Activation of Alkyl Chlorides Enabled by Zirconocene and Photoredox Catalysis

Toshimasa Okita, Kazuhiro Aida,[§] Keisuke Tanaka,[§] Eisuke Ota,[*] and Junichiro Yamaguchi[*]

Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan.

KEYWORDS Zirconocene, Alkyl chloride, Halogen atom transfer, Borylation, Photoredox catalysis

ABSTRACT: C–Cl bond cleavage of unactivated alkyl chlorides with zirconocene and photoredox catalysis has been achieved. The present protocol exhibited a broader scope of alkyl chlorides compared to the preceding methods with titanocene. This scope expansion could be attributed to the zirconium metal center rendering the C–Cl bond cleavage more endergonic and lowering the transition states.

Alkyl chlorides are ubiquitous structural motifs found in natural products, and synthetic intermediates,[1–5] and these can be readily prepared using common synthetic transformations. The activation mode for alkyl chlorides is broadly classified as two-electron processes such as nucleophilic substitution, halogen-metal exchange, and cross-coupling, or one-electron processes generating radicals as represented by single electron transfer (SET) or halogen atom transfer (XAT).[6–8] In these one-electron processes, alkyl chlorides are less prevalent radical precursors compared to alkyl bromides and iodides due to their strongly negative potentials (ca. –2.8 V vs SCE)[9] and high bond dissociation energies (BDE)(ca. 84 kcal/mol)[10] hampering access to carbon radicals. Compared to activated chlorides such as benzyl chlorides, α-chloro carbonyls, and trichloromethyl compounds, unactivated alkyl chlorides are particularly challenging substrates. Classical approaches for the generation of carbon radicals from unactivated alkyl chlorides are typically limited to the reactions requiring strong reductants including active metals and metal hydrides,[11] or stoichiometric reductants such as SmI_2,[12,13] organotin hydrides,[14] and organosilanes.[15]

Modern visible light photocatalysis have emerged as a preeminent strategy for the catalytic activation of unactivated chlorides (Figure 1A).[16] Unactivated alkyl chlorides have successfully proven to be a practical radical source by a series of SET-based approaches.[17–21] These elegant approaches provide a powerful platform to generate carbon radicals from alkyl chlorides but potentially erode more reducible bonds such as aryl C–Cl and C–Br bonds due to their strong reducing power.[22] As a unique activation for unactivated alkyl chlorides, formation of metal–carbon bonds from C–Cl bonds using nucleophilic low-valent metals (Co^I and Ni^I) followed by photolysis is effective, but substrates have been restricted to primary and a few secondary alkyl chlorides.[23,24] XAT-based activation exhibits a distinct mechanism for generating carbon radicals, where the chemoselectivity depends on the BDE and polarity of the C–Cl bond. Nickel/photoredox[25] and copper/photoredox[26] dual catalysis successfully engaged unactivated alkyl chlorides with the aid of organosilane reagents. These methods exhibited broad substrate scope, however, no examples of tertiary alkyl chlorides were demonstrated. Recently, photo-induced Pd catalysis has emerged as a valuable tool for the activation of unactivated alkyl chlorides. Although a broad range of alkyl chlorides could be accommodated to couple with styrenes and electron-deficient olefins, this catalysis has been only applied to Mizoroki–Heck type reactions.[27,28]

Meanwhile, titanocenes have been widely used for the variety of radical transformations of alkyl chlorides.[29–37,38–46] Regarding unactivated chlorides, Tufariello reported a dehalogenation of linear chloroalkanes using stochiometric Cp_2TiCl_2 and excess magnesium,[47] nonetheless, catalytic protocols for the unactivated alkyl chlorides have remained a long-standing challenge. Recently, Lin and coworkers have achieved the alkylation of a broad range of secondary and tertiary unactivated alkyl chlorides by XAT using less bulky Cp^*TiCl_3.[48] The Wu and Xia groups demonstrated a titanocene-catalyzed borylation of unactivated alkyl halides.[49] These successful examples significantly improved the potential of titanocene catalysis for unactivated alkyl chlorides, however, the activation of primary unactivated alkyl chlorides is currently limited by the requirement of high temperature under basic conditions and narrow substrate scopes of linear chloroalkane.[49] We envisioned that a mild photochemical XAT-based protocol applicable to broad types of chlorides can expand the potential of unactivated alkyl chlorides as a practical and versatile radical precursor.

Recently, we have developed zirconocene and photoredox catalysis enabling the ring opening of epoxides to furnish less stable radicals.[50] Based on our previous investigations, we hypothesized that lowering the kinetic barrier of chlorine atom transfer by changing the metal center of the metallocene would facilitate access to the unactivated primary chlorides. The bond dissociation energy (BDE) of Zr–Cl (116 kcal/mol) is higher than that of Ti–Cl (93 kcal/mol).[10] This difference results in the C–Cl bond homolysis being more exothermic, and decreases the activation energy (ΔE_{TS}) considering the Bell–Evans–Polanyi principle (Figure 1C).[51,52] For example, the activation energy of chlorine atom transfer from ethyl chloride to $Cp_2Zr(III)Cl$ is dramatically lower than that for $Cp_2Ti(III)Cl$ (calculated ΔG_{TS} = 4.5 kcal/mol for Zr, 16.6 kcal/mol for Ti, see SI for details). Here, we report the successful execution of these ideas and a new catalytic protocol for chlorine atom transfer from a series of unactivated alkyl chlorides.

