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

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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.

◆ *Catalytic homocoupling of benzyl chlorides*   ◆ *Chlorine atom transfer by zirconocene*
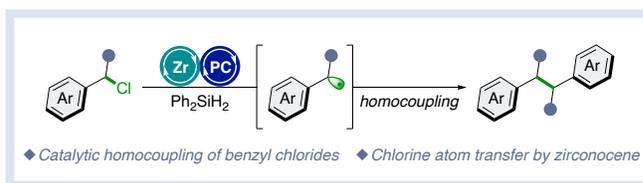
■ INTRODUCTION

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^3)–C(sp^3) 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,[1,2] and *N*-heterocyclic carbene(NHC)-based radical catalysis.[3,4–6] Visible light-mediated radical–radical coupling reactions are 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).[7–9] Traditionally, bibenzyls are synthesized stepwise through the reduction of stilbenes, which are prepared by the Wittig, Horner–Wadsworth–Emmons, or Mizoroki–Heck reactions. Recently, new synthetic methods for these compounds have also emerged.[10,11] The radical–

radical coupling provides a straightforward approach, and the catalytic reductive homocoupling of benzyl halides has been intensively developed.[12] While visible light-mediated variants have also been developed, applicable substrates are primarily limited to bromide[13–19] (Figure 1A). Other specially designed radical precursors, including sulfone,[20] phosphonium salt,[21] organozinc,[22] and others[23,24] 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,[25] and some inorganic photocatalysis, such as home-made Nickel/graphitic carbon nitride (Ni/gCN)[26] or UV light-induced Cu-loaded ZnO nanoparticle[27] have also accomplished homocoupling (Figure 1B). The vast majority of other studies have focused on α-chlorotoluene.[28–33] Leveraging benzyl chloride, known for its abundance and chemical stability, 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.[34–36] Strategies based on single electron transfer (SET),[37–40] photoexcited transition metal,[41–45] nucleophilic metal,[46–49] or halogen atom transfer (XAT)[50–53] have been established.
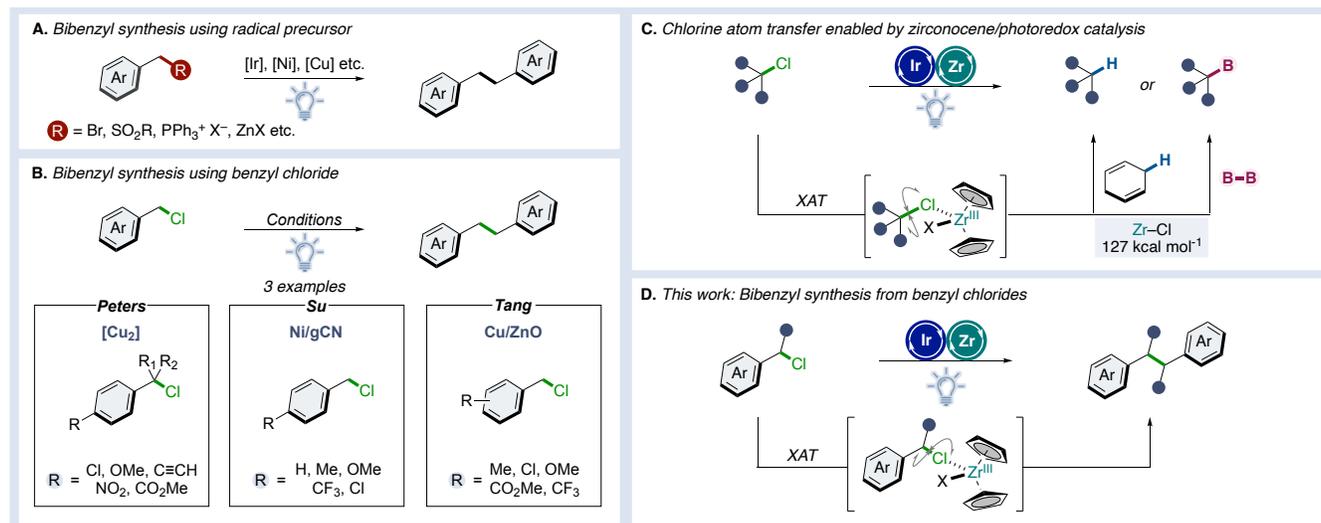
Figure 1. Visible light-mediated bibenzyl synthesis via catalytic reductive homocoupling.

Recently, we developed a catalytic protocol for generating carbon radicals from alkyl chlorides[54] using zirconocene and photoredox catalysis (Figure 1C).[55–57]

The formation of a strong Zr–Cl bond (127 kcal mol^{-1}) 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 redox potential. Despite the electronically mild feature of the XAT-based approach, its application to forming C(sp^3)–C(sp^3) bond through radical–radical coupling has not been realized so far.[50–53] Herein, we report a catalytic reductive homocoupling of benzyl chlorides using zirconocene and photoredox catalysis (Figure 1D).

■ RESULTS AND DISCUSSION

We hypothesized that the activation of benzyl chlorides to produce stabilized benzyl radicals allows the formation of a new C(sp^3)–C(sp^3) bond by radical–radical coupling.[58,59] 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.[60] Using Ir(4-MeOppy)$_3$, Cp$_2$Zr(OTs)$_2$, 1,3-di(*p*-tolyl)thiourea, and 1,4-cyclohexadiene (1,4-CHD) under visible light irradiation, the reaction of 4-*tert*-butylbenzyl chloride afforded the homocoupling product **2A** and the hydrogenated product **3A** in 10% and 24% yield, respectively (entry 1). The change of hydrogen atom donor 1,4-CHD to Ph$_2$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 Cp$_2$Zr(OTf)$_2$·THF inhibited the product formation, Cp$_2$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 reactivity (entries 9 and 10). Further screening of hydrosilane and photocatalyst diminished conversion to the desired coupling product

3A (see the Supporting Information). 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).

Table 1. Condition screening[a]
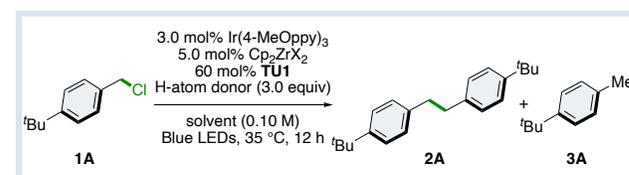
entry	Cp$_2$ZrX$_2$	solvent	H-atom donor	2A/ %	3A/ %
1	Cp$_2$Zr(OTs)$_2$	PhCF$_3$	1,4-CHD	10	24
2	Cp$_2$Zr(OTs)$_2$	PhCF$_3$	Ph$_2$SiH$_2$	10	20
3[b]	Cp$_2$Zr(OTs)$_2$	PhCF$_3$	Ph$_2$SiH$_2$	66	9
4[b]	Cp$_2$Zr(OTf)$_2$·THF	PhCF$_3$	Ph$_2$SiH$_2$	0	0
5[b]	Cp$_2$ZrCl$_2$	PhCF$_3$	Ph$_2$SiH$_2$	54	0
6[b]	Cp$_2$ZrCl$_2$	PhMe	Ph$_2$SiH$_2$	0	0
7[b]	Cp$_2$ZrCl$_2$	DME	Ph$_2$SiH$_2$	74	5
8[b]	Cp$_2$ZrCl$_2$	THF	Ph$_2$SiH$_2$	85	2
9[b]	Cp$_2$ZrCl$_2$	THF	^{t}Bu$_2$SiH$_2$	0	0
10[b]	Cp$_2$ZrCl$_2$	THF	PhSiH$_3$	59	9
11[b]	none	THF	Ph$_2$SiH$_2$	8	2
12[b]	Cp$_2$ZrCl$_2$	THF	none	0	0
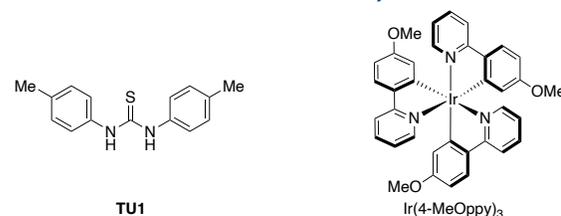
[a]Conditions: 1A (0.10 mmol), Cp$_2$ZrX$_2$ (5.0 mol%), Ir(4-MeOppy)$_3$ (3.0 mol%), thiourea (60 mol%), H-atom donor (3.0 equiv), solvent (1.0 mL). [b]Without **TU1**. Yields were determined by ^{1}H NMR using an internal standard (see the Supporting Information). DME = 1,2-dimethoxyethane.

