# Rapid and Scalable Photocatalytic C($sp^2$)–C($sp^3$) Suzuki−Miyaura Cross-Coupling of Aryl Bromides with Alkyl Boranes

Ting Wan,[a,‡] Luca Capaldo,[a,‡] Jonas Djossou,[a] Angela Staffa,[a,b] Felix J. de Zwart,[c] Bas de Bruin,[c] Timothy Noël[a,*]

[a] *Flow Chemistry Group, van 't Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam, 1098 XH Amsterdam, The Netherlands;*

[b] *Merck Healthcare KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany*

[c] *Homogeneous, Supramolecular and Bioinspired Catalysis Group (HomKat), van 't Hoff Institute for Molecular Sciences (HIMS), Universiteit van Amsterdam (UvA), 1098 XH Amsterdam, The Netherlands;*

** Corresponding author: t.noel@uva.nl*

‡ These authors contributed equally to the work

## Abstract

In recent years, there has been a growing demand for drug design approaches that incorporate a higher number of $sp^3$-hybridized carbons, necessitating the development of innovative cross-coupling strategies to reliably introduce aliphatic fragments. Here, we present a novel and powerful approach for the light-mediated B-alkyl Suzuki−Miyaura cross-coupling between alkyl boranes and aryl bromides. Alkyl boranes can be easily generated via hydroboration from readily available alkenes, exhibiting excellent regioselectivity and enabling the selective transfer of a diverse range of primary alkyl fragments onto the arene ring. This methodology eliminates the need for expensive catalytic systems and sensitive organometallic compounds, operating efficiently at room temperature within just 30 minutes. Interestingly, our mechanistic studies reveal an unexpected mechanistic scenario that operates through transmetalation rather than alkyl radical formation, setting it apart from established metallaphotoredox protocols. Moreover, we demonstrate the advantageous translation of the present protocol to continuous-flow conditions, enhancing scalability, safety, and overall efficiency of the method. This versatile approach offers significant potential for accelerating drug discovery efforts by enabling the introduction of complex aliphatic fragments in a straightforward and reliable manner.

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

## Introduction

The development of highly efficient transition metal-catalyzed cross-coupling reactions has significantly benefited the synthesis of pharmaceuticals and agrochemicals. These transformations have demonstrated remarkable fidelity, but their success has led to an overreliance on producing structurally similar compounds, introducing bias in small molecule drug design. However, a new trend has emerged in recent years, aiming to design drugs with a greater number of $sp^3$-hybridized carbons that align more effectively with the 3D-shaped protein targets.[1] This approach enhances the selectivity and efficacy of drugs while minimizing the potential for off-target side effects. Consequently, these insights have sparked a growing need for novel synthetic methods capable of incorporating $sp^3$-fragments. However, despite notable advancements in the field, introducing $C(sp^3)$-hybridized fragments through transition-metal catalyzed cross-coupling reactions remains a significant challenge in organic synthesis.

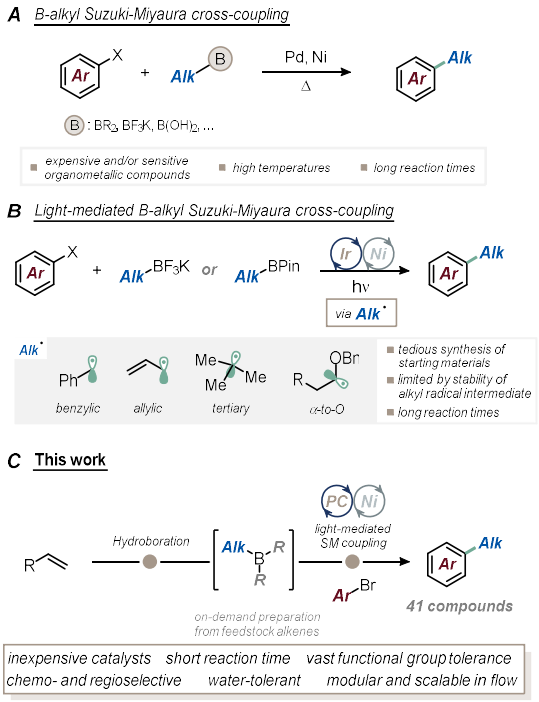
Amongst the different potential strategies, the B-alkyl Suzuki−Miyaura cross-coupling (SMC) reaction (Scheme 1A) presents a powerful method for creating $C(sp^3)$−$C(sp^2)$ bonds through the coupling of alkyl borane compounds with aryl or vinyl (pseudo)halides.[2,3] Notably, it offers advantages such as the mild and facile generation of the alkyl borane coupling partner (e.g., via hydroboration), great functional group tolerance,[4] manageable toxicity of boron-derived by-products, and the ability to perform the reaction under non-dry conditions. However, several limitations, including the requirement for expensive and/or sensitive organometallic compounds, high temperatures, and long reaction times, hinder the practical utility of these transformations in routine medicinal or process chemistry applications.[5] Consequently, the development of mild and selective B-alkyl SMC reactions becomes an attractive option to facilitate access to three-dimensional structures.

Recently, the utilization of light-mediated synthesis, employing photonic energy to trigger chemical reactions, has gained increasing significance in both academic and industrial organic synthetic settings.[6] This approach has revolutionized chemists' retrosynthetic thinking by providing a mild and controlled access to open-shell intermediates. Notably, elegant methods utilizing light-mediated approaches for B-alkyl SMC have been reported, primarily relying on single-electron transmetalation.[7-9] In these methods, a photocatalyst is employed to generate carbon-centered radicals from boron derivatives (such as trifluoroborate potassium salts and boronic esters), which are subsequently captured by a metal complex (typically nickel) to form the desired $C(sp^3)$−$C(sp^2)$ bond (Scheme 1B). However, a comprehensive analysis reveals certain limitations in their general applicability. For instance, these approaches are often more suitable for the arylation of stabilized alkyl radicals (e.g., benzylic, allylic, α-alkoxy- and α-acyloxyalkyl),[9-12] thereby restricting their utility for unactivated primary carbon centers. Additionally, some of these methods require extended irradiation times,[11] which can hinder their practical usefulness and scalability. It is important to note that while commercially available trifluoroborate salts and simple boronic acid ester derivatives exist, complex molecule derivatives are not readily accessible due to the use of harsh reaction conditions or metal catalysis required for their synthesis, which may not always be compatible with the diverse functionalities present in complex organic structures. Given these

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

considerations, the development of a general, practical and mild light-mediated B-alkyl SMC method would be of great value in diverse synthetic contexts, including total synthesis and medicinal chemistry. At the outset of our investigations, we identified alkyl boranes as captivating alkyl coupling partners, as they can be readily generated by hydroboration of commercially available alkenes. In addition, hydroboration exhibits the appealing attribute of remarkable regioselectivity, enabling reliable functionalization of the less hindered side of the carbon-carbon double bond (anti-Markovnikov). Interestingly, despite their widespread utilization in thermal chemistry,[2,13-20] the use of alkyl boranes in photocatalytic reactions has hitherto been overlooked. In this study, we present the convenient utilization of said alkyl boranes as versatile coupling partners, establishing a robust and scalable platform for constructing $C(sp^3)–C(sp^2)$ bonds via Suzuki–Miyaura cross-coupling (SMC), made possible by integrating photocatalysis and nickel catalysis (Scheme 1C). Our protocol specifically caters to the introduction of non-activated alkyl fragments, making it complementary to other metallaphotoredox strategies. The effectiveness of this coupling strategy is exemplified by successfully incorporating complex alkyl fragments derived from natural products. Interestingly, our mechanistic studies reveal a unique activation strategy that operates through polar transmetalation rather than alkyl radical formation, setting it apart from established metallaphotoredox protocols. Additionally, we demonstrate the potential of flow technology in realizing a scalable, safe and streamlined process, combining both the hydroboration and the light-mediated B-alkyl SMC reaction.[21]

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0




Scheme 1. A) The B-alkyl Suzuki−Miyaura cross-coupling is a powerful approach for the formation of C($sp^3$)-C($sp^2$) bonds. B) Light-mediated B-alkyl Suzuki−Miyaura cross-coupling reaction via single-electron transmetalation. C) This work.

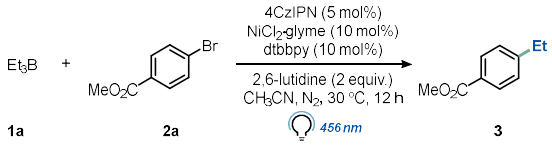
# Results

## Method optimization

We initiated our research by investigating the cross-coupling of commercially-available triethyl borane **1a** with methyl 4-bromobenzoate **2a** to yield alkyl arene **3**. Through a preliminary screening of various photocatalysts (Table 1, Entries 1−3) under blue light irradiation (λ = 456 nm), we discovered that the organic photocatalyst 4CzIPN outperformed the benchmark Ir-based photocatalyst used in previous reports on light-mediated B-alkyl SMC reactions.[7-9,22] In contrast, the highly oxidizing acridinium photocatalyst did not prove as effective (Table 1, Entry 3). Notably, even under non-dry conditions (Table 1, Entry 4), we obtained product **3** with only a slight reduction in yield, which demonstrates the robustness of the protocol. Diminished yields were observed when using a sub-stoichiometric amount of the base or lower amounts of the alkyl borane (Table 1, Entries 5 and 6 , underscoring the significance of the base for efficient catalysis and confirming that only one of the alkyl groups transfers to nickel. Changing the nickel source minimally impacted the reaction, as nickel bromide delivered nearly identical yields (Table 1, Entry 7). Encouragingly, the reaction was found to be complete after 30 minutes of irradiation (Table 1, Entry 8). Extended irradiation times did not result in any detectable product decomposition, even after 3 hours of irradiation. Therefore, for the sake of generality, we established 3 hours as the ideal reaction time to carry out the reaction scope. Notably, the transformation proceeded smoothly even with reduced loading of both the photocatalyst and the nickel catalyst (Table

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

1, Entry 9). The aforementioned results highlight the robustness of this B-alkyl SMC methodology, which is particularly useful to facilitate process chemistry applications.[23] Next, several control experiments were conducted, demonstrating that the absence of either the photocatalyst or the nickel catalytic system resulted in no product formation (Table 1, Entries 10 and 11). Furthermore, omission of the base yielded only traces of **3** (Table 1, Entry 12); a similar result was obtained when performing the reaction at elevated temperatures in the dark (Table 1, Entry 13). Additional details and optimization experiments can be found in the Supplementary Information.



1a 2a 3

| Entry | Variation from conditions | Yield (3)[a] |
|---|---|---|
| **1** | *None* | 93 |
| **2** | $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (5 mol%) as the photocatalyst | 82 |
| **3** | Mes-AcrClO$_4$ (5 mol%) as the photocatalyst | 23 |
| **4** | In the presence of $H_2O$ (10 equiv.) | 85 |
| **5** | 2,6-lutidine (0.2 equiv.) | 21 |
| **6** | $Et_3B$ (0.33 equiv.) | 33 |
| **7** | $NiBr_2$·glyme (10 mol%) | 90 |
| **8** | Reaction time: 3h | 92 |
| **9** | 4CzIPN (2 mol%), $NiCl_2$·glyme (5 mol%), dtbbpy (5 mol%), 3 h | 82 |
| **10** | No photocatalyst | n.d. |
| **11** | No $NiCl_2$·glyme nor dtbbpy | n.d. |
| **12** | No 2,6-lutidine | 8[b] |
| **13** | No light, T: 80 °C | 7[c] |

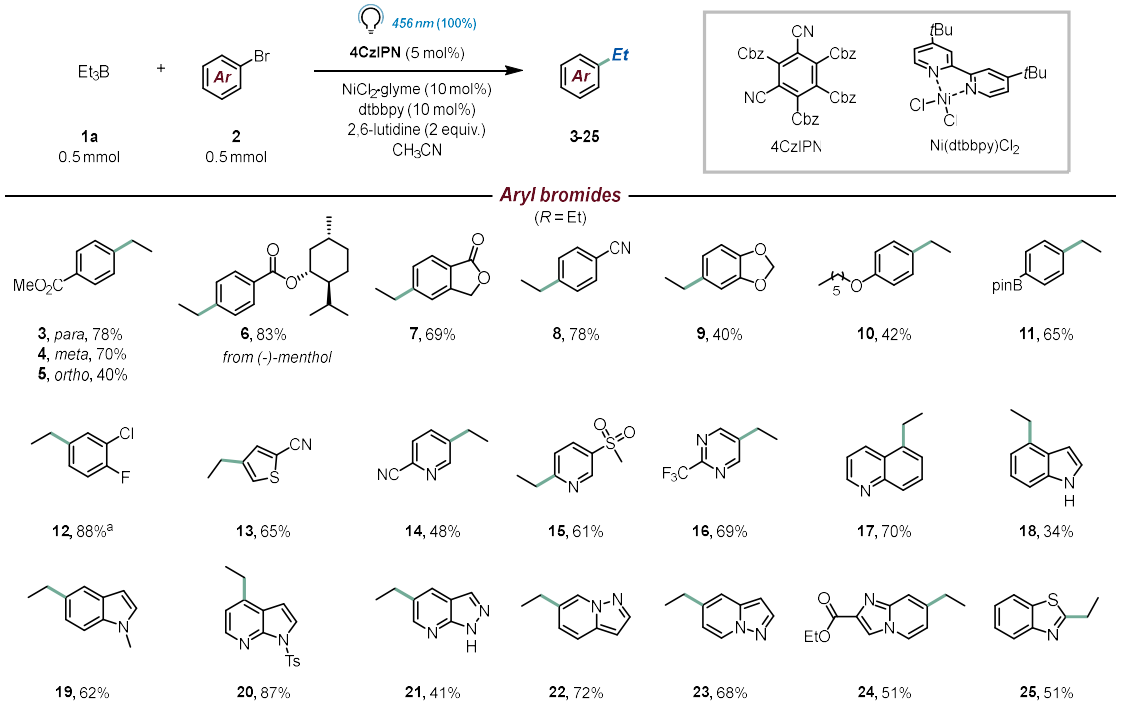
**Table 1**. [a] Yields determined by $^1$H-NMR, $CH_2Br_2$ as external standard. [b] 74% recovery of starting material. [c] 63% recovery of starting material. 4CzIPN: 2,4,5,6-tetrakis(9H-carbazol-9-yl) isophthalonitrile. Mes-AcrClO$_4$: 9-Mesityl-10-methylacridinium perchlorate. Dtbbpy: 4,4′-di-*tert*-butyl-2,2′-dipyridyl. PC: photocatalyst. n.d.: not detected.

