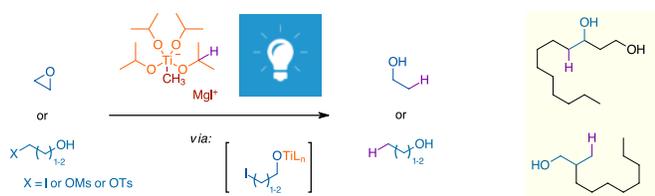


Visible-Light-Promoted Reduction of Epoxides, Hydroxysulfonates and Halohydrines with Alkyltitanium Alkoxides

Artyom Mikhailiov, Aliaksei Flerko, Dzyiana Atroshchanka, Aliaksei Harakhouski, Arsenii Budko, Kirill Stasko, Andrei Bialkevich, Siarhei Shepialevich, Yahor Rusakovich and Alaksiej Hurski*



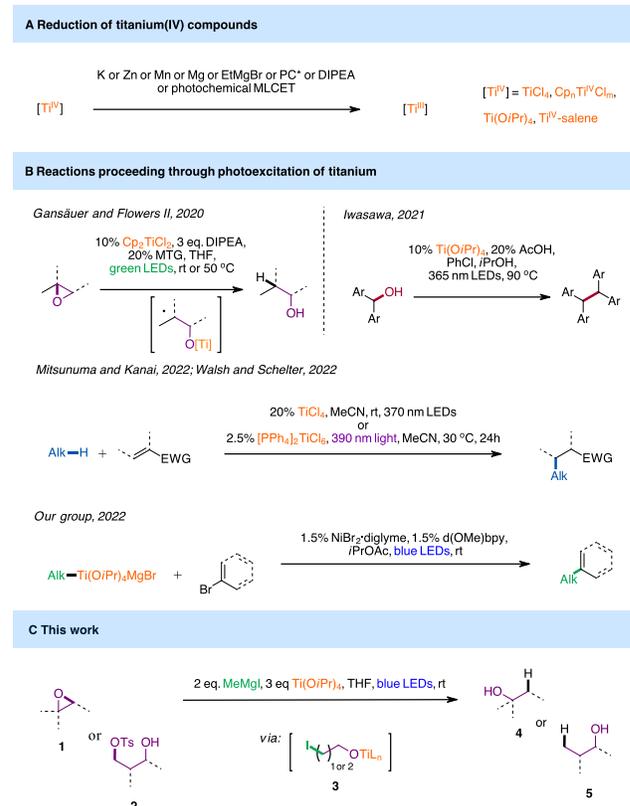
ABSTRACT: Alkyltitanium alkoxides generally serve as nucleophiles in the reactions with carbonyl compounds and cross-coupling. Their application as reductants is known but remains underdeveloped. Here, we report that irradiation with visible light makes these organometallic compounds efficient reducing agents for the dehalogenation of 1,2- and 1,3-haloalcohols. This was utilized for the reduction of epoxides and hydroxysulphonates, which started with the *in situ* formation of haloalkoxies and followed by the photochemical dehalogenation step. Ester, amide, alkyne, sulphone, and remote bromide groups were stable under the reaction conditions.

Being readily available and non-toxic, titanium reagents and catalysts have been employed in remarkably diverse organic transformations including oxidation, reduction and C-C bond forming reactions.¹⁻⁴ Low valent titanium species, especially Ti^{III} compounds, are powerful reducing agents capable of reacting with carbonyl, imine, oxime, epoxide, acylaziridine, halide, hydroxyl, oxazoline and other functional groups (Scheme 1A).⁵⁻¹⁰ These reagents are air-sensitive and typically prepared *in situ* by the reduction of an available Ti^{IV} compound with a suitable reductant such as K, Zn, Mn, Mg metals or a Grignard reagent. Recently, Ti^{III/IV} catalysis was successfully merged with photoredox catalysis, where reduction of Ti^{IV} was achieved by the oxidative quenching of a photocatalyst.¹¹

Direct photoexcitation of a titanium reagent is another attractive tool for the generation of low-valent titanium compounds (Scheme 1B). This was utilized by Gansäuer and Flowers II in the reductive cleavage of epoxides.¹² Photoexcitation of Cp₂Ti^{IV}Cl₂ complex enabled its reduction to Cp₂Ti^{III}Cl with a very mild reducing agent, diisopropylethylamine. Subsequent ring-opening of an epoxide by Ti^{III} complex proceeded regioselectively at the more substituted carbon because this led to a more stable radical intermediate. Alternatively, photoexcitation of titanium compounds can lead to Ti^{IV}-X bond homolysis, which delivers Ti^{III} and X radical. Iwasawa described deoxygenative dimerization of benzylic alcohols promoted by a Ti^{III} reagent generated by the light-driven homolysis of Ti^{IV}-O*i*Pr bond.¹³ Photolysis of Ti-Cl bond was deployed by Mitsunuma and Kanai¹⁴ as well as by Walsh and Schelter¹⁵ in C-H functionalization of alkanes. In these approaches, both Ti^{III} and chlorine radical were essential for the reactions. While chlorine radical abstracted H-atom from the substrate, Ti^{III} species were necessary in the subsequent Giese addition stage for the reduction of radical center to anion. In our group, a light-promoted cross-coupling of alkyltitanium alkoxides with organic halides was recently developed.¹⁶ The reaction proceeded through the light

induced Ti-C bond homolysis and then both alkyl radical and Ti^{III} species were engaged in the nickel catalytic cycle.

Scheme 1 Reduction with low-valent titanium compounds

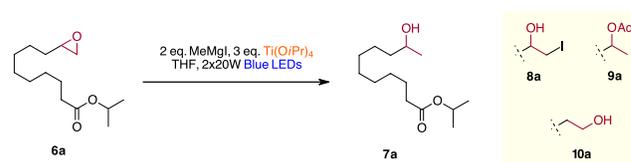


Here, we report that under visible light irradiation, the *in situ* generated alkyltitanium alkoxides are efficient reagents for the

reduction of epoxides **1** to alcohols **4** (Scheme 1C). Hydroxytosylates **2** can also be reduced under the same conditions affording alcohols **5**. Both these reactions begin with a nucleophilic substitution step and follows by the dehalogenation of intermediate **3** with photoexcited low-valent titanium species. Therefore, the reduction of epoxides proceeded at the less substituted bond in the ring, which is opposite to the common regioselectivity in Ti^{III}-promoted reactions.

First, we found that blue-light-promoted reduction of epoxide **6a** with methylmagnesium iodide and Ti(O*i*Pr)₄ in THF at ambient temperature delivered secondary alcohol **7a** in a high 89% yield (Table 1, entry 1). Ester group in the substrate was non-reactive under these conditions. The experiment in dark led to iodohydrin **8a** in 90% yield indicating that the reaction begins with regioselective nucleophilic ring-opening of the epoxide at the more sterically available carbon (entry 2). When this reaction mixture was further subjected to blue light irradiation, secondary alcohol **7a** was formed in 81% yield (entry 3). Notably, direct reduction of the epoxide by an alkyltitanium alkoxide is also possible. When a halogen-free dibutylmagnesium was used instead of methylmagnesium iodide, regioselectivity of the ring-opening became the same as in Ti^{III}-promoted reactions. Primary alcohol **10a** became a major product forming in 75% yield along with 20% of secondary alcohol **7a** (entry 4). The presence of a Grignard reagent was crucial for the dehalogenation. When MgI₂ was used instead of MeMgI, only iodohydrine **8a** was isolated (entry 5). Two-fold decrease of the light intensity led to a little decline in both yield and regioselectivity (entry 6). UV/vis spectroscopy revealed that the titanium reagent absorbs broad spectrum of UV and visible light without any distinct absorption peak (see SI). This suggested that other than blue light source can also promote the reaction. Indeed, upon irradiation with fluorescent light, product formed in 71% yield (entry 7). Changing the solvent to ether caused significant decrease in yield of **7a** to 61% (entry 8). Unexpectedly, when the reduction was carried out in isopropyl acetate, ester product **9a** was obtained in a good 72% yield. Its formation was a result of transesterification of the solvent with **7a** catalyzed by the titanium alkoxide (entry 9). The use of methylmagnesium bromide instead of methylmagnesium iodide caused a slight decrease in yield and regioselectivity (entry 10). This experiment indicated that not only iodohydrine but also bromohydrine intermediates undergo efficient photochemical reduction with methyltitanium isopropoxide. When ethylmagnesium iodide was employed instead of methyl Grignard reagent, the yield of **7a** declined to 60% (entry 11). Moreover, the reaction was accompanied by Kulinkovich cyclopropanation of the ester unit and deoxygenation of epoxide to alkene. Only trace amounts of cyclopropanation by-products were observed when isopropylmagnesium iodide or *n*-butylmagnesium chloride were used, but the outcome of the reaction was worse than under the standard conditions (entries 12-13). The most reproducible results were obtained when 2 equivalents of methylmagnesium iodide and 3 equivalents of titanium isopropoxide were employed. Decreasing the relative amounts of titanium isopropoxide led to significant decline of the yield (entries 14-15). When 1 equivalent of methylmagnesium iodide was used, the yield lowered insignificantly to 80% (entry 16).

Table 1. Optimization of the reaction conditions



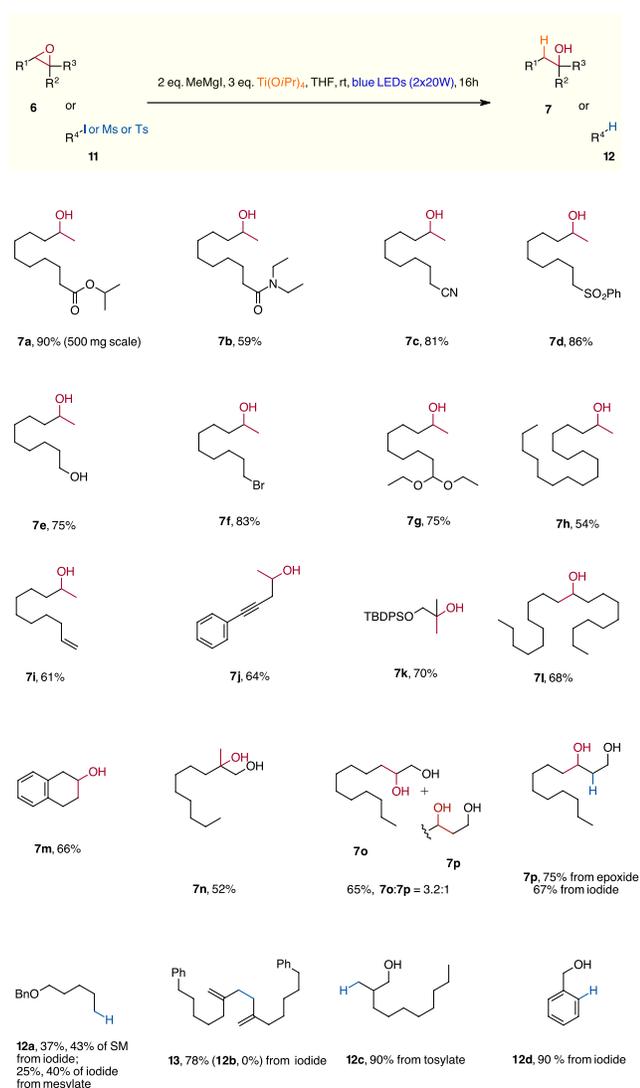
Entry	Deviation from the standard conditions	Yield of 7a ^a (7a : 10a) ^b
1	-	89% (99:1)
2	No light	0%; 90% of 8a
3	No light (12h) then blue LEDs (15h)	81% (99:1)
4	<i>n</i> Bu ₂ Mg	20%; 75% of 10a
5	MgI ₂ instead of MeMgI	0%; 69% ^c of 8a
6	20W Blue LED light source	85% (97:3)
7	15W CFL bulb	71% (98:2)
8	in Et ₂ O	61% (91:9)
9	in <i>i</i> PrOAc	4%; 72% ^c of 9a
10	MeMgBr	81% (87:13)
11	EtMgI	60% ^d (100:0)
12	<i>i</i> PrMgI	70% (100:0)
13	<i>n</i> BuMgCl	73% (84:16)
14	2 eq MeMgI, 2 eq Ti(O <i>i</i> Pr) ₄	68% (96:4)
15	2 eq MeMgI, 1 eq Ti(O <i>i</i> Pr) ₄	43% (89:11)
16	1 eq MeMgI, 2 eq Ti(O <i>i</i> Pr) ₄	80% (95:5)

^aNMR yields; 4-bromoanisole was used as an internal standard. ^bDetermined by GC analysis. ^cIsolated yield. ^dAlkene and cyclopropanol formed in 9% and 27% yields.

Having optimized the reaction conditions, we investigated the scope of photochemical reduction (Scheme 2). Not only ester but also amide, nitrile and sulfone groups were tolerated and products **7a**, **7b-d** were isolated in 90% (500 mg, 2.07 mmol scale), 59%, 46% and 72% yields, respectively. Diol **7e** was successfully prepared in 75% yield from the epoxide bearing an unprotected hydroxyl moiety. While a halide group in the halohydrin intermediate underwent smooth reduction, remote bromide moiety in **6f** was non-reactive and **7f** was isolated in a high 83% yield. Epoxide **6g** containing acetal protecting group reacted smoothly delivering **7g** in a good 75% yield. Non functionalized epoxide with a long linear hydrocarbon chain was transformed to alcohol **7h** in a moderate 54% yield. Being reactive with Ti^{III} complexes, alkene and alkyne units did not interfere with the reduction and corresponding alcohols **7i** and **7j** were isolated in 61% and 64% yields, respectively. 1,1-Disubstituted epoxide bearing a silyl protecting group was efficiently reduced to tertiary alcohol **7k**. Both mono- and bicyclic 1,2-disubstituted epoxides underwent smooth reduction giving alcohols **7l** and **7m** in 68% and 66% yields. Next, we studied reduction of α,β - and β,γ -epoxy alcohols to diols. 1,2-Diol **7n** was prepared regioselectively from the 1,1-disubstituted epoxide in 52% yield. Reduction of linear epoxy alcohol **6n** delivered an inseparable 3.2:1 mixture of 1,2- and 1,3-diols **7o** and **7p** in 65% overall yield. Conversely, reduction of linear β,γ -epoxy alcohol **6p** proceeded with good regioselectivity affording 1,3-diol **7p** in 75% yield. The same product was obtained by the reduction of 2-iodododecan-1,3-diol in 67% yield. Proximity of hydroxyl group was crucial for the dehalogenation. Deiodination of **11a**, which lacks the directing group, proceeded incompletely furnishing alkane **12a** in 37% yield only

and 43% of the recovered starting material. Iodide **11a** can be also generated *in situ* from the corresponding mesylate under the reaction conditions. This experiment led to alkane **12a** and iodide **11a** in 25% and 40% yields, respectively. Increasing the reaction time and amounts of methyltitanium reagent did not allow us to achieve the complete reduction. When a more reactive allyl iodide was tested, dimerization product **13** was isolated instead of the expected dehalogenated hydrocarbon. A tosylate with directing hydroxyl group at β -position underwent smooth reduction like it was observed for α -halohydrins. Alcohol **12c** was isolated in high 90% yield from the corresponding 3-hydroxytosylate **11c**. Dehalogenation of aryl iodide **11d** that bears a directing hydroxyl group also proceeded efficiently giving benzyl alcohol **12d** in a high 91% yield. Control experiments revealed that presence of the directing group was crucial for the reaction, but reduction of the aryl iodide group in **11d** was not photochemical and proceeded with the same efficiency in dark.

Scheme 2 Scope of the photochemical reduction

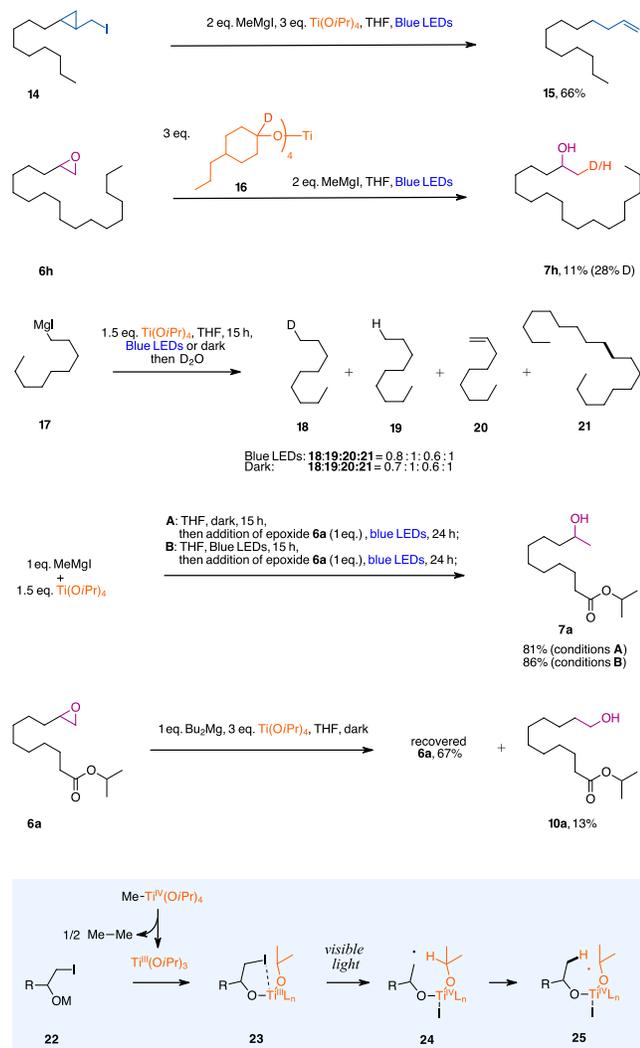


To gain insight into mechanism of the dehalogenation step, we carried out additional control experiments (Scheme 3). Reduction of iodomethyl cyclopropane **14** under the standard conditions gave ring-opening product **15** in 66% yield indicating the formation of alkyl radical intermediates. Such a radical

could further undergo oxidative addition to a Ti^{III} complex or abstract H-atom from another molecule. D₂O quenching of the reaction mixture after epoxide **6h** reduction gave no deuterated product, which showed that HAT follows by the radical formation. Reaction in THF-d₈ gave no deuterated product as well. Finally, we detected 28% incorporation of the isotopic label in **7h** when titanium alkoxide **16** was used instead of Ti(OiPr)₄. This outcome indicated that isopropoxy group served as a H-donor like it was previously observed by Okamoto.¹⁷ Next, we studied stability of the alkyltitanium reagent under the reaction conditions. When a mixture of nonylmagnesium iodide **17** and titanium isopropoxide was irradiated for 15 h and then quenched with D₂O, a mixture of deuterated nonane **18**, nonane **19**, nonene **20** and dimerization product **21** were formed in 0.8:1:0.6:1 ratio. Formation of the deuterated alkane **18** in a low 24% yield indicated that only minor amounts of the alkyltitanium isopropoxide remained in the solution, while formation of hydrocarbons **19-21** suggested that the alkyl ligand reduced Ti^{IV} center to Ti^{III}. Remarkably, the ratio of hydrocarbons **18-21** was almost the same in the identical control experiment run in the dark. This result suggested that the formation of Ti^{III} species was not photochemical and the light-promoted step was likely to be alkyl iodide reduction with low-valent titanium species. A control experiments with the equimolar amounts of methylmagnesium iodide confirmed this assumption. First, the *in situ* generated methyltitanium isopropoxide was stirred overnight in dark or under the blue light irradiation. Then, epoxide **6a** was added to both experiments and the reactions were further subjected to visible light irradiation. Both reactions delivered product **7a** in similar yields. Considering that most of the alkyltitanium reagent decomposed during the first stage of the experiments, high 81% and 86% yields of **7a** suggested that visible light is likely activate Ti^{III} species during the dehalogenation step. Next, we found that light also assisted direct reduction of epoxide **6a** to primary alcohol **10a** by the low-valent titanium species generated in the absence of halide anions. It was not vital like in the dehalogenation reaction, but the reductive ring-opening of **6a** with Ti(OiPr)₄ and Bu₂Mg in dark proceeded significantly less efficient giving **10a** along with recovered **6a** in 13% and 67% yields, respectively.

Based on the control experiments, we proposed a mechanism of the reduction. First, Ti^{IV} center in alkyltitanium alkoxides undergoes reduction by the alkyl ligand to Ti^{III} species. Then, iodohydrine **22** formed by the nucleophilic ring opening of the epoxide substitutes isopropoxide ligand in Ti^{III} alkoxide. Under visible light irradiation, one electron reduction of a pendant iodide group by Ti^{III} center occurs in **23**. Next, hydrogen transfer from isopropoxy unit to the primary radical center in **24** leads to intermediate **25**. Its further transformation remains unclear, but it is likely that **25** undergo the pinacol coupling. Formation of ketone like it was reported by Okamoto¹⁷ is unlikely because we detected only trace amounts of this product in the reduction of **6h** by MeMgI and titanium alkoxide **16**. We also did not observe a product of the Grignard reagent addition to the ketone.

Scheme 3 Control experiments and plausible mechanism



In conclusion, we have found that 1,2- and 1,3-haloalcohols undergo efficient light-induced hydroxyl-directed dehalogenation by low-valent titanium species generated from methylmagnesium iodide and titanium(IV) isopropoxide. The reaction was successfully utilized for the reduction of epoxides and hydroxytosylates to alcohols. These substrates first underwent nucleophilic substitution under the reaction conditions and then the dehalogenation step. Mechanistic studies revealed that alkyltitanium reagent undergoes decomposition delivering low-valent titanium complexes that further reduce the halide group under irradiation with visible light.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data of synthesized compounds and NMR spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

Alaksiej Hurski – Republican Scientific Center of Human Issues of Belarusian State University, Kurčatava 7, Minsk 220064, Belarus; Scientific Testing Center Campilab Ltd., Centralnaja 30A, Dynaraŭka 222202, Belarus <https://orcid.org/0000-0002-8599-2621>

E-mail: alaksiej.hurski@gmail.com

Authors

Artyom Mikhaliov - Republican Scientific Center of Human Issues of Belarusian State University, Kurčatava 7, Minsk 220064, Belarus

Aliaksei Flerko - Department of chemistry, Belarusian State University Niezaliežnasci 4, Minsk 220030, Belarus

Dziyana Atroshchanka - Republican Scientific Center of Human Issues of Belarusian State University, Kurčatava 7, Minsk 220064, Belarus

Aliaksei Harakhouski - Republican Scientific Center of Human Issues of Belarusian State University, Kurčatava 7, Minsk 220064, Belarus

Arsenii Budko - Department of chemistry, Belarusian State University Niezaliežnasci 4, Minsk 220030, Belarus

Kirill Stasko - Department of chemistry, Belarusian State University Niezaliežnasci 4, Minsk 220030, Belarus

Andrei Bialkevich - Department of chemistry, Belarusian State University Niezaliežnasci 4, Minsk 220030, Belarus

Siarhei Shepialevich - Department of chemistry, Belarusian State University Niezaliežnasci 4, Minsk 220030, Belarus

Yahor Rusakovich - Republican Scientific Center of Human Issues of Belarusian State University, Kurčatava 7, Minsk 220064, Belarus

Author Contributions

The manuscript was written through contributions of all authors.

ACKNOWLEDGMENT

Financial support was provided by the State Program for Scientific Research (Belarus) (project 2.2.01.07 (520/42)). We thank Dr. Vitaly Syakhovich and his group (National Anti-Doping Laboratory) for the HRMS analysis, Dmitri Tarasau (A. N. Sevchenko Institute of Applied Physical Problems of Belarusian State University) for UV-vis spectra, Yulia Konik for GC-MS analysis.

REFERENCES

- (1) Marek, Prof. I. Titanium and Zirconium in Organic Synthesis. 2019.
- (2) Manßen, M.; Schafer, L. L. Titanium Catalysis for the Synthesis of Fine Chemicals – Development and Trends. *Chem. Soc. Rev.* **2020**, *49*, 6947–6994.
- (3) Katsuki, T.; Martin, V. Asymmetric Epoxidation of Allylic Alcohols: the Katsuki–Sharpless Epoxidation Reaction. *Organic Reactions.* **2012**, 1–299.
- (4) Wartmann, C.; Nandi, S.; Neudörfl, J.; Berkessel, A. Titanium Salalen Catalyzed Enantioselective Benzylic Hydroxylation. *Angew. Chem. Int. Ed.* **2023**, e202306584.
- (5) Wu, X.; Chang, Y.; Lin, S. Titanium Radical Redox Catalysis: Recent Innovations in Catalysts, Reactions, and Modes of Activation. *Chem* **2022**, *8*, 1805–1821.
- (6) Okamoto, S. Synthetic Reactions Using Low-valent Titanium Reagents Derived from $Ti(OR)_4$ or $CpTiX_3$ ($X = O\text{-}i\text{-Pr}$ or Cl) in the Presence of Me_3SiCl and Mg . *Chem. Rec.* **2016**, *16*, 857–872.
- (7) McCallum, T.; Wu, X.; Lin, S. Recent Advances in Titanium Radical Redox Catalysis. *J. Org. Chem.* **2019**, *84* (22), 14369–14380.
- (8) Matiushenkov, E. A.; Sokolov, N. A.; Kulinkovich, O. G. Alkylative Reduction of Titanium(IV) Isopropoxide with $EtMgBr$: Convenient Method for the Generation of Subvalent Titanium Alkoxide

Reagents and Their Reactivity in Pinacol Coupling Reactions. *Synlett* **2004**, 77–80.

(9) Churykau, D.; Zinovich, V.; Kulinkovich, O. A Convenient and Chemoselective Method for the Reductive Ring Cleavage of Isoxazoles and Isoxazolines with EtMgBr/Ti(Oi-Pr)₄ Reagent. *Synlett* **2004**, 2004, 1949–1952.

(10) Li, H.; Li, Y.; Yuan, W.; Qu, A.; Chen, K.; Zhu, Y. Photoredox/Ti Dual-Catalyzed Dehydroxylative Ring-Opening Giese Reaction of Cyclobutanone Oximes. *Green Synth. Catal.* **2023**.

(11) Fermi, A.; Gualandi, A.; Bergamini, G.; Cozzi, P. G. Shining Light on TiIV Complexes: Exceptional Tools for Metallaphotoredox Catalysis. *Eur. J. Org. Chem.* **2020**, 2020, 6955–6965.

(12) Zhang, Z.; Hilche, T.; Slak, D.; Rietdijk, N. R.; Oloyede, U. N.; Flowers, R. A.; Gansäuer, A. Titanocenes as Photoredox Catalysts Using Green-Light Irradiation. *Angew. Chem. Int. Ed.* **2020**, 59, 9355–9359.

(13) Sumiyama, K.; Toriumi, N.; Iwasawa, N. Use of Isopropyl Alcohol as a Reductant for Catalytic Dehydroxylative Dimerization of

Benzylic Alcohols Utilizing Ti–O Bond Photolysis. *Eur. J. Org. Chem.* **2021**, 2021, 2474–2478.

(14) Yamane, M.; Kanzaki, Y.; Mitsunuma, H.; Kanai, M. Titanium(IV) Chloride-Catalyzed Photoalkylation via C(Sp³)–H Bond Activation of Alkanes. *Org. Lett.* **2022**, 24, 1486–1490.

(15) Panetti, G. B.; Yang, Q.; Gau, M. R.; Carroll, P. J.; Walsh, P. J.; Schelter, E. J. Discovery and Mechanistic Investigation of Photoinduced Sp³ C–H Activation of Hydrocarbons by the Simple Anion Hexachlorotitanate. *Chem Catal.* **2022**, 2, 853–866.

(16) Leushukou, A. A.; Krech, A. V.; Hurski, A. L. Visible-Light-Promoted Nickel-Catalyzed Cross-Coupling of Alkyltitanium Alkoxides with Aryl and Alkenyl Halides. *Org. Lett.* **2022**, 24, 6277–6281.

(17) Kawaji, T.; Shohji, N.; Miyashita, K.; Okamoto, S. Non-Cp Titanium Alkoxide-Based Homolytic Ring-Opening of Epoxides by an Intramolecular Hydrogen Abstraction in β-Titanoxy Radical Intermediates. *Chem. Commun.* **2011**, 47, 7857–7859.