{*c*} Using NaHCO₃ (1.0 equiv). ^{*d*} 1.8:1 regioisomeric ratio. ^{*e*} 2.2:1 regioisomeric ratio.

The sp^3 C–H arylation could also be conducted in benzene as solvent using 10-20 equiv of C-H precursor, giving rise to 1, and 48-52 in good yields (Table 5). While in lower yields, the reaction could also be executed with stoichiometric amounts (2.0 equiv) of C-H precursor (1, 47), thus holding promise for designing future photochemical sp^3 C–H functionalizations with improved practicality, flexibility and generality. Although the results compiled in Tables 3-4 showed the viability for a sp³ C-H arylation event with alkanes possessing low C-H bond-dissociation energies, it was unclear whether such technique could be extended to unactivated, yet particularly strong, sp^3 C–H bonds possessing high bond-dissociation energies. Gratifyingly, we found that the sp^3 C–H arylation of cyclohexane is within reach (51, 52), constituting a stepforward for the functionalization of particularly unactivated sp^3 C–H bonds.^{36,37}

Table 5. sp³ C–H Arylation in Benzene as Solvent.^{*a,b*}



^{*a*} Reaction conditions: as Table 2 (entry 1), in benzene as solvent (0.075 M). ^{*b*} Isolated yields, average of at two independent runs. ^{*c*} NaHCO₃ (1 equiv). ^{*d*} A1 (50 %) was used. ^{*e*} Cyclohexane:benzene (1:1, 0.05 M).



Figure 1. Late-stage Diversification and Site-Selectivity. ^{*a*} As Table 2, with benzene as solvent (0.06M) and C–H precursor (10 equiv). ^{*b*} dr = 12:1. ^{*c*} dr = 10:1. ^{*d*} Minor regioisomer corresponds to the arylation at the primary sp^{3} C–H bond.

Prompted by the generality of our photochemical sp^3 C–H arylation, we anticipated that our protocol might hold promise to streamline the synthesis of complex molecules within the context of late-stage functionalization.³⁸ To this end, we found that (–)–Ambroxide underwent late-stage sp^3 C–H functionalization with a different set of (hetero)aryl bromides in benzene as solvent, giving rise to **53-55** in high yields and excellent diastereoselectivities (Figure 1).³⁹ We also found that the sp^3 C–H arylation of NMP (*N*-methylpyrrolidone) with 3-bromopyridine rapidly afforded Cotinine (**56**), a potential therapeutic agent against Alzheimer's disease,⁴⁰ in high yields and excellent site-selectivity. Likewise, a variety of valuable, yet not easily accessible, Cotinine analogues such as **57**⁴¹ or **58-59** could also be accessed under otherwise identical reaction conditions from cheap starting precursors.

Scheme 4. Enantioselective sp³ C–H Arylation.



Encouraged by our results, we wondered whether the merger of triplet excited ketones and nickel catalysis might enable the development of an asymmetric sp^3 C–H arylation with appropriate chiral ligands. Gratifyingly, we found that **60** could be accessed in moderate enantioselectivities and yields when utilizing a Ni/L5 couple (Scheme 4).⁴² This result is particular-

ly noteworthy, as it constitutes the first example of an enantioselective C–C bond-forming reaction of native sp^3 C–H bonds within the metallaphotoredox arena.

sp³ C-H alkylation of saturated hydrocarbons. Taken together, the data summarized above advocate the notion that the interface between triplet excited ketones and nickel catalysis might be a fertile ground within the sp^3 C–H functionalization arena. After establishing the ability to enable a sp^3 C–H arylation, we set out to investigate whether an otherwise related sp^3 C-H alkylation would be within reach. We recognized that such a platform might constitute an excellent opportunity to couple two sp^3 carbon fragments with readily accessible precursors and catalysts.⁴³ Despite the lower propensity for $C(sp^3)$ - $C(sp^3)$ bond-reductive elimination,⁴⁴ and the natural proclivity of transient alkyl metal species for parasitic homodimerization or β -hydride elimination, we found that a regime based on Ni(acac)₂, L4 (4,4'-diterbutyl-2,2'bipyridine) and A1 was particularly suited for our purposes (Table 6).²⁸ Although the presence of CF_3CO_2Na was not strictly necessary,⁴⁵ its inclusion significantly improved both the reaction rate and the yields of the targeted sp^{3} C–H alkyla-