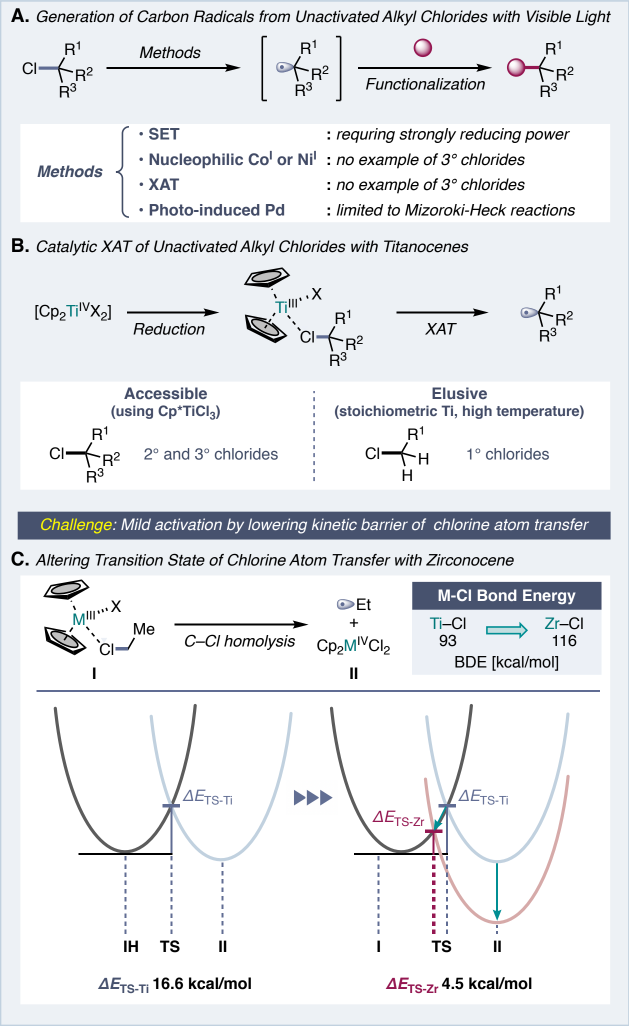


Figure 1. Reductive activation of alkyl chlorides (A) General scheme of the activation of alkyl chlorides (B) Titanocene(III)-catalyzed C–Cl bond cleavage (C) Lowering ΔE_{TS} by changing metal center from Ti to Zr.

Our working hypothesis is briefly described in Figure 2. Cp_2ZrX_2 would be reduced by an excited photocatalyst to furnish zirconocene (III) with elimination of the ligand. The alkyl chloride could then undergo C–Cl bond cleavage with zirconocene (III) to provide carbon radical species. Hydrogen atom transfer (HAT) from cyclohexadiene would then give the hydrogenated product and cyclohexadienyl radical which would undergo oxidation by Ir(IV). The resulting cation and anion X would act as a Brønsted acid to produce benzene and HCl, along with ligand exchange on zirconocene, then completing the catalytic cycle.[53]

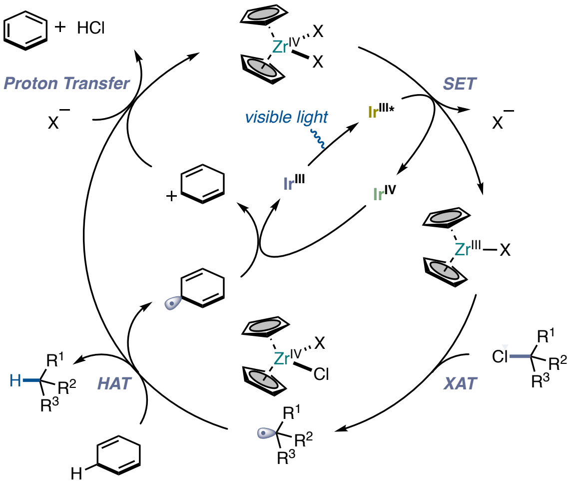
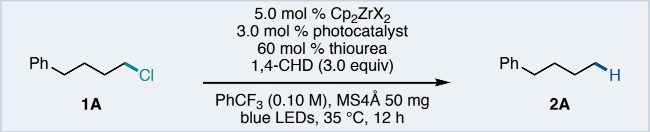


Figure 2. Working hypothesis for reductive activation of alkyl chlorides.

