

Synergistic Merger of Ketone, Halogen Atom Transfer (XAT), and Nickel-Mediated C(sp³)–C(sp²) Cross-Electrophile Coupling Enabled by Light

Alisha Rani Tripathy,[#] Akash Bisoyi,[#] Arya P, Sreelakshmi Venugopal, and Veera Reddy Yatham*Cite This: *ACS Org. Inorg. Au* 2024, 4, 229–234

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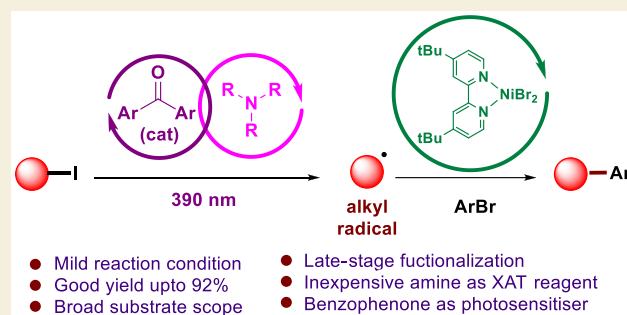
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ABSTRACT: In the present manuscript, we have developed a unique catalytic system by merging photoexcited ketone catalysis, halogen atom transfer (XAT), and nickel catalysis to forge C(sp³)–C(sp²) cross-electrophile coupling products from unactivated iodoalkanes and (hetero)aryl bromides. The synergistic catalytic system works under mild reaction conditions and tolerates a variety of functional groups; moreover, this strategy allows the late-stage modification of medicinally relevant molecules. Preliminary mechanistic studies reveal the role of the α -aminoalkyl radical, which further participates in the XAT process with alkyl iodides to generate the desired alkyl radical, which eventually intercepts with the nickel catalytic cycle to liberate the products in good to excellent yields.

KEYWORDS: ketone, halogen atom transfer, nickel, cross-coupling, photoredox

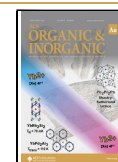


Over the past decade, with the development of metal-lathotoredox catalysis, several synthetic methodologies have been developed to forge various C–C and C–X (X = heteroatom) bonds.^{1–4} The synergy between photocatalysts and a variety of metal catalysts is the key to the success of this strategy. Various radical precursors have been employed in the presence of metal-based or organo-based photosensitizers to generate the desired radical entities through either a single-electron transfer (SET) process or an energy transfer (ET) process.^{5–7} The generated carbon radicals under visible-light photocatalysis were efficiently integrated with transition metal catalysts.^{1–4} With the advancement of this strategy, further research was explored by employing unreactive C(sp³)–H bonds as carbon radical precursors through the hydrogen atom transfer (HAT) process, which led to various cross-coupling products.^{8–15} Recently, it has been demonstrated that commercially available inexpensive ketones are utilized as organophotocatalysts in the presence of light.¹⁶ The photoexcited triplet ketone acts as a hydrogen-atom-abstracting agent, a single-electron acceptor, or can participate in energy transfer processes with the substrates to generate the radical entities that are efficiently merged with transition metal catalysts for versatile functionalization of C–H or C–X bonds. During this process, the photoexcited ketone is converted to an entity that is easily transformed to the ground-state ketones upon synergy with metal.¹⁷ In this direction, a few groups recently demonstrated synergistic

photoexcited ketone/nickel catalysis to forge C(sp³)–C(sp²) and C(sp³)–C(sp³) bonds (Scheme 1 a).^{18–22}

