Dihydroquinazolinones as adaptative C(sp³) handles in arylations and alkylations via dual catalytic C–C bond-functionalization

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C–C bond forming cross-couplings are convenient technologies for the construction of functional molecules. Consequently, there is continual interest in approaches that can render traditionally inert functionality as cross-coupling partners, included in this are ketones which are widely-available commodity chemicals and easy to install synthetic handles. Herein, we describe a dual catalytic strategy that utilizes dihydroquinazolinones derived from ketone congeners as adaptative one-electron handles for forging C(sp³) architectures via α C–C cleavage with aryl and alkyl bromides. Our approach is achieved by combining the flexibility and modularity of nickel catalysis with the propensity of photoredox events for generating open-shell reaction intermediates. This method is distinguished by its wide scope and broad application profile—including chemical diversification of advanced intermediates—, providing a catalytic technique complementary to existing C(sp³) cross-coupling reactions that operates within the C–C bond-functionalization arena.
Transition-metal-catalyzed cross-coupling reactions of nucleophilic and electrophilic components are powerful methods for rapidly forming carbon-carbon bonds\textsuperscript{1-3}. These approaches have been widely applied to the preparation of biologically-relevant molecules and functional materials, by academic and industrial institutions alike\textsuperscript{4-7}. Consequently, great interest exists for the development of new cross-coupling synthons that operate under ambient conditions, as this increases the structural diversity of accessible molecules within drug discovery programs\textsuperscript{8-12}. The broad utility of ketones as chemical precursors\textsuperscript{13,14}, the plethora of methods for their preparation\textsuperscript{15-17}, and their prevalence as medicinal and commodity chemicals make them ideal targets for chemical innovation\textsuperscript{18-21}. Synthetic manipulations of ketones generally rely on their latent polarity, specifically the electronegativity of $\text{C}=\text{O}$ bonds and nucleophilicity of enolate related structures (Fig. 1a, path a). In sharp contrast, the selective and catalytic cleavage of ketone $\alpha$–$\text{C}$ bonds as a platform for installing chemical functionality still remains challenging (Fig. 1a, path b). However, such techniques hold promise for creating conceptually new disconnects during retrosynthetic analysis to achieve $\alpha$-ketone functionalities. The broad utility of ketones as chemical precursors\textsuperscript{18-21}, the plethora of methods for their preparation\textsuperscript{15-17}, and their prevalence as medicinal and commodity chemicals make them ideal targets for chemical innovation\textsuperscript{18-21}. Synthetic manipulations of ketones generally rely on their latent polarity, specifically the electronegativity of $\text{C}=\text{O}$ bonds and nucleophilicity of enolate related structures (Fig. 1a, path a). In sharp contrast, the selective and catalytic cleavage of ketone $\alpha$–$\text{C}$ bonds as a platform for installing chemical functionality still remains challenging (Fig. 1a, path b). However, such techniques hold promise for creating conceptually new disconnects during retrosynthetic analysis to achieve $\alpha$-ketone functionalities.

Metallaphotoredox catalysis has gained momentum as a powerful synthetic tool\textsuperscript{38-40}, in particular by allowing alcohol\textsuperscript{41-43} primary amines\textsuperscript{44,45} and aldehydes\textsuperscript{46-48} to be used as adaptative $\text{C}(sp^3)$ handles in $\text{C}$-$\text{C}$ bond-formations. These approaches generally rely on the conversion of traditionally inert chemical functionality into groups susceptible to single-electron activation. Despite this, the $\alpha$–$\text{C}$ bond activation of ketone derivatives has not yet been fully realized within metallaphotoredox catalysis, but if were so would expand the synthetic chemist’s repertoire for forging $\text{C}(sp^3)$ linkages.

In this work we use ketone derived dihydroquinazolinones as radical precursors in metallaphotoredox events, to formally deliver ketone $\alpha$–$\text{C}$ cleavage driven by the formation of aromaticity via single-electron-oxidation (Fig. 1d)\textsuperscript{49-53}. Our strategy allows for abundant ketones to be formally used as cross-coupling synthons with aryl and alkyl bromide electrophiles in the construction of $\text{C}(sp^3)$ architectures—currently a need in medicinal chemistry programs\textsuperscript{54-57}.