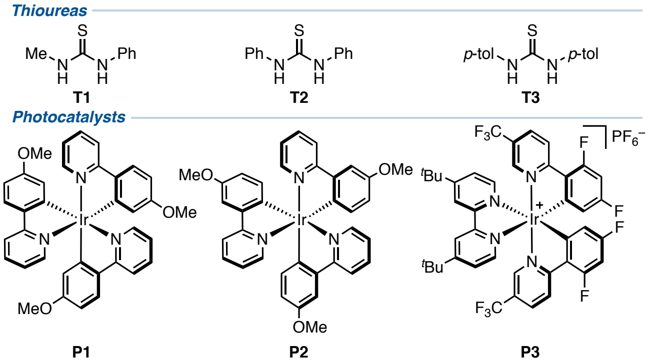
We initially tested the feasibility of C–Cl bond cleavage using zirconocene and photocatalyst by screening reaction conditions. Our initial attempts focused on reductive dehalogenation of unactivated primary alkyl chlorides (Table 1). Notably, our optimized conditions from our previous report on the zirconocene-catalyzed reductive ring opening of epoxides, which utilized $Cp_2Zr(OTf)_2 \cdot THF$, Ir[(4-MeO)ppy]$_3$ (**P1**), 1-methyl-3-phenyl thiourea (**T1**), and 1,4-cyclohexadiene (CHD) proved unsuccessful but furnished measurable product formation (entry 1). A change to $Cp_2Zr(OTs)_2$ resulted in the hydrogenated product **2A** in 58% yield (entry 2). Further optimization of thiourea derivatives revealed that 1,3-di(*p*-tolyl)thiourea (**T3**) provides superior yields (entries 3 and 4). Other photocatalysts were ineffective in this dechlorinative protocol (entries 5 and 6). The control experiments indicated that zirconocene, photocatalyst, 1,4-CHD, or visible light irradiation was essential while the lack of thiourea dramatically decreased the yield of the desired product **2A** and the recovery of alkyl chloride **1A** (entries 7–11).

Table 1. Screening of reaction conditions[a]



entry	Cp_2ZrX_2	photocatalyst	thiourea	**2A** (%)[a]
1	$Cp_2Zr(OTf)_2 \cdot THF$	P1	T1	29
2	$Cp_2Zr(OTs)_2$	P1	T1	58
3	$Cp_2Zr(OTs)_2$	P1	T2	73
4	$Cp_2Zr(OTs)_2$	P1	T3	96
5	$Cp_2Zr(OTs)_2$	P2	T3	0
6	$Cp_2Zr(OTs)_2$	P3	T3	0
7	none	P1	T3	0
8	$Cp_2Zr(OTs)_2$	none	T3	0

9	$Cp_2Zr(OTs)_2$	P1	none	11
10[b]	$Cp_2Zr(OTs)_2$	P1	T3	0
11[c]	$Cp_2Zr(OTs)_2$	P1	T3	0

