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CONTRIBUTORS TO THIS ISSUE (本特集号の寄稿者)

Shiroh Futaki
二木 史朗, Kyoto University

Azusa Kondoh and Masahiro Terada*
近藤 梓, 寺田 眞浩, Tohoku University

Subrata Mukherjee, Shintaro Kawamura,* and Mikiko Sodeoka*
スブラタ ムカジー, 河村 伸太郎, 袖岡 幹子, RIKEN

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General Correspondence
Editor: Sharbil J. Firsan, Ph.D.
Sharbil.Firsan@milliporesigma.com

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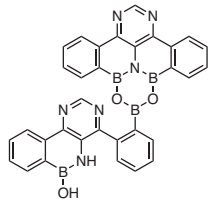

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ABOUT OUR COVER

What immediately comes to mind when you see a row of cherry trees in bloom? For us it is Japan! ***Cherry Blossom Viewing*** (ink and color on silk panel, 37.6 x 64.8 cm) is attributed to Katsushika Hokusai* (葛飾北斎,1760–1849). He was a renowned, prodigious, and much sought-after artist in Japan. Hokusai initially trained in woodblock prints of actors and courtesans. He later shifted his interest to depictions of landscapes, plants, animals, and the daily lives of the Japanese. Possibly the most famous of his landscapes are *Under the Great Wave Off Kanagawa* and his numerous depictions of Mount Fuji. Hokusai did not achieve international fame and influence until after his death when Japan became more accessible to the rest of the world.

Detail from ***Cherry Blossom Viewing***. Photo courtesy The Freer Gallery of Art, Washington, DC.

Another type of year-round bloom in Japan is scientific research, in particular chemistry research. Is it any wonder that in the past two decades over half a dozen Japanese researchers working at home and abroad have been awarded the Nobel Prize in Chemistry? This issue celebrates the achievements of Japanese chemistry research by showcasing vignettes from prestigious research groups at three renowned Japanese scientific institutions.

Katsushika Hokusai / Freer Gallery of Art, Smithsonian Institution, Washington, DC: Gift of Charles Lang Freer, F1902.2.

* *Interestingly, the artist Hokusai was known by many other names. To find out more, visit* ***SigmaAldrich.com/acta***

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Peptide-Mediated Strategies for Intracellular Protein Delivery

ペプチドを利用した細胞内へのタンパク質送達戦略

Prof. S. Futaki

Shiroh Futaki†
二木 史朗

Institute for Chemical Research
Kyoto University
Uji, Kyoto 611-0011, Japan

Email: futaki@scl.kyoto-u.ac.jp

Keywords. cell-penetrating peptide; arginine; cell membrane; intracellular delivery; endocytosis; macropinocytosis; membrane lysis; endosomal escape; attenuated cationic amphiphilic lytic (ACAL) peptide; antibody.

キーワード. 細胞透過ペプチド; アルギニン; 細胞膜; 細胞内送達; エンドサイトーシス; マクロピノサイトーシス; 膜溶解; エンドソーム脱出; 弱毒型カチオン性両親媒性膜溶解ペプチド (ACALペプチド); 抗体.

Abstract. Establishing methodologies that allow protein delivery into cells has an impact both on the design of membrane-interacting molecular systems and on their practical applications to modulate cellular functions. Here we introduce our approaches for intracellular delivery using peptides that have unique modes of membrane interaction and perturbation.

細胞内へのタンパク質導入のための方法論の確立は、膜と相互作用する分子システムの設計ならびにこれらの細胞機能調節への応用の双方の観点から大きな意味を持ちます。ここでは、ユニークな膜相互作用様式と膜構造破壊能を有するプチドを用いた私達の細胞内送達の試みを紹介します.

Outline

1. Introduction
2. Arginine-Rich, Cell-Penetrating Peptides
3. Attenuated Cationic Amphiphilic Lytic (ACAL) Peptides for Intracellular Protein Delivery
4. Combination Approach of Macropinocytosis-Inducing Peptides and Endosomolytic Peptides
5. Conclusion and Outlook
6. References

1. Introduction

The cell membrane (plasma membrane) acts as a barrier to separate the interior from the exterior of cells. Thus, cellular components needed for cellular activity such as proteins and peptides as well as nucleic acids are retained inside cells without leaking out to the outside. On the other hand, there is a strong demand for delivering such biologically relevant molecules into cells because of their potential therapeutic effects. The approaches that enable intracellular delivery of such molecules are also beneficial for basic studies on the elucidation and modulation of cellular functions. Mechanical means to deliver such molecules into cells, such as microinjection, electroporation, and glass-bead transfection[1] have been employed for these purposes. However, such means are often accompanied by severe damage to cells, or suffer from inefficiency in handling. Therefore, more efficient and safer approaches, preferably ones that can be extended to therapeutic applications, are needed. Numerous approaches based on polymers and lipid nanoparticles have been reported.[2-4] These approaches often yield satisfactory results at least at the cellular level for gene and nucleic acid delivery. However, in terms of protein and peptide delivery, the incorporation of these biomolecules into such particles is generally not easy.

As a new means to achieve facile intracellular delivery, an approach to employ peptides having membrane permeability (cell-penetrating peptides or CPPs) has been introduced.[5-8] Examples of such intracellular delivery include formation of conjugates or stable complexes of CPPs with the proteins of interest to obtain the desired activities of the proteins (**Figure 1**, Part (a)).[9] This approach is not limited to protein delivery, but has been extended to delivery of various peptides,

nanoparticles, and nucleic acids. Our group is interested in understanding the internalization processes of CPPs, especially those rich in arginine (arginine-rich peptides),[2,9] and creating more efficient delivery peptides based on this understanding. Complementary approaches have been developed for delivering relatively large proteins such as antibodies (i.e., immunoglobulin G, IgG) with the assistance of endosomolytic peptides (Figure 1, Part (b)).[10–12] These and related topics are reviewed and discussed in this article.

2. Arginine-Rich, Cell-Penetrating Peptides

The origin of CPPs goes back to the finding of cellular internalization of the Tat protein of the human immunodeficiency virus type 1 (HIV-1).[13,14] The Tat protein is involved in the transcription regulation of the virus. Since the protein is endogenous, a control experiment to examine the effect of externally added Tat protein on transcription was carried out by Frankel and Pabo.[13] Although no effect was originally expected, activation of transcription was observed, which suggested the internalization of externally added Tat protein. A similar effect was also observed by Green and Loewenstein.[14] It bears mentioning that the Tat protein does not play any role in HIV-1 infection of host cells. A later study by Fawell et al. demonstrated that delivery of proteins into cells was feasible through chemical conjugation of the partial sequences of the Tat protein with exogenous proteins.[15] Lebleu and co-workers demonstrated that the RNA-binding segment of the Tat protein corresponding to positions 48–60 (GRKKRRQRRRPPQ, designated as Tat peptide in this article) plays a crucial role in the delivery of the protein to the cell.[16] As is often observed with DNA- and RNA-binding segments, the Tat sequence is rich in basic amino acids (i.e., arginine and lysine) and is hydrophilic. In spite of this fact, there have been many reports that demonstrated the practicality of using Tat for intracellular peptide and protein delivery to yield the expected activities.[6,17] This raised the question of why such a segment, possessing basic and hydrophilic properties, can penetrate through the hydrophobic lipid bilayer core.

Through the synthesis of the D-form of Tat, oligoarginine, and branched-chain oligoarginines, our group demonstrated the importance of clusters of arginine or guanidino functions for membrane translocation.[18] A comparison of the translocation ability of different lengths of oligoarginine identified marked translocation abilities of the 6- to 12-mers of arginine. Similar findings were independently reported by Wender's research group at Stanford University.[19,20] Comparing the cellular uptake efficacy among unmodified mono-methylated and di-methylated arginine peptides, the Stanford group clearly established that the guanidino structure—which can potentially form two hydrogen bonds with phosphate, carboxylate, sulfate, and other functional groups—is more important than basicity (**Figure 2**).[21] The same group suggested that the membrane potential (difference in voltage on both sides of the membrane) also plays an important role in the transport across the membrane.[21] Several peptides having different physicochemical characteristics but sharing membrane permeability have also been reported. Examples of such peptides are penetratin[7] and transportan.[22] The former peptide is derived from the DNA-binding region of the antennapedia homeobox protein and has a potentially amphiphilic structure.[7] The latter peptide is a chimera of the

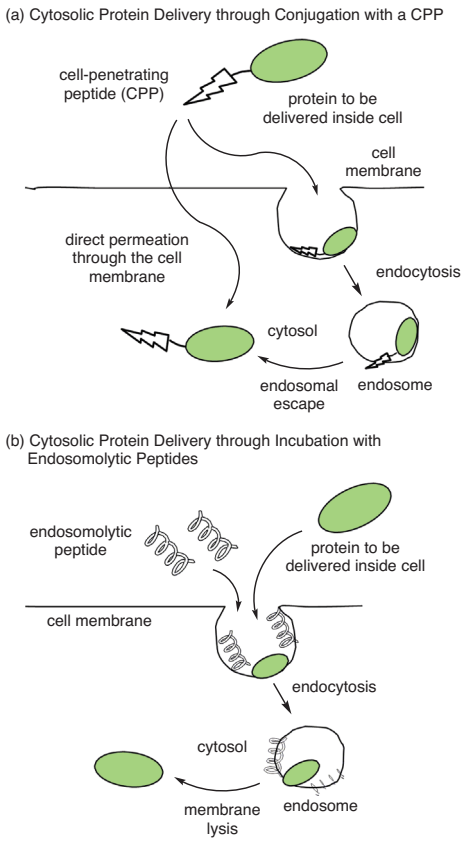

Figure 1. Two Representative Approaches of Cytosolic Protein Delivery. (a) By Conjugation with a Cell-Penetrating Peptide (CPP): (i) Protein May Permeate through the Cell Membrane, or (ii) Is Taken Up by the Cell via Endocytosis, Followed by Endosomal Escape to Reach the Cytosol. (b) Cytosolic Protein Delivery Is Also Possible by Incubating the Protein with Endosomolytic Peptides. *(Ref. 9,10)*

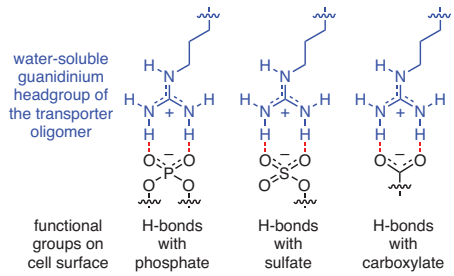

Figure 2. Possible Divalent Hydrogen Bond Formation by the Side-Chain Guanidino Moiety of Arginine with Phosphate, Sulfate, and Carboxylate Functional Groups in Cell-Membrane-Associated Molecules. *(Ref. 21)*

neuropeptide "galanin" and a bee venom "mastoparan", having a primary amphipathic structure.[22] On the other hand, arginine-rich peptides do not include a notable hydrophobic part in their sequence.[23] Since each peptide has membrane permeability and is capable of intracellular delivery by conjugation or by complex formation with cargo molecules, it would be reasonable to consider different methods for internalization.

Later studies demonstrated that, depending on administration conditions, arginine-rich peptides and their conjugates with cargos can penetrate a cell membrane (plasma membrane) directly, especially when cargos are peptides or small molecules and when a high concentration of peptides accumulates on cell surfaces.[24,25] The addition of appropriate hydrophobic moieties (e.g., a hexanoyl group or a tetra(phenylalanine) sequence) to arginine-rich peptides enhances their direct-penetration ability.[26–28] It is worth noting that an excessive increase in hydrophobicity may increase membrane perturbation ability and make the peptides rather toxic. The increase in hydrophobicity may also increase the serum binding of the peptides, and thus reduce the effective peptide concentration on cell surfaces leading to reduced permeation efficacy.

Lebleu's study of the Tat peptide indicated that the internalization process is not inhibited at 4 °C,[16] and that endocytosis—cellular uptake machinery of extracellular materials and solutes into cells using intracellular vesicular transport—is not involved. However, later studies demonstrated that this was due to an artifact in microscopic observation and that Tat and the conjugates are also taken up by the cells via endocytosis.[29] We and others have reported the involvement of micropinocytosis in the cellular uptake of arginine-rich peptides including Tat.[30,31] Macropinocytosis is actin-driven fluid-phase endocytosis, and interaction of arginine-rich peptides with the cell surface activates this form of endocytosis (**Figure 3**).[32] The interaction of arginine-rich peptides with membrane-associated proteoglycans (membrane proteins decorated with sulfated polysaccharides) is critical for the activation.[30,33] The extracellular materials are delivered into cells while encapsulated in vesicular compartments (i.e., endosomes). Endocytosed materials are usually delivered into lysosomes to be digested. Therefore, they must escape from endosomes to exert the expected activity. Endocytosed arginine-rich peptides and their conjugates escape from endosomes, but it is thought that only a small proportion of endocytosed arginine-rich peptides and the conjugates can go into the cytosol.[34] Although a detailed understanding of the methods of endosomal escape should contribute to the creation of more efficient delivery systems, little is known about the actual mechanism. In this context, a potential role has been proposed for bis(monoacylglycero)-phosphate (BMP), a negatively charged phospholipid specifically localized in endosomal membranes, in the escape of CPPs into the cytosol.[35]

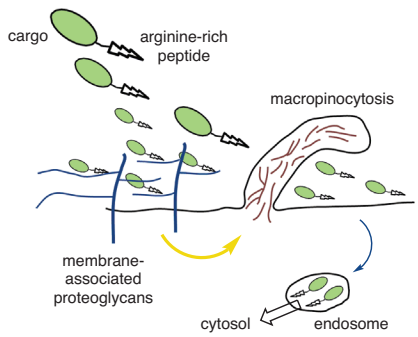

Figure 3. The Interaction of Arginine-Rich CPPs with Membrane-Associated Proteoglycans Displayed on Cell Surfaces Leads to Macropinocytosis, Which Involves Actin Reorganization, Membrane Ruffling, and Fluid-Phase Massive Uptake of Extracellular Liquid and Solutes. Leakage through the Endosomal Membranes Achieves Cytosolic Translocation. *(Ref. 32)*

3. Attenuated Cationic Amphiphilic Lytic (ACAL) Peptides for Intracellular Protein Delivery

Although arginine-rich peptides are a useful tool for delivering extracellular materials into cells, the efficacy of endosomal escape may not be very high especially when the peptide is conjugated with large proteins (e.g., >30 kDa) or other macromolecules. As described in the preceding section, arginine-rich peptides do not have marked hydrophobic domains. On the other hand, cationic amphiphilic peptides often exhibit membrane lytic activity, and the interaction of the membrane with the hydrophobic domain of the cationic peptides is important for the activity (**Figure 4**, Part (a)).[36] If one were to suppress the hydrophobic interaction of the lytic peptides on cell surfaces but allow it inside endosomes, effective perturbation of the endosomal membrane could be achieved. It is known that the interior of endosomes has a reduced pH (~5) compared with that (neutral) on the outside of cells.[37] Aiming at utilizing this pH difference as a switch of the lytic activity, many pH-responsive peptides and polymers have been reported.[38] However, in our view, the resultant lytic activities in endosomes may not be high enough. We thus considered using instead peptides of high lytic activity by replacing the hydrophobic amino acids on the potential hydrophobic face of the amphiphilic lytic peptide with glutamic acid (negatively charged amino acid bearing a carboxy moiety), which would reduce the membrane lytic activity on cell surface (Figure 4, Part (b)). In this case, since the cell surface is negatively charged by the presence of proteoglycans or sialic acid, if we could keep the net positive charges of the peptide, the peptide would effectively adsorb on the cell surface and would then be endocytosed. Under the reduced pH in endosomes, the carboxy group of the glutamic acid may become more protonated, and the lytic activity of the peptide is then recovered. This may lead to rupture of the endosomal membrane, stimulating the endosomal escape of the molecules of interest (cargo molecules).

To ascertain the validity of the above idea, we selected the Carolina wolf spider derived amphiphilic peptide, M-lycotoxin (M-LCTX),[39] as the template. We then substituted a series of amino acids on the potential hydrophobic face of the peptide with glutamic acid, and compared the cytotoxicity of the

resulting lytic peptides. We found a mutant L17E (leucine at position 17 of M-lycotoxin was replaced with glutamic acid: IWLTALKFLGKHAAKHEAKQQLSKL-amide) to have the desired activity.[10] By placing glutamic acid at position 17, the

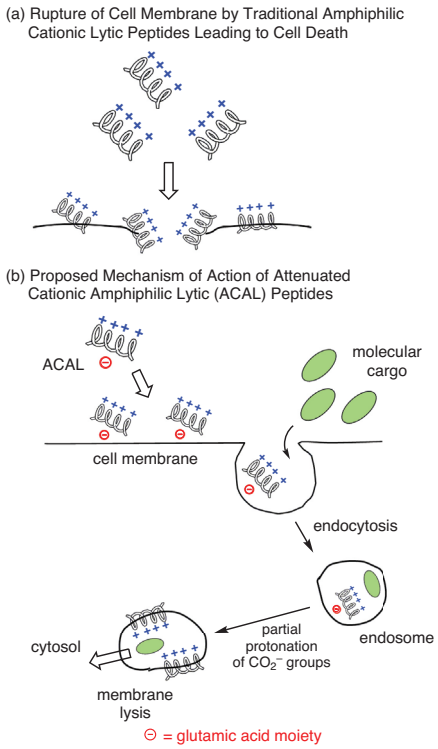

Figure 4. (a) Rupture of Cell Membrane by Amphiphilic Cationic Lytic Peptides, Leading to Cell Death. (b) Design Concept of Attenuated Cationic Amphiphilic Lytic (ACAL) Peptides. By Placing a Negatively Charged Amino Acid (e.g., Glu) in Cationic Amphiphilic Lytic Peptides, the Lytic Activity toward the Cell Membrane Is Greatly Suppressed and the Peptides Are Effectively Adsorbed on the Cell Surface, Leading to Endocytic Uptake of the Peptides and Cargo Molecules. The Reduced pH in Endosomes Should Reduce the Negative Charges of ACAL at Low pH, Resulting in the Recovery of the Lytic Activity of ACAL and Cytosolic Delivery of the Cargo. *(Ref. 10)*

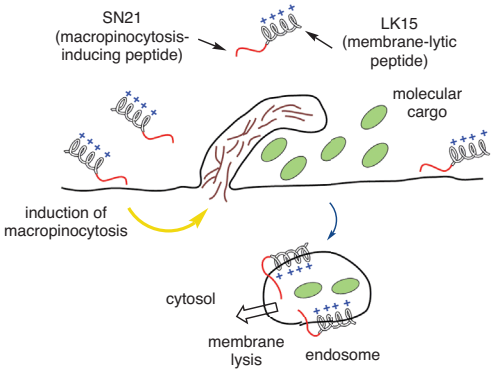

Figure 5. Combination of a Macropinocytosis-Inducing Peptide (SN21, Stimulating Cellular Uptake) and a Membrane-Lytic Peptide (LK15, Rupturing Endosomal Membrane) for Cytosolic Delivery of Bioactive Cargoes. *(Ref. 12)*

EC_{50} (concentration that yields 50% cell death) of L17E was reduced to >40 μM compared to that of M-lycotoxin (1.36 μM). On the other hand, treatment of cells with the model macromolecules polydextran (10 kDa) and immunoglobulin G (IgG, ~150 kDa) in the presence of L17E yielded apparent cytosolic appearance of these molecules in 50% of cells.[10] A later study demonstrated that the cytosolic appearance was accomplished in 5 min, suggesting cytosolic translocation at the very early stages of endocytosis.[40] A design modification that was conducted to increase hydrophobicity and enhance the helical structure at low pH yielded an improved peptide HAad [IWLTALKFLGKAAAKAXAKQXLSKL-amide; X = L-2-aminoadipic acid (Aad)], and this achieved a cytosolic appearance of IgG in 75% of cells, ~25% higher than that obtained by L17E.[11] Using L17E and HAad, successful cytosolic protein delivery was attained, which was confirmed by protein activity exerted in the cell. It is worth mentioning that, at the current stage, proteins and delivery peptides are administrated to cells simply by mixing them together; however, conjugation or complex formation should be considered in order to extend this approach further.

4. Combination Approach of Macropinocytosis-Inducing Peptides and Endosomolytic Peptides

To achieve intracellular delivery via endocytosis, promoting endosomal escape is of course important; however, as a prerequisite, the molecules of interest have to be taken up into the endosomes. To recruit molecules of interest in endosomes, we thought that massive-uptake methods of macropinocytosis may be preferable. Our laboratory had previously identified CXCR4 as a receptor that induces macropinocytosis.[41] Stromal cell-derived factor 1α (SDF-1α) is a natural ligand of CXCR4. We thus prepared the peptides corresponding to the N-terminal sequence of SDF-1α and found that the peptide corresponding to the N-terminal 21 residues (SN21: KPVSLSYRCPCRFFESHVARA-amide) induces macropinocytosis.[12] It is known that Tat and R8 have the ability to induce macropinocytosis, but, in terms of stimulation effect of 70 kDa polydextran uptake, SN21 has a higher macropinocytosis induction ability than that of Tat and R8. LK15 is a cationic membrane-lytic peptide comprised of only leucine and lysine (KLLKLLLKLLLKLLK-amide). A tandem peptide bearing sequences of SN21 and LK15 was prepared (KPVSLSYRCPCRFFESHVARA-GG-KLLKLLLKLLLKLLK-amide) and found to have a marked ability to deliver bioactive proteins and IgGs into cells (**Figure 5**).[12,42] The needed amounts of the proteins are much smaller than those that are needed for the delivery of L17E and HAad. Moreover, SN21–LK15 was able to deliver plasmid and siRNA to an extent comparable to that of lipofectamine, a commercially available, efficient transfection agent. Therefore, the validity of this approach was confirmed. Although similar combinations of macropinocytosis-inducing peptides and endosomolytic peptides have been reported,[31,43] SN21–LK15 has a higher ability than these peptides presumably because of the more potent macropinocytosis induction and membrane-lytic abilities of SN21 and LK15, respectively.

5. Conclusion and Outlook

We introduced in this short review some of our strategies for intracellular delivery of biomacromolecules, in particular bioactive peptides and proteins. With respect to direct penetration through cell membranes, we have proposed the possible transient membrane permeabilization or lipid packing loosening induced by peptide–membrane interaction. This permeabilization may take place either by a physicochemical or physiological process of membrane structural alteration. As is seen in the internalization of arginine-rich peptides, cellular internalization via direct cell-membrane penetration and endocytic uptake followed by endosomal escape can be conducted simultaneously, although one aspect may become more apparent depending on conditions. One possible explanation for the factors that make each pathway more dominant is the kinetics of membrane penetration. If the molecules of interest have relatively small molecular sizes and appropriate physicochemical properties, they tend to go through membranes. However, if they lack high efficacy in permeation, they are eventually trapped in endosomes and endocytosed. Based on these insights, the design of more suitable systems for intracellular delivery should be of great interest.

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(†) The author declares no conflict of interest.
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About the Author

Shiroh Futaki obtained his Ph.D. degree in 1989 from Kyoto University, Japan. Following his appointment as Research Associate and Associate Professor at the University of Tokushima, he moved to Kyoto University in 1997. Meanwhile, he spent 16 months (1989–1991) in the U.S. as Postdoctoral Associate in the Department of Biochemistry, Rockefeller University. He has been Professor of Biochemistry at the Institute of Chemical Research, Kyoto University, since 2005. His research interests include the design of bioactive peptides that possess unique functions (cell penetration, membrane structural organization, and so on). Shiroh has been honored with, among others, The Japanese Peptide Society Award for Young Scientists (1997), The Pharmaceutical Society of Japan Award for Young Scientists (1998), and The Pharmaceutical Society of Japan (PSJ) Award (2020). He was appointed Invited Professor at Pierre and Marie Curie University in 2010 and has been Honorary Member of the Hungarian Academy of Sciences since 2019.

Chiral Organosuperbase Catalysts as Useful Tools for Developing Enantioselective Reactions

キラル超強塩基性有機触媒を用いた不斉反応の開発


Prof. A. Kondoh


Prof. M. Terada

Azusa Kondoh[a] and Masahiro Terada[*,b]
近藤 梓, 寺田 眞浩

[a] Research and Analytical Center for Giant Molecules
Graduate School of Science
Tohoku University
Aoba-ku, Sendai 980-8578, Japan

[b] Department of Chemistry
Graduate School of Science
Tohoku University
Aoba-ku, Sendai 980-8578, Japan

Email: mterada@tohoku.ac.jp

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Abstract. In the field of chiral Brønsted base catalysis, a long-standing challenge has been the expansion of the scope of pronucleophiles that can be applied in enantioselective reactions. In this review, we summarize our recent efforts to overcome this challenge and expand the scope of viable enantioselective transformations that are available under this type of catalysis. We accomplished this by developing two types of chiral organosuperbase catalyst and applying them in enantioselective reactions.

Outline

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3. Applications of Chiral Bis(guanidino)iminophosphorane Catalysts
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4. Development of Chiral Cooperative Binary Base Catalysts
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1. Introduction

Brønsted base catalysis is a fundamental and reliable methodology in the field of synthetic chemistry. Over the past decades, the development of enantioselective reactions by using chiral uncharged organobase catalysts has attracted considerable attention because the methodology enables the direct transformation of pronucleophiles into enantio-enriched compounds in a highly atom-economical fashion under mild reaction conditions.[1] Traditionally, chiral tertiary amines have been employed as the chiral organobase catalyst. Cinchona alkaloid based catalysts and bifunctional catalysts consisting of tertiary amines and hydrogen-bond donors, such as (thio)ureas and squaramides, are widely used, and a large number of enantioselective reactions have been developed so far.[2] However, diversity of the applied pronucleophiles is lacking: the scope of the pronucleophiles applicable to the reactions is highly dependent on the basicity of the catalyst molecules, and the basicity of tertiary amines is considerably low. Recently, chiral uncharged organobases—such as chiral guanidines,[3] P1-phosphazenes,[4] iminophosphoranes,[5] and cyclopropenimines[6]—possessing higher basicities than those of tertiary amines have emerged as efficient chiral Brønsted base catalysts, and considerable progress has been achieved in the development of a variety of enantioselective reactions by

employing these catalysts.[7] However, even with these "strong" organobase catalysts, the applicable pronucleophiles are still limited to compounds that have a highly acidic proton, such as 1,3-dicarbonyl compounds and nitroalkanes. In order to expand the scope of viable enantioselective transformations that are available under Brønsted base catalysis, we have focused on the development of chiral uncharged organosuperbase catalysts that possess much higher basicities than those of the aforementioned conventional chiral catalysts (**Figure 1**).[3–8] In the rest of this article, we present our recent studies on the development of two types of chiral organosuperbase catalyst and their applications to enantioselective reactions.

2. Development of Chiral Bis(guanidino)-iminophosphorane Catalysts

For the purpose of developing chiral organobase catalysts possessing exceptionally high basicity, we envisioned utilizing a higher order phosphazene as a new motif of the chiral catalyst. Phosphazenes are pentavalent phosphorus compounds that contain a P=N double bond and have a high basicity. Whereas the basicity of P1-phosphazenes—which have secondary amine groups attached to the iminophosphorane core—is similar to that of guanidines, replacing the secondary amine groups with phosphazene or guanidine subunit(s) enhances the basicity owing to better delocalization of the positive charge formed through protonation. Thus, the higher order phosphazenes would exhibit a much higher basicity than that of P1-phosphazenes and other conventional organobases (Figure 1).[8] We anticipated that the development of chiral organobases in which a higher order phosphazene is embedded as a core structure would open up a new avenue in asymmetric Brønsted base catalysis by exploiting their high basicity. Specifically, we designed and synthesized pseudo-C_2-symmetric bis(guanidino)-iminophosphoranes (*M*)-**1**, in which two guanidine subunits were introduced to the central iminophosphorane core, as a novel family of chiral organosuperbases (**Figure 2**).[9]

The characteristic feature of the newly designed catalysts (*M*)-**1** is underscored by their helical chirality that is based on the 7,7-memberd spirocyclic system along with their carbon center based chirality resulting from (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediamine ((*S*,*S*)-DPEN). In this catalyst design, we arranged the hydrogen-bond donor and acceptor sites around the central phosphorus atom: the nitrogen atom of the iminophosphorane moiety (P=N) functions as the hydrogen-bond acceptor, while the N–H moiety attached to the iminophosphorane core functions as the hydrogen-bond donor. The side-by-side arrangement of the donor and acceptor sites has been proven to be a fundamental approach to designing efficient chiral organobase catalysts, such as chiral guanidines and P1-phosphazenes, to achieve high enantioselectivity.[3,4] Importantly, in this case, the conjugate acid of the catalyst generated through deprotonation of a pronucleophile can simultaneously interact with an anionic nucleophile (Nu) and an electrophile (X=Y) through hydrogen bonding by using two adjacent N–H moieties to form a cyclic transition state. To validate the catalytic performance of bis(guanidino)iminophosphoranes (*M*)-**1** as chiral organosuperbases, a series of (*M*)-**1** were tested in the electrophilic amination of 2-alkyltetralone (e.g., **2a**; as a less acidic pronucleophile) with azodicarboxylate **3**. (*M*)-**1a**, possessing methyl groups on the nitrogen of the guanidine moieties, efficiently catalyzed the reaction of **2a** with **3**, and

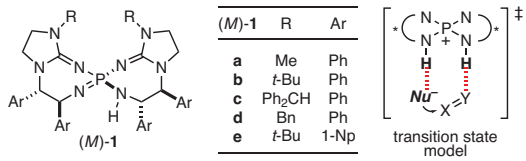


Figure 2. Chiral, Pseudo-C_2-Symmetric Bis(guanidino)iminophosphoranes as Novel, Brønsted Organosuperbase Catalysts. *(Ref. 9)*

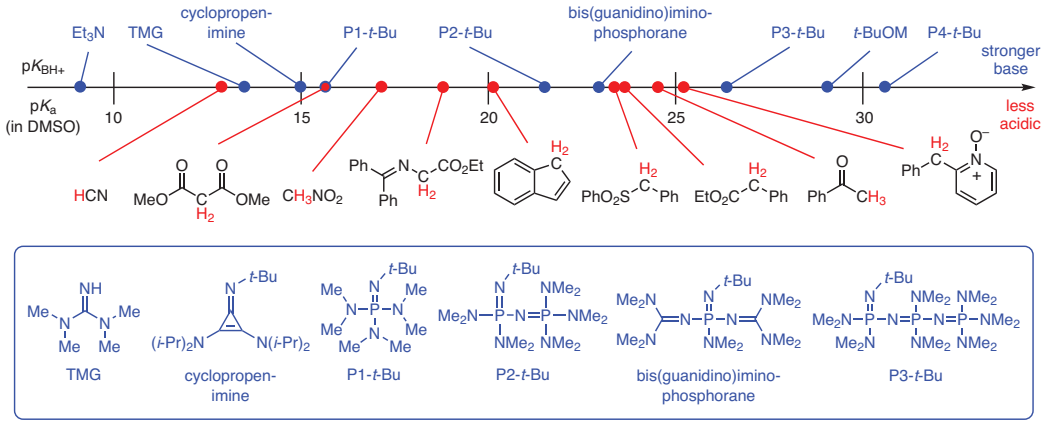


Figure 1. Relationship between Basicity of Uncharged Organobases and Acidity of Representative Pronucleophiles. *(Ref. 3–8)*

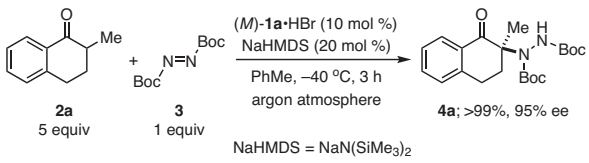
the corresponding adduct **4a** was obtained in high yield and with high enantioselectivity (**eq 1**).[9a] Thus, the higher-order phosphazene-based (*M*)-**1** were confirmed as a superb class of uncharged chiral organosuperbase catalysts that facilitate the enantioselective reactions of less acidic pronucleophiles.

3. Applications of Chiral Bis(guanidino)-iminophosphorane Catalysts

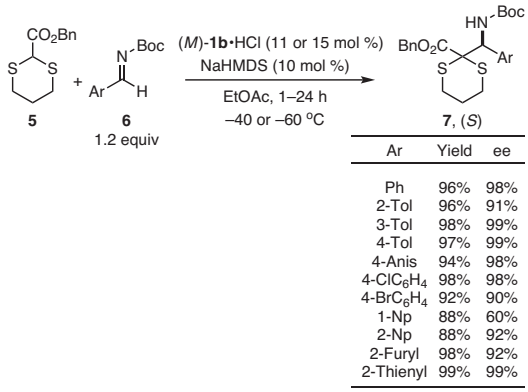
3.1. Enantioselective Addition of Less Acidic Pronucleophiles

In order to extend the utility of chiral bis(guanidino)-iminophosphoranes, particularly in synthetically useful transformations, we first focused our attention on 2-alkoxycarbonyl-1,3-dithianes as a less acidic pronucleophile class. The anion of 1,3-dithiane is a useful synthetic intermediate which can be regarded as an acyl anion equivalent.[10] Generally, a stoichiometric amount of a strong Brønsted base is employed for generating the dithiane anion prior to its reaction with electrophiles because of the low acidity of the hydrogen at C-2, even when it is α to an ester moiety.[11] In particular, the enantioselective addition reactions of the dithiane anion have not been reported.[12] Thus, we envisioned that the direct enantioselective addition of 2-alkoxycarbonyl-1,3-dithianes to imines by using our newly developed catalyst class would provide enantio-enriched α-amino-1,3-dithiane derivatives, which are known as valuable versatile building blocks. Currently, the synthesis of these compounds relies on methods involving asymmetric additions in which stoichiometric amounts of the achiral Brønsted base and a chiral auxiliary are required.[13] As a result of our investigation, chiral bis(guanidino) iminophosphorane (*M*)-**1b** (R = *t*-Bu, Ar = Ph) promoted the addition of 2-benzyloxycarbonyl-1,3-dithiane (**5**) to *N*-Boc imines **6** in a highly enantioselective manner (**eq 2**).[14] Imines with various functionalities on the benzene ring as well as heteroaromatic imines were applicable to the reaction, and the resulting adducts **7** were obtained in high yields and with high enantioselectivities.

Next, we envisioned utilizing chiral bis(guanidino)-iminophosphoranes to develop diastereo- and enantioselective addition reactions for the construction of vicinal quaternary stereogenic centers. The catalytic asymmetric construction of vicinal quaternary stereogenic centers, which are commonly found as a core structure in bioactive compounds, is a topic of profound interest in synthetic chemistry. This is because of the difficulty encountered in not only forming the carbon–carbon bond in the presence of steric congestion, but also in controlling the requisite stereochemical outcome.[15] The nucleophilic 1,2 addition of trisubstituted carbon pronucleophiles to ketones and ketimines is one of the potential straightforward methods for constructing vicinal quaternary stereogenic centers under Brønsted base catalysis.[16] Thus, we investigated the enantioselective direct Mannich-type reaction of α-imino esters with α-alkyl-substituted thionolactones as less acidic pronucleophiles by employing chiral bis(guanidino)-iminophosphoranes (**eq 3**).[17] The screening of the reaction conditions revealed that the substituents on the nitrogen of the guanidine moieties of the catalyst and the benzoyl moiety of the α-imino ester highly influence the stereoselectivity, in particular the diastereoselectivity, of the reaction. Using *para*-trifluoromethylbenzoyl-substituted α-imino esters as electrophiles, we achieved the construction of vicinal quaternary stereogenic centers in a highly diastreo- and enantioselective manner by employing (*M*)-**1c** (R = Ph_2CH, Ar =Ph), which incorporates sterically hindered diphenylmethyl groups on the two nitrogens of the guanidino group. The newly developed enantioselective Mannich-type reaction provides efficient access to densely functionalized and complex amino acid derivatives, such as **11**, which are difficult to prepare by prior methods.

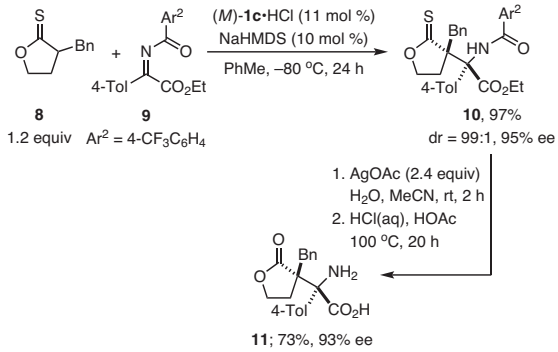


eq 1 *(Ref. 9a)*



Ar	Yield	ee
Ph	96%	98%
2-Tol	96%	91%
3-Tol	98%	99%
4-Tol	97%	99%
4-Anis	94%	98%
4-ClC_6H_4	98%	98%
4-BrC_6H_4	92%	90%
1-Np	88%	60%
2-Np	88%	92%
2-Furyl	98%	92%
2-Thienyl	99%	99%

eq 2 *(Ref. 14)*



eq 3 *(Ref. 17)*

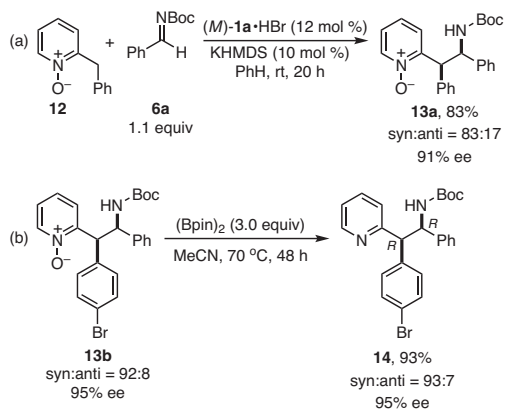
Most enantioselective reactions under Brønsted base catalysis, including our previous reactions, had involved enolate formation from the corresponding carbonyl-based pronucleophiles. We envisioned the development of an enantioselective reaction involving direct α deprotonation of 2-alkylazaarenes,[18] which is a potentially useful approach because it can directly provide 2-substituted azaarenes with a stereogenic center at the α position, which are commonly encountered motifs in natural products and pharmaceuticals. However, the main obstacle to developing the reaction is the low acidity of the α protons in the 2-alkyl substituents, which impedes the deprotonation required for initiation of the catalytic process. To overcome this difficulty, we utilized azaarene *N*-oxides as azaarene surrogates possessing higher electron-deficient properties[19] (**Scheme 1**, Part (a)).[20] Control experiments suggested that the primary role of the *N*-oxide moiety is not limited to enhancing the acidity of the α protons to facilitate the requisite deprotonation. It also acts as an additional coordination site for the chiral bis(guanidino)-iminophosphorane catalyst, where the orientation of the nucleophilic 2-benzylpyridine *N*-oxides would be well-organized in the chiral environment created by the catalyst. The *N*-oxide moiety of the products can be readily removed under mild conditions without any loss in the diastereomeric ratio and enantiomeric excess (Scheme 1, Part (b)).[20] This reaction is a rare example of the direct construction of a stereogenic center at the less acidic α position of an azaarene derivative under Brønsted base catalysis.

3.2. Enantioselective Protonation

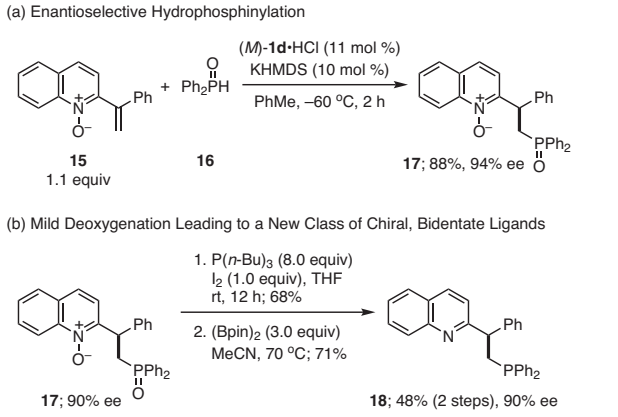
In addition to the enantioselective carbon–carbon bond forming reactions, we have applied chiral bis(guanidino)-iminophosphoranes to the construction of stereogenic centers through the enantioselective protonation of transient prochiral carbanions. In the past decade, the enantioselective protonation of transient enolates under Brønsted base catalysis has received considerable attention.[21] The transient enolate can be readily generated in a catalytic fashion by 1,4 addition of anionic nucleophiles to α,β-unsaturated carbonyl compounds. Moreover, the reaction can be performed under metal-free conditions and utilizing a simple procedure. In light of this, we reasoned that enantioselective protonation under the influence of chiral organosuperbase catalysts could markedly broaden the utility of the methodology by expanding the scope of possible transient carbanions resulting from the deprotonation of less acidic pronucleophiles. Toward this aim, we investigated the hydrophosphinylation reaction of diarylphosphine oxides with 2-vinyl azaheterocyclic *N*-oxides.[22] We found that chiral catalyst (*M*)-**1d** (R = Bn, Ar = Ph) facilitated the reaction of 2-(1-arylvinyl)quinoline *N*-oxides with diarylphosphine oxides—represented by **15** and **16**, respectively—to provide the desired adducts in high yields and high enantioselectivities (**Scheme 2**, Part (a)).[22] Some experimental results strongly suggested that the weak conjugate acid of the chiral organosuperbase, not the diarylphosphine oxides, acts as the active protonating agent in this reaction system. Enantio-enriched phosphine oxide **17** thus obtained could be easily deoxygenated under mild conditions to produce trivalent phosphine **18** (Scheme 2, Part (b)),[22] thereby affording a new class of chiral bidentate P,N ligands for forming chiral transition-metal complexes.

3.3. Enantioselective Formal [3 + 2] Cycloaddition of Epoxides

The [3 + 2] cycloaddition is a powerful method for the synthesis of densely functionalized five-membered-ring heterocyclic compounds containing oxygen.[23] Recently, the development of the enantioselective formal variant of the reaction has been advanced by using either transition-metal or Lewis acid catalysts with chiral ligands.[24,25] However, few catalytic systems exist that assemble multiple stereogenic centers in a highly stereoselective manner by utilizing this approach. In this context, we anticipated that the development of a catalytic



Scheme 1. Enantioselective Direct Mannich-Type Reaction of Azaarene *N*-Oxides as Azaarene Surrogates with Enhanced Acidity of the α Protons. *(Ref. 20)*



Scheme 2. (a) Representative Enantioselective Protonation through Hydrophosphinylation of a 2-Vinylquinoline *N*-Oxide. (b) Deoxygenation under Mild Conditions, Producing Trivalent Phosphine and a New Class of Chiral Bidentate P,N Ligands for Transition Metals. *(Ref. 22)*

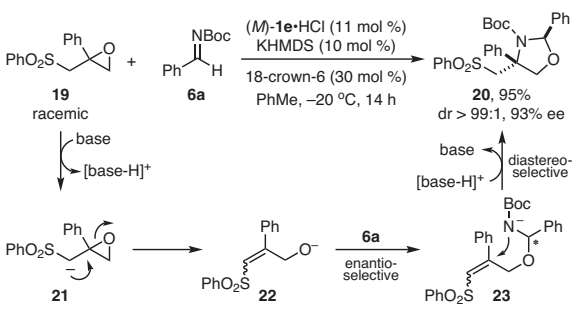
system employing a chiral Brønsted base would expand the range of the methodology. Therefore, we investigated the enantioselective reaction of β,γ-epoxy sulfone **19** with *N*-Boc imine **6a** by using chiral bis(gunanidino)iminophosphoranes. Screening of these organosuperbases revealed that (*M*)-**1e** (R = *t*-Bu, Ar = 1-Np) is the best catalyst for providing 1,3-oxazolidine **20** as a single diastereomer in an enantioselective formal [3 + 2] cycloaddition (**Scheme 3**).[26]

The reaction is initiated by the catalytic ring-opening of racemic β,γ-epoxy sulfone **19** leading to alkoxide **22**, which possesses an electron-deficient alkene moiety. Intermediate **22** formally serves as the synthetic equivalent of a 1,3-dipole, and its stereoselective cycloaddition with imine **6a** proceeds in a stepwise fashion: The enantioselective addition of **22** to **6a** is followed by a diastereoselective intramolecular aza-Michael addition of the hemiaminal ether anion **23** to afford enantioenriched 1,3-oxazolidine **20**.[27] The main challenge of the overall reaction is stereocontrol of the two stereogenic centers one of which is a quaternary one. Control experiments indicated that, in this tandem catalytic process, the key roles the chiral bis(guanidino)iminophosphorane plays are: (i) facilitating the reaction with its high basicity, (ii) controlling the enantioselectivity in the addition of alkoxide intermediate **22** to the *N*-Boc imine, and (iii) assisting the diastereocontrol of the intramolecular aza-Michael addition of anion **23**.

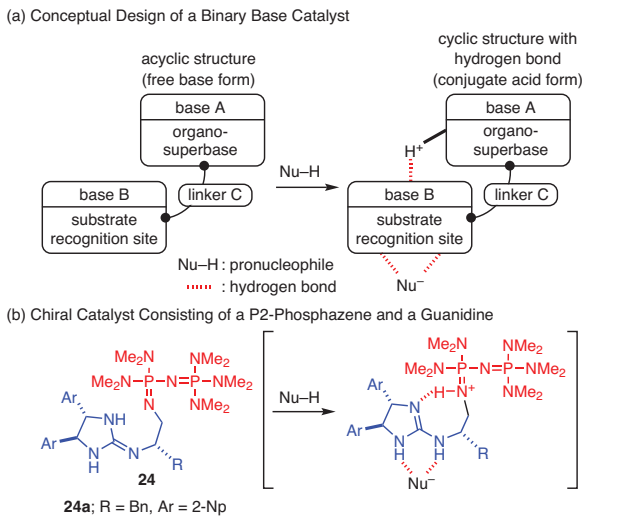
4. Development of Chiral Cooperative Binary Base Catalysts

Our preceding studies with chiral bis(guanidino)-iminophosphorane catalysts revealed the benefit of employing chiral organosuperbases possessing high basicity in developing new catalytic enantioselective reactions and in expanding the scope of pronucleophiles. However, the development of chiral organosuperbase catalysts and related chiral strong Brønsted base catalysts, which would lead to significant progress in the field of enantioselective catalysis, is still less advanced because of the difficulty in designing catalyst molecules that possess both high basicity and high stereocontrol ability.[28] In this regard, we have developed a conceptually new molecular design of a "chiral cooperative binary base" for chiral organosuperbases: a chiral acyclic organic molecule having two different organobase functional groups, one of which functions as an organosuperbase and the other as the substrate recognition site (**Scheme 4**, Part (a)).[29]

The key feature of this design is the distinctive cooperative function of the two organobases in a single chiral catalyst molecule. We expected that the conjugate acid of the catalyst, which is the actual key species in the stereochemistry-determining step of the enantioselective reaction, would form a chiral cyclic structure with an intramolecular hydrogen bond between the two organobase functionalities.[30] Thus, these functional groups would work cooperatively to form an effective chiral environment around the substrate recognition site by limiting the conformational flexibility in the conjugate acid form. The newly designed catalyst molecule **24** possesses a P2-phosphazene as an organosuperbase and a chiral guanidine as a hydrogen-bond donor for substrate recognition (Scheme 4, Part (b)). The two organobase functional groups are connected by a chiral two-carbon linker derived from an α-amino acid. A series of such binary molecules were prepared in a convergent manner from three readily accessible components: (i) a triaminophosphonium salt as a P2-phosphazene precursor, (ii) a chiral cyclic thiourea as a guanidine precursor, and (iii) a chiral 1,2-diaminoethane derivative as a linker. This approach would make it easy to optimize the catalyst structure to suit a variety of enantioselective reactions. The prominent catalytic activity of the chiral cooperative binary base catalyst was demonstrated in the unprecedented enantioselective direct Mannich-type reaction of an α-(phenythio)acetate as a less acidic pronucleophile with *N*-Boc imines to construct, in a highly enantioselective manner, a β-amino-α-thiocarbonyl scaffold, which is a synthetically useful building block incorporated into a number of sulfur-containing biologically active compounds (**eq 4**).[29]



Scheme 3. Representative Example of the Enantioselective Formal [3 + 2] Cycloaddition of Epoxides with Imines under Brønsted Base Catalysis. *(Ref. 26)*



Scheme 4. Chiral Cooperative Binary Base Catalyst. *(Ref. 29)*

5. Conclusion

In the field of chiral Brønsted base catalysis, a long-standing issue has been the expansion of the scope of pronucleophiles that can be applied to enantioselective reactions. To address this issue, we have developed two new types of chiral organosuperbase catalyst: chiral bis(guanidino)iminophosphorane catalysts and chiral cooperative binary base catalysts, both of which possess a much higher basicity than conventional chiral organobase catalysts as well as a high stereocontrol ability. Their prominent catalytic activity was demonstrated in several enantioselective transformations, including the direct enantioselective addition of less acidic pronucleophiles, the enantioselective protonation, and the enantioselective formal [3 + 2] cycloaddition of epoxides. Our results provide, not only new methods for the synthesis of enantio-enriched compounds which are difficult to prepare by using other methods, but a new guiding principle for the design and development of new chiral Brønsted base catalysts that would broaden their usefulness in organic synthesis. Further studies are in progress to develop novel catalytic enantioselective transformations with less acidic pronucleophiles and to develop highly efficient catalysts based on our molecular design.

6. Acknowledgments

The authors thank all their co-workers for their contributions to the chemistry described in this article. This research was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (No. 23105002) and "Hybrid Catalysis for Enabling Molecular Synthesis on Demand" (No. 17H06447) from MEXT (Japan), and a Grant-in-Aid for Scientific Research (No. 16H06354, No. 16K05680, and No. 25810057) from the JSPS.

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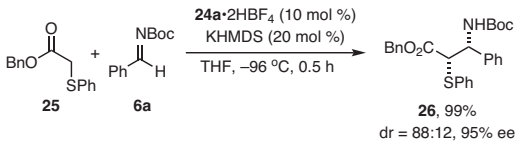

25 **6a** **26**, 99%
dr = 88:12, 95% ee

eq 4 *(Ref. 29)*

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About the Authors

Azusa Kondoh was born in 1982 in Osaka, Japan. He earned his B.S. and Ph.D. degrees in 2005 and 2010, respectively, from Kyoto University under the supervision of Prof. Koichiro Oshima. He then joined the group of Prof. Alois Fürstner at the Max-Plank-Institut für Kohlenforschung as a postdoctoral fellow. In 2012, he became Assistant Professor at Tohoku University, working with Prof. Masahiro Terada, and was promoted to Associate Professor in 2020. His current research program focuses on the development of new synthetic methods on the basis of organocatalysis as well as transition-metal catalysis. He received the Chemical Society of Japan Award for Young Chemists (2018) and the Young Scientists' Award, The Commendation for Science and Technology by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) (2020).

Masahiro Terada received his B.S. degree in 1986 from the Department of Applied Chemistry, and completed his Ph.D. degree in 1993 at the Tokyo Institute of Technology. During his Ph.D. study, he was appointed Assistant Professor at the Tokyo Institute of Technology (1989–2001). Between 1999 and 2000, he was a postdoctoral fellow at Harvard University and, in 2001, he accepted a position as Associate Professor at Tohoku University. In 2006, he was promoted to Professor of Chemistry at the Graduate School of Science, Tohoku University, and was appointed Dean of the Graduate School of Science and Faculty of Science in 2017. His current research interests focus on the development of useful synthetic methods by designing novel chiral Brønsted acid and base catalysts as well as the utilization of transition-metal catalysts. He is the recipient of The incentive Award in Synthetic Organic Chemistry, Japan (2003), The Chemical Society of Japan Award for Creative Work (2008), the Mukaiyama Award (2010), the Daiichi-Sankyo Award for Medicinal Organic Chemistry (2011), The Nagoya Silver Medal (2012), the Molecular Chirality Award (2015), and the Synthetic Organic Chemistry Award, Japan (2017).

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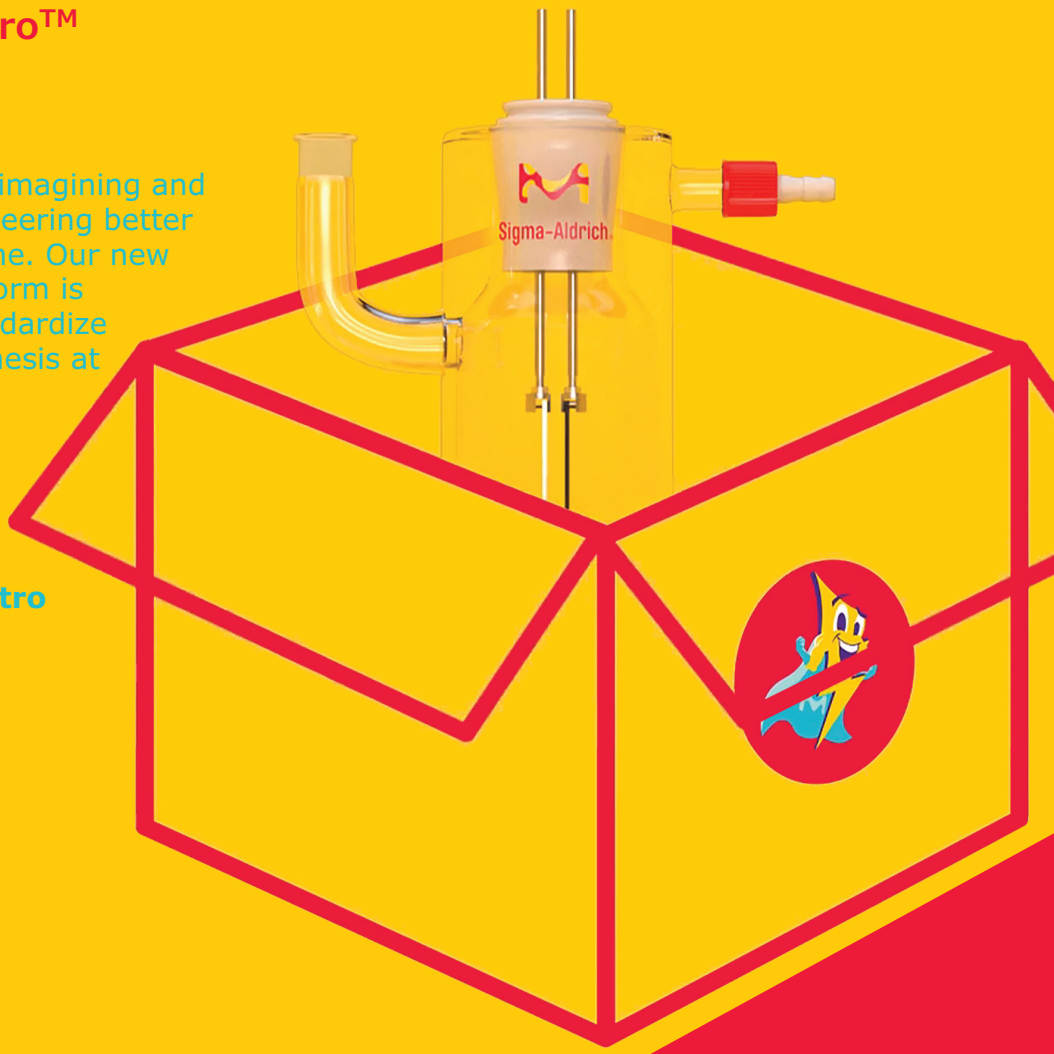

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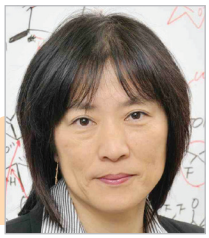
Difunctionalization-Type Fluoroalkylations of Alkenes via Intramolecular Carbo- or Heterocycle Formation

炭素環およびヘテロ環の分子内形成を伴うアルケンの二官能基化型フルオロアルキル化反応


Dr. S. Mukherjee


Dr. S. Kawamura


Prof. M. Sodeoka

Subrata Mukherjee,[a] Shintaro Kawamura,*[,a,b] and Mikiko Sodeoka*[,a,b]
スブラタ ムカジー, 河村 伸太郎, 袖岡 幹子

[a] Catalysis and Integrated Research Group
RIKEN Center for Sustainable Resource Science
2-1 Hirosawa, Wako, Saitama, 351-0198, Japan

[b] Synthetic Organic Chemistry Laboratory
RIKEN Cluster for Pioneering Research
2-1 Hirosawa, Wako, Saitama 351-0198, Japan

Email: skawamura@riken.jp, sodeoka@riken.jp

Keywords. perfluoroalkylation; trifluoromethylation; radical reaction; difunctionalization of alkenes; intramolecular cyclization; Togni reagent; perfluorocarboxylic anhydride; copper catalyst; carbocycle; heterocycle.

キーワード. ペルフルオロアルキル化; トリフルオロメチル化; ラジカル反応; アルケンの二官能基化; 分子内環化; Togni試薬; ペルフルオロカルボン酸無水物; 銅触媒; 炭素環; ヘテロ環.

Abstract. Fluoroalkylation is often an effective strategy for improving the drug-like properties and bioactivities of compounds such as pharmaceuticals and agrochemicals. Efficient and practical fluoroalkylation methods are therefore important tools in the synthetic chemist's tool chest. In particular, difunctionalization-type fluoroalkylations of alkenes—installing a fluoroalkyl group and constructing a cyclic skeleton simultaneously—pose a significant challenge for synthetic organic chemists. Focusing mainly on work in our laboratory, this mini-review summarizes intramolecular difunctionalization-type fluoroalkylations of alkenes with Togni reagent and fluorine-containing carboxylic anhydrides. These reactions lead to a variety of fluoroalkyl-group-containing carbo- and heterocycles as potentially bioactive molecules and building blocks suitable for further elaboration.

Outline

1. Introduction
2. Trifluoromethylation with Togni Reagent
   2.1. Synthesis of CF_3-Containing Carbocycles
   2.2. Synthesis of CF_3-Containing Heterocycles
3. Fluoroalkylation with Fluorine-Containing Carboxylic Anhydrides
   3.1. Fluorine-Containing Carboxylic Anhydrides as Fluoroalkyl Sources
   3.2. Catalytic Fluoroalkylations
   3.3. Transition-Metal-Free Fluoroalkylations
4. Conclusion and Outlook
5. Acknowledgments
6. References and Notes

1. Introduction

Introduction of fluoroalkyl groups is a common strategy in the development of drug candidates and agrochemicals (**Figure 1**).[1] For example, a fluorinated thymidine analogue, trifluridine, gained FDA approval for the treatment of metastatic colorectal cancer in 2015.[2a,b] Efavirenz, containing a tertiary stereogenic center, is used to treat human immunodeficiency virus (HIV) patients.[2c] Fulvestrant (trade name: Faslodex®) is a pentafluoroethylated drug molecule used for the treatment

of breast cancer.[2d] Fluralaner, containing two trifluoromethyl groups and marketed as Bravecto®, is a pesticide that is employed to treat companion animals and poultry for fleas, ticks, and mites.[2e,f] Flupoxam, bearing a pentafluoroethyl group, is a herbicide that acts by inhibiting cellulose biosynthesis.[2g]

A major reason for the remarkable increase in fluoroalkyl-containing drugs and agrochemicals is that the introduction of fluoroalkyl groups into bioactive molecules often improves their lipophilicity, membrane permeability, metabolic stability, and pharmacokinetics.[1] Moreover, the presence of the strongly electronegative fluorine atom in the fluoroalkyl group sometimes enables new hydrogen bonding, dipole–electrostatic, or dipole–dipole interactions that lead to enhanced or novel biological activities.

While there is strong interest in fluoroalkyl compounds as drug candidates and agrochemicals, only a few naturally occurring fluorine-containing organic molecules are known.[3] Consequently, electrophilic fluoroalkylation methods have rapidly advanced in the past decade to expand the chemical space of fluoroalkyl compounds. Among them, the intramolecular difunctionalization-type fluoroalkylation of alkenes—involving electrophilic addition of a fluoroalkyl group and intramolecular carbo- or heterocycle formation—is an efficient synthetic strategy (**eq 1**).[4] In the rest of this article, we cover these fluoroalkylation reactions that employ Togni reagent and fluorine-containing carboxylic anhydrides, focusing mainly on our work in this field.[5]

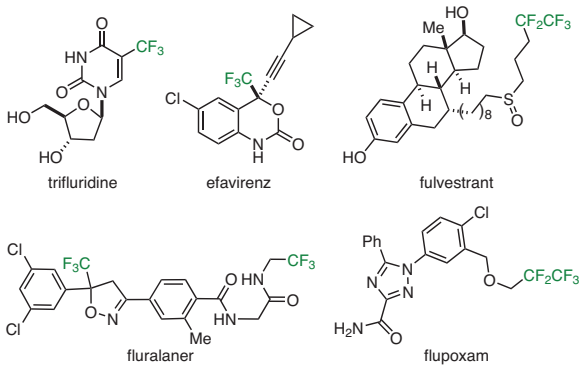
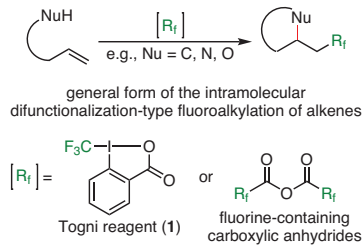


Figure 1. Examples of Drugs and Agrochemicals Incorporating One or More Fluoroalkyl Groups. *(Ref. 1,2)*



eq 1 *(Ref. 4,5)*

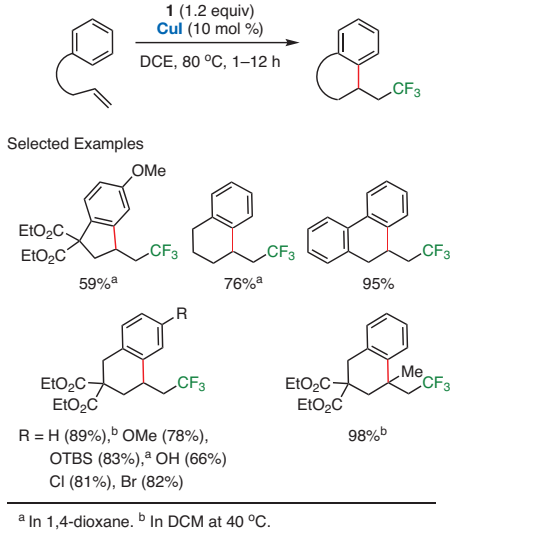
2. Trifluoromethylation with Togni Reagent

In 2010, Togni's group[6a] and our group[6b] independently discovered that zinc and copper salts can activate Togni reagent and catalyze C–CF_3 bond formation in the electrophilic trifluoromethylation of indoles.[7] Later, it was reported that the combination of Togni reagent and transition-metal catalysts, mostly copper catalysts, can promote various difunctionalization-type trifluoromethylation reactions of alkenes.[4,5]

2.1. Synthesis of CF_3-Containing Carbocycles

In 2013, we reported the first example of intramolecular carbo-trifluoromethylation of alkenes with Togni reagent in the presence of a Cu(I) catalyst. In this transformation, alkenes bearing an aromatic ring as the nucleophilic motif at an appropriate position of the carbon side chain, afforded CF_3-containing benzo-fused carbocycles in high yields (**eq 2**).[8] This was an interesting result, since related previous work had found that the reaction of alkenes with Togni reagent in the presence of copper catalyst resulted in allylic trifluoromethylation.[9] We found that the use of CuI as the catalyst, together with a judicious choice of solvent, such as 1,2-dichloroethane (DCE), 1,4-dioxane, or dichloromethane (DCM), was key to the success of this novel intramolecular carbo-trifluoromethylation. Since then, a variety of conditions for alkene trifluoromethylations with Togni reagent have been uncovered by many research groups, enabling the synthesis of a diverse array of CF_3-containing carbocycles.[4,5]

We recently developed a method for synthesizing CF_3-containing tetrahydrocarbazoles by carbo-trifluoromethylation



eq 2 *(Ref. 8)*

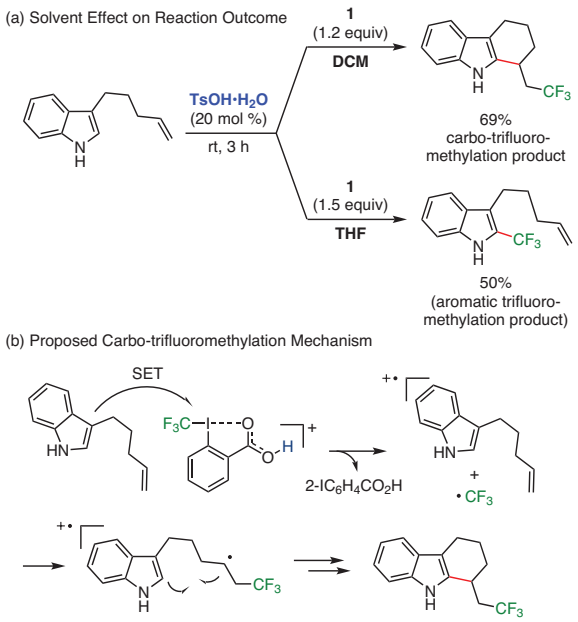
of indoles bearing a pentenyl group at the C-3 position with Togni reagent.[10] In this reaction, a simple Brønsted acid, TsOH, exhibited a higher catalytic reactivity than CuI.Notably, this was the first synthesis of these compounds, although some related work on trifluoromethylation of indoles bearing an alkene side-chain had been reported.[11] The resulting CF_3-substituted compounds are potential drug candidates since the tetrahydrocarbazole motifs are often found in bioactive molecules.[12] In addition, it was observed that the site-selectivity of the trifluoromethylation could be controlled by changing the reaction solvent; specifically, carbo-trifluoromethylation proceeded in dichloromethane, while aromatic trifluoromethylation products were mostly formed in THF. Mechanistic studies suggested that the tetrahydrocarbazole-forming reaction proceeds via single-electron transfer (SET) between the indole substrate and the protonated Togni reagent; addition of the trifluoromethyl radical to the alkene double bond leads to a key radical cation intermediate which undergoes the carbocyclization (**Scheme 1**).[10]

2.2. Synthesis of CF_3-Containing Heterocycles

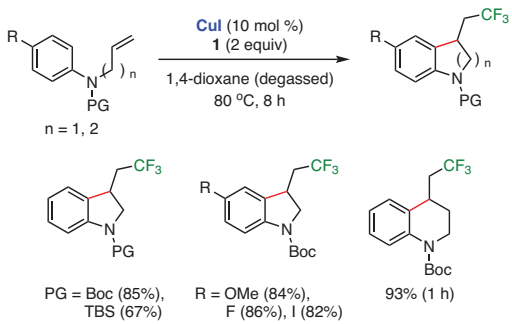
Heterocycles are privileged motifs of bioactive molecules and have a vast range of applications in medicinal chemistry and the agrochemicals industry.[13] More than 85% of all biologically active chemicals contain a heterocyclic fragment, and thus trifluoromethylated heterocycles are of interest in drug discovery and medicinal chemistry.

In this context, we applied our carbo-trifluoromethylation of alkenes with Togni reagent to the synthesis of CF_3-containing heterocycles. We employed alkenes possessing a heteroatom in the side chain in order to construct benzo-fused aliphatic heterocyclic skeletons.[8] Indeed, the reactions of N-protected allylaniline and homoallylaniline derivatives furnished CF_3-containing indolines and tetrahydroquinolines, respectively (**eq 3**).[8] We also extended our protocol to the synthesis of CF_3-containing oxindole derivatives from acryloanilides under mild reaction conditions (**eq 4**).[14,15] Later, further progress in intramolecular carbo-trifluoromethylation reactions for the construction of CF_3-containing heterocycles was made by other research groups.[4,5]

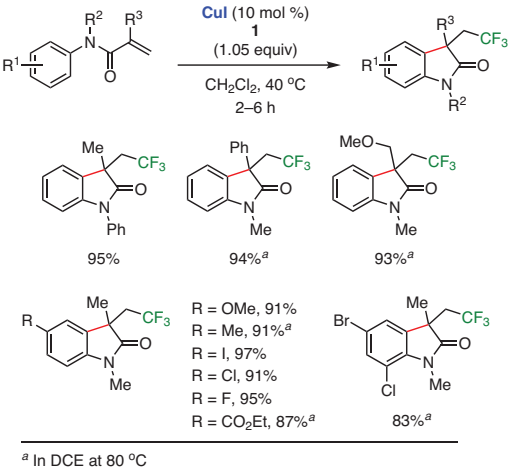
Carbo-trifluoromethylations of alkenes possessing a heteroatom in the side chain are useful for providing the corresponding heterocycles; however, these are limited to benzo-fused compounds. To broaden the range of available CF_3-containing aza-heterocyclic compounds, we envisioned an analogous intramolecular amino-trifluoromethylation reaction of aminoalkenes. In 2013, our group described the first amino-trifluoromethylation of alkenyl amines with Togni reagent to synthesize CF_3-containing aza-heterocycles.[16,17] The reaction of allylamines with Togni reagent in the presence of 1–5 mol % CuI gave the corresponding CF_3-containing



Scheme 1. Formation of Trifluoromethyl-Containing Tetrahydrocarbazoles by Carbo-trifluoromethylation. *(Ref. 10)*



eq 3 *(Ref. 8)*

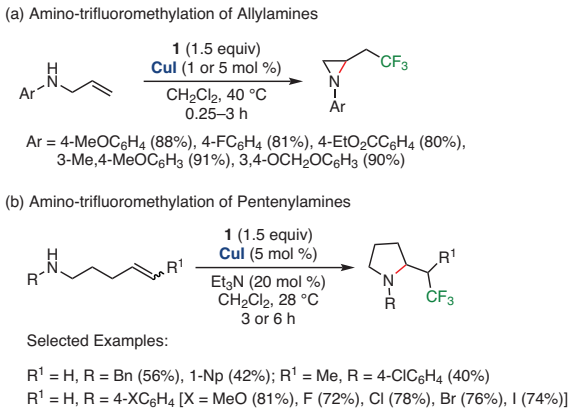


eq 4 *(Ref. 14)*

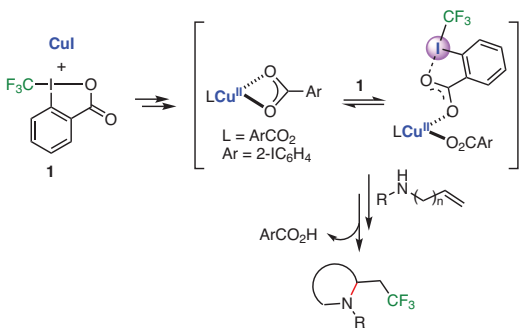
aziridines in excellent yields (**Scheme 2**, Part (a)).[16] We also found that the use of Et_3N as a co-catalyst enabled the smooth amino-trifluoromethylation of pentenylamines, affording CF_3-containing pyrrolidines (Scheme 2, Part (b)).[18]

Our mechanistic experiments, including kinetic studies, ^{19}F NMR, and ESI-MS analyses, showed that a Cu(II) species generated in situ from CuI serves as a Lewis acid to activate Togni reagent (**Scheme 3**).[18] The synthesis of CF_3-containing aza-heterocycles has also been achieved under a variety of conditions by several other research groups.[4,5]

We next focused on the synthesis of trifluoromethylated oxazolines (**Scheme 4**),[19] because the oxazoline motif is frequently found in natural products, and thus their trifluoromethyl analogues are expected to show interesting bioactivity.[20,21] We initially examined our previously reported conditions for the Cu-catalyzed intermolecular oxy-trifluoromethylation reaction of alkenes.[22] Specifically, we expected to construct the oxazoline ring together with introduction of the CF_3 group by intramolecular cyclization of *N*-allylamides with Togni reagent in the presence of $[Cu(MeCN)_4]PF_6$ as catalyst. Unfortunately, this was not successful with the model compound *N*-allylbenzamide; a complex mixture was formed containing only a small amount of the desired oxazoline. Next, we considered another approach based on our iodotrifluoromethylation reaction;[23] the oxazoline was expected to be formed by the iodotrifluoromethylation of the alkene followed by nucleophilic cyclization. When KI was used as an electron donor to activate Togni reagent, the desired 2-phenyl-5-(2,2,2-trifluoro)ethyloxazoline was formed in 75% yield. We examined various *N*-allyl arylamides as well as *N*-allyl alkylamides as substrates under these reaction conditions, and synthesized a wide range of oxazoline derivatives (see Scheme 4).[19] Moreover, this methodology was also applied to the late-stage trifluoromethylation of telmisartan and lithocholic acid analogues.



Scheme 2. Amino-trifluoromethylation Reaction of Allylamines and Alkenylamines with **1**. *(Ref. 16,18)*

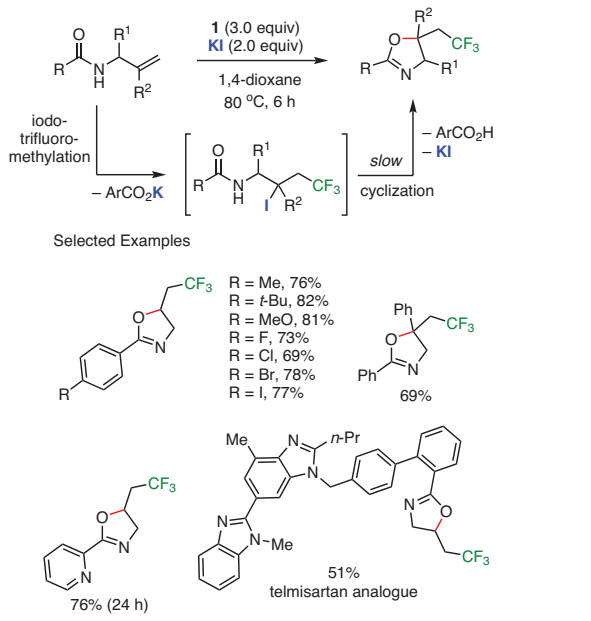


Scheme 3. Mechanism of the Copper-Catalyzed Amino-trifluoromethylation Reaction. *(Ref. 18)*

3. Fluoroalkylation with Fluorine-Containing Carboxylic Anhydrides

3.1. Fluorine-Containing Carboxylic Anhydrides as Fluoroalkyl Sources

Sophisticated electrophilic trifluoromethylating reagents such as Togni, Umemoto, and Langlois reagents have enabled the development of various difunctionalization-type trifluoromethylations of alkenes;[4,5] however, high cost and/or multistep preparation of these reagents sometimes limit their synthetic applications, particularly in large-scale synthesis. To address this issue, we focused on the class of fluorine-containing carboxylic anhydrides as a fluoroalkyl source. In addition to their low cost, various fluorine-containing carboxylic anhydrides—possessing not only a trifluoromethyl group, but also other fluoroalkyl groups such as C_2F_5, C_3F_7, and CF_2Cl—are commercially available. Nevertheless, it has been a long-standing challenge to utilize them as fluoroalkyl sources in fluoroalkylations of unactivated alkenes.[24] Recently, we



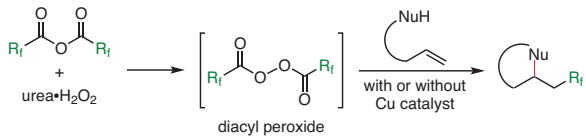
Scheme 4. Oxazoline-Forming Trifluoromethylation Using **1**. *(Ref. 19)*

achieved difunctionalization-type fluoroalkylations of alkenes via intramolecular carbo/heterocycle formation with fluorine-containing carboxylic anhydrides (**Scheme 5**).[5b,c] The key to success in this reaction was the in situ generation of diacyl peroxide from the carboxylic anhydride and urea-hydrogen peroxide, as well as precise control of the reactivity of the radical species formed during the reaction with the aid of copper catalysts or appropriate substrate structures.

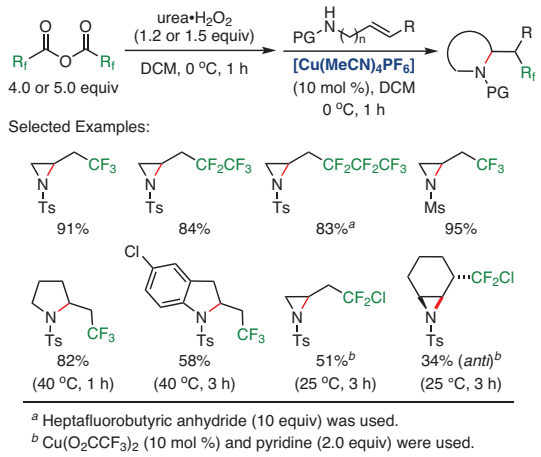
3.2. Catalytic Fluoroalkylations

In 2017, we achieved the first amino-perfluoroalkylation of alkenylamines by using perfluorocarboxylic anhydrides.[25] Specifically, diacyl peