

# Catalytic Reductive Homocoupling of Benzyl Chlorides Enabled by Zirconocene and Photoredox Catalysis

Ryota Tajima,<sup>§</sup> Keisuke Tanaka,<sup>§</sup> Kazuhiro Aida, Eisuke Ota,\* and Junichiro Yamaguchi\*



Cite This: *Precis. Chem.* 2025, 3, 43–50



Read Online

ACCESS |

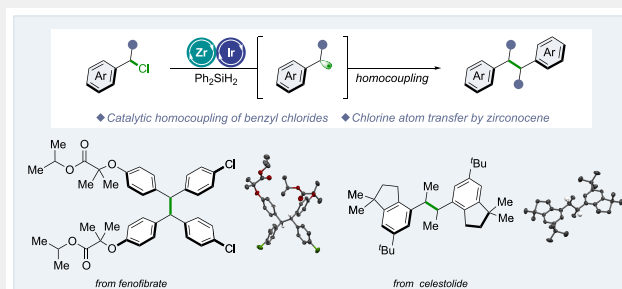
Metrics & More

Article Recommendations

Supporting Information

**ABSTRACT:** The bibenzyl skeleton is prevalent in numerous natural products and other biologically active compounds. Radical homocoupling provides a straightforward approach for synthesizing bibenzyls in a single step with the reductive homocoupling of benzyl halides undergoing extensive development. Unlike benzyl bromides and other tailored precursors used in visible-light-mediated homocoupling, benzyl chlorides offer greater abundance and chemical stability. Nevertheless, achieving chemoselective cleavage of the C–Cl bond poses significant challenges, with only a limited number of studies reported to date. Herein, we demonstrate a catalytic reductive homocoupling of benzyl chlorides facilitated by zirconocene and photoredox catalysis. This cooperative catalytic system promotes C–Cl bond cleavage in benzyl chlorides under mild conditions and supports the homocoupling of a wide range of benzyl chlorides, including those derived from pharmaceutical agents. Our preliminary mechanistic investigations highlight the pivotal role of hydrosilane in the catalytic cycle.

**KEYWORDS:** Zirconocene, Photoredox catalysis, Radical–radical coupling, Benzyl chlorides, Silane



## INTRODUCTION

The development of new strategies for C–C bond formation remains a pivotal focus in advancing synthetic organic chemistry. Despite a plethora of established methodologies for C–C bond formation, the quest for more straightforward and efficient strategies continues, aiming to synthesize a diverse array of target molecules. Recently, radical–radical coupling has been recognized as a robust approach forming C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bonds, leveraging the high reactivity of radical intermediates to construct sterically hindered C–C bonds. The recent advances in photoredox chemistry have led to the development of cutting-edge methodologies for novel bond formation, which includes metallaphotoredox chemistry<sup>1,2</sup> and *N*-heterocyclic carbene(NHC)-based radical catalysis.<sup>3–6</sup> Visible-light-mediated radical–radical coupling reactions stand out as a preeminent approach, operating under relatively mild conditions, while often achieving high selectivity and functional group tolerance.

The bibenzyl skeleton is prevalent in natural products and biologically active compounds, including pharmaceuticals (Figure 1).<sup>7–9</sup> Traditionally, bibenzyls are synthesized stepwise through the reduction of stilbenes, which are prepared by Wittig, Horner–Wadsworth–Emmons, or Mizoroki–Heck reactions. Recently, new synthetic methods for these compounds have also emerged.<sup>10,11</sup> The radical–radical coupling provides a straightforward approach, and the catalytic reductive homocoupling of benzyl halides has been intensively developed.<sup>12</sup> While visible-light-mediated variants have also

been developed, applicable substrates are primarily limited to bromide (Figure 1A).<sup>13–19</sup> Other specially designed radical precursors, including sulfone,<sup>20</sup> phosphonium salt,<sup>21</sup> organozinc,<sup>22</sup> and others,<sup>23,24</sup> have been continuously developed. However, benzyl chloride remains an elusive substrate in visible light catalysis. Activation of benzyl chloride has been achieved with a dinuclear copper catalyst with an electrophotochemical setting,<sup>25</sup> and some inorganic photocatalysis, such as homemade Nickel/graphitic carbon nitride (Ni/gCN),<sup>26</sup> UV light-induced Cu-loaded ZnO nanoparticle,<sup>27</sup> and divalent europium generated with the aid of organic chromophore<sup>28</sup> have also accomplished homocoupling (Figure 1B). The vast majority of other studies have only focused on *o*-chlorotoluene.<sup>29–34</sup> Leveraging benzyl chloride, known for its abundance and chemical stability compared to benzyl bromide, in visible light catalysis could significantly enhance the practicality of catalytic homocoupling and facilitate late-stage functionalization.

Visible-light activation of alkyl chlorides has emerged as a vivid area of research, enabling innovative new bond cleavage modes.<sup>35–37</sup> Strategies based on single electron transfer

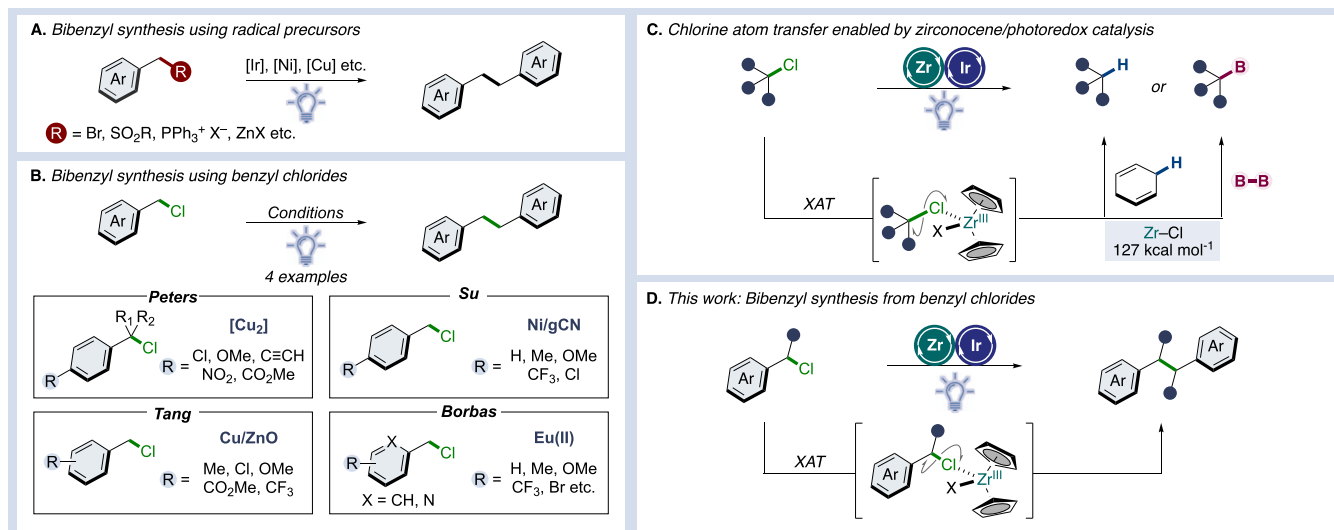
**Received:** September 28, 2024

**Revised:** October 31, 2024

**Accepted:** October 31, 2024

**Published:** November 7, 2024





**Figure 1.** (A) Bibenzyl synthesis using radical precursors. (B) Bibenzyl synthesis using benzyl chlorides. (C) Chlorine atom transfer enabled by zirconocene/photoredox catalysis. (D) This work: Bibenzyl synthesis from benzyl chlorides.