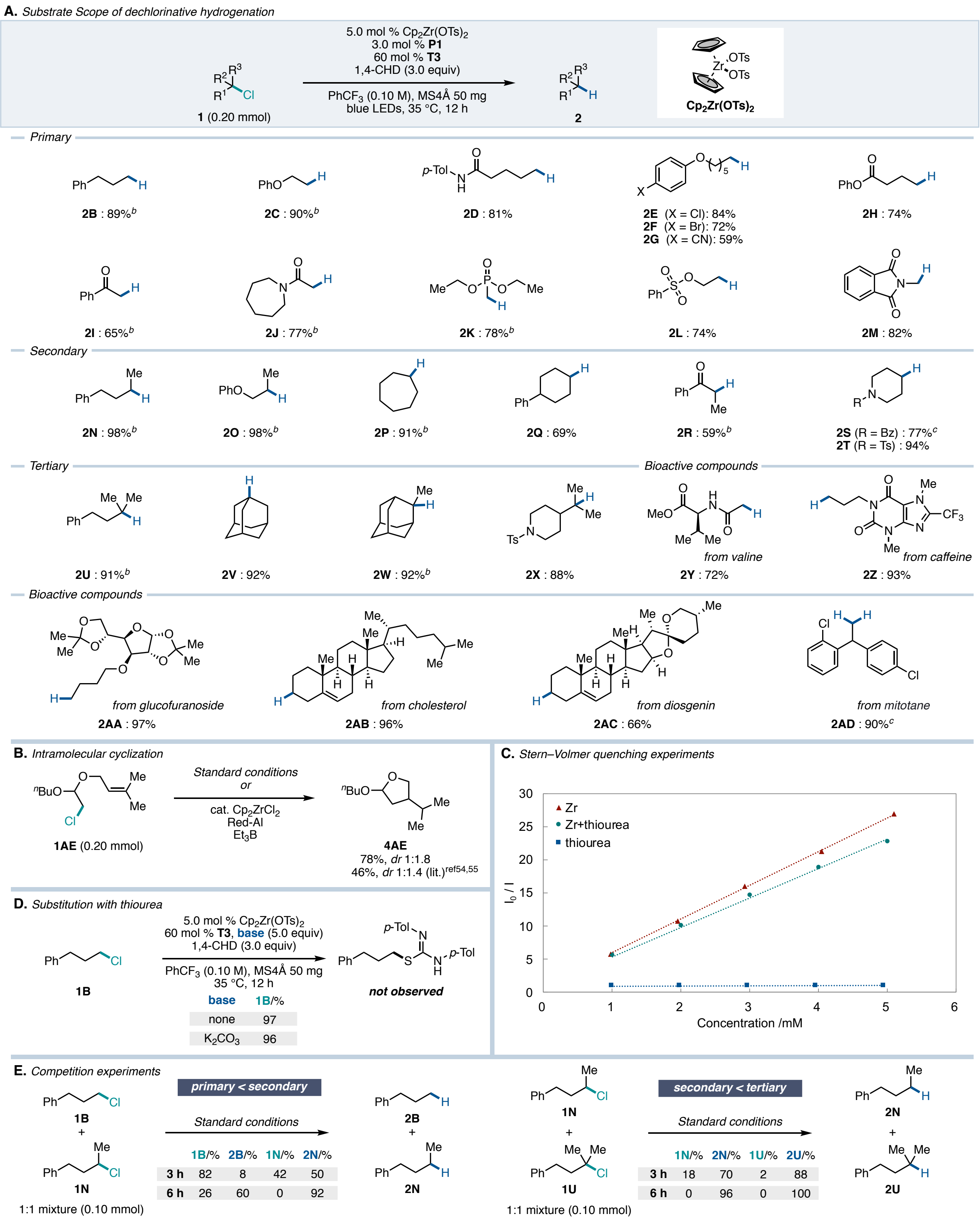


[a] Reactions were conducted on a 0.10 mmol scale and yields were determined by NMR analysis. [b] Without irradiation. [c] Without 1,4-CHD. See also the SI for more information.

With these optimized conditions in hand, we next examined the substrate scope of this protocol (Figure 3A). First, we examined primary alkyl chlorides with a variety of functional groups. In addition to phenyl (**1B**), phenoxy (**1C**) and amide (**1D**) were tolerated and afforded the corresponding dechlorinated products **2B–2D** in high yields. Aryl chloride (**1E**) ($E_{1/2}$ = –2.6 V vs SCE)[9] and aryl bromide (**1F**) ($E_{1/2}$ = –2.2 V vs SCE)[9] functional groups both remained intact, despite the susceptibility to strongly reducing photocatalysis[18–20]. A cyano group (**1G**) was also tolerated to give the product **2G** in moderate yield. A diverse array of electrophiles, including phenyl ester (**1H**), carbonyls (**1I** and **1J**), phosphonate (**1K**), sulfonate (**1L**), and phthalimide (**1M**) remained intact. The present protocol was also applicable to both acyclic and cyclic secondary alkyl chlorides (**1N–1Q**). α-Chloro ketone (**1R**) and protected piperidine derivatives (**1S** and **1T**) were found to be suitable substrates. We next evaluated tertiary alkyl chlorides. The present protocol converted a branched alkyl chloride (**1U**), adamantanes with chlorine atoms at different positions (**1V** and **1W**), and a sulfonamide (**1X**) to the corresponding reduced products **2U–2X** in excellent yields. Additionally, our reaction conditions were applicable to the derivatives of natural products or medicinal agents. C–Cl bond cleavage in biologically important architectures such as amino acid (**1Y**), purine (**1Z**), sugar (**1AA**), as well as steroids (**1AB** and **1AC**) smoothly proceeded to afford the products **2Y–2AC** in good yields. It is noted that a drug for the treatment of adrenocortical carcinoma, mitotane (**1AD**), was successfully underwent two C–Cl cleavages to furnish methyl derivative **2AD**.

With the scope of the reductive dehalogenation shown to be broad across a range of substrates, we next turned our attention to the mechanism of this reaction. To gain insights into the reaction mechanism, intermolecular cyclization of alkyl chloride **1AE** was carried out (Figure 3B). Under our optimized conditions, THF derivative **4AE** was obtained from **1AE** in 78% yield. A comparable result was observed with Oshima's conditions using zirconocene(III) prepared from Cp_2ZrCl_2, Red-Al, and Et_3B, suggesting the involvement of a zirconocene(III) species.[54,55] To better understand the mechanism of C–Cl bond cleavage, we made use of luminescence quenching studies (Figure 3C). Stern-Volmer analysis showed that the excited photocatalyst is efficiently quenched by zirconocene and not thiourea, which is in agreement with the reduction of zirconocene by the excited photocatalyst. Next, thiouronium formation via an S_N2 process was investigated (Figure 3D). The possibility of reductive radical generation emerged from recent reports from the Melchiorre group.[56–58] An experiment without light irradiation revealed that the starting chloride remains intact even in the presence of base: the corresponding thiouronium was not observed. To further investigate the C–Cl bond cleavage, we compared the reactivity between unactivated alkyl chlorides (Figure 3E). When a competitive experiment was carried out with a 1:1 mixture of **1B** and **1N**, the hydrogenation was faster for the secondary chloride. Tertiary chloride **1U** was more reactive than the secondary chloride **1N**, thus the rate of C–Cl bond cleavage is in the order of tertiary > secondary > primary, which is consistent with the order of the calculated kinetic barrier of chlorine atom transfer with zirconocene (III) (0.6, 1.7, and 4.5 kcal/mol, see the SI for details). A series of mechanistic studies are in agreement with the hypothesis that chlorine atom transfer from alkyl chloride to zirconocene(III) occurred with the assistance of the photocatalyst.

We next sought to expand the synthetic utility of the newly developed C–Cl bond cleavage. Alkyl boronic esters are high-value synthetic precursors due to their synthetic versatility allowing for a diverse array of transformations as well as their utility in chemical biology and drug discovery.[59] Despite the tremendous advances in photochemical dechlorinative transformations, borylation of unactivated alkyl chlorides remains elusive.[60] To our delight, we found that our protocol is applicable to the photochemical borylation of alkyl chlorides (Scheme 1). The exposure of alkyl chlorides to Cp_2ZrCl_2 in the presence of **P1**, 1,3-dicyclohexylurea, and $B_2(cat)_2$ under visible light irradiation smoothly provided the desired boronic esters after the treatment with pinacol under basic condition. It is noteworthy that 1,3-dicyclohexylurea is more effective than **T3** and other thioureas in the borylation (see the SI for details), presumably due to a better coordinating ability of the carbonyl oxygen toward $B_2(cat)_2$ than sulfur.[61–63] Aliphatic primary borates including neopentyl borate were successfully obtained in good yields (**3A–3D**). As well as aryl chloride **1E**, readily reducible aryl bromide **1F** was tolerated to afford borylated compounds **3E** and **3F**. Secondary chlorides, possessing either acyclic or cyclic alkyl substituents efficiently underwent borylation under the optimized conditions (**3G-3J**). The C–Cl bond cleavage of tertiary chloride **1V** also proceeded successfully to afford borylated adamantane **3K**. In addition to cholesterol derivatives (**3L**), caffein derivatives (**3M**) was successfully borylated. Notably, 1,4-dichloro butane was found to be a suitable substrate, and diborylated compound **3N** was obtained. It should be noted that mixtures of diastereomers (**3H** and **3L**) were obtained from diastereomerically pure starting materials. This observation provides further support for radical-mediated C–Cl bond cleavage.



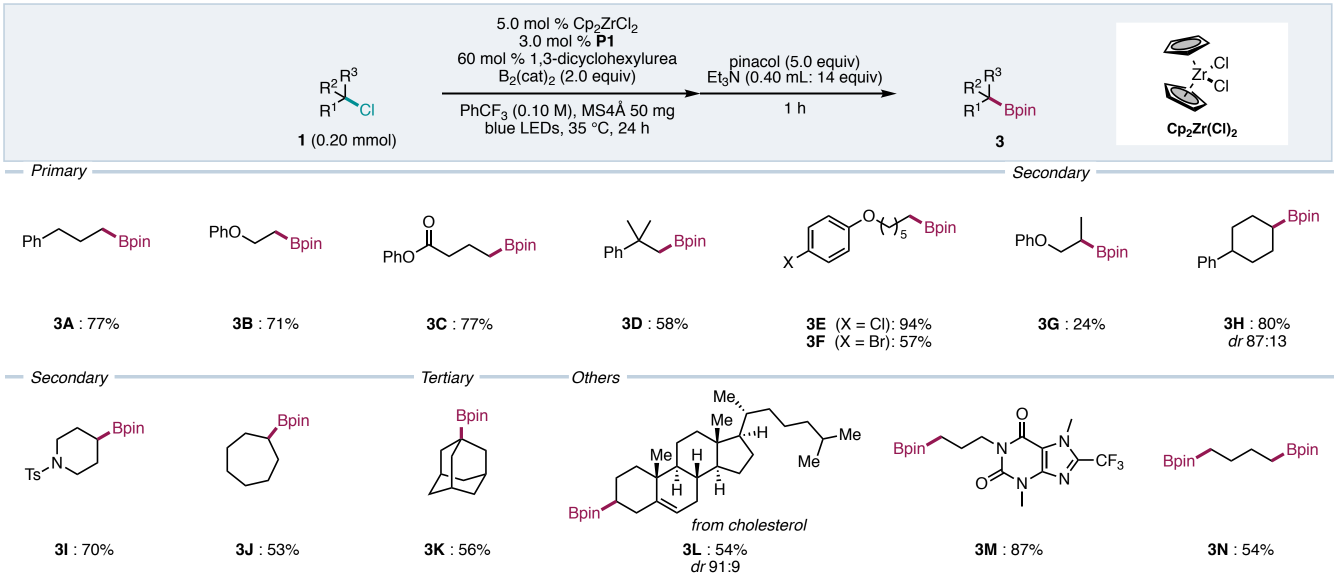
base	1B/%
none	97
K_2CO_3	96

	1B/%	2B/%	1N/%	2N/%
3 h	82	8	42	50
6 h	26	60	0	92

	1N/%	2N/%	1U/%	2U/%
3 h	18	70	2	88
6 h	0	96	0	100

Figure 3. Reductive activation of alkyl chlorides (A) Substrate scope. [a]Reactions were conducted on a 0.20 mmol scale and yields are for isolated material unless otherwise noted. All data are the average of two experiments. [b]Yields were determined by GC analysis due to volatility. [c]Reaction was run for 24 h. (B) Intramolecular cyclization. (C) Stern–Volmer quenching experiments. (D) Substitution of thiourea. (E) Competitive experiments. See the SI for details.

Scheme 1. Substrate Scope[a]



[a]Reactions were conducted on a 0.20 mmol scale and yields are for isolated material. All data are the average of two experiments. See the SI for details.

In summary, we succeeded in the development of zirconocene-photoredox cooperative catalysis for the reductive hydrogenation and borylation of unactivated alkyl chlorides. Our protocol accommodated primary, secondary, and tertiary chlorides, in the presence of substituents that are commonly susceptible to strong reductants. A variety of experimental observations were consistent with a radical-mediated C–Cl bond cleavage. We believe that changing the metal center in the metallocene influences the energy profile of C–Cl bond cleavage, which is useful in the context of halogen atom abstraction. Efforts towards exploring transformations with this new cooperative catalysis and further mechanistic investigations are ongoing in our laboratory.[64]

AUTHOR INFORMATION

Corresponding Author

* Eisuke Ota – Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan;
orcid.org/0000-0002-3436-9768; Email: eota@aoni.waseda.jp
* Junichiro Yamaguchi – Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan;
orcid.org/0000-0002-3896-5882; Email: junyamaguchi@waseda.jp

Author

Toshimasa Okita – Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan
Kazuhiro Aida – Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan
Keisuke Tanaka – Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Number JP21H05213 (Digitalization-driven Transformative Organic Synthesis) (to J.Y.), JP20K15290 (to E.O.). This work was partly supported by JST ERATO Grant Number JPMJER1901 (to J.Y.). Materials Characterization Central Laboratory in Waseda University is acknowledged for the support of HRMS measurement. A part of computations was performed at the Research Center for Computational Science, Okazaki, Japan.

Author Contributions

§(K.A., K.T.) These authors contributed equally to this work.

REFERENCES

(1) Ashby, J. Naturally Occurring Organohalogen Compounds. *Mutat. Res. Mol. Mech. Mutagen.* **1996**, *356*, 297.

(2) Gribble, G. W. *Naturally Occurring Organohalogen Compounds - A Comprehensive Update*, 1st ed.; Fortschritte der Chemie organischer Naturstoffe / Progress in the Chemistry of Organic Natural Products; Springer Vienna: Vienna, 2010; Vol. 91.

(3) Gribble, G. W. A Recent Survey of Naturally Occurring Organohalogen Compounds. *Environ. Chem.* **2015**, *12*, 396–405.

(4) Gál, B.; Bucher, C.; Burns, N. Z. Chiral Alkyl Halides: Underexplored Motifs in Medicine. *Mar. Drugs* **2016**, *14*, 1–11.

(5) Ertl, P.; Schuhmann, T. A Systematic Cheminformatics Analysis of Functional Groups Occurring in Natural Products. *J. Nat. Prod.* **2019**, *82*, 1258–1263.

(6) *The Carbon-Halogen Bond (1973)*; Patai, S., Ed.; John Wiley & Sons, Ltd.: Chichester, UK, 1973.

(7) Crespi, S.; Fagnoni, M. Generation of Alkyl Radicals: From the Tyranny of Tin to the Photon Democracy. *Chem. Rev.* **2020**, *120*, 9790–9833.

(8) 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.

(9) Lambert, F. L.; Ingall, G. B. Voltammetry of Organic Halogen Compounds. IV. The Reduction of Organic Chlorides at the Vitreous (Glassy) Carbon Electrode. *Tetrahedron Lett.* **1974**, *15*, 3231–3234.

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

(11) Alonso, F.; Beletskaya, I. P.; Yus, M. Metal-Mediated Reductive Hydrodehalogenation of Organic Halides. *Chem. Rev.* **2002**, *102*, 4009–4092.

(12) Krief, A.; Laval, A.-M. Coupling of Organic Halides with Carbonyl Compounds Promoted by SmI_2 , the Kagan Reagent. *Chem. Rev.* **1999**, *99*, 745–778.

(13) Szostak, M.; Spain, M.; Procter, D. J. Recent Advances in the Chemoselective Reduction of Functional Groups Mediated by Samarium(Ii) Iodide: A Single Electron Transfer Approach. *Chem. Soc. Rev.* **2013**, *42*, 9155–9183.

(14) Davies, A. G. Organotin Hydrides. In *Organotin Chemistry*; Wiley Online Books; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, FRG, 2004; pp 244–265.

(15) Chatgilialoglu, C. *Organosilanes in Radical Chemistry*; John Wiley & Sons, Ltd: Chichester, UK, 2004.

(16) Cybularczyk-Cecotka, M.; Szczepanik, J.; Giedyk, M. Photocatalytic Strategies for the Activation of Organic Chlorides. *Nat. Catal.* **2020**, *3*, 872–886.

(17) 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.

(18) 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.

(19) 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.

(20) 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.

(21) 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.