Scheme 1. Substrate scope[a]

Primary

2A (X = *t*Bu): 70% **2C** (X = CN): 69%
2B[a] (X = SMe): 50% **2D** (X = CO2Me): 82%
2E (X = F): 70%

2F : 72%

2G : 68%

2H : 71%

2I : 53%

Primary   **Secondary**

2J : 40%

2K[b] : 55%

2L (X = H): 64%
2M (X = F): 57%

2N : 30%

2O : 77%

Bioactive compounds

from celestolide
2P[b] : 65%

X-ray

from probenecid
2Q : 80%

X-ray

from fenofibrate
2R : 39%

X-ray

from ketoprofen
2S[b] : 55%

Brittonin A
2T : 81%
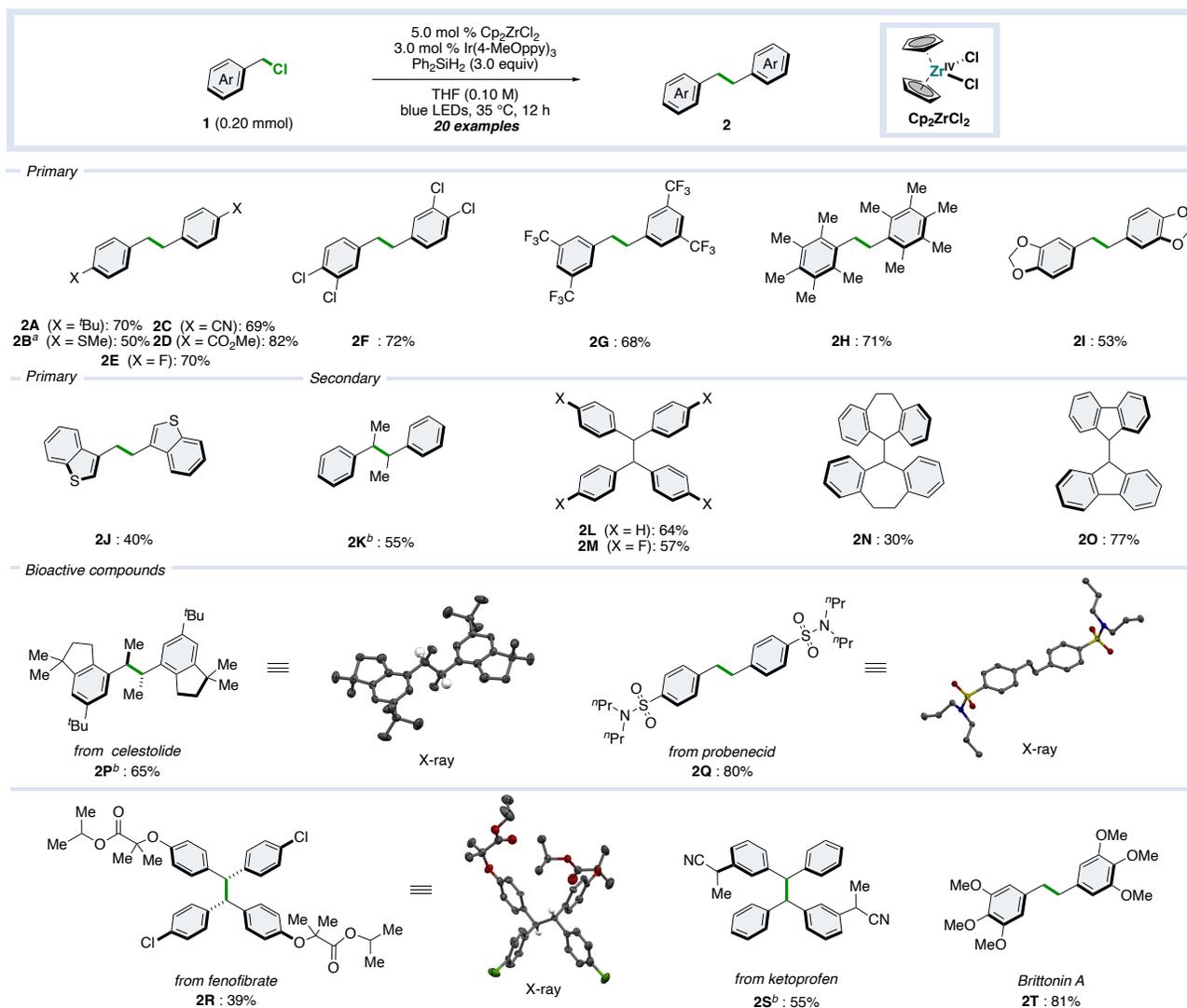
[a]Conditions: **1** (0.20 mmol), 5.0 mol% Cp2ZrCl2, 3.0 mol% Ir(4-MeOppy)3, Ph2SiH2 (3.0 equiv), THF (2.0 mL), 456 nm LEDs (kessil lamp), 35 °C, 12 h. [b]The reaction was conducted for 24 h.