## Reaction Scope

Having established optimal reaction conditions (Table 1, Entry 8), our next objective was to assess the scope of the light-mediated B-alkyl SMC reaction (Scheme 2). As expected, aryl bromides with electron-withdrawing groups displayed favorable performance, resulting in good isolated yields for compounds **3**-**8** (40-78%). Regarding the substitution pattern on the aromatic ring (**3**-**5**), we observed that the presence of an ortho substituent led to lower yields. Subsequently, we shifted our attention to electron-rich aryl bromides, known for their reluctance to undergo oxidative addition by the nickel catalyst. Although challenging, we obtained satisfactory yields for compounds **9** and **10** (40-42%). The cross-coupling reaction also tolerated a BPin functional group (compound **11**, 65%), providing opportunities for further diversification. Notably, this particular substrate would have posed inherent difficulties for previously developed approaches (Scheme 1B).[8,9] When subjected to the optimized reaction conditions, 4-bromo-2-chloro-1-fluorobenzene underwent functionalization solely at the C−Br

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

bond, yielding compound **12** in excellent yield (88%). Recognizing the significance of heterocycles in pharmaceutical compound synthesis, we applied our reaction conditions to a wide range of heteroaryl bromides, including pyridines, quinolines, indoles, indazoles, and pyrazolopyridines. All of these substrates yielded the expected products in good to excellent yields (**13**-**25**, 34-87%).




**Scheme 2**. Survey of the aryl bromides. Conditions: 4CzIPN (5 mol %), $NiCl_2$·glyme (10 mol %), dtbbpy (10 mol %), 2,6-lutidine (2 equiv.), **1a** (1.0 equiv.) and **2** (0.5 mmol) in $CH_3CN$ (0.1 M). The solution was $N_2$-bubbled and subsequently irradiated with a blue LED (λ = 456 nm) for 3 hours (see Section 7 in Supplementary Information). Yields reported are after isolation, unless otherwise stated. [a] NMR yield is given because of the volatility of the compound.

Next, our focus shifted to the alkyl borane coupling partner, which can be conveniently synthesized on demand through the hydroboration of readily available or easily prepared alkenes with $BH_3$ (known as Brown hydroboration).[24] Upon subjecting alkyl boranes derived from 1,1-disubstituted olefins to the optimized conditions (referred to as Method A in Scheme 3), the desired products were obtained with excellent yields and exhibited high anti-Markovnikov regioselectivity (54-77%, > 20:1 regioisomeric ratio, **26**-**27**). Remarkably, an allyl chloride could also participate in the transformation, resulting in a 47% yield of product **28**. Alkyl boranes derived from cycloalkenes underwent smooth arylation, affording products **29** and **30** in very good yields (67-83%), thus demonstrating the compatibility of secondary carbons with the transformation. Notably, even an estradiol derivative served as a suitable substrate under these conditions, leading to the isolation of compound **31** with a 43% yield and exquisite regioselectivity.

As anticipated, regioselectivity issues arose when sterically unhindered alkenes with long aliphatic chains were subjected to the conditions of Method A. For instance, ether **32** could be obtained in a good

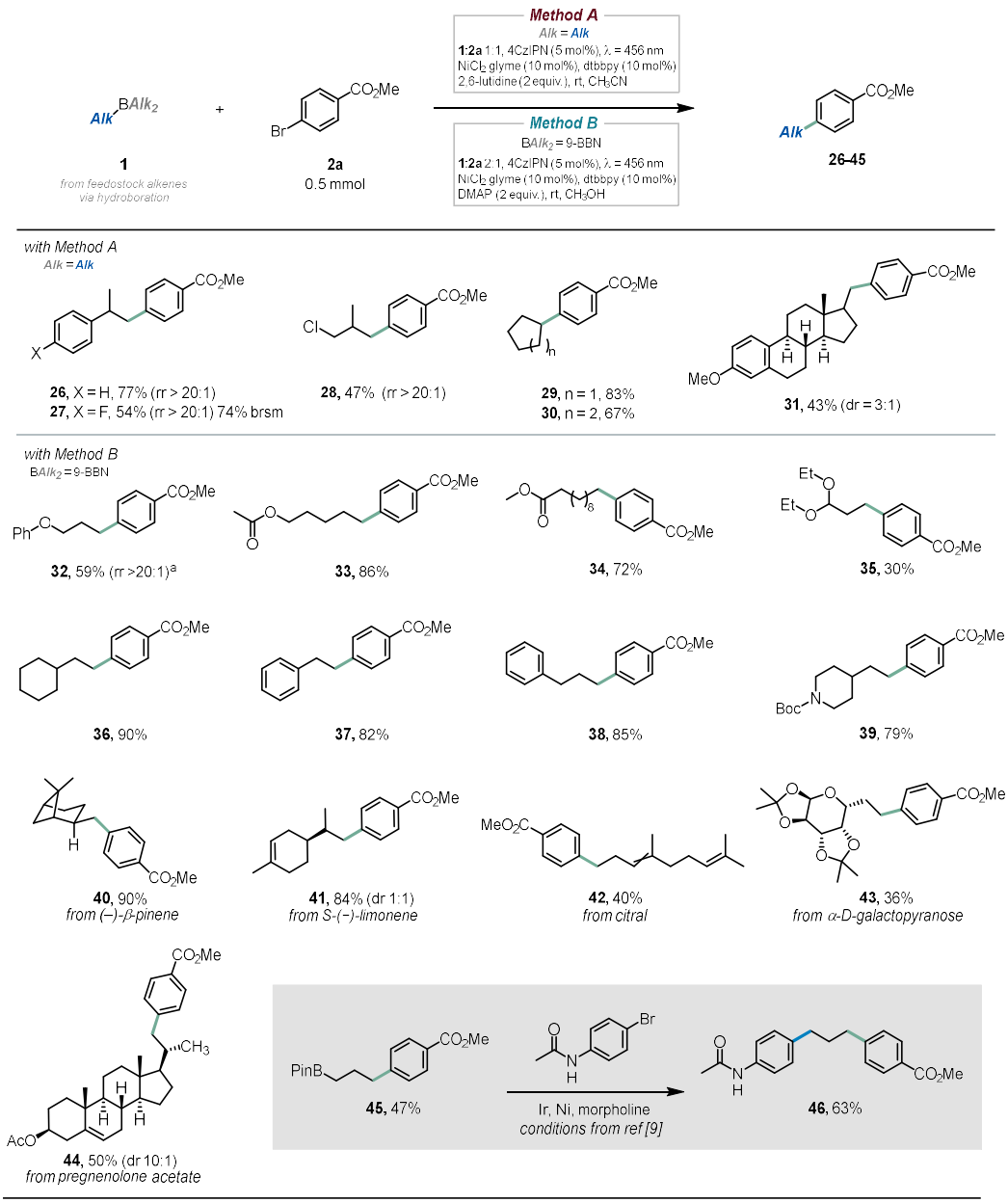
https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