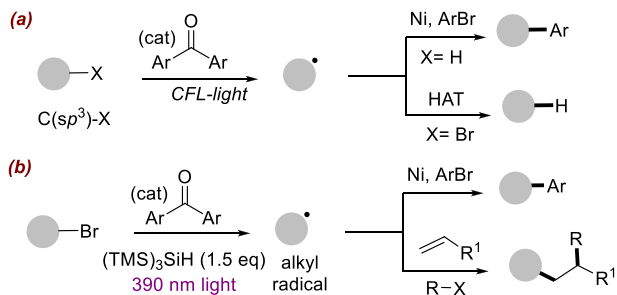
Recently, the concept of halogen atom transfer (XAT) under visible-light photocatalysis gained significant momentum.^{23,24} This strategy allows the radical dehalogenative functionalization of haloalkanes and haloarenes.^{25–30} Furthermore, this concept was successfully merged with metal catalysis, which eventually led to a variety of cross-coupling products.³¹ Initially, Macmillan and co-workers enormously contributed by employing silicon-based reagents as XAT reagents in the presence of photosensitizer,^{32–40} and later, the Doyle and Leonori groups independently demonstrated the employment of α -aminoalkyl radicals as XAT reagents and further applications in a number of C–C bond formation reactions in the presence of visible light photocatalysis.^{25–28,41–44} In this direction, our group also first demonstrated C(sp³)–C(sp²) and C(sp³)–C(sp) cross-electrophile coupling reactions using iodoalkanes, aryl bromides, and phenylethynyl bromides.^{30,43} Very recently, Noël and co-workers further exploited the merger of a photoexcited ketone, HAT, and XAT with nickel

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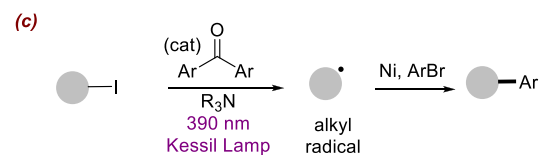


Scheme 1. Known Strategies for Photoexcited Triplet Ketone-Enabled C–C and C–H Bond Formation Reactions

Known reports



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catalysis to forge C–C bond formation by employing bromoalkane and bromoarenes through a silyl radical generated in situ (Scheme 1b).⁴⁵ In the present manuscript, we have developed cross-electrophile coupling between unactivated iodoalkanes and (hetero)aryl bromides by merging nickel–photoexcited ketone catalysis using inexpensive amines as XAT reagents (Scheme 1c).

We started our investigations by selecting iodocyclohexane **1a** and methyl 4-bromobenzoate **2a** as model substrates. After the different conditions were thoroughly investigated (see the Supporting Information), we realized that using 20 mol% of 4,4'-dichlorobenzophenone **B**, 3 equiv of ^tBu₃N, and 5 mol% of Ni(dtbbpy)Br₂ (dtbbpy = 4,4'-di-tert-butyl-2,2'-bipyridine) in acetonitrile (0.1 M) in the presence of Kessil light (390 nm) resulted in isolation of the product **3a** in 87% yield (Table 1, entry 1). Using benzophenone **A** and 4,4'-dimethoxybenzophenone **C** observed a slight reduction in the yield (Table 1, entries 2 and 3), while using ketone **D** produced a comparable yield (Table 1, entry 4) with ketone **B**.¹⁸ Because of the commercial availability and inexpensive nature of ketone **B**, further optimization reactions proceeded with ketone **B**. When we decreased the loading of ketone catalyst and nickel catalyst and employed different bipyridine ligands, we observed a slightly lower yield of the product **3a** (see the Supporting Information). By employing different solvents (EtOAc, DMF) and amines (Et₃N and DIPEA), we observed moderate to good yields of the products (Table 1, entries 5–8). Interestingly, the presence of other amines, such as Hantzsch ester, 1,4-diazabicyclo[2.2.2]octane (DABCO), and TMP (2,2,6,6-tetramethylpiperidine), did not lead to any product formation (Table 1, entries 9–11). Finally, controlled reactions clearly indicate that all components, such as ketone, NiBr₂(dtbbpy), amine, and light are necessary for the product formation (Table 1, entries 12–15).