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 halogen (**2E** and **2F**) are all tolerated in this reaction to yield the corresponding bibenzyl derivatives. Additionally, we found that benzyl chlorides with electron-deficient arene could be dimerized in a moderate yield (**2G**). Moreover, sterically hindered benzyl chloride possessing pentamethyl group also yielded the product (**2H**), which highlights that the steric hindrance does not strongly influence the reaction efficiency. Benzodioxole (**2I**) and benzothiophene (**2J**) also gave the dimerized products in good yields. Moreover, secondary benzyl chloride (**2K**) afforded the homocoupling product in a moderate yield. This catalytic homocoupling could be applied to tetraarylethane synthesis (**2L**, and **2M**). Fused cyclic compounds (**2N** and **2O**) also reacted regardless of their ring size. Furthermore, dimerized products of flavor chemical and pharmaceutical agents, such as celestolide (**2P**), probenecid (**2Q**), fenofibrate (**2R**), and ketoprofen

(**2S**) are successfully obtained from the corresponding benzyl chloride in a single step. We report the synthesis of tetraarylethane through the dimerization of diaryl ketones, this method that can be used complementarily with the reaction.[61] Finally, this catalytic reductive homocoupling provides ready access to bibenzyl natural product Brittonin A (**2T**) isolated from *Frullaniu* species[62] in good yield, enhancing the practicality of this method.