**Table 1. Condition Screening<sup>a</sup>**

entry	Cp <sub>2</sub> ZrX <sub>2</sub>	solvent	H atom donor	2A/ %	3A/ %
1	Cp <sub>2</sub> Zr(OTs) <sub>2</sub>	PhCF <sub>3</sub>	1,4-CHD	10	24
2	Cp <sub>2</sub> Zr(OTs) <sub>2</sub>	PhCF <sub>3</sub>	Ph <sub>2</sub> SiH <sub>2</sub>	10	20
3 <sup>b</sup>	Cp <sub>2</sub> Zr(OTs) <sub>2</sub>	PhCF <sub>3</sub>	Ph <sub>2</sub> SiH <sub>2</sub>	66	9
4 <sup>b</sup>	Cp <sub>2</sub> Zr(OTf) <sub>2</sub> ·THF	PhCF <sub>3</sub>	Ph <sub>2</sub> SiH <sub>2</sub>	0	0
5 <sup>b</sup>	Cp <sub>2</sub> ZrCl <sub>2</sub>	PhCF <sub>3</sub>	Ph <sub>2</sub> SiH <sub>2</sub>	54	0
6 <sup>b</sup>	Cp <sub>2</sub> ZrCl <sub>2</sub>	PhMe	Ph <sub>2</sub> SiH <sub>2</sub>	0	0
7 <sup>b</sup>	Cp <sub>2</sub> ZrCl <sub>2</sub>	DME	Ph <sub>2</sub> SiH <sub>2</sub>	74	5
8 <sup>b</sup>	Cp <sub>2</sub> ZrCl <sub>2</sub>	THF	Ph <sub>2</sub> SiH <sub>2</sub>	85	2
9 <sup>b</sup>	Cp <sub>2</sub> ZrCl <sub>2</sub>	THF	<sup>t</sup> Bu <sub>2</sub> SiH <sub>2</sub>	0	0
10 <sup>b</sup>	Cp <sub>2</sub> ZrCl <sub>2</sub>	THF	PhSiH <sub>3</sub>	59	9
11 <sup>b</sup>	none	THF	Ph <sub>2</sub> SiH <sub>2</sub>	8	2
12 <sup>b</sup>	Cp <sub>2</sub> ZrCl <sub>2</sub>	THF	none	0	0

— Thiourea

TU1

— Photocatalyst

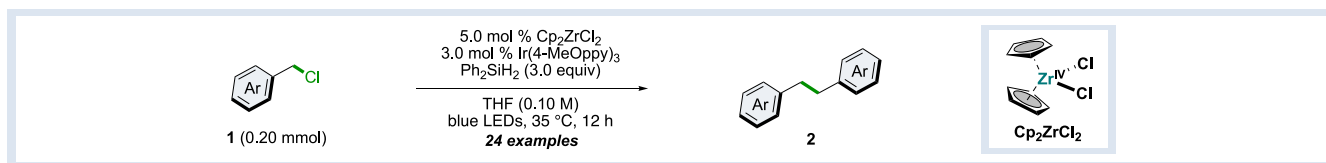
Ir(4-MeOppy)<sub>3</sub>

<sup>a</sup>Conditions: **1A** (0.10 mmol), Cp<sub>2</sub>ZrX<sub>2</sub> (5.0 mol %), Ir(4-MeOppy)<sub>3</sub> (3.0 mol %), **TU1** (60 mol %), H-atom donor (3.0 equiv), solvent (1.0 mL), 456 nm LEDs (Kessil lamp), 35 °C, 12 h. <sup>b</sup>Without **TU1**. Yields were determined by <sup>1</sup>H NMR using an internal standard. See the [Supporting Information](#) for more details (Figure S1, Tables S1–4). DME = 1,2-dimethoxyethane.

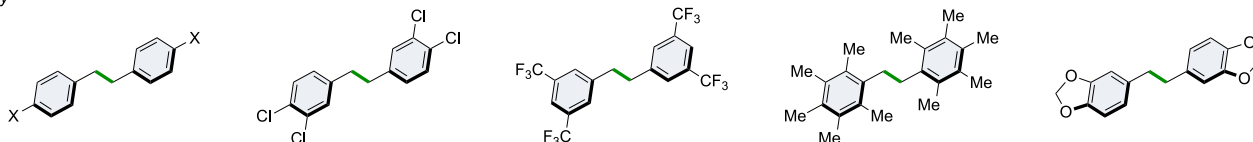
(SET),<sup>38–41</sup> photoexcited transition metal,<sup>42–46</sup> nucleophilic metal,<sup>47–50</sup> or halogen atom transfer (XAT)<sup>51–54</sup> have been established. Recently, we developed a catalytic protocol for generating carbon radicals from alkyl chlorides<sup>55</sup> using zirconocene and photoredox catalysis (Figure 1C).<sup>56–58</sup>

The formation of a strong Zr–Cl bond (127 kcal mol<sup>−1</sup>) facilitates the challenging C–Cl bond cleavage in an XAT fashion. Contrary to the approaches relying on strongly

reducing conditions, reactivity is not governed by the redox potential. Despite the electronically mild feature of the XAT-based approach, its application to forming C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bond through radical–radical coupling has not been realized so far.<sup>51–54</sup> Herein, we report a catalytic reductive homocoupling of benzyl chlorides using zirconocene and photoredox catalysis (Figure 1D).

Scheme 1. Substrate Scope<sup>a</sup>

Primary



2A (X = <sup>t</sup>Bu): 70%    2D (X = CO<sub>2</sub>Me): 82%  
2B<sup>b</sup> (X = SMe): 50%    2E (X = F): 70%  
2C (X = CN): 69%    2F<sup>c</sup> (X = Br): 47%

2G : 72%

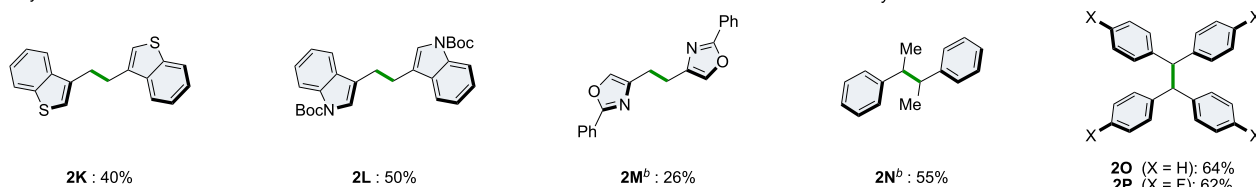
2H : 68%

2I : 71%

2J : 53%

Primary

Secondary



2K : 40%

2L : 50%

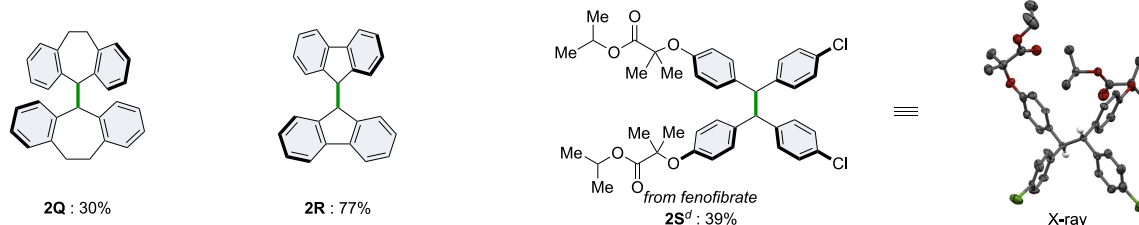
2M<sup>b</sup> : 26%2N<sup>b</sup> : 55%

2O (X = H): 64%

2P (X = F): 62%

Secondary

Bioactive compounds



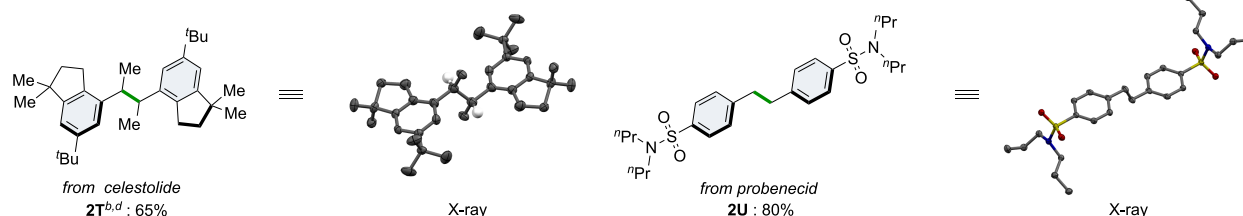
2Q : 30%

2R : 77%

2S<sup>d</sup> : 39%

X-ray

Bioactive compounds

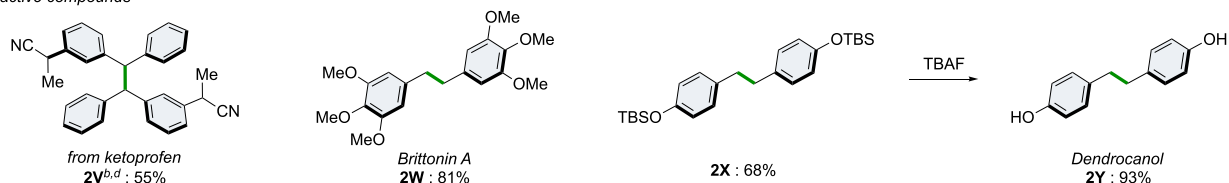
from celestolide  
2T<sup>b,d</sup> : 65%

X-ray

from probenecid  
2U : 80%

X-ray

Bioactive compounds

from ketoprofen  
2V<sup>b,d</sup> : 55%Brittonin A  
2W : 81%

2X : 68%

Dendrocannabinol  
2Y : 93%

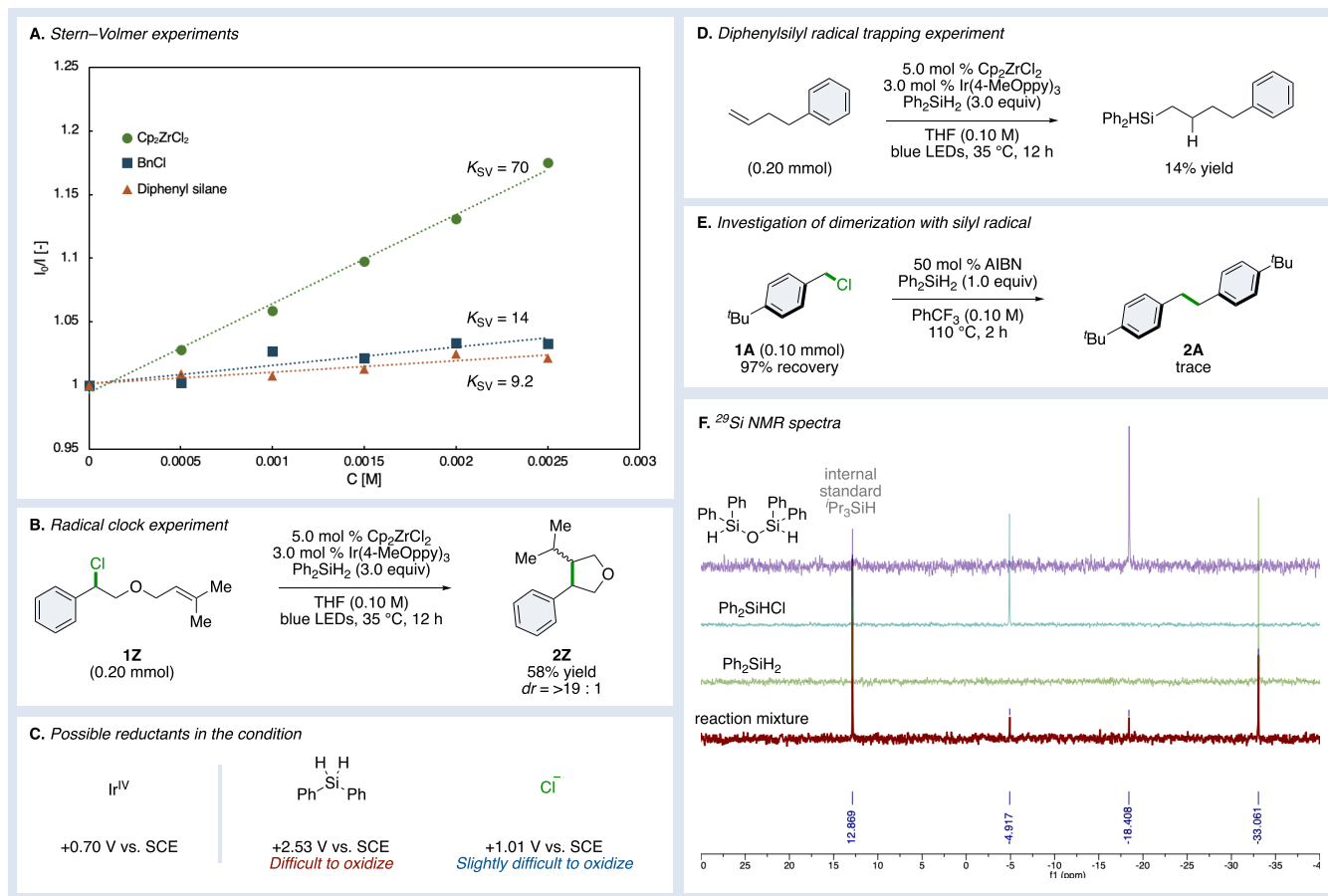
TBAF

<sup>a</sup>Conditions: 1 (0.20 mmol), 5.0 mol %  $\text{Cp}_2\text{ZrCl}_2$ , 3.0 mol %  $\text{Ir}(4\text{-MeOppy})_3$ ,  $\text{Ph}_2\text{SiH}_2$  (3.0 equiv), THF (2.0 mL), 456 nm LEDs (Kessil lamp), 35 °C, 12 h. <sup>b</sup>The reaction was conducted for 24 h. <sup>c</sup>The reaction was conducted for 8 h. <sup>d</sup>The product was obtained as a mixture of diastereomers. All data are the average of two experiments. See the [Supporting Information](#) for the details of the experiments.