yield, albeit as a mixture of regioisomers (74%, rr 10:1). To address this challenge, we capitalized on existing knowledge of hydroboration methods,[25] and introduced 9-BBN as the hydroboration agent (referred to as Method B, see also Section 7.3 in the Supplementary Information). Armed with this new set of conditions, we successfully achieved excellent regioselectivity in the synthesis of compound **32** (59%, rr >20:1). Similarly, a series of long-chain alkenes incorporating multiple functional groups proved amenable to these conditions, yielding the expected products as single regioisomers with excellent yields (**33-34**, 72-86%). The presence of an acetal functionality was also tolerated, leading to the formation of product **35** in a 30% yield. Moreover, the transformation worked well with vinylcyclohexene, affording compound **36** in an excellent yield of 90%. Intriguingly, when phenyl-containing alkenes were employed as substrates, the formation of alkylarenes **37** and **38** was observed (82-85%), while significant migration of the nickel center to the benzylic position was not detected.[26] Once again, this underscores the potential of our methodology for functionalizing alkyl chain termini.

Our focus then shifted towards the functionalization of biologically and medicinally relevant scaffolds. Interestingly, protected piperidine was well tolerated within the protocol. Specifically, when 4-vinyl piperidine was subjected to the optimized reaction conditions (Method B), compound **39** was obtained in a 79% yield after isolation. The functionalization of β-pinene proceeded smoothly, providing a single diastereomer in excellent yield (**40**, 90%). The hydroarylation of (−)-limonene resulted in a mixture of diastereomers (**41**, 84%, dr 1:1). However, the regioselectivity exhibited was remarkable, functionalizing only the exocyclic olefin. A similar trend was observed for the citral-derived alkene, wherein selective functionalization of the primary olefin position occurred (**42**, 40%), leaving the more substituted olefins untouched. Finally, a sugar and a glucocorticoid derivative underwent efficient functionalization, providing the targeted products **43** (36%) and **44** (50%, dr 10:1).

As a final observation, we found that utilizing the pinacol ester of allyl boronic acid as the substrate in the hydroboration-cross-coupling process resulted in a 47% yield for the isolated product **45**. This outcome underscores the tolerance of our method towards BPin functional groups. Product **45** is highly compatible with the amino radical transfer strategy recently reported by scientists at Sanofi.[8] Interestingly, when subjected to the conditions outlined in their study, we successfully obtained product **46** with a yield of 63%. This consecutive transformation highlights the orthogonal nature of these two approaches.

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0




**Scheme 3**. Survey of the alkyl boranes. Conditions for Method A: 4CzIPN (5 mol %), $NiCl_2$·glyme (10 mol %), dtbbpy (10 mol %), 2,6-lutidine (2 equiv.), **1** (1.0 equiv.) and **2** (0.5 mmol) in $CH_3CN$ (0.1 M). The solution was $N_2$-bubbled and irradiated with a blue LED (λ = 456 nm) for 3 hours. Conditions for Method B: 4CzIPN (5 mol %), $NiCl_2$·glyme (10 mol %), dtbbpy (10 mol %), 4-dimethylaminopyridine (2 equiv.), **1** (2.0 equiv.) and **2** (0.5 mmol) in $CH_3OH$ (0.1 M). The solution was $N_2$-bubbled and irradiated with a blue LED (λ = 456 nm) for 3 hours. Alkyl boranes were generated on-demand from the corresponding alkenes via hydroboration with $BH_3$ (for Method A) or 9-BBN (for Method B). Yields reported are after isolation. [a] with Method A: 74%, rr 10:1. See Section 9 in the Supplementary Information for additional details. rr: regioisomeric ratio. dr: diastereomeric ratio. Brsm: based on recovered starting material.