**Results**

**Optimization of reaction conditions.** We began our investigation by evaluating the reaction of aryl bromide $\text{I}$ with dihydroquinazolinone $\text{2a}$ (Table 1), accessed on large scale by the condensation of cyclohexyl methyl ketone with 2-amino benzamide (2-AB). A combination of $\text{Ni(OAc)}_2$-$\text{H}_2\text{O}$, 4-CzIPN photocatalyst, tetrypyridine ligand $\text{L}_4$, $\text{Na}_2\text{CO}_3$ and NaBr in NMP under blue light-emitting diodes (LEDs) irradiation at 40°C provided the best results, affording cross-coupling product $\text{3a}$ in 93% isolated yield (entry 1). Under the limits of detection, no methyl 4-methylbenzoate arising from $\text{C}(sp^3)$–Me cleavage was observed, thus tacitly indicating that $\text{C}$–$\text{C}$ cleavage is dictated by the relative stability of the resulting radical intermediate. As expected, the nature of the ligand played a crucial role. Lower levels of $\text{3a}$ productivity were attained with 2,2’-bipyridine ligands (entries 2 and 3), while tetrypyridines other than ligand $\text{L}_4$ were deleterious, highlighting the electronic and steric subtleties of our ligand backbone (entries 4 and 5). Similarly, inferior results were found for nickel pre-catalysts, solvents and bases other than $\text{Ni(OAc)}_2$-$\text{H}_2\text{O}$, NMP and $\text{Na}_2\text{CO}_3$ (entries 6–9). Although iridium photocatalysts were competent en route to cross-coupling product $\text{3a}$ (entry 10), the use of photocatalyst 4-CzIPN constituted a bonus from an accessibility standpoint\textsuperscript{58}. As expected, no cross-coupling product $\text{3a}$ was found under the omittance of nickel pre-catalyst, tetrypyridine ligand $\text{L}_4$, 4-CzIPN photocatalyst or light (entry 11).

**Substrate scope.** With optimal conditions in hand, we next explored the generality of this $\text{C}(sp^3)$ arylation method of ketone derivatives via dihydroquinazolinone activation for $\text{C}$–$\text{C}$ bond-cleavage. As shown in Fig. 2 (Left), the $\text{C}(sp^3)$ arylation could be accomplished independently on whether dihydroquinazolinones were decorated with primary or secondary alkyl residues. Interestingly, site-selectivity can be easily dictated and modulated by an appropriate selection of the substituents on the dihydroquinazolinone core. Specifically, the coupling of secondary alkyl radicals ($\text{3a}$–$\text{3f}$), secondary oxygen-stabilized radicals ($\text{3g}$, $\text{3h}$ or oxygen- or nitrogen-stabilized primary radical congeners ($\text{3i}$–$\text{3l}$) could all easily be within reach for Me-substituted analogues. Additionally, it is worth noting that ethyl-substituted dihydroquinazolinones were applicable without deviation in cross-coupling productivity from their methyl-congeners ($\text{3a}$, $\text{3l}$). The arylation of a primary butyl residue to form $\text{3m}$ was found to operate with dihydroquinazolinone cores decorated with methyl groups; note, however, that superior yields were afforded when using aryl-substituted analogues. As such, primary alkyl residues were simply transferred using dihydroquinazolinone cores containing phenyl groups ($\text{3n}$–$\text{r}$). It is worth noting this preference for alkyl bond scission over $\text{C}(sp^3)$-aromatic cleavage provides an alternative selectivity to transition-metal-catalyzed $\text{C}$–$\text{C}$ activations.
Table 1 Optimization of the reaction conditions.

| Entry | Deviation standard conditions | 3a (%)^c |
|-------|-------------------------------|----------|
| 1     | none                          | 99 (93)^a|
| 2     | L1 instead of L4              | 36       |
| 3     | L2 instead of L4              | <1       |
| 4     | L3 instead of L4              | <1       |
| 5     | L5 instead of L4              | <1       |
| 6     | Using Ni(COD)₂                  | 61       |
| 7     | Using NiCl₂·DME               | 92       |
| 8     | using MeCN instead of NMP     | 63       |
| 9     | using K₂PO₄ instead of Na₂CO₃  | 81       |
| 10    | using [Ir(CF₃)(ppy)(dpym)(PF₆)]  | 59       |
| 11    | no Ni, no L4, or in the darkness | <1     |

Fig. 2 Dihydroquinazolinones as sp³ handles via a C–C cleavage. As Table 1 (entry 1), using aryl bromide (0.20 mmol). Isolated yields, average of at least two independent runs. Unless stated otherwise, R¹ = Me in the ketone derivative. ^R² = Et in the ketone derivative. Using NiCl₂·DME as Ni source in NMP (0.2 M). ^Using 5-CzBN (2 mol%) as photocatalyst, LiBr (1.2 eq.) as additive. ^H NMR yield using CH₂Br₂ as standard. ^R₁ = Ph in the ketone derivative. ^R₁ = 4-methoxyphenyl in the ketone derivative. ^R₁ = benzo[d][1,3]dioxol-5-yl in the ketone derivative. ^Aryl bromide (0.20 mmol), ketone derivative (0.30 mmol), NiBr₂·diglyme (10 mol%), L1 (15 mol%), LiHMDS (1.5 eq.), in dioxane (0.1 M).
of ketones, which generally give the more stable metal-aryl complex over alkyl species.39-62