We then turned our attention to the reaction mechanism. Initially, we conducted Stern–Volmer quenching experiments (Figure 2A). Cp2ZrCl2 (K_{SV} = 70) strongly quenches the excited photocatalyst Ir(4-MeOppy)3, compared to benzyl chloride **1A** and Ph2SiH2. These results support the chlorine atom transfer mechanism rather than direct one-electron reduction of benzyl chloride (–2.21 V vs SCE)[63] may be operative. Subsequently, we performed a radical clock experiment (Figure 2B). Benzyl chloride **1V** which possesses a prenyl group, smoothly converted to the cyclized product **2V** in 58% yield
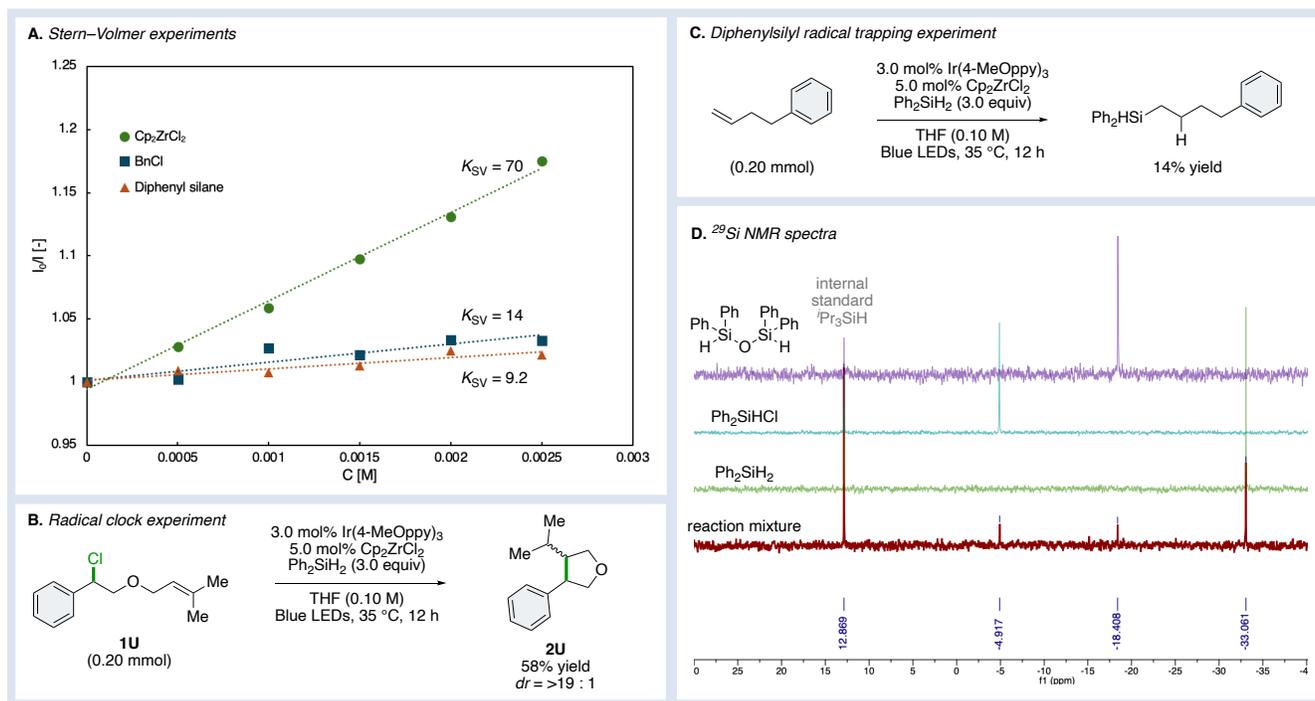
Figure 2. (A) Stern–Volmer experiments. (B) Radical clock experiment. (C) Silyl radical trapping experiment. (D) ^{29}Si NMR spectra red: reaction mixture, green: Ph$_2$SiHCl, blue: Ph$_2$SiH$_2$, purple: (Ph$_2$SiH)$_2$O.