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

**Mechanistic investigation**

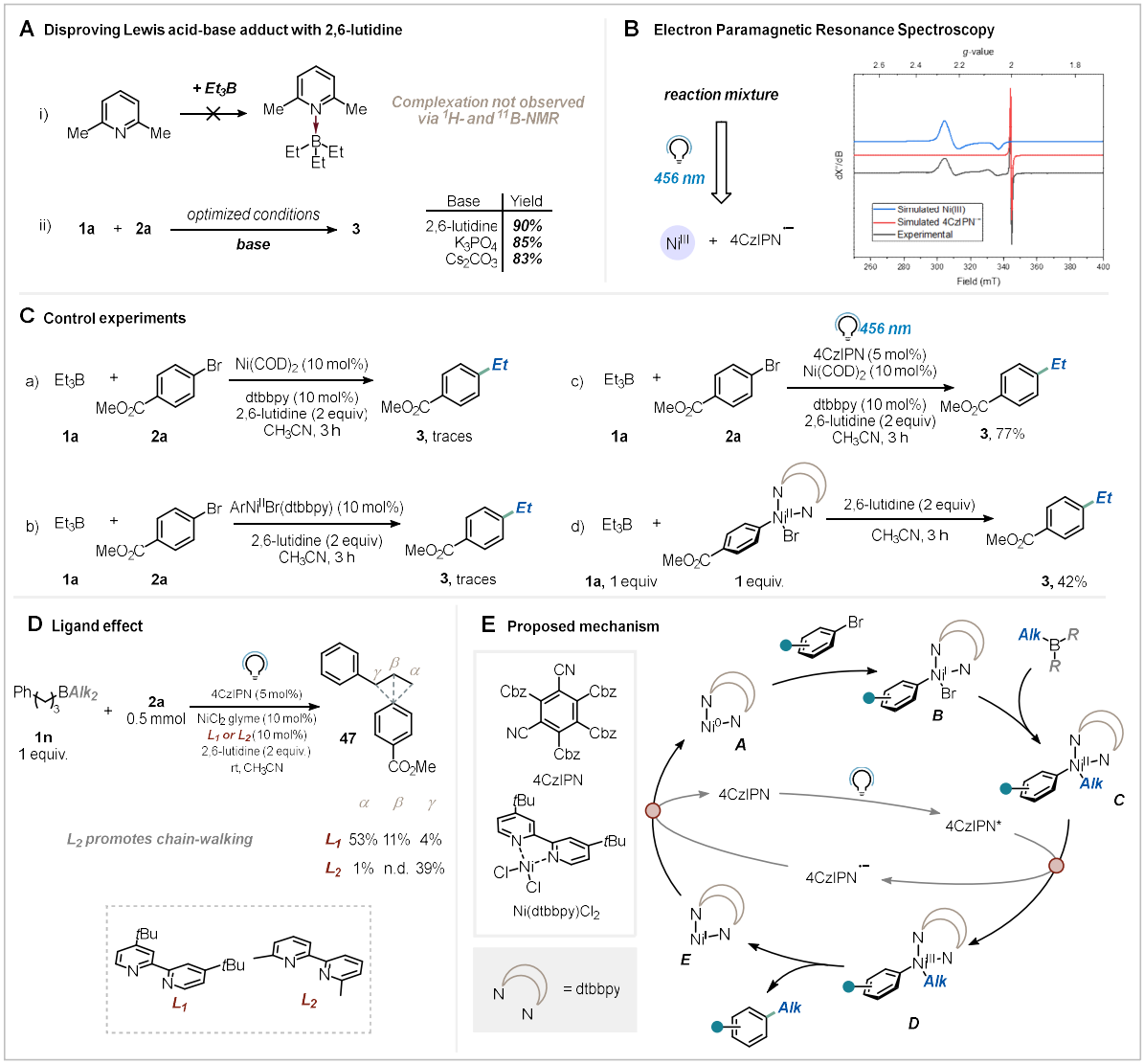
In order to gain insights into the mechanistic aspects of the developed photocatalytic B-alkyl SMC, a series of experiments were conducted. First, we investigated whether alkyl boranes formed "ate" complexes with 2,6-lutidine. However, it is worth noting that 2,6-lutidine is considered a weak Lewis base, which raised doubts about direct complexation of the borane by the heterocycle.[22] To investigate this further, titration experiments were performed and followed both via $^{1}$H-NMR and $^{11}$B-NMR. Surprisingly, no apparent NMR signal shifts were observed when mixing 2,6-lutidine and triethyl borane (1:1), providing initial evidence against complexation (Scheme 4A). Additionally, when the organic base was replaced with inorganic bases, such as $K_3PO_4$ and $Cs_2CO_3$, very similar yields were obtained (85% and 83%, respectively), thus indicating the absence of any specific interaction between 2,6-lutidine and the borane (Scheme 4A).

We proceeded to investigate whether alkyl radicals are generated under our reaction conditions. To this end, we employed Electron Paramagnetic Resonance (EPR) spectroscopy at low temperature (10 K). Inside a J-Young EPR tube, the catalytic mixture was irradiated with 456 nm light for 30 seconds and then rapidly cooled in liquid nitrogen while still under irradiation, allowing for the acquisition of the spectrum presented in Scheme 4B (black trace). Analysis of the spectrum revealed two doublet components, corresponding to an isotropic organic radical with $g_{iso}$=2.002, derived from the photocatalyst, and a nearly axial metal-centered radical with $g_{xyz}$=[2.265 2.23 2.047].[27] The g-values of the axial signal closely matched those reported for other $Ni^{III}$ species in literature, strongly suggesting the formation of a $Ni^{III}$-centered radical upon irradiation.[28-31] In contrast, despite several attempts, we were unable to detect or trap ethyl radicals derived from **1a** (see Section 6.6 in Supplementary Information). Furthermore, several representative reactions were conducted in the presence of an excess of butylated hydroxytoluene (BHT), a well-known radical scavenger. Remarkably, the presence of BHT did not impede the cross-coupling reaction, and the expected products were obtained with unaltered yields (see Section 6.5 in Supplementary Information). Collectively, these results point towards a more conventional scenario based on polar transmetalation to the nickel center, rather than single-electron transmetalation.

The determination of the quantum yield of the process via ferrioxalate actinometry[32,33] revealed a value of 0.27, indicating that a self-sustained $Ni^{I/III}$ cycle[32] is unlikely to be the primary scenario for this B-alkyl SMC. Moreover, we observed that the reaction did not proceed in the absence of light, even after a short initial irradiation period of 3 minutes. To gain further insights into the dual catalytic system, we conducted additional experiments (Scheme 4C). When the reaction was performed under inert conditions, replacing the photocatalyst/$Ni^{II}$ system with $Ni(COD)_2$ (10 mol%) and excluding light, only traces of product **3** were obtained. Similarly, when the reaction was carried out in the absence of light and photocatalyst, using 10 mol% of the oxidative addition complex Ar–$Ni^{II}$–Br as the active metal species, the result was again negligible. Conversely, when the $Ni(COD)_2$ experiment was performed in

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

the presence of the photocatalyst and light, reactivity was restored, yielding a 77% $^{1}$H-NMR yield of product **3**. Furthermore, in a stoichiometric experiment, where 1 equivalent of the oxidative addition complex Ar–Ni$^{II}$–Br was stirred in the dark without photocatalyst for 3 hours, a 42% $^{1}$H-NMR yield of compound **3** was obtained. When substrate **1n** was subjected to our optimized conditions, we detected traces of a product resulting from chain-walking via reiterated β-hydride elimination and migratory insertion (compound **47γ**). Notably, when ligand **L2**, known to promote chain-walking,[34,35] was employed, selectivity was completely shifted towards the benzylic position (Scheme 4D). This observation supports our proposal that chain-walking occurs prior to reductive elimination, aligning well with the control experiments mentioned earlier. Taken together, these experiments provide evidence that the photocatalytic system plays a crucial role in enhancing nickel catalysis, likely by accelerating the reductive elimination step.