Our dual catalytic platform was found to be widely applicable for an array of aryl bromides regardless of their electronic and steric environment (5a–5p) (Fig. 2, Right). As evident from the results compiled in Fig. 2, our method displays an excellent chemoselectivity profile, including accommodation of structures containing aldehyde (5a), acetal (3h), N-aryl amines (3r), thioether (3q), amides (3i, 3p, 3q, 3r), nitrile (5b), ketone (5c), sulfonamide (5g) and alkyl esters (3d, 3j, 3n). As shown for cross-coupling products 5h and 3g, the reaction could be extended to vinyl bromides or acyl-type radicals with similar ease. Notably, oxygen- and nitrogen-containing heterocycles were compatible in this cross-coupling arylation regime turned out to be particularly applicable for the coupling of secondary alkyl radicals (8i–8l). Gratifyingly, after a brief re-optimization a protocol based on the Ni/L4 complex performed well for the coupling of aryl bromide 4j, which was observed (8o–8p) as a mixture of the linear (12) and cyclized (13) arylation products, which presumably arise from radical 5-exo-trig cyclisation of the intermediary primary hex-1-ynyl radical (Fig. 5b, Bottom). The oxidation potential of dihydroquinazolinone 2e (E1/2ox = +1.07 V vs SCE in NMP) was measured using cyclic voltammetry and was shown to be within the oxidizing power of 4-CzIPN (+1.43 V vs SCE) (See Supplementary Fig. 21 and 22)).268, Stern–Volmer fluorescence quenching experiments verified that the excited state of 4-CzIPN was effectively quenched by dihydroquinazolinone 2e and not by aryl bromide 4d (See Supplementary Fig. 17). These observations suggest a canonical reductive quenching scenario where single-electron transfer from dihydroquinazolinone to photoexcited 4-CzIPN occurs, initiating formal C–C cleavage en route to alkyl radical driven by the formation of an aromatic by-product.

Mechanistic studies. To gain insight into the possible reaction pathway of this cross-coupling process a set of preliminary mechanistic experiments have been carried out (Fig. 5). Firstly, the cross-coupling of aryl bromide 1 with dihydroquinazolinone 2e was completely inhibited in the presence of a stoichiometric amount of TEMPO radical scavenger, with only the TEMPO-tetrahydropryan adduct (9) being observed (Fig. 5a). Subjection of our metallaphotoredox reaction conditions to a cyclopropane containing dihydroquinazolinone (2t) yielded only the ring-opened cross-coupling product (10) along with quinazolin-4-one by-product (11) (Fig. 5b, Top). Furthermore, use of dihydroquinazolinone 2u gave a mixture of the linear (12) and cyclized (13) arylation products, which presumably arise from radical 5-exo-trig cyclisation of the intermediary primary hex-1-ynyl radical (Fig. 5b, Bottom). The oxidation potential of dihydroquinazolinone 2e (E1/2ox = +1.07 V vs SCE) was measured using cyclic voltammetry and was shown to be within the oxidizing power of 4-CzIPN (+1.43 V vs SCE) (See Supplementary Fig. 21 and 22)).268, Stern–Volmer fluorescence quenching experiments verified that the excited state of 4-CzIPN was effectively quenched by dihydroquinazolinone 2e and not by aryl bromide 4d (See Supplementary Fig. 17). These observations suggest a canonical reductive quenching scenario where single-electron transfer from dihydroquinazolinone to photoexcited 4-CzIPN occurs, initiating formal C–C cleavage en route to alkyl radical driven by the formation of an aromatic by-product.

Terpypidine ligated nickel complex (Ni-I) was obtained by exposure of Ni(COD)2/PPh3 to aryl bromide 4d followed by ligand exchange with terpyridine L499, with the structure of this complex confirmed by X-ray diffraction. As anticipated, isolated complex Ni-I was found to be catalytically competent in the cross-coupling of dihydroquinazolinone 21 with aryl bromide 4dh (Fig. 5c, Right). Next, we performed the stoichiometric reaction between dihydroquinazolinone 21 and isolated complex Ni-I affording the cross-coupling product 5d in 25% yield. This suggests that Ni-I and similar nickel complexes can capture radicals and undergo reductive elimination under our established conditions (Fig. 5c, left). A positive linear relationship between Ni-I catalyst concentration and linear selectivity in the cross-coupling of dihydroquinazolinone 2u with 4d was observed (Fig. 6). This is consistent with the formation of C(sp3)-centred hex-1-ynyl radical from dihydroquinazolinone 2u, which is captured by Ni-I. Higher concentrations of Ni-I shortens the lifetime of the alkyl radical in solution resulting in diminished cyclization product 13 formation and greater selectivity for the linear product (12).