With the suitable optimized conditions in hand, we next evaluated the substrate scope of the transformation by employing a wide range of unactivated alkyl iodides and (hetero)aryl bromides. As shown in Scheme 2, a variety of secondary unactivated iodoalkanes were coupled with aryl bromides (**2a**, **2q**, and **2k**) and afforded the corresponding

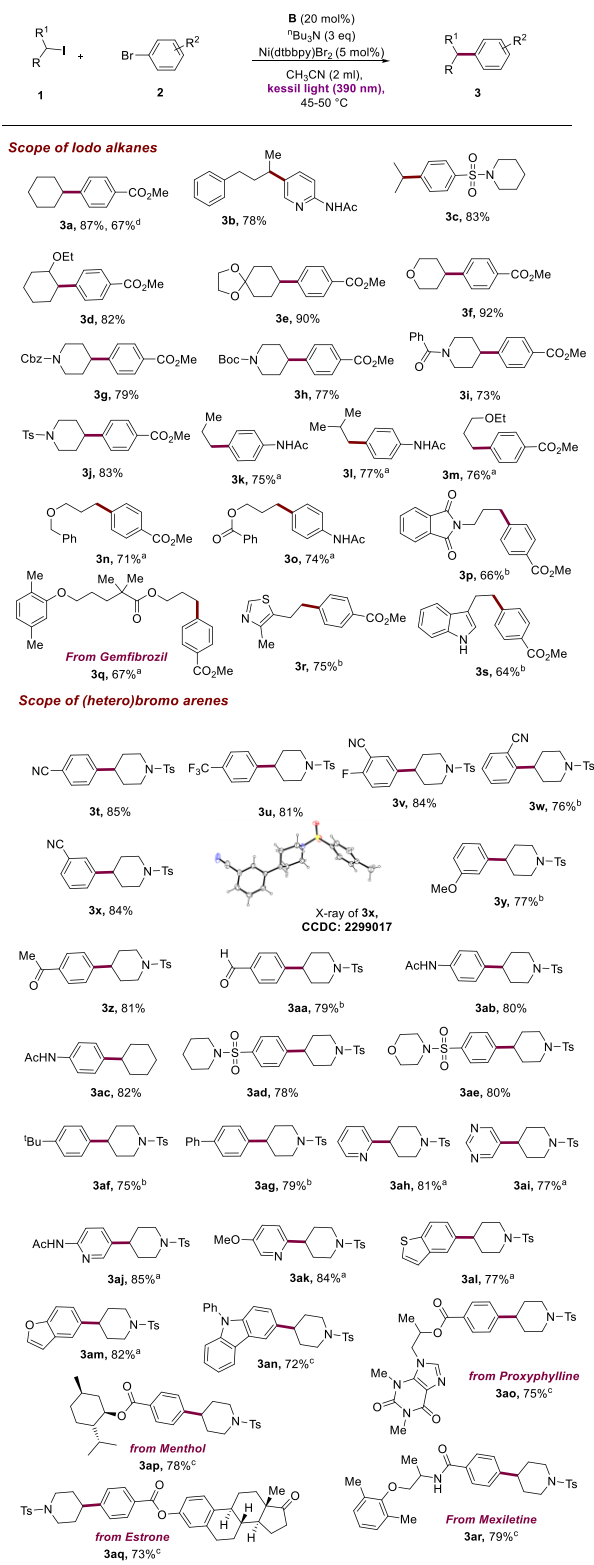
Table 1. Optimization of the Reaction Conditions^a

entry	optimization of reaction parameters	3a (%) ^b
1	none	94(87) ^c
2	using A instead of B	85
3	using C instead of B	78
4	using D instead of B	94
5	EtOAc as a solvent	65
6	DMF as a solvent	71
7	using DIPEA	76
8	using Et ₃ N	66
9	using Hantzsch ester	0
10	using DABCO	0
11	using TMP	0
12	without ^t Bu ₃ N	0
13	without light	0
14	without Ni(dtbbpy)Br ₂	0
15	without ketone	0

^aReaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), **B** (20 mol%), and CH₃CN (0.1 M) at 45–50 °C, 2 h. ^bNMR yields using benzyl benzoate as an internal standard. ^cIsolated yield. TMP = –2,2,6,6-tetramethylpiperidine.

coupling products (**3a–3c**) in good to excellent yields (78–87%). Secondary iodoalkanes containing an ether moiety were coupled with methyl 4-bromobenzoate **2a** in excellent yields (**3d–3f**, 82–92%). Also, it is noteworthy to mention that no competing HAT byproducts were observed in our reaction conditions. Medicinally relevant *N*-protected (*N*-Boc, *N*-Cbz, *N*-Bz, and *N*-Ts) 4-iodopiperidines were converted to secondary alkyl radical and efficiently intercepted with nickel catalysis in our methodology to afford corresponding products (**3g–3j**) in good yields (73–83%). Primary alkyl iodides containing different functional groups, such as alkyl ether, benzylic ether, ester, and amide, were proven to be excellent coupling partners in our reaction conditions and reacted with aryl bromides (**2a**, **2j**) to result in desired products in good yields (**3k–3p**, 66–77%). A medicinally relevant alkyl iodide derived from gemfibrozil, 4-methyl-5-thiazolethanol (used in kinase inhibitors), and tryptophol were efficiently coupled with aryl bromide **2a** in our conditions and led to the desired products **3q**, **3r**, and **3s**, respectively, in 64–75% yield.

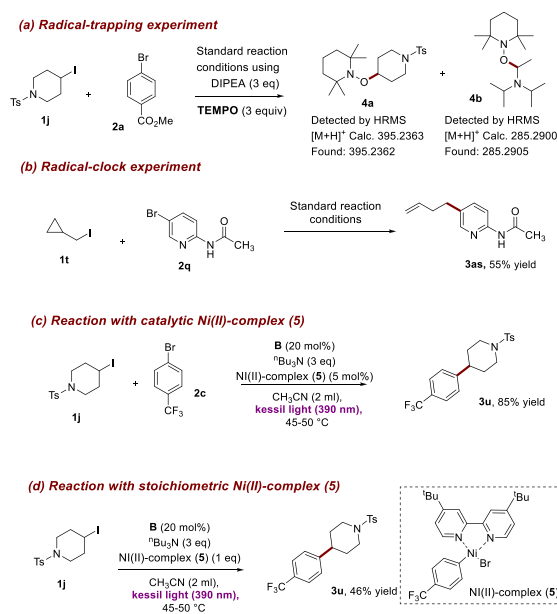
Next, we turned our attention to the scope of the (hetero)aryl bromides. *para*-, *meta*-, and *ortho*-substituted electron-poor aryl bromides were efficiently reacted with iodoalkane (**1j**) in our catalysis and converted into the corresponding products (**3t–3y**) in excellent yields (76–85%). Aryl bromides bearing different functional groups, such as ketone, aldehyde, amides, and sulfonamides, were well tolerated (**3z–3ae**, 78–82%). Electron-donating aryl bromides reacted slowly in our reaction protocol, and desired coupling products (**3af–3ag**) were obtained in good yields (75–79%). Notably, electronically different (hetero)aryl bromides readily transformed into targeted coupling products in our photocatalytic conditions in good yields. For example, electron-

Scheme 2. Substrate Scope^e

^aFor 8 h. ^bFor 10 h. ^cReactions were carried out using 0.15 mmol of **1** and 0.1 mmol of **2** for 6 h. ^dReactions were carried out using 7.5 mmol of **1a** and 5 mmol of **2a** for 48 h. Isolated yields are an average of at least two independent runs. ^eReaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), ketone **B** (20 mol%), and CH₃CN (2 mL) at 45–50 °C, 4 h.