**Scheme 4.** Mechanistic investigation. CW X-Band EPR spectrum of catalytic mixture in 5:1 PrCN:MeCN at 10 K, after 30 s irradiation with blue light (Mw Freq= 9.6503 GHz). Experimental spectrum (black), simulated

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

spectrum $Ni^{III}$ (blue, S=1/2, g=[2.265 2.23 2.047]), simulated spectrum 4CzIPN radical anion (red, S=1/2, $g_{iso}$=2.002). $L_1$: 4,4′-di-*tert*-butyl-2,2′-dipyridyl ; $L_2$: 6,6′-dimethyl-2,2′-dipyridyl.

To further explore the reaction kinetics, we conducted an investigation into the dependence of the initial rate on various factors, including substrate concentration, nickel catalyst concentration, and base concentration in the reaction between **1a** and **2a**. The progress of the reaction and the formation of product **3** were monitored using $^1$H-NMR. This study revealed that, under the optimized conditions, the reaction operates in a photon-limited regime, indicating that the rate is primarily determined by the availability of photons. Intriguingly, the reaction exhibited zeroth order kinetics with respect to all other reaction components. A related Hammett plot[36] supported the conclusion of a photon-limited regime (see Section 6.3 Supplementary Information). It is worth noting that the rate-limiting step shifted to oxidative addition only in the case of electron-rich aryl bromides, such as 4-bromoanisole.

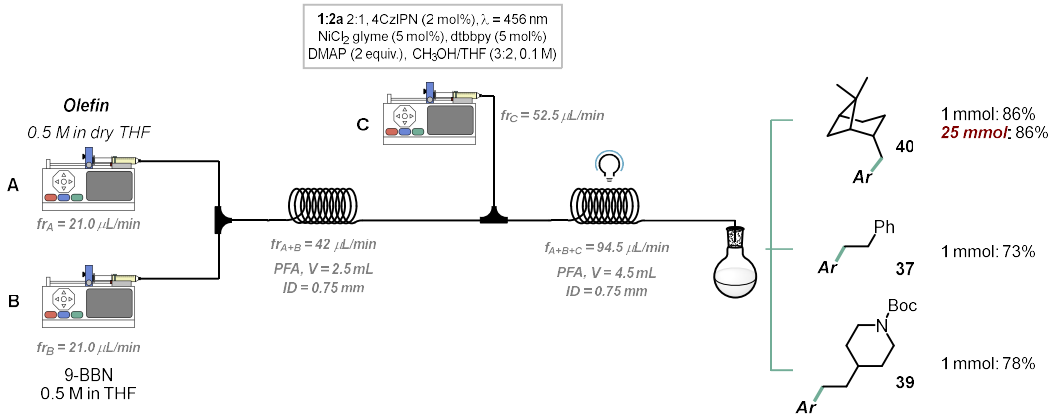
Based on our experimental findings and the relevant literature, we propose a mechanistic scenario outlined in Scheme 4E. Initially, the aryl bromide is activated through oxidative addition by low-valent nickel species (**A**), leading to the formation of an aryl–$Ni^{II}$ species (**B**). Subsequently, this complex undergoes transmetalation with the alkyl borane, resulting in the formation of species **C**.[3] The excited state of the photocatalyst is reductively quenched, generating a high-valent $Ni^{III}$ species (**D**), which readily undergoes reductive elimination to yield the desired alkyl arene and $Ni^{I}$ species **E**.[7,29,37] Finally, the reduced photocatalyst closes the catalytic cycle by reducing **E** back to **A** ($E(PC/PC_{red})$ = -1.21 V vs SCE;[38] $E(Ni^{I}/Ni^{0})$ > -1.1 vs SCE[39]).

**Experiments in continuous flow**

Based on the observation of a photon-limited regime in our batch reactions, it becomes apparent that microreactor technology, with its higher photon fluxes, offers significant advantages in terms of rate acceleration. This, in turn, leads to increased throughput and improved scalability of the chemistry.[40-42] Moreover, by integrating the hydroboration step with the metallaphotoredox B-alkyl SMC reaction, the alkyl boranes can be generated on demand and immediately utilized, thereby reducing the handling, purification, and storage requirements for these coupling partners.[43-47] Following a brief optimization of reaction conditions on a 0.1 mmol scale (as described in Section 5.3 of the Supplementary Information), we successfully connected the hydroboration and B-alkyl SMC steps. To achieve this, two syringe pumps were employed, each containing a 0.5 M THF solution of β-pinene and a commercially available 0.5 M THF solution of 9-BBN, respectively. The solutions were combined in a PEEK T-mixer, and the resulting reaction mixture was introduced into a 2.5 mL PFA capillary ($t_R$ = 60 min) maintained at an ambient temperature of 22 °C. Subsequently, the stream containing the alkyl borane was merged with another stream containing the necessary reactants for the B-alkyl SMC reaction and introduced into a flow photoreactor ($t_R$ = 48 min, see Section 7.4 in Supplementary Information).

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

By employing this streamlined flow process, compound **40** was obtained with an 86% yield after isolation through column chromatography. It is noteworthy that the use of flow conditions allowed for a reduction in both the nickel (5 mol%) and photocatalyst loading (2 mol%), while still yielding comparable results to the batch process. Importantly, this flow approach facilitated easy scalability of the transformation to a 25 mmol scale without the need for reoptimization of the reaction conditions. Finally, we applied this flow approach to other representative scaffolds (**37** and **39**), resulting in good yields ranging from 73% to 86% (Scheme 5).




**Scheme 5.** Translation to continuous-flow conditions (see GP5 in the Supplementary Information) and scale-up (see Section 8 in the Supplementary Information). Ar: (4-$CO_2Me$)-$C_6H_4$.

## Conclusions

We have developed a fast, robust, and scalable photocatalytic B-alkyl Suzuki−Miyaura cross-coupling method that overcomes the limitations of previous approaches. Our protocol allows for room temperature reactions, utilizes an inexpensive catalytic system, and can be completed in just a few minutes. By employing alkyl boranes as alkyl fragments, we have addressed the challenge of arylation at primary C($sp^3$) centers, expanding the synthetic possibilities of this methodology. The straightforward synthesis of alkyl boranes via hydroboration enables greater synthetic creativity and makes our approach particularly suitable for functionalizing biologically relevant alkyl substrates in medicinal chemistry or total synthesis. Notably, our reaction operates through conventional transmetalation rather than alkyl radical formation, distinguishing it from other metallaphotoredox protocols. Furthermore, we have demonstrated the benefits of continuous-flow technology in terms of scalability, modularity, and reliability. In conclusion, our versatile and efficient method for C($sp^3$)–C($sp^2$) bond formation is poised to find rapid adoption in pharmaceutical route scouting campaigns, offering accelerated drug development opportunities through its inherent modularity and wide availability of starting materials.

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

## Author contributions

L.C. and T.W. contributed equally in the conceptualization of the project and performed the optimization experiments and the reaction scope. F.J.d.Z. and B.d.B. carried out and analyzed the EPR experiments. L.C., J.D. and A.S. performed experiments on the mechanistic investigation and the reaction scope. L.C. and T.N. directed the project and wrote the manuscript with input from all co-authors.