Based on the aforementioned mechanistic experiments and literature precedent70, a plausible mechanism was proposed.
NaHCO₃ (1.0 eq.) in DMF (0.1 M) at 40 °C for 24 h. Isolated yields, average of two independent runs. Unless stated otherwise, R₂ is a derivative.

(Fig. 7). Oxidative single-electron transfer from dihydroquinazolinone (I) to excited photocatalyst triggers a C–C scission driven by the formation of aromatic by-product, forming alkyl radical II and reduced photocatalyst. Ni(II) pre-catalyst III can be reduced to the Ni(0) form IV and then to the catalytically active Ni(0) state V by consecutive single electron transfer events with the photocatalyst using dihydroquinazolinone (I) as a sacrificial reductant in a catalytic quantity. Oxidative addition of an aryl or alkyl bromide to Ni(0)L₅(V) generates NiII species (VI). Radical recombination of NiII species (VI) with alkyl radical II generates discrete NiIII species VII, which upon reductive elimination forms the targeted cross-coupling product (VIII) and L₅Ni(II)Br IX. The two catalytic cycles are then simultaneously closed with a final single-electron transfer between the radical anion of the photocatalyst and L₅Ni(II)Br IX, recovering both Ni(0)L₅V and ground-state photoredox catalyst.

**Discussion**

In summary, we have developed a catalytic blueprint for forging C(sp3)-C(sp3) and C(sp3)-C(sp3) bonds by using ketone derived dihydroquinazolines as one-electron C(sp3) handles via a C–C bond cleavage. This technology offers an unconventional disconnection within the retrosynthetic planning phase of synthesis by enabling C(sp3)-arylations and C(sp3)-alkylations with an excellent chemoselectivity profile while operating under ambient temperature. In addition, a judicious choice of the starting precursor allows to control the site-selectivity of C–C bond-cleavage. Mechanistic experiments were conducted, all of which are consistent with the operation of a reductive quenching photoredox cycle, beginning with oxidative single-electron transfer of dihydroquinazolinone radical precursor by excited-state photocatalyst resulting in radical fragmentation driven by formation of an aromatic by-product. Further extensions to other related processes are underway in our laboratories.

**Methods**

**General procedure for nickel-catalyzed coupling with aryl bromides.** An oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with 4-CzIPN (3.2 mg, 2 mol%), Ni(OAc)₂·4H₂O (3.0 mg, 15 mol%), NaBr (21.2 mg, 1.2 eq.), aryl bromide (1.5 eq.). The test tube was introduced in a nitrogen-filled glovebox where Na₂CO₃ (21.2 mg, 1.0 eq.) was added. The reaction vessel was sealed with a screw cap and removed from the glovebox. Afterwards, alkyl bromide I (if liquid) and NMP (2 mL, 0.1 M) were added by syringe. Paraflin was used to seal the pierced cap. The reaction mixture was stirred at rt for 1 min, then exposed to blue LED irradiation at 40 °C for 24 hours. The reaction mixture was quenched with water/brine (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel chromatography to afford the desired product 3 or 5.

**General procedure for nickel-catalyzed coupling with alkyl bromides.** An oven-dried 8 mL screw-cap test tube containing a stirring bar was charged with Ir(fppy)₂(bpy)PF₆ (1.6 mg, 1 mol%), 2,6-di(1-pyrazolyl)pyridine (12.1 mg, 15 mol%), NaBr (24.7 mg, 1.2 eq.), alkyl bromide I (if solid, 1.0 eq., 0.2 mmol) and ketone derivative 2 (1.2 eq.). The test tube was introduced in a nitrogen-filled glovebox where Na₂CO₃ (21.2 mg, 1.0 eq.) was added. The reaction vessel was sealed with a screw cap and removed from the glovebox. Afterwards, alkyl bromide I (if liquid) and DMF (2 mL, 0.1 M) were added by syringe. Paraflin was used to seal the pierced cap. The reaction mixture was stirred at rt for 1 min, then exposed to blue LED irradiation at 40 °C for 24 hours. The reaction mixture was quenched with water/brine (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel chromatography to afford the desired product 8.


**Fig. 6 Radical cyclization as a function of catalyst loading.**

2u (0.12 mmol), 4d (0.10 mmol), Ni(OAc)₂·4H₂O (10 mol%), L₄ (15 mol %), 4-CzIPN (2 mol%), NaBr (1.2 eq.), Na₂CO₃ (1.0 eq.) in NMP (0.10 M) at 40 °C, for 24 h.

**Data availability**

The data supporting the findings of this study are available within the article and its Supplementary Information file. CCDC 2102869 (Ni-I) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. Any further relevant data are available from the authors on request.

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**Author contributions**
R.M. and X.-Y.L. conceived and designed the study. X.-Y.L. and R.A. performed the experiments and collected the data. R.M. and R.A. wrote the manuscript and all authors commented on the paper.

**Competing interests**
The authors declare no competing interests.

**Additional information**

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