deficient six-membered (hetero)arylbromides, such as pyridines and pyrimidines, were efficiently converted into the desired coupling products (**3ah–3ak**, 77–85%). Moreover, electron-rich (hetero)aryl bromides, such as benzothiophene, benzofuran, and *N*-phenyl carbazole, proved to be suitable substrates for the process and led to the products (**3al–3an**) in good yields (72–82%). To further showcase the application of this protocol, we have synthesized some medically relevant aryl bromides derived from menthol, proxiphylline, estrone, and mexiletine, which were employed as coupling partners in our protocol to isolate the desired products (**3ao–3ar**) in good yields (73–79%).

With a decent substrate scope, next we carried out a few preliminary mechanistic studies to reveal the reaction pathway (Scheme 3). The ON-OFF experiment indicates the

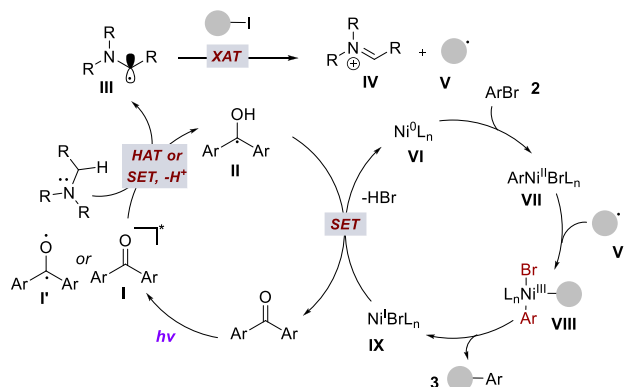
Scheme 3. Preliminary Mechanistic Studies of (a) Reaction in Presence of TEMPO, (b) Radical Clock Experiment, (c) Reaction with Catalytic Ni(II) Complex (**5**), and (d) Reaction with Stoichiometric Ni(II) Complex (**5**)

importance of continuous irradiation of light throughout the reaction (see the Supporting Information). In the presence of DIPEA and a radical trapping agent, such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), under the standard reaction conditions, a TEMPO-adducts **4a,4b** were detected by HRMS (Scheme 3a). A radical clock experiment using cyclopropyl methyl iodide (**1t**) in the presence of (hetero)aryl bromide **2q** led to ring-opening product **3as** in 55% yield (Scheme 3b). These experiments suggested the involvement of an alkyl radical and an α -amino alkyl radical in our catalysis. Finally, we carried out the reaction using catalytic and stoichiometric amounts of Ni(II) complex (**5**), as shown in Scheme 3c,d, which led to the product **3u** in 85% yield and 46% yield, respectively, according to ¹H NMR (see the Supporting Information for crude proton NMR) (Scheme 3c,d). These two experiments suggested the potential involvement of the Ni(II) intermediate in our catalysis. It is noteworthy to mention amines (Hantzsch ester, DABCO, and TMP) that are unable to be involved in a XAT process did not lead to the formation of product **3a** (Table 1, entries 9–

11), which might also suggest the role of the α -aminoalkyl radical in our catalysis.

On the basis of our preliminary mechanistic studies and previous literature precedents,^{46–51} we propose a tentative mechanism, as shown in Scheme 4. Initially, in the presence of