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

(23) 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

(24) 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 $C(sp^3)$-C(sp) Bond Formation Catalyzed by a B12 Complex. *Chem. Commun.* **2019**, *55*, 13070–13073.

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

(26) 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.

(27) Lee, G. S.; Kim, D.; Hong, S. H. Pd-Catalyzed Formal Mizoroki–Heck Coupling of Unactivated Alkyl Chlorides. *Nat. Commun.* **2021**, *12*, 1–12.

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

(29) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Oltra, J. E. Cp_2TiCl in Natural Product Synthesis. In *Radicals in Synthesis II*; Springer-Verlag: Berlin/Heidelberg, 2006; Vol. 37, pp 63–91.

(30) Krische, M. J. Radicals in Synthesis III. In *Topics in Current Chemistry*; Heinrich, M., Gansäuer, A., Eds.; Topics in Current Chemistry; Springer Berlin Heidelberg: Berlin, Heidelberg, 2012; Vol. 320.

(31) Streuff, J. Reductive Umpolung Reactions with Low-Valent Titanium Catalysts. *Chem. Rec.* **2014**, *14*, 1100–1113.

(32) Rosales, A.; Rodríguez-García, I.; Muñoz-Bascón, J.; Roldan-Molina, E.; Padial, N. M.; Morales, L. P.; García-Ocaña, M.; Oltra, J. E. The Nugent Reagent: A Formidable Tool in Contemporary Radical and Organometallic Chemistry. *Eur. J. Org. Chem.* **2015**, *2015*, 4567–4591.

(33) Streuff, J.; Gansäuer, A. Metal-Catalyzed β-Functionalization of Michael Acceptors through Reductive Radical Addition Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 14232–14242.

(34) Castro Rodríguez, M.; Rodríguez García, I.; Rodríguez Maecker, R. N.; Pozo Morales, L.; Oltra, J. E.; Rosales Martínez, A. Cp_2TiCl: An Ideal Reagent for Green Chemistry? *Org. Process Res. Dev.* **2017**, *21*, 911–923.

(35) Zweig, J. E.; Kim, D. E.; Newhouse, T. R. Methods Utilizing First-Row Transition Metals in Natural Product Total Synthesis. *Chem. Rev.* **2017**, *117*, 11680–11752.

(36) McCallum, T.; Wu, X.; Lin, S. Recent Advances in Titanium Radical Redox Catalysis. *J. Org. Chem.* **2019**, *84*, 14369–14380.

(37) Martínez, A. R.; Morales, L. P.; Ojeda, E. D.; Rodríguez, M. C.; Rodríguez-García, I. The Proven Versatility of Cp_2TiCl. *J. Org. Chem.* **2021**, *86*, 1311–1329.

(38) Parrish, J. D.; Shelton, D. R.; Little, R. D. Titanocene(III)-Promoted Reformatsky Additions. *Org. Lett.* **2003**, *5*, 3615–3617.

(39) Rosales, A.; Oller-López, J. L.; Justicia, J.; Gansäuer, A.; Oltra, J. E.; Cuerva, J. M. Unprecedented Barbier-Type Reactions Catalysed by Titanocene(iii). *Chem. Commun.* **2004**, 2628–2629.

(40) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Diéguez, H. R.; Sánchez, E. M. Mild Ti^{III}- and Mn/Zr^{IV} -Catalytic Reductive Coupling of Allylic Halides: Efficient Synthesis of Symmetric Terpenes. *J. Org. Chem.* **2007**, *72*, 2988–2995.

(41) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Akssira, M.; El Hanbali, F.; Arteaga, J. F.; Diéguez, H. R.; Sánchez, E. M. Couplings of Benzylic Halides Mediated by Titanocene Chloride: Synthesis of Bibenzyl Derivatives. *J. Org. Chem.* **2007**, *72*, 2251–2254.

(42) Estévez, R. E.; Paradas, M.; Millán, A.; Jiménez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. Ti-Catalyzed Reformatsky-Type Coupling between α-Halo Ketones and Aldehydes. *J. Org. Chem.* **2008**, *73*, 1616–1619.

(43) Justicia, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Oltra, J. E.; Cuerva, J. M. Efficient Propargylation of Aldehydes and Ketones Catalyzed by Titanocene(III). *Adv. Synth. Catal.* **2009**, *351*, 2295–2300.

(44) Muñoz-Bascón, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Rosales, A.; Oltra, J. E. Highly Selective Barbier-Type Propargylations and Allenylations Catalyzed by Titanocene(III). *Chem. Eur. J.* **2012**, *18*, 14479–14486.

(45) Muñoz-Bascón, J.; Hernández-Cervantes, C.; Padial, N. M.; Álvarez-Corral, M.; Rosales, A.; Rodríguez-García, I.; Oltra, J. E. Ti-Catalyzed Straightforward Synthesis of Exocyclic Allenes. *Chem. Eur. J.* **2014**, *20*, 801–810.

(46) González-Delgado, J. A.; Prieto, C.; Enríquez, L.; Jaraíz, M.; López-Pérez, J. L.; Barrero, A. F.; Arteaga, J. F. Ti-Mediated Efficient

Reductive Dehalogenation of Carbon-Halogen Bonds. *Asian J. Org. Chem.* **2016**, *5*, 991–1001.