## Acknowledgements

T.W. has received support from the China Scholarship Council (CSC) for her PhD studies. J.D. and T.N. thank the European Union for funding (GreenDigiPharma, No. 101073089, J.D. and T.N.). We also wish to acknowledge Dr. Dietrich Böse for fruitful discussions (Merck Healthcare KGaA).


## References


1 Lovering, F., Bikker, J. & Humblet, C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **52**, 6752-6756, doi:10.1021/jm901241e (2009).

2 El-Maiss, J. *et al.* Recent Advances in Metal-Catalyzed Alkyl–Boron (C(sp3)–C(sp2)) Suzuki-Miyaura Cross-Couplings. *Catalysts* **10**, doi:10.3390/catal10030296 (2020).

3 Chemler, S. R., Trauner, D. & Danishefsky, S. J. The B-Alkyl Suzuki-Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis. *Angew. Chem. Int. Ed.* **40**, 4544-4568, doi:10.1002/1521-3773(20011217)40:24<4544::Aid-anie4544>3.0.Co;2-n (2001).

4 Jana, R., Pathak, T. P. & Sigman, M. S. Advances in transition metal (Pd, Ni, Fe)-catalyzed cross-coupling reactions using alkyl-organometallics as reaction partners. *Chem. Rev.* **111**, 1417-1492, doi:10.1021/cr100327p (2011).

5 Brown, D. G. & Bostrom, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **59**, 4443-4458, doi:10.1021/acs.jmedchem.5b01409 (2016).

6 Noël, T. & Zysman-Colman, E. The promise and pitfalls of photocatalysis for organic synthesis. *Chem Catal.* **2**, 468-476, doi:10.1016/j.checat.2021.12.015 (2022).

7 Tellis, J. C., Primer, D. N. & Molander, G. A. Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. *Science* **345**, 433-436, doi:10.1126/science.1253647 (2014).



https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

8 Speckmeier, E. & Maier, T. C. ART horizontal line An Amino Radical Transfer Strategy for C(sp(2))-C(sp(3)) Coupling Reactions, Enabled by Dual Photo/Nickel Catalysis. *J. Am. Chem. Soc.* **144**, 9997-10005, doi:10.1021/jacs.2c03220 (2022).

9 Lima, F. *et al.* Visible Light Activation of Boronic Esters Enables Efficient Photoredox C(sp2)–C(sp3) Cross-Couplings in Flow. *Angew. Chem. Int. Ed.* **55**, 14085-14089, doi:10.1002/anie.201605548 (2016).

10 Primer, D. N., Karakaya, I., Tellis, J. C. & Molander, G. A. Single-electron transmetalation: an enabling technology for secondary alkylboron cross-coupling. *J. Am. Chem. Soc.* **137**, 2195-2198, doi:10.1021/ja512946e (2015).

11 Tellis, J. C., Amani, J. & Molander, G. A. Single-Electron Transmetalation: Photoredox/Nickel Dual Catalytic Cross-Coupling of Secondary Alkyl beta-Trifluoroboratoketones and -esters with Aryl Bromides. *Org. Lett.* **18**, 2994-2997, doi:10.1021/acs.orglett.6b01357 (2016).

12 Tellis, J. C. *et al.* Single-Electron Transmetalation via Photoredox/Nickel Dual Catalysis: Unlocking a New Paradigm for sp(3)-sp(2) Cross-Coupling. *Acc. Chem. Res.* **49**, 1429-1439, doi:10.1021/acs.accounts.6b00214 (2016).

13 Nicolaou, K. C., Bulger, P. G. & Sarlah, D. Palladium-catalyzed cross-coupling reactions in total synthesis. *Angew. Chem. Int. Ed.* **44**, 4442-4489, doi:10.1002/anie.200500368 (2005).

14 Baumgartner, Y. & Baudoin, O. One-Pot Alkene Hydroboration/Palladium-Catalyzed Migratory Suzuki–Miyaura Cross-Coupling. *ACS Catal.* **10**, 10508-10515, doi:10.1021/acscatal.0c02755 (2020).

15 Sun, H.-X., Sun, Z.-H. & Wang, B. B-Alkyl Suzuki–Miyaura cross-coupling of tri-n-alkylboranes with arylbromides bearing acidic functions under mild non-aqueous conditions. *Tetrahedron Lett.* **50**, 1596-1599, doi:10.1016/j.tetlet.2009.01.090 (2009).

16 Saito, B. & Fu, G. C. Alkyl-alkyl suzuki cross-couplings of unactivated secondary alkyl halides at room temperature. *J. Am. Chem. Soc.* **129**, 9602-9603, doi:10.1021/ja074008l (2007).

17 Miyaura, N., Ishiyama, T., Ishikawa, M. & Suzuki, A. Palladium-catalyzed cross-coupling reactions of B-alkyl-9-BBN or trialkylboranes with aryl and 1-alkenyl halides. *Tetrahedron Lett.* **27**, 6369-6372, doi:10.1016/s0040-4039(00)87811-9 (1986).

18 Chatupheeraphat, A. *et al.* Ligand-Controlled Chemoselective C(acyl)-O Bond vs C(aryl)-C Bond Activation of Aromatic Esters in Nickel Catalyzed $C(sp^2)$-$C(sp^3)$ Cross-Couplings. *J. Am. Chem. Soc.* **140**, 3724-3735, doi:10.1021/jacs.7b12865 (2018).

19 Hu, X., Di Franco, T. & Boutin, N. Suzuki-Miyaura Cross-Coupling Reactions of Unactivated Alkyl Halides Catalyzed by a Nickel Pincer Complex. *Synthesis* **45**, 2949-2958, doi:10.1055/s-0033-1338544 (2013).

20 Di Franco, T., Stojanovic, M., Keller, S. C., Scopelliti, R. & Hu, X. A Structure-Activity Study of Nickel NNN Pincer Complexes for Alkyl-Alkyl Kumada and Suzuki-Miyaura Coupling Reactions. *Helv. Chim. Acta* **99**, 830-847, doi:10.1002/hlca.201600165 (2016).

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

21 Atkins, W. J., Burkhardt, E. R. & Matos, K. Safe Handling of Boranes at Scale. *Org. Proc. Res. Dev.* **10**, 1292-1295, doi:10.1021/op0680111 (2006).

22 Lima, F. *et al.* A Lewis Base Catalysis Approach for the Photoredox Activation of Boronic Acids and Esters. *Angew. Chem. Int. Ed.* **56**, 15136-15140, doi:10.1002/anie.201709690 (2017).

23 Zhang, T. Y. Process chemistry: The science, business, logic, and logistics. *Chem. Rev.* **106**, 2583-2595, doi:10.1021/cr040677v (2006).