Scheme 4. Mechanistic Hypothesis



390 nm light, the ketone is converted to either photoexcited ketone (I) or diradical (I') intermediate. Next, the amine is converted to α -aminoalkyl radical either in the presence of diradical (I') intermediate through hydrogen atom transfer (HAT) or by single-electron transfer (SET) from amine to the photoexcited ketone (I) followed by deprotonation, which leads to the formation of α -aminoalkyl radical (II) and ketyl radical (III).^{46,47} Next, the generated α -aminoalkyl radical (III) engages in the halogen atom transfer (XAT) process with unactivated alkyl iodides to lead to the formation of an alkyl radical (V) intermediate. Concurrently, the Ni^0L_n complex, which might be generated from $\text{Ni}^{\text{II}}\text{Br}_2\text{L}_n$ complex ($E_{\text{red}}[\text{Ni}^{\text{II}}/\text{Ni}^0] = -1.2$ V versus SCE in DMF)⁵² through two successive single-electron transfer events from ketyl radical (II) [$E_{\text{red}}(\text{Ph}_2\text{CO}) = -2.20$ V vs Ag/AgNO₃ in MeCN],^{18,53} undergoes oxidative addition with aryl bromides to generate the $\text{ArNi}^{\text{II}}\text{Br}$ complex (VII). Then, the trapping of an alkyl radical (V) with the Ni(II) complex (VII) leads to a high-valence Ni(III) complex (VIII). Also, there is a possibility that alkyl radical is first trapped by the $\text{L}_n\text{Ni}(0)$ complex followed by oxidative addition with ArBr to afford the Ni(III) complex (VIII). However, the stoichiometric reaction with presynthesized Ni(II) complex (5) (Scheme 3d) suggests that the nickel cycle is more likely to proceed via Ni(II) intermediate. The Ni(III) complex (VIII) then, upon reductive elimination, furnishes the cross-coupling product (3) and the Ni(I) complex (IX). Finally, SET between ketyl radical (II) [$E_{\text{red}}(\text{Ph}_2\text{CO}) = -2.20$ V vs Ag/AgNO₃ in MeCN]⁵³ and $\text{Ni}^{\text{I}}\text{BrL}_n$ complex [$E_{\text{red}}(\text{Ni}^{\text{I}}/\text{Ni}^0) \approx -1.13$ V vs Ag/AgNO₃ in DMF]^{54,55} results in a recovery of both the propagating diaryl ketone and $\text{Ni}(0)\text{L}_n$ catalyst for the next catalytic cycle.

In conclusion, we developed an operationally simple and convenient protocol for the direct cross-electrophile coupling of unactivated alkyl iodides and (hetero)aryl bromides. The synergistic combination of diarylketone catalysis and XAT with nickel catalysis is the key to success. Given the wide substrate scope, good functional group tolerance, scale-up (gram-scale reaction) of the reaction, and the ability to engage medicinally relevant alkyl iodides and (hetero)aryl bromides, we believe that the reported findings are of interest to many synthetic chemists from academic research to chemical industry.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscorginorgau.3c00062>.

General experimental procedures; mechanism studies; and ¹H, ¹³C, and ¹⁹F NMR spectra of all compounds (PDF)

Accession Codes

CCDC 2299017 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Veera Reddy Yatham – School of Chemistry, Indian Institute of Science Education and Research, Thiruvananthapuram 695551, India; orcid.org/0000-0002-3967-5342; Email: reddy@iisertvm.ac.in

Authors

Alisha Rani Tripathy – School of Chemistry, Indian Institute of Science Education and Research, Thiruvananthapuram 695551, India

Akash Bisoyi – School of Chemistry, Indian Institute of Science Education and Research, Thiruvananthapuram 695551, India

Arya P – School of Chemistry, Indian Institute of Science Education and Research, Thiruvananthapuram 695551, India

Sreelakshmi Venugopal – School of Chemistry, Indian Institute of Science Education and Research, Thiruvananthapuram 695551, India

Complete contact information is available at:

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Author Contributions

#A.R.T. and A.B. contributed equally. CRediT: A.R.T., conceptualization (lead), data curation (lead), formal analysis (lead), investigation (lead), writing-review and editing (supporting); A.B., data curation (lead), formal analysis (lead), investigation (lead), writing-review and editing (supporting); A.P., data curation (supporting); S.V., data curation (supporting); V.R.Y., data curation (supporting), formal analysis (supporting), funding acquisition (lead), project administration (lead), resources (lead), supervision (lead), writing-original draft (lead).

Notes

The authors declare no competing financial interest.

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