Division of Synthetic Chemistry
– Synthetic Organic Chemistry –

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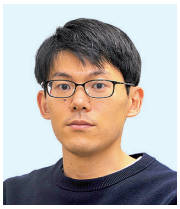

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Scope of Research

Our group has been carrying out innovative research on the radical-based organic synthesis by designing catalysts and chemical reactions as well as molecules. Our current research projects include (1) radical-mediated organocatalysis such as N-heterocyclic carbene catalysis or organophotoredox catalysis; (2) radical modification of nucleic acids; and (3) molecular imaging based on boron chemistry.

KEYWORDS

Synthetic Reactions
Photoredox Catalysis
Organocatalysis
Radical Reaction
Boron Molecule

Recent Selected Publications

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.*, **14**, 6856 (2023).

Goto, Y.; Sano, M.; Sumida, Y.; Ohmiya, H., N-Heterocyclic Carbene- and Organic Photoredox-Catalysed meta-Selective Acylation of Electron-Rich Arenes, *Nat. Synth.*, **2**, 1037-1045 (2023).

Nakamura, R.; Yamazaki, T.; Kondo, Y.; Tsukada, M.; Miyamoto, Y.; Arakawa, N.; Sumida, Y.; Kiya, T.; Arai, S.; Ohmiya, H., Radical Caging Strategy for Cholinergic Optopharmacology, *J. Am. Chem. Soc.*, **145**, 10651-10658 (2023).

Kodo T.; Nagao K.; Ohmiya H., Organophotoredox-Catalyzed Semipinacol Rearrangement via Radical-Polar Crossover, *Nat. Commun.*, **13**, 2684 (2022).

Nakagawa M.; Matsuki Y.; Nagao K.; Ohmiya H., A Triple Photoredox/Cobalt/Brønsted Acid Catalysis Enabling Markovnikov Hydroalkoxylation of Unactivated Alkenes, *J. Am. Chem. Soc.*, **144**, 7953-7959 (2022).

Synthesis of Tertiary Alkylphosphonate Oligonucleotides through Light-Driven Radical-Polar Crossover Reactions

Chemical modification of nucleotides can improve the metabolic stability and target specificity of oligonucleotide therapeutics, and alkylphosphonates have been employed as charge-neutral replacements for naturally-occurring phosphodiester backbones in these compounds. However, at present, the alkyl moieties that can be attached to phosphorus atoms in these compounds are limited to methyl groups or primary/secondary alkyls, and such alkylphosphonate moieties can degrade during oligonucleotide synthesis. The present work demonstrates the *tertiary* alkylation of the phosphorus atoms of phosphites bearing two 2'-deoxynuclosides. This process utilizes a carbocation generated via a light-driven radical-polar crossover mechanism. This protocol provides *tertiary* alkylphosphonate structures that are difficult to synthesize using existing methods. The conversion of these species to oligonucleotides having charge-neutral alkylphosphonate linkages through a phosphoramidite-based approach was also confirmed in this study.

N-Heterocyclic Carbene- and Organic Photoredox-Catalysed meta-Selective Acylation of Electron-Rich Arenes

meta-Selective functionalization of electron-rich arenes provides a complementary route to that of traditional organic synthesis. In classical electrophilic aromatic substitution reactions of electron-donating group-pendant arenes, C–H functionalization occurs at the *ortho*- or *para*-positions. There have been numerous efforts to overcome this selectivity, and various synthetic methods have been developed, typically using transition metal catalysis. Here we report a combined N-heterocyclic carbene- and organic photoredox-catalysed method for *meta*-selective acylation of electron-rich arenes, using acyl imidazoles as acylating reagents. This approach proceeds without directing groups or steric factors required in transition metal-catalysed processes, resulting in the opposite regioselectivity to conventional approaches such as Friedel–Crafts acylation. Mechanistic studies reveal the process involves a sequence of single-electron oxidation of an electron-rich arene followed by the radical–radical coupling between a ketyl radical and an arene radical cation.

Radical Caging Strategy for Cholinergic Optopharmacology

Photo-caged methodologies have been indispensable for elucidating the functional mechanisms of pharmacologically active molecules at the cellular level. A photo-triggered removable unit enables control of the photo-induced expression of pharmacologically active molecular function, resulting in a rapid increase in the concentration of the bioactive compound near the target cell. However, caging the target bioactive compound generally requires specific heteroatom-based functional groups, limiting the types of molecular structures that can be caged. We have developed an unprecedented methodology for caging/uncaging on carbon atoms using a unit with a photo-cleavable carbon–boron bond. The caging/uncaging process requires installation of the CH_2–B group on the nitrogen atom that formally assembles an *N*-methyl group protected with a photoremovable unit. *N*-Methylation proceeds by photoirradiation via carbon-centered radical generation. Using this radical caging strategy to cage previously uncageable bioactive molecules, we have photocaged molecules with no general labeling sites, including acetylcholine, an endogenous neurotransmitter. Caged acetylcholine provides an unconventional tool for optopharmacology to clarify neuronal mechanisms on the basis of photo-regulating acetylcholine localization. We demonstrated the utility of this probe by monitoring uncaging in HEK cells expressing a biosensor to detect ACh on the cell surface, as well as Ca^{2+} imaging in *Drosophila* brain cells (ex vivo).

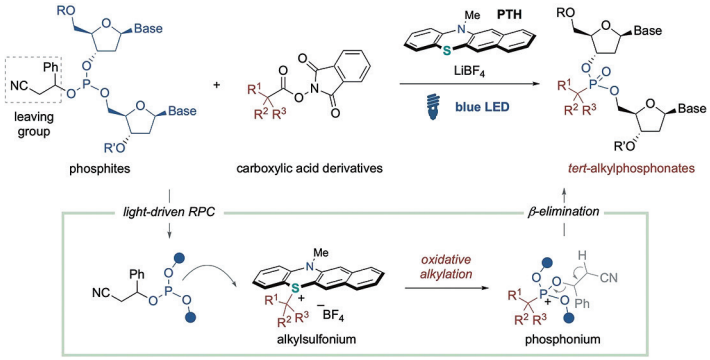

Figure 1. Synthesis of Tertiary Alkylphosphonate Oligonucleotides through Light-Driven Radical-Polar Crossover Reactions.

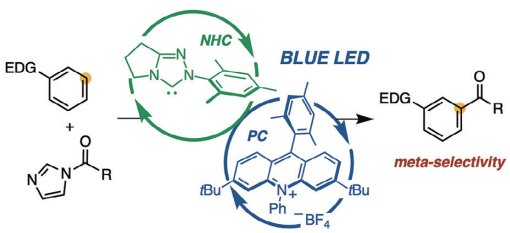

Figure 2. N-Heterocyclic Carbene- and Organic Photoredox-Catalysed meta-Selective Acylation of Electron-Rich Arenes.

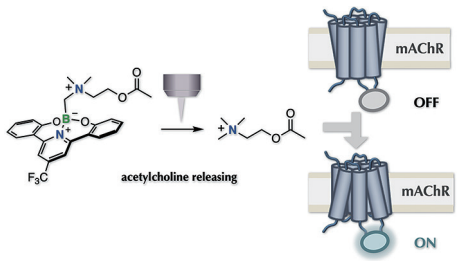

Figure 3. Radical Caging Strategy for Cholinergic Optopharmacology.