(47) Nelsen, T. R.; Tufariello, J. J. Reduction of Organic Halides by the System Titanocene Dichloride-Magnesium. *J. Org. Chem.* **1975**, *40*, 3159–3160.

(48) Wu, X.; Hao, W.; Ye, K. Y.; Jiang, B.; Pombar, G.; Song, Z.; Lin, S. Ti-Catalyzed Radical Alkylation of Secondary and Tertiary Alkyl Chlorides Using Michael Acceptors. *J. Am. Chem. Soc.* **2018**, *140*, 14836–14843.

(49) Wang, X.; Cui, P.; Xia, C.; Wu, L. Catalytic Boration of Alkyl Halides with Borane without Hydrodehalogenation Enabled by Titanium Catalyst. *Angew. Chem., Int. Ed.* **2021**, *60*, 12298–12303.

(50) 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**. https://doi.org/10.1016/j.chempr.2022.04.010.

(51) Bell, R. P. The Theory of Reactions Involving Proton Transfers. *Proc. R. Soc. London. Ser. A - Math. Phys. Sci.* **1936**, *154*, 414–429.

(52) Evans, M. G.; Polanyi, M. Further Considerations on the Thermodynamics of Chemical Equilibria and Reaction Rates. *Trans. Faraday Soc.* **1936**, *32*, 1333–1360.

(53) Klare, S.; Gordon, J. P.; Gansäuer, A.; RajanBabu, T. V.; Nugent, W. A. The Reaction of β,γ–epoxy Alcohols with Titanium(III) Reagents. A Proposed Role for Intramolecular Hydrogen Bonding. *Tetrahedron* **2019**, *75*, 130662.

(54) Fujita, K.; Nakamura, T.; Yorimitsu, H.; Oshima, K. Triethylborane-Induced Radical Reaction with Schwartz Reagent. *J. Am. Chem. Soc.* **2001**, *123*, 3137–3138.

(55) Fujita, K.; Yorimitsu, H.; Oshima, K. Development of Radical Reactions with Zirconocene Complexes as Electron Transfer Reagents. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1727–1736.

(56) Schweitzer-Chaput, B.; Horwitz, M. A.; de Pedro Beato, E.; Melchiorre, P. Photochemical Generation of Radicals from Alkyl Electrophiles Using a Nucleophilic Organic Catalyst. *Nat. Chem.* **2019**, *11*, 129–135.

(57) Cuadros, S.; Horwitz, M. A.; Schweitzer-Chaput, B.; Melchiorre, P. A Visible-Light Mediated Three-Component Radical Process Using Dithiocarbamate Anion Catalysis. *Chem. Sci.* **2019**, *10*, 5484–5488.

(58) Mazzarella, D.; Magagnano, G.; Schweitzer-Chaput, B.; Melchiorre, P. Photochemical Organocatalytic Borylation of Alkyl Chlorides, Bromides, and Sulfonates. *ACS Catal.* **2019**, *9*, 5876–5880.

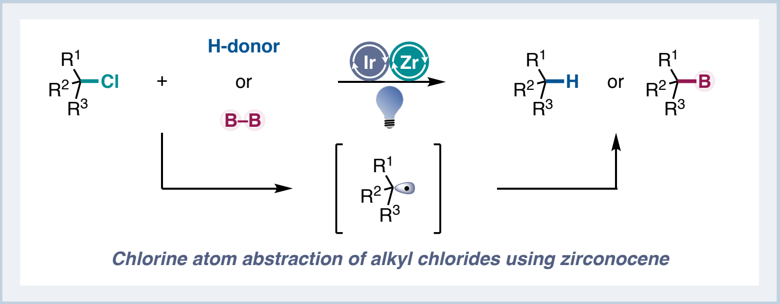
(59) Hall, D. G. *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011.

(60) Jiao, Z. F.; Tian, Y. M.; Guo, X. N.; Radius, U.; Braunschweig, H.; Marder, T. B.; Guo, X. Y. Visible-Light-Driven Graphene Supported Cu/Pd Alloy Nanoparticle-Catalyzed Borylation of Alkyl Bromides and Chlorides in Air. *J. Catal.* **2021**, *395*, 258–265.

(61) Kepp, K. P. A Quantitative Scale of Oxophilicity and Thiophilicity. *Inorg. Chem.* **2016**, *55*, 9461–9470.

(62) Previous studies of radical borylation indicates the coordination of oxygen to boron atom is essential to activate diboron agents, see; Fawcett, A.; Pradeilles, J.; Wang, Y.; Mutsuga, T.; Myers, E. L.; Aggarwal, V. K. Photoinduced Decarboxylative Borylation of Carboxylic Acids. *Science* **2017**, *357*, 283–286. See also reference 63.

(63) Cheng, Y.; Mück-Lichtenfeld, C.; Studer, A. Transition Metal-Free 1,2-Carboboration of Unactivated Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 6221–6225.



Chlorine atom abstraction of alkyl chlorides using zirconocene