24 Brown, H. C. & Zweifel, G. A Stereospecific Cis Hydration of the Double Bond in Cyclic Derivatives. *J. Am. Chem. Soc.* **81**, 247-247, doi:10.1021/ja01510a059 (2002).

25 Brown, H. C., Knights, E. F. & Scouten, C. G. Hydroboration. XXXVI. Direct route to 9-borabicyclo[3.3.1]nonane via the cyclic hydroboration of 1,5-cyclooctadiene. 9-Borabicyclo[3.3.1]nonane as a uniquely selective reagent for the hydroboration of olefins. *J. Am. Chem. Soc.* **96**, 7765-7770, doi:10.1021/ja00832a025 (2002).

26 Li, Y. *et al.* Reaction scope and mechanistic insights of nickel-catalyzed migratory Suzuki-Miyaura cross-coupling. *Nat. Commun.* **11**, 417, doi:10.1038/s41467-019-14016-1 (2020).

27 Xu, J. *et al.* Unveiling Extreme Photoreduction Potentials of Donor-Acceptor Cyanoarenes to Access Aryl Radicals from Aryl Chlorides. *J. Am. Chem. Soc.* **143**, 13266-13273, doi:10.1021/jacs.1c05994 (2021).

28 Diccianni, J. B., Hu, C. & Diao, T. Binuclear, High-Valent Nickel Complexes: Ni−Ni Bonds in Aryl–Halogen Bond Formation. *Angew. Chem.* **129**, 3689-3693, doi:10.1002/ange.201611572 (2017).

29 Zheng, B. *et al.* Organometallic nickel(III) complexes relevant to cross-coupling and carbon-heteroatom bond formation reactions. *J. Am. Chem. Soc.* **136**, 6499-6504, doi:10.1021/ja5024749 (2014).

30 Lee, H., Borgel, J. & Ritter, T. Carbon-Fluorine Reductive Elimination from Nickel(III) Complexes. *Angew. Chem. Int. Ed.* **56**, 6966-6969, doi:10.1002/anie.201701552 (2017).

31 Griego, L., Chae, J. B. & Mirica, L. The Magic of Triisopropyl-1,4,7-Triazacyclononane: Probing the Role of Ni(III) and Ni(I) Centers in Cross-Coupling Catalysis. *ChemRxiv*, doi:10.26434/chemrxiv-2023-fpf1n (2023).

32 Sun, R., Qin, Y. & Nocera, D. G. General Paradigm in Photoredox Nickel-Catalyzed Cross-Coupling Allows for Light-Free Access to Reactivity. *Angew. Chem. Int. Ed.* **59**, 9527-9533, doi:10.1002/anie.201916398 (2020).

33 Cismesia, M. A. & Yoon, T. P. Characterizing Chain Processes in Visible Light Photoredox Catalysis. *Chem Sci* **6**, 5426-5434, doi:10.1039/C5SC02185E (2015).

34 Sommer, H., Julia-Hernandez, F., Martin, R. & Marek, I. Walking Metals for Remote Functionalization. *ACS Cent Sci* **4**, 153-165, doi:10.1021/acscentsci.8b00005 (2018).

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

35 Janssen-Müller, D., Sahoo, B., Sun, S. Z. & Martin, R. Tackling Remote $sp^3$ C–H Functionalization via Ni-Catalyzed "chain-walking" Reactions. *Isr. J. Chem.* **60**, 195-206, doi:10.1002/ijch.201900072 (2019).

36 Hansch, C., Leo, A. & Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **91**, 165-195, doi:10.1021/cr00002a004 (2002).

37 Zuo, Z. *et al.* Dual catalysis. Merging photoredox with nickel catalysis: coupling of alpha-carboxyl sp(3)-carbons with aryl halides. *Science* **345**, 437-440, doi:10.1126/science.1255525 (2014).

38 Shang, T. Y. *et al.* Recent advances of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) in photocatalytic transformations. *Chem. Commun.* **55**, 5408-5419, doi:10.1039/c9cc01047e (2019).

39 Cannes, C., Labbé, E., Durandetti, M., Devaud, M. & Nédélec, J. Y. Nickel-catalyzed electrochemical homocoupling of alkenyl halides: rates and mechanisms. *J. Electroanal. Chem.* **412**, 85-93, doi:10.1016/0022-0728(96)04605-0 (1996).

40 Buglioni, L., Raymenants, F., Slattery, A., Zondag, S. D. A. & Noel, T. Technological Innovations in Photochemistry for Organic Synthesis: Flow Chemistry, High-Throughput Experimentation, Scale-up, and Photoelectrochemistry. *Chem. Rev.* **122**, 2752-2906, doi:10.1021/acs.chemrev.1c00332 (2022).

41 Zondag, S. D. A., Mazzarella, D. & Noel, T. Scale-Up of Photochemical Reactions: Transitioning from Lab Scale to Industrial Production. *Annu. Rev. Chem. Biomol. Eng.* **14**, 283-300, doi:10.1146/annurev-chembioeng-101121-074313 (2023).

42 Wan, T. *et al.* Accelerated and Scalable C(sp(3))-H Amination via Decatungstate Photocatalysis Using a Flow Photoreactor Equipped with High-Intensity LEDs. *ACS Cent. Sci.* **8**, 51-56, doi:10.1021/acscentsci.1c01109 (2022).

43 Webb, D. & Jamison, T. F. Continuous flow multi-step organic synthesis. *Chem. Sci.* **1**, doi:10.1039/c0sc00381f (2010).

44 Capaldo, L., Wen, Z. & Noel, T. A field guide to flow chemistry for synthetic organic chemists. *Chem. Sci.* **14**, 4230-4247, doi:10.1039/d3sc00992k (2023).

45 Capaldo, L., Bonciolini, S., Pulcinella, A., Nuno, M. & Noel, T. Modular allylation of C($sp^3$)-H bonds by combining decatungstate photocatalysis and HWE olefination in flow. *Chem. Sci.* **13**, 7325-7331, doi:10.1039/d2sc01581a (2022).

46 Jiao, J. *et al.* Multi-Step Continuous-Flow Organic Synthesis: Opportunities and Challenges. *Chem.-Eur. J.* **27**, 4817-4838, doi:10.1002/chem.202004477 (2021).

47 Dallinger, D., Gutmann, B. & Kappe, C. O. The Concept of Chemical Generators: On-Site On-Demand Production of Hazardous Reagents in Continuous Flow. *Acc. Chem. Res.* **53**, 1330-1341, doi:10.1021/acs.accounts.0c00199 (2020).

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

https://doi.org/10.26434/chemrxiv-2023-4g3xz **ORCID:** https://orcid.org/0000-0002-3107-6927 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0