Table 6. Scope of the sp^3 C–H alkylation.^{*a,b*}

tion products. Under these optimized reaction conditions, a wide variety of unactivated alkyl bromides possessing alkenes (62), free alcohols (63), silvl ethers (64), esters (66), nitrogencontaining heterocycles (66), nitriles (70), amides (71, 73), aldehydes (72) or ketones (74) could all be perfectly accommodated. Although chemoselectivity issues arise in the presence of alkyl chlorides (67), exhaustive or selective sp^3 C–H alkylation could be accomplished when 1,6-dibromohexane was employed as substrate (68, 69). Notably, the sp^3 C–H alkylation could also be conducted with a variety of ethereal C-H precursors (75-77). Although we anticipated that a C-C bond reductive elimination between two fragments derived from secondary sp^3 C–H bonds would be even more problematic, we found that our protocol could be integrated with more challenging secondary alkyl bromides (73, 74). As for the sp³ C-H arylation (Table 1), particularly noteworthy was the ability to enable a rather challenging $C(sp^3)-C(sp^3)$ bondformation at unactivated sp^3 C–H bonds possessing particularly high bond-dissociation energies (78-80). These results tacitly suggest that our Ni/A1 regime might complement existing metallaphotoredox scenarios based on the utilization of noble iridium polypyridyl photocatalysts for the functionalization of process.14-16,34,43 sp C-H via HAT



^{*a*} Reaction conditions: alkyl bromide (0.30 mmol), Ni(acac)₂ (10 mol%), **L6** (10 mol%), **A1** (20 mol%), C-H precursor as solvent (0.075 M), Na₂CO₃ (1.0 equiv), CF₃CO₂Na (1 equiv), CFL (32W), 25 °C. ^{*b*} Isolated yields, average of at least two independent runs. ^{*c*} Without CF₃CO₂Na. ^{*d*} Benzene as cosolvent (1:1, 0.05 M), **A1** (50 mol%). ^{*e*} NaHCO₃ (1.0 equiv).

Mechanistic studies. The data summarized above provides compelling evidence that triplet excited ketone catalysts exploit an unrecognized opportunity in the field of metalcatalyzed sp^3 C–H functionalization. However, it was unclear whether the promiscuous photoreactivity of triplet excited ketones would allow to understand how the C–H bondcleavage operates at the molecular level. Prompted by the seminal studies from Chow^{10} , Molander¹⁵ and Doyle¹⁶, we turned our attention to unravelling the mode of action by which A1 enable sp^3 C–H arylation. Although we corroborated by control experiments the efficient photoreduction of Ni(acac)₂ by A1 under CFL irradiation,²⁸ various scenarios

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might a priori be conceivable for the results highlighted above (Scheme 5): (a) single-electron oxidation of the aryl-Ni(II)(L1)-Br oxidative addition with A1* followed by Ni(III)-Br homolysis and HAT towards III/V (*path a*);^{15,16} (b) triplet-triplet ET from A1* to the transient aryl-Ni(II)(L1)-Br oxidative addition complex followed by Ni(II)-Br homolysis and HAT en route to III/VII (*path b*);^{15,16} (c) charge-transfer (CT) from A1* to in situ generated aryl-Ni(II)(L1)-acac, resulting in acac radical that triggers a HAT process followed by recombination to end up in VII (*path c*);¹⁰ (d) triplet-triplet ET from A1* to aryl-Ni(II)(L1)-Br species followed by σ -bond metathesis of the C-H precursor to deliver VII (*path* d)¹⁵ or (e) generation of III upon HAT from A1* to ultimately generate V by recombination with aryl-Ni(II)(L1)-Br (*path e*).

Scheme 5. Proposed Pathways for *sp*³ C–H Cleavage.