## RESULTS AND DISCUSSION

We hypothesized that the activation of benzyl chlorides to produce stabilized benzyl radicals allows the formation of a new  $\text{C}(sp^3)\text{-C}(sp^3)$  bond by radical–radical coupling.<sup>59,60</sup> Initially, we evaluate the feasibility of zirconocene and photoredox catalysis for a radical–radical coupling reaction with the optimized conditions in our previous dechlorinative hydrogenation.<sup>55</sup> Using  $\text{Ir}(4\text{-MeOppy})_3$ ,  $\text{Cp}_2\text{Zr}(\text{OTf})_2$ , 1,3-di(*p*-tolyl)thiourea, and 1,4-cyclohexadiene (1,4-CHD) under visible light irradiation, the reaction of 4-*tert*-butylbenzyl chloride (1A) afforded the homocoupling product 2A and the hydrogenated product 3A in 10% and 24% yield,

respectively (Table 1, entry 1). The change of the hydrogen atom donor 1,4-CHD to  $\text{Ph}_2\text{SiH}_2$  slightly suppressed the formation of 3A (entry 2). Our previous study demonstrated that the addition of thiourea accelerates the hydrogenation. Thus, we performed the reaction in the absence of thiourea additive, which improves the selectivity effectively (entry 3). While  $\text{Cp}_2\text{Zr}(\text{OTf})_2\cdot\text{THF}$  inhibited the product formation,  $\text{Cp}_2\text{ZrCl}_2$  was identified as an effective zirconocene catalyst (entries 4 and 5). Contrasting to using PhMe, employing etheric solvents such as DME and THF resulted in good yields (entries 6, 7, and 8). Screening hydrosilanes indicated that a phenyl group at the silicone atom is critical for efficient



**Figure 2.** (A) Stern–Volmer experiments. (B) Radical clock experiment. (C) Possible reductants. (D) Silyl radical trapping experiment. (E) Dimerization with stoichiometric radical initiator. (F)  $^{29}\text{Si}$  NMR spectra red: reaction mixture, blue:  $\text{Ph}_2\text{SiHCl}$ , green:  $\text{Ph}_2\text{SiH}_2$ , purple:  $(\text{Ph}_2\text{SiH})_2\text{O}$ . See the [Supporting Information](#) for the details of the experiments.

reactivity (entries 9 and 10). Further screening of hydrosilane and photocatalyst diminished conversion to desired coupling product **3A** (Tables S2 and S3). Control experiments conducted in the absence of photocatalyst, zirconocene, or hydrosilane resulted in almost no products, emphasizing the essential roles of these components in this homocoupling (entries 11 and 12).

With the optimized conditions in hand, we next investigated the substrate scope (Scheme 1). Various functional groups, such as alkyl (**2A**), sulfide (**2B**), nitrile (**2C**), ester (**2D**), and fluorine (**2E**), are all tolerated in this reaction to yield the corresponding bibenzyl derivatives. Aryl bromide was accommodated to afford a homocoupling product with a shorter reaction time (**2F**) (see the [Supporting Information](#), Section 9). Additionally, we found that benzyl chlorides with electron-deficient arenes could be dimerized in good yields (**2G** and **2H**). Moreover, sterically hindered benzyl chloride possessing a pentamethyl group also yielded the product (**2I**), which highlights that the steric hindrance does not strongly influence the reaction efficiency. Benzodioxole and benzothiophene also gave dimerized products (**2J** and **2K**) in good yields. Additionally, nitrogen-containing heteroaromatic benzyl chlorides, such as indole and oxazole derivatives, although giving moderate yields, also underwent homocoupling (**2L** and **2M**). Moreover, secondary benzyl chloride afforded homocoupling product **2N** in a moderate yield. This catalytic homocoupling could be applied to the synthesis of tetraarylethane (**2O** and

**2P**). Fused cyclic compounds (**2Q** and **2R**) also reacted, regardless of their ring size. Furthermore, dimerized products of flavor chemical and pharmaceutical agents, such as fenofibrate (**2S**), celestolide (**2T**), probenecid (**2U**), and ketoprofen (**2V**), are successfully obtained from the corresponding benzyl chloride in a single step. The structures were confirmed by X-ray crystallographic analysis (Figures S12–S14, Table S5). We previously reported the synthesis of tetraarylethanes through the dimerization of diaryl ketones, and the current method serves as a complementary approach.<sup>61</sup> Finally, this catalytic reductive homocoupling provides ready access to bibenzyl natural product brittonin A (**2W**) isolated from *Frullania* species<sup>62</sup> in good yield, enhancing the practicality of this method. Furthermore, the synthesis of unsymmetrical bibenzyl natural product chrysotobibenzyl was accomplished using the current protocol, albeit in low yield (see the [Supporting Information](#), Section 7).<sup>63</sup> Although a simple compound, the homocoupling of benzyl chloride afforded **2X**, from which the removal of the TBS group led to the bibenzyl natural product, dendrocanol (**2Y**). Additionally, we attempted the conversion of various allyl chlorides, which exhibit reactivity similar to that of benzyl chloride. However, while the starting materials were consumed, the reactions became complex. The reaction also proceeded with benzyl bromide, and while the yield was low, benzyl fluoride exhibited slight reactivity, leading to the formation of a small

amount of the bibenzyl compound. (see the Supporting Information, Section 8).

We then turned our attention to the reaction mechanism. Initially, we conducted Stern–Volmer quenching experiments (Figures 2A, S2–S4).  $\text{Cp}_2\text{ZrCl}_2$  ( $K_{\text{SV}} = 70$ ) strongly quenches the excited photocatalyst  $\text{Ir}(4\text{-MeOppy})_3$ , compared to benzyl chloride 1A and  $\text{Ph}_2\text{SiH}_2$ . These results support the chlorine atom transfer mechanism rather than direct one-electron reduction of benzyl chloride ( $-2.21$  V vs SCE)<sup>64</sup> may be operative. Subsequently, we performed a radical clock experiment (Figure 2B). Benzyl chloride 1Z which possesses a prenyl group, smoothly converted to the cyclized product 2Z in 58% yield under our optimal conditions. This finding suggests that the reaction proceeds via a radical mechanism, highlighting the generation and involvement of radical intermediates. Next, we investigated the role of the hydrosilane additive. Given the redox-neutral character of the photocatalysts, it prompted us to question which species is oxidized to complete the catalytic cycle. Given the oxidation potential of  $\text{Ph}_2\text{SiH}_2$  is  $+2.53$  V (vs SCE),<sup>65</sup> oxidation of this compound is unlikely (Figure 2C). Additionally, the  $\text{p}K_{\text{a}}$  value of  $\text{Ph}_2\text{SiH}_2$  (29.2)<sup>66</sup> implies that oxidation of the diphenylsilyl anion, formed through deprotonation by chloride anion may also be difficult. Taken together, although the oxidation of chloride anion ( $+1.01$  V vs SCE)<sup>67</sup> seems slightly hard by  $\text{Ir}^{\text{IV}}$  ( $\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}} = +0.70$  V vs SCE),<sup>68</sup> we assumed that the oxidation of chloride anion would produce chlorine radical and complete catalytic cycle to regenerate  $\text{Ir}^{\text{III}}$ . In this scenario, the electrophilic chlorine radical likely abstracts a hydrogen atom from  $\text{Ph}_2\text{SiH}_2$  ( $\text{H}-\text{Cl}$  BDE =  $102$  kcal mol<sup>-1</sup>,  $\text{Ph}_2\text{SiH}_2$  BDE =  $90.6$  kcal mol<sup>-1</sup>).<sup>69</sup> To verify the generation of the diphenylsilyl radical, but-3-en-1-ylbenzene was subjected to the optimal conditions. The reaction provided the hydrosilylated product in 14% yield, consistent with radical-mediated hydrosilylation (Figure 2D).<sup>70</sup> Exploiting the stoichiometric radical initiator did not afford the dimerized product (Figure 2E). Following these surveys, we next sought to determine the products derived from the silyl radical in the homocoupling reaction. Using <sup>29</sup>Si NMR spectroscopy, unstable silane-containing final products were detected (Figure 2F). After the reaction had completed, two new significant signals were observed. We identified these signals are  $\text{Ph}_2\text{SiHCl}$  ( $\delta = -4.92$  ppm) and  $(\text{Ph}_2\text{SiH})_2\text{O}$  ( $\delta = -18.41$  ppm). This observation suggested that the silyl radical would be further oxidized by  $\text{Ir}^{\text{IV}}$  to afford the silyl cation, leading to  $\text{Ph}_2\text{SiHCl}$  by combining with a chloride anion. The conversion of  $\text{Ph}_2\text{SiHCl}$  to  $(\text{Ph}_2\text{SiH})_2\text{O}$  in the presence of  $\text{H}_2\text{O}$  was confirmed by the reported procedure.<sup>71</sup> Additionally,  $\text{Ph}_2\text{SiH}_2$  is known to react with  $\text{HCl}$  to produce  $\text{Ph}_2\text{SiHCl}$  and  $\text{H}_2$ .<sup>72</sup> This is consistent with the requirement of  $\text{Ph}_2\text{SiH}_2$  more than 1 equiv in our optimized conditions to completely consume the starting benzyl chloride (Figures S5–S10). The reaction between  $\text{Ph}_2\text{SiH}_2$  and  $\text{HCl}$  was also supported by the detection of  $\text{H}_2$  gas in our homocoupling reaction (Figure S11).

According to these experimental results, the proposed mechanism is outlined in Figure 3. An excited photocatalyst would initially reduce  $\text{Zr}^{\text{IV}}$  to  $\text{Zr}^{\text{III}}$ , followed by chlorine atom transfer from benzyl chloride to furnish the corresponding benzyl radical and  $\text{Zr}^{\text{IV}}$ . The chloride anion arising from the reduction of  $\text{Zr}^{\text{IV}}$  could be oxidized by  $\text{Ir}^{\text{IV}}$  to reproduce  $\text{Ir}^{\text{III}}$  and to form a chlorine radical. Then, the chlorine radical may abstract a hydrogen atom from  $\text{Ph}_2\text{SiH}_2$ , and the subsequent oxidation of the resultant diphenylsilyl radical affords

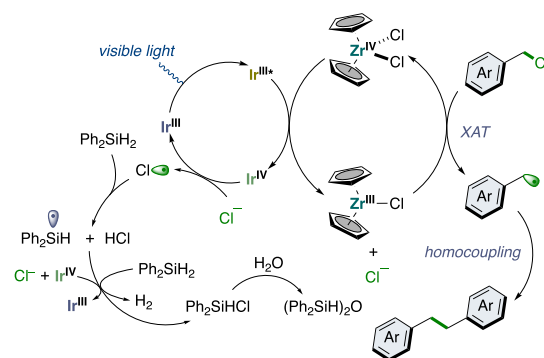


Figure 3. Proposed reaction mechanism.

$\text{Ph}_2\text{SiHCl}$  through combining a chloride anion. Additionally,  $\text{Ph}_2\text{SiH}_2$  can also work as a scavenger of  $\text{HCl}$  leading to the formation of  $\text{Ph}_2\text{SiHCl}$ . Finally, the bimolecular benzyl radical produces the desired homocoupling product. Totally, two oxidation and reduction cycles occur to generate two benzyl radicals. At this stage, other mechanisms, such as the  $\text{S}_{\text{N}}2$  mechanism between the benzyl chloride and the benzyl anion formed by the reduction of benzyl radical ( $-1.34$  V vs SCE) or chlorine atom transfer by diphenylsilyl radical, are possible. However, further investigation revealed that these mechanisms are unlikely (see the Supporting Information, Section 10.6 and 10.7).

## CONCLUSIONS

In conclusion, we have developed a catalytic protocol for the reductive homocoupling of benzyl chlorides utilizing zirconocene and photoredox catalysis.<sup>73</sup> This method demonstrates tolerance to a broad range of functional groups, facilitating the homocoupling of biologically active compounds and the synthesis of naturally occurring bibenzyls. A series of mechanistic studies have elucidated the role of hydrosilane additive. Efforts to explore additional transformations using this approach are currently underway.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/prechem.4c00077>.

Crystallographic data (CIF)

Experimental procedures and spectroscopic data for compounds including <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F and <sup>29</sup>Si spectra and crystallographic data (PDF)

## AUTHOR INFORMATION

### Corresponding Authors

Eisuke Ota – Waseda Institute for Advanced Study, Waseda University, Shinjuku, Tokyo 162-0041, Japan; [orcid.org/0000-0002-3436-9768](https://orcid.org/0000-0002-3436-9768); Email: [eota@aoni.waseda.jp](mailto:eota@aoni.waseda.jp)

Junichiro Yamaguchi – Department of Applied Chemistry, Waseda University, Shinjuku, Tokyo 162-0041, Japan; [orcid.org/0000-0002-3896-5882](https://orcid.org/0000-0002-3896-5882); Email: [junyamaguchi@waseda.jp](mailto:junyamaguchi@waseda.jp)

### Authors

Ryota Tajima – Department of Applied Chemistry, Waseda University, Shinjuku, Tokyo 162-0041, Japan

Keisuke Tanaka – Department of Applied Chemistry, Waseda University, Shinjuku, Tokyo 162-0041, Japan  
Kazuhiro Aida – Department of Applied Chemistry, Waseda University, Shinjuku, Tokyo 162-0041, Japan

Complete contact information is available at:  
<https://pubs.acs.org/10.1021/prechem.4c00077>

### Author Contributions

<sup>§</sup>R.T. and K.T. contributed equally.

### Notes

The authors declare no competing financial interest.

### ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Numbers JP21H05213 (Digi-TOS) (to J.Y.), JP20K15290 (to E.O.), Daiichi Kigenso Kagaku Kogyo (to E.O.), and Satomi Foundation (to E.O.). This work was partly supported by JST ERATO Grant No. JPMJER1901 (to J.Y.). We thank Dr. Kenta Kato for helping X-ray crystallographic analysis. Materials Characterization Central Laboratory in Waseda University is acknowledged for the support of NMR and HRMS measurement. We acknowledge Kessil Lighting for the lights used in this study.

### REFERENCES

- (1) Twilton, J.; Le, C. C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The Merger of Transition Metal and Photocatalysis. *Nat. Rev. Chem.* **2017**, *1*, 0052.
- (2) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis. *Chem. Rev.* **2022**, *122*, 1485–1542.
- (3) Ishii, T.; Nagao, K.; Ohmiya, H. Recent Advances in N-Heterocyclic Carbene-Based Radical Catalysis. *Chem. Sci.* **2020**, *11*, 5630–5636.
- (4) Ota, K.; Nagao, K.; Ohmiya, H. Synthesis of Sterically Hindered  $\alpha$ -Hydroxycarbonyls through Radical–Radical Coupling. *Org. Lett.* **2021**, *23*, 4420–4425.
- (5) Sato, Y.; Goto, Y.; Nakamura, K.; Miyamoto, Y.; Sumida, Y.; Ohmiya, H. Light-Driven N-Heterocyclic Carbene Catalysis Using Alkylborates. *ACS Catal.* **2021**, *11*, 12886–12892.
- (6) Ota, K.; Nagao, K.; Hata, D.; Sugiyama, H.; Segawa, Y.; Tokunoh, R.; Seki, T.; Miyamoto, N.; Sasaki, Y.; Ohmiya, H. Synthesis of Tertiary Alkylphosphonate Oligonucleotides through Light-Driven Radical–Polar Crossover Reactions. *Nat. Commun.* **2023**, *14*, 1–9.
- (7) Harrowven, D. C.; Kostiuk, S. L. Macrocyclic Bisbenzyl Natural Products and Their Chemical Synthesis. *Nat. Prod. Rep.* **2012**, *29*, 223–242.
- (8) Keylor, M. H.; Matsuura, B. S.; Stephenson, C. R. J. Chemistry and Biology of Resveratrol-Derived Natural Products. *Chem. Rev.* **2015**, *115*, 8976–9027.
- (9) Zhang, X.; Chen, W.; Du, Y.; Su, P.; Qiu, Y.; Ning, J.; Liu, M. Phytochemistry and Pharmacological Activities of *Arundina Graminifolia* (D. Don) Hochr. and Other Common Orchidaceae Medicinal Plants. *J. Ethnopharmacol.* **2021**, *276*, No. 114143.
- (10) Cao, D.; Li, C. C.; Zeng, H.; Peng, Y.; Li, C. J. C(sp<sup>3</sup>)–C(sp<sup>3</sup>) Bond Formation via Nickel-Catalyzed Deoxygenative Homocoupling of Aldehydes/Ketones Mediated by Hydrazine. *Nat. Commun.* **2021**, *12*, 1–8.
- (11) Jiang, H.; Lu, R.; Luo, X.; Si, X.; Xu, J.; Lu, F. Molybdenum-Catalyzed Deoxygenation Coupling of Lignin-Derived Alcohols for Functionalized Bibenzyl Chemicals. *Chem.—Eur. J.* **2021**, *27*, 1292–1296.
- (12) Chen, S.; Zhao, Y. C(sp<sup>3</sup>)–C(sp<sup>3</sup>) Bond Formation via Transition-Metal Mediated and Catalyzed Reductive Homocouplings. *Chin. J. Org. Chem.* **2020**, *40*, 3078–3093.
- (13) Huther, N.; McGrail, P. T.; Parsons, A. F. Radical Reactions Using Decacarbonyldimanganese under Biphasic Conditions. *Eur. J. Org. Chem.* **2004**, *2004*, 1740–1749.
- (14) Wiesner, S.; Walter, P.; Wagner, A.; Kaifer, E.; Himmel, H. J. Photochemical Reductive C–C Coupling with a Guanidine Electron Donor. *Eur. J. Org. Chem.* **2016**, *2016*, 5045–5054.
- (15) Park, G.; Yi, S. Y.; Jung, J.; Cho, E. J.; You, Y. Mechanism and Applications of the Photoredox Catalytic Coupling of Benzyl Bromides. *Chem.—Eur. J.* **2016**, *22*, 17790–17799.
- (16) Zhang, Y.; Petersen, J. L.; Milsman, C. Photochemical C–C Bond Formation in Luminescent Zirconium Complexes with CNN Pincer Ligands. *Organometallics* **2018**, *37*, 4488–4499.
- (17) Li, Y.; Zhang, D.; Ye, J.; Mai, Y.; Wang, C.; Yang, Y.; Li, Y.; Besenbacher, F.; Niemantsverdriet, H.; Rosei, F.; Pan, F.; Su, R. A Modular Tubular Flow System with Replaceable Photocatalyst Membranes for Scalable Coupling and Hydrogenation. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202302979.
- (18) Rosa-Pardo, I.; Zhu, D.; Cortés-Villena, A.; Prato, M.; De Trizio, L.; Manna, L.; Galian, R. E.; Pérez-Prieto, J. The Dark Side of Lead-Free Metal Halide Nanocrystals: Substituent-Modulated Photocatalytic Activity in Benzyl Bromide Reduction. *ACS Energy Lett.* **2023**, *8*, 2789–2798.
- (19) Rosa-Pardo, I.; Casadevall, C.; Schmidt, L.; Claros, M.; Galian, R. E.; Lloret-Fillol, J.; Pérez-Prieto, J. The Synergy between the CsPbBr<sub>3</sub> Nanoparticle Surface and the Organic Ligand Becomes Manifest in a Demanding Carbon–Carbon Coupling Reaction. *Chem. Commun.* **2020**, *56*, 5026–5029.
- (20) Ohkura, R.; Ohtsuka, M.; Yim, J. C. H.; Nambo, M.; Crudden, C. M. Photocatalytic Desulfonylative Homocoupling of Benzylic Sulfone Derivatives. *Synlett* **2023**, *34*, 81–85.
- (21) Boldt, A. M.; Dickinson, S. I.; Ramirez, J. R.; Benz-Weeden, A. M.; Wilson, D. S.; Stevenson, S. M. Reactions of Benzyltriphenylphosphonium Salts under Photoredox Catalysis. *Org. Biomol. Chem.* **2021**, *19*, 7810–7815.
- (22) Levin, V. V.; Agababayan, D. P.; Struchkova, M. I.; Dilman, A. D. Dimerization of Benzyl and Allyl Halides via Photoredox-Mediated Disproportionation of Organozinc Reagents. *Synthesis* **2018**, *50*, 2930–2935.
- (23) Seong, C. M.; Ansel, A. Q.; Roberts, C. C. Redox Inversion: A Radical Analogue of Umpolung Reactivity for Base- and Metal-Free Catalytic C(sp<sup>3</sup>)–C(sp<sup>3</sup>) Coupling. *J. Org. Chem.* **2023**, *88*, 3935–3940.
- (24) Chen, J.; Wang, F.; Li, X.; Wang, L.; Yu, W.; Sun, K.; Yang, J. Homocoupling of Benzyl Pyridyl Ethers via Visible Light-Mediated Deoxygenation. *Chem. Commun.* **2023**, *59*, 11409–11412.
- (25) Zott, M. D.; Canestraight, V. M.; Peters, J. C. Mechanism of a Luminescent Dicopper System That Facilitates Electrophotocatalytic Coupling of Benzyl Chlorides via a Strongly Reducing Excited State. *ACS Catal.* **2022**, *12*, 10781–10786.
- (26) Li, Y.; Li, Y.; Hu, C.; Wen, X.; Xiang, H.; Li, Y.; Niemantsverdriet, H.; Su, R. Efficient Heterogeneous Photocatalytic C–C Coupling of Halogenated Arenes Mediated by Metal Cocatalyst. *Green Chem.* **2022**, *24*, 7622–7629.
- (27) Yang, Q.; Li, X.; Chen, L.; Han, X.; Wang, F. R.; Tang, J. Effective Activation of Strong C–Cl Bonds for Highly Selective Photosynthesis of Bibenzyl via Homo-Coupling. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202307907.
- (28) Tomar, M.; Bhimpuria, R.; Kocsi, D.; Thapper, A.; Borbas, K. E. Photocatalytic Generation of Divalent Lanthanide Reducing Agents. *J. Am. Chem. Soc.* **2023**, *145*, 22555–22562.
- (29) Chow, P. K.; Cheng, G.; Ong, G. S. M. T.; To, W. P.; Kwong, W. L.; Kowk, C. C.; Ma, C.; Che, C. M. Luminescent Pincer Platinum(II) Complexes with Emission Quantum Yields up to Almost

Unity: Photophysics, Photoreductive C–C Bond Formation, and Materials Applications. *Angew. Chem., Int. Ed.* **2015**, *54*, 2084–2089.

(30) Tran, H.; McCallum, T.; Morin, M.; Barriault, L. Homocoupling of Iodoarenes and Bromoalkanes Using Photoredox Gold Catalysis: A Light Enabled Au(III) Reductive Elimination. *Org. Lett.* **2016**, *18*, 4308–4311.

(31) Kohlmann, T.; Kerzig, C.; Goetz, M. Laser-Induced Wurtz-Type Syntheses with a Metal-Free Photoredox Catalytic Source of Hydrated Electrons. *Chem.—Eur. J.* **2019**, *25*, 9991–9996.

(32) Li, Y.; Ren, P.; Zhang, D.; Qiao, W.; Wang, D.; Yang, X.; Wen, X.; Rummeli, M. H.; Niemantsverdriet, H.; Lewis, J. P.; Besenbacher, F.; Xiang, H.; Li, Y.; Su, R. Rationally Designed Metal Cocatalyst for Selective Photosynthesis of Bibenzyls via Dehalogenative C–C Homocoupling. *ACS Catal.* **2021**, *11*, 4338–4348.

(33) Barraza, R.; Sertage, A. G.; Kajjam, A. B.; Ward, C. L.; Lutter, J. C.; Schlegel, H. B.; Allen, M. J. Properties of Amine-Containing Ligands That Are Necessary for Visible-Light-Promoted Catalysis with Divalent Europium. *Inorg. Chem.* **2022**, *61*, 19649–19657.

(34) Sun, J.; Liu, Z.; Jin, J. Modular Synthesis of Triarylamines and Poly(Triarylamine)s through a Radical Mechanism. *Eur. J. Org. Chem.* **2023**, *26*, 1–6.

(35) Juliá, F.; Constantin, T.; Leonori, D. Applications of Halogen-Atom Transfer (XAT) for the Generation of Carbon Radicals in Synthetic Photochemistry and Photocatalysis. *Chem. Rev.* **2022**, *122*, 2292–2352.

(36) Ji, C. L.; Zhai, X.; Fang, Q. Y.; Zhu, C.; Han, J.; Xie, J. Photoinduced Activation of Alkyl Chlorides. *Chem. Soc. Rev.* **2023**, *52*, 6120–6138.

(37) Juliá, F. New Synthetic Strategies Based on Photoinduced Halogen-Atom Transfer (XAT). In *Photochemistry*; Crespi, S., Protti, S., Eds.; Royal Society of Chemistry, 2023; pp 361–383.

(38) Matsubara, R.; Yabuta, T.; Md Idros, U.; Hayashi, M.; Ema, F.; Kobori, Y.; Sakata, K. UVA- and Visible-Light-Mediated Generation of Carbon Radicals from Organochlorides Using Nonmetal Photocatalyst. *J. Org. Chem.* **2018**, *83*, 9381–9390.

(39) Giedyk, M.; Narobe, R.; Weiß, S.; Touraud, D.; Kunz, W.; König, B. Photocatalytic Activation of Alkyl Chlorides by Assembly-Promoted Single Electron Transfer in Microheterogeneous Solutions. *Nat. Catal.* **2020**, *3*, 40–47.

(40) Li, Y.; Ye, Z.; Lin, Y.-M.; Liu, Y.; Zhang, Y.; Gong, L. Organophotocatalytic Selective Deuterodehalogenation of Aryl or Alkyl Chlorides. *Nat. Commun.* **2021**, *12*, 2894.

(41) Wei, D.; Li, X.; Shen, L.; Ding, Y.; Liang, K.; Xia, C. Phenolate Anion-Catalyzed Direct Activation of Inert Alkyl Chlorides Driven by Visible Light. *Org. Chem. Front.* **2021**, *8*, 6364–6370.

(42) Ratani, T. S.; Bachman, S.; Fu, G. C.; Peters, J. C. Photoinduced, Copper-Catalyzed Carbon–Carbon Bond Formation with Alkyl Electrophiles: Cyanation of Unactivated Secondary Alkyl Chlorides at Room Temperature. *J. Am. Chem. Soc.* **2015**, *137*, 13902–13907.

(43) Lee, G. S.; Kim, D.; Hong, S. H. Pd-Catalyzed Formal Mizoroki–Heck Coupling of Unactivated Alkyl Chlorides. *Nat. Commun.* **2021**, *12*, 991.

(44) Muralirajan, K.; Kancherla, R.; Gimnkhani, A.; Rueping, M. Unactivated Alkyl Chloride Reactivity in Excited-State Palladium Catalysis. *Org. Lett.* **2021**, *23*, 6905–6910.

(45) Ji, C. L.; Han, J.; Li, T.; Zhao, C. G.; Zhu, C.; Xie, J. Photoinduced Gold-Catalyzed Divergent Dechloroalkylation of Gem-Dichloroalkanes. *Nat. Catal.* **2022**, *5*, 1098–1109.

(46) Ji, C. L.; Chen, H.; Gao, Q.; Han, J.; Li, W.; Xie, J. Dinuclear Gold-Catalyzed Divergent Dechlorinative Radical Borylation of Gem-Dichloroalkanes. *Nat. Commun.* **2024**, *15*, 1–12.

(47) Chen, L.; Kametani, Y.; Imamura, K.; Abe, T.; Shiota, Y.; Yoshizawa, K.; Hisaeda, Y.; Shimakoshi, H. Visible Light-Driven Cross-Coupling Reactions of Alkyl Halides with Phenylacetylene Derivatives for C(sp<sup>3</sup>)–C(sp) Bond Formation Catalyzed by a B<sub>12</sub> Complex. *Chem. Commun.* **2019**, *55*, 13070–13073.