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 Ph$_2$SiH$_2$ is +2.53 V (vs. SCE),[64] oxidation of this compound is unlikely. Additionally, the pKa value of Ph$_2$SiH$_2$ (29.2)[65] 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)[66] seems slightly hard by Ir^{IV} (Ir^{III}/Ir^{IV} = 0.70 V vs. SCE),[67] we assumed that the oxidation of chloride anion would produce chlorine radical and complete catalytic cycle to regenerate Ir^{III}. In this scenario, the chlorine radical likely abstracts a hydrogen atom from Ph$_2$SiH$_2$ (H−Cl BDE = 102 kcal mol^{-1}, Ph$_2$SiH$_2$ BDE = 90.6 kcal mol^{-1}).[68] To verify the generation of 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 2C).[69] Following these surveys, we next sought to determine the products derived from silyl radical in the homocoupling reaction. Using ^{29}Si NMR analysis, unstable silane-containing final products were detected (Figure 2D). After the reaction completion, two new significant signals were observed. We identified these signals are Ph$_2$SiHCl (δ = −4.92 ppm) and (Ph$_2$SiH)$_2$O (δ = −18.41 ppm). This observation suggested that the silyl radical would be further oxidized by Ir^{IV} to afford the silyl cation,

leading to Ph$_2$SiHCl by combining with chloride anion. The conversion of Ph$_2$SiHCl to (Ph$_2$SiH)$_2$O in the presence of H$_2$O was confirmed by the reported procedure.[70] Additionally, Ph$_2$SiH$_2$ is known to react with HCl to produce Ph$_2$SiHCl and H$_2$.[71] This is consistent with the requirement of Ph$_2$SiH$_2$ more than 1 equivalent in our optimized conditions to completely consume the starting benzyl chloride (see the Supporting Information). The reaction between Ph$_2$SiH$_2$ and HCl was also supported by the detection of H$_2$ gas in our homocoupling reaction (see the Supporting Information).

According to these experimental results, the proposed mechanism is outlined in Figure 3. An excited photocatalyst would initially reduce Zr^{IV} to Zr^{III}, followed by chlorine atom transfer from benzyl chloride to furnish the corresponding benzyl radical and Zr^{IV}. The Cl anion arising from the reduction of Zr^{IV} could be oxidized by Ir^{IV} to reproduce Ir^{III} and to form Cl radical. Then, the Cl radical may abstract a hydrogen atom from Ph$_2$SiH$_2$, and the subsequent oxidation of the resultant diphenylsilyl radical affords Ph$_2$SiHCl through combining Cl anion. Additionally, Ph$_2$SiH$_2$ can also work as a scavenger of HCl leading to the formation of Ph$_2$SiHCl. Finally, the bimolecular of the benzyl radical produces the desired homocoupling product. Totally, two couple of oxidation and reduction occur to generate two benzyl radicals. At this stage, other mechanisms, such as the S$_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).
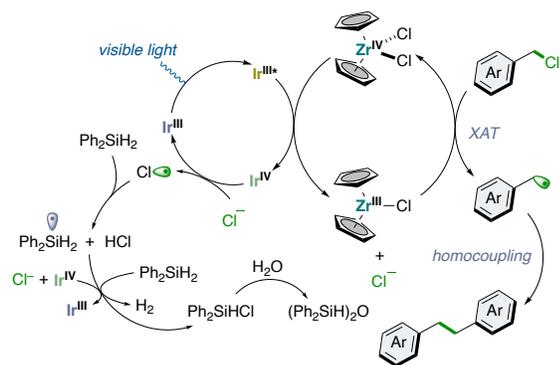
Figure 3. Proposed reaction mechanism.

■ CONCLUSIONS

In conclusion, we have developed a catalytic protocol for the reductive homocoupling of benzyl chlorides utilizing zirconocene and photoredox catalysis. 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 the hydrosilane additive. Efforts to explore additional transformations using this approach are currently underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for compounds including ^{1}H, ^{13}C, ^{19}F and ^{29}Si spectra and crystallographic data (PDF)

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◆ *Catalytic homocoupling of benzyl chlorides*　　◆ *Chlorine atom transfer by zirconocene*

8