SET or ET

path a & b

nath e

СТ

VII

Ni^I−Ar

acac

path c

acac

ET & σ-bond

metathesis

path d

B

SET or ET

Br

bromine

radical

HAT/SET o-bond metathesis (ET) At first sight, it is not particularly straightforward to rigorously distinguish between the mechanistic scenarios highlighted in Scheme 5. Although HAT might indeed occur via bromine radicals that are released from in situ generated aryl-Ni(II)(L1)-Br complexes (*pathways a & b*),^{15,16} we believe that this manifold makes a minor contribution to productive sp^3 C-H arylation, if any. Taking into consideration the mismatch of bond-dissociation energies (BDE)46 of H-Br (87 Kcal/mol) and the C-H bond of cyclohexane (98 Kcal/mol), one might argue that the sp^3 C–H arylation of the latter with bromoarenes should a priori not take place (Scheme 8). However, the successful formation of 51-52 (Table 3) and 78-80 (Table 4) indicates otherwise. The interpretation for the lack of Nihalogen homolysis gains credence by the non-negligible reactivity found when promoting the sp^3 C–H arylation of both tetrahydroduran (C-H: 85 Kcal/mol) and cyclohexanes (C-H: 98 Kcal/mol) with iodoarenes (H-I: 71 Kcal/mol) as substrates, delivering 3 and 51 in moderate yields. Furthermore, deuterium labelling studies showed an exothermic radical sp³ C-H abstraction.⁴⁸ Putting everything into perspective, these experiments suggest that a pathway consisting of the intermediacy of halogen radical species may not be populated.⁴⁹





Next, we turned our attention to explore the viability of a triplet-triplet ET followed by σ -bond metathesis (Scheme 5, pathway d). If such a pathway intervenes, we anticipated that exposure of 1-bromo-4-(trifluoromethyl)benzene in THF under UV-irradiation with Ni/L1 in the absence of A1 might result in non-negligible amounts of sp^3 C–H arylation. However, not even traces of 1 were observed under irradiation by a dark lamp ($\lambda_{max} = 365 \text{ nm}$).⁵⁰ Further support for the lack of σ bond metathesis is evident from the sp^3 C–H arylation of a mixture of cis/trans 2,5-dimethyl tetrahydrofuran (1:1 ratio) with methyl 4-bromobenzoate (Scheme 7). A statistical mixture of products was anticipated for a mechanism consisting of a concerted σ -bond metathesis; on the contrary, a nonconcerted scenario by capturing radical intermediates generated by SET or HAT would be expected to exert a certain control on diastereoselectivity. As shown in Scheme 7, 40 was obtained as a single diastereoisomer, suggesting that pathways other than σ -bond metathesis seem to be the most plausible avenue for our *sp*³ C–H arylation event.⁵¹

Scheme 7. Assessing Intramolecular σ-Bond Metathesis.



Although the available data likely indicates that scenarios based on bromine radicals (Scheme 5, *pathway a & b*) or σ bond metathesis (*pathway d*) might not be operative, a clearcut choice between the two remaining options (*pathways c & e*) still remained elusive. Aiming at shedding light into such overly complex reaction, we set out to explore the reactivity of the putative aryl-Ni(II)(L1)-Br oxidative addition complex (Figure 2). To this end, simple exposure of 4-trifluoromethyl bromobenzene to Ni(COD)₂ and L1 in THF at rt resulted in Ni-1, the structure of which was univocally confirmed by X-ray diffraction (Figure 2, *top*).²⁸ Particularly noteworthy was the observation that Ni-1 underwent the targeted sp^{3} C–H arylation of tetrahydrofuran en route to 1 *only* in the presence of A1 under CFL irradiation. Indeed, control experiments revealed that no reaction occurred in the absence of A1 whereas exclusive homodimerization was observed if Ni-1 was exposed under UVA irradiation ($\lambda_{max} = 365$ nm), thus providing additional evidence that a σ -bond metathesis regime (*pathway d*) might not be operative.



Figure 2. Mechanistic Experiments with Ni-1. All reactions were conducted with **Ni-1:A1** in a 1:1 ratio. ^{*a*} GC yields, using decane as internal standard. ^{*b*} Exclusive homodimerization was observed in the crude mixtures.

In line with our expectations, Ni-1 turned out to be catalytically competent, furnishing 3 in 35% yield together with nonnegligible amounts of 1 derived from Ni-1 (Figure 2, *middle*). At present, the markedly decrease in reactivity of Ni-1 when compared to our *in situ* protocol based on Ni(acac)₂/L1 can tentatively be attributed to (a) the stunning absorption of Ni-1 in the visible light region,²⁸ and/or (b) the absence of acac anion, as the photoreduction of Ni(acac)₂ via charge-transfer (CT) might have a direct correlation with the generation of acac-radical species (Scheme 5, *pathway c*).¹⁰ The latter assumption was assessed by conducting the *sp*³ C–H arylation of methyl 4-bromobenzoate and Ni-1 (1 mol%) with or without additional Na(acac) (20 mol%). Although in lower yields, the results are particularly illustrative (Figure 2, *middle*); specifically, significant inhibition was observed in the presence of Na(acac)⁵² whereas an improved turnover number (TON) was observed in the absence of such additive, leaving a reasonable doubt that *pathway c* (Scheme 7) based on a CT event might be operative. As a consequence, the presence of acac in our catalytic protocol does not have an influence on product formation, suggesting that acac may merely facilitate the initial photoreduction of Ni(acac)₂ to deliver the catalytically competent nickel intermediates. In line with this context, it is worth noting that no significant deleterious effect was observed when replacing Ni(acac)₂ by other Ni(II) precatalysts²⁸ or Ni(COD)₂ (Table 2, entry 5). Although our empirical observations may not be taken as a definitive proof that other pathways might not be populated,⁵³ the available data is consistent with *pathway* e based on a HAT process from the triplet excited state of A1 followed by SET to recover back the propagating A1 and low-valent Ni(0)L species (Scheme 4). Unfortunately, it was not possible to unambiguously unravel the most basic features of such intertwined scenarios, as the interaction of A1 and Ni-1 in either THF or benzene was exacerbated by the high absorption of Ni-1 in the (n,π^*) excitation region of A1. Additionally, Stern-Volmer analysis or flash photolysis could not be conducted due the propensity of Ni-1 to decomposition pathways, even under highly diluted conditions.^{54,55} Aimed at providing indirect evidence about the mode of action of A1, we decided to monitor a stoichiometric reaction of Ni-1 and A1 in dioxane by EPR spectroscopy with constant irradiation (>300 nm) (Figure 2, bottom). A direct comparison with the known g-values on related scenarios^{10b,28} revealed the formation of Ni(I) intermediates and the corresponding ketyl radical together with the corresponding sp^3 C–H arylation of dioxane (83).²⁸ Taken together, these control mechanistic experiments contribute to the perception that a HAT & SET pathway seems the most plausible avenue for the merger of triplet excited ketones and Ni catalysis.

CONCLUSION

In summary, we have designed a catalytic platform that employs a synergistic combination of nickel salts and diaryl ketone catalysts for the utilization of saturated feedstocks as functional handles in sp³ C-H arylation and alkylation events with aryl or alkyl halides as starting precursors. This dual catalytic scenario makes use of simple, modular and versatile triplet diaryl ketones as catalysts to activate sp^3 C–H bonds, even in the context of late-stage functionalization or in an asymmetric manner. The available data suggest that the merger of cheap, modular and widely accessible triplet excited ketones and nickel catalysts might represent a powerful alternative to classical inner-sphere sp^3 C-H functionalization techniques or existing photochemical metallaphotoredox scenarios based on commonly employed iridium polypyridyl photoredox catalysts. Mechanistic experiments suggest a new activation mode by which triplet excited ketones serve as both HAT and SET catalysts, with catalytic turnover effected by an intertwined scenario with nickel catalysts. We expect that the broader consequences of this concept will foster systematic investigations for a more prolific use of simple ketones as photocatalysts for streamlining synthetic sequences that rapidly build-up molecular complexity from simple chemical feedstocks.

ASSOCIATED CONTENT

Supporting Information

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The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectral and crystallographic data (PDF)

Data for Ni-1 (CCDC 1851145) (CIF)

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- 47) Oxidative addition of aryl bromides or iodides to Ni(0) may a priori occur via radical cage mechanisms en route to aryl-Ni(II) halide complexes or by the formation of Ni(I) halide species with concomitant formation of aryl radicals capable of triggering HAT with C–H donors. In line with this context, it is worth noting that trace amounts of reduced arene were observed when using aryl iodides as substrates in THF (or d_8 -THF), suggesting that the latter pathway does not intervene under our standard reaction conditions; after prolonged reac-

tion times, however, small amounts of reduced arene could be observed in the crude mixtures (see ref. 28). For selected mechanistic considerations with either bipyridine or phosphine ligands, see: (a) ref. 16. (b) Tsou, T. T.; Kochi, J. K. Mechanism of Oxidative Addition. Reaction of Nickel(0) Complexes with Aromatic Halides. J. Am. Chem. Soc. **1979**, *101*, 6319. (c) Funes-Ardoiz, I.; Nelson, D. J.; Maseras, F. Halide Abstraction Competes with Oxidative Addition in the Reactions of Aryl Halides with [Ni(PMe_nPh_{(3-n)4}]. Chem. Eur. J. **2017**, *23*, 16728.

- (a) Deneś, F.; Pichowicz, M.; Povie, G.; Renaud, P. Thiyl Radicals in Organic Synthesis. *Chem. Rev.* 2014, *114*, 2587.
 (b) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C-H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem. Int. Ed.* 2012, *51*, 3066.
- 49) For the generation of halogen radical from high valent Ni complex, see: Mondal, P.; Pirovano, P.; Das, A.; Farquhar, E. R.; McDonald, A. R. Hydrogen Atom Transfer by A High-Valent Nickel Chloride Complex. J. Am. Chem. Soc. 2018, 140, 1834.
- 50) These results are in sharp contrast to a recent arylation of toluene under UV irradiation, see: Ishida, N.; Masuda, Y.; Ishikawa, N.; Murakami, M. Cooperative of A Nickel-Bipyridine Complex with Light for Benzylic C-H Arylation of Toluene Derivatives. *Asian. J. Org. Chem.* **2017**, *6*, 669.
- 51) In this context, not even traces of intramolecular sp^3 C–H functionalization were observed en route to either **68** or **81** and **82** using 2,2'-dibromo-1,1'-biphenyl as starting precursor (see Supporting information for details). Although the site-selectivity observed for **42** or **43** favoring secondary *vs* primary sp^3 C–H sites may argue against a σ -bond metathesis regime, we cannot rigorously rule out this pathway due to the reversibility of high valent Ni–C bonds. For a computational study, see: Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A. Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015**, *137*, 4896.
- 52) In line with this notion, the sp^3 C–H arylation of THF with 4trifluoromethyl bromobenzene was inhibited in the presence of Na-acac (1 equiv). See ref. 28 for details.
- 53) For a fundamental study of photochemical properties of bipyridine ligated Ni(II) complex, see: Shields, B. J.; Kudisch, B.; Scholes, G. D.; Doyle, A. G. Long-Lived Charge-Transfer States of Ni(II) Aryl Halide Complexes Facilitate Bimolecular Photoinduced Electron Transfer. J. Am. Chem. Soc. 2018, 140, 3035.
- 54) It is worth considering the quenching rate of triplet benzophenone by Ni(acac)₂ (2.9*10⁹ M¹sec⁻¹ in MeOH) and nPr₂O (9.2*10⁶ M¹sec⁻¹ in bencene). See: (a) Guttenplan, J.; Cohen, S. G. Triplet Energies, Reduction Potential, and Ionization potentials in Carbonyl-Donor Partial Charge-Transfer Interactions. J. Am. Chem. Soc. 1972, 94, 4040. (b) ref. 10b. Although tentative, these quenching rates might be responsible for the observed efficiency of our Ni/A1 regime
- 55) Although Ni-1 turned out to be particularly prone to decomposition pathways, the presence of an aryl bromide significantly increased its stability.