(48) Claros, M.; Ungeheuer, F.; Franco, F.; Martin-Diaconescu, V.; Casitas, A.; Lloret-Fillol, J. Reductive Cyclization of Unactivated Alkyl

Chlorides with Tethered Alkenes under Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 4869–4874.

(49) Claros, M.; Casitas, A.; Lloret-Fillol, J. Visible-Light Reductive Cyclization of Nonactivated Alkyl Chlorides. *Synlett* **2019**, *30*, 1496–1507.

(50) Aragón, J.; Sun, S.; Pascual, D.; Jaworski, S.; Lloret-Fillol, J. Photoredox Activation of Inert Alkyl Chlorides for the Reductive Cross-Coupling with Aromatic Alkenes. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202114365.

(51) Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Juliá, F.; Leonori, D. Aminoalkyl Radicals as Halogen-Atom Transfer Agents for Activation of Alkyl and Aryl Halides. *Science* **2020**, *367*, 1021–1026.

(52) Sakai, H. A.; Liu, W.; Le, C. C.; MacMillan, D. W. C. Cross-Electrophile Coupling of Unactivated Alkyl Chlorides. *J. Am. Chem. Soc.* **2020**, *142*, 11691–11697.

(53) Dow, N. W.; Cabré, A.; MacMillan, D. W. C. A General N-Alkylation Platform via Copper Metallaphotoredox and Silyl Radical Activation of Alkyl Halides. *Chem.* **2021**, *7*, 1827–1842.

(54) Kostromitin, V. S.; Sorokin, A. O.; Levin, V. V.; Dilman, A. D. Aminals as Powerful XAT-Reagents: Activation of Fluorinated Alkyl Chlorides. *Chem. Sci.* **2023**, *14*, 3229–3234.

(55) Okita, T.; Aida, K.; Tanaka, K.; Ota, E.; Yamaguchi, J. Chlorine Atom Transfer of Unactivated Alkyl Chlorides Enabled by Zirconocene and Photoredox Catalysis. *Precis. Chem.* **2023**, *1*, 112–118.

(56) Aida, K.; Hirao, M.; Funabashi, A.; Sugimura, N.; Ota, E.; Yamaguchi, J. Catalytic Reductive Ring Opening of Epoxides Enabled by Zirconocene and Photoredox Catalysis. *Chem.* **2022**, *8*, 1762–1774.

(57) Aida, K.; Ota, E.; Yamaguchi, J. Regioselective Ring Opening of Oxetanes Enabled by Zirconocene and Photoredox Catalysis. *Synlett* **2024**, *35*, 451–454.

(58) Ota, E.; Aida, K.; Yamaguchi, J. Harnessing Zirconocene (III) for Photoinduced Carbon Radical Generation. *Chem. Lett.* **2024**, *53*, No. upae095.

(59) Leifert, D.; Studer, A. The Persistent Radical Effect in Organic Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 74–108.

(60) Meng, Q. Y.; Lezius, L.; Studer, A. Benzylic C–H Acylation by Cooperative NHC and Photoredox Catalysis. *Nat. Commun.* **2021**, *12*, 2068.

(61) Kurosawa, M. B.; Kato, K.; Muto, K.; Yamaguchi, J. Unified Synthesis of Multiply Arylated Alkanes by Catalytic Deoxygenative Transformation of Diarylketones. *Chem. Sci.* **2022**, *13*, 10743–10751.

(62) Asakawa, Y.; Matsuda, R.; Toyota, M.; Hattori, S.; Ourisson, G. Terpenoids and Bibenzyls of 25 Liverwort *Frullania* Species. *Phytochem.* **1981**, *20*, 2187–2194.

(63) Pettit, G. R.; Singh, S. B.; Schmidt, J. M.; Nixen, M. L.; Hamel, E.; Lin, C. M. Isolation, Structure, Synthesis, and Antimitotic Properties of Combretastatins B-3 and B-4 from *Combretum Caffrum*. *J. Nat. Prod.* **1988**, *51*, 517–527.

(64) Li, K.; Wan, Q.; Yang, C.; Chang, X. Y.; Low, K. H.; Che, C. M. Air-Stable Blue Phosphorescent Tetradentate Platinum(II) Complexes as Strong Photo-Reductant. *Angew. Chem., Int. Ed.* **2018**, *57*, 14129–14133.

(65) Liang, H.; Wang, L.; Ji, Y.; Wang, H.; Zhang, B. Selective Electrochemical Hydrolysis of Hydrosilanes to Silanols via Anodically Generated Silyl Cations. *Angew. Chem., Int. Ed.* **2021**, *60*, 1839–1844.

(66) Takamori, A.; Ito, S.; Naruse, Y. Deprotonation-From-Diphenylsilane-With-Organosilyllithium-Agents. *ChemRxiv*, 2022. DOI: 10.26434/chemrxiv-2022-kqbw.

(67) Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. *Synlett* **2016**, *27*, 714–723.

(68) Nacsa, E. D.; MacMillan, D. W. C. Spin-Center Shift-Enabled Direct Enantioselective  $\alpha$ -Benzoylation of Aldehydes with Alcohols. *J. Am. Chem. Soc.* **2018**, *140*, 3322–3330.

(69) Luo, Y.-R. *Comprehensive Handbook of Chemical Bond Energies*; Luo, Y.-R., Ed.; CRC Press: Boca Raton, 2007.

(70) Yu, Z.; Dai, Z.; Bai, Y.; Li, J.; Yan, Y.; Peng, J. Metal-Free Photocatalytic Hydrosilylation of Olefins in the Presence of Photoinitiators. *New J. Chem.* **2021**, *45*, 10383–10387.

(71) Straus, D. A.; Zhang, C.; Quimbata, G. E.; Grumbine, S. D.; Heyn, R. H.; Don Tilley, T.; Rheingold, A. L.; Geib, S. J.; Straus, D. A.; Zhang, C.; Quimbata, G. E.; Grumbine, S. D.; Heyn, R. H.; Tilley, T. D.; Rheingold, A. L.; Geib, S. J. Silyl and Diphenylsilylene Derivatives of  $(\eta^5\text{-C}_5\text{Me}_5)(\text{PMe}_3)_2\text{Ru}$ . Evidence for the Base-Free Silylene Complex  $[(\eta^5\text{-C}_5\text{Me}_5)(\text{PMe}_3)_2\text{Ru} = \text{SiPh}_2]^+$ . *J. Am. Chem. Soc.* **1990**, *112*, 2673–2681.

(72) Sturm, A. G.; Schweizer, J. I.; Meyer, L.; Santowski, T.; Auner, N.; Holthausen, M. C. Lewis Base Catalyzed Selective Chlorination of Monosilanes. *Chem.—Eur. J.* **2018**, *24*, 17796–17801.

(73) An initial version of this work was deposited in ChemRxiv on June 6, 2024. DOI: [10.26434/chemrxiv-2024-bw02j](https://doi.org/10.26434/chemrxiv-2024-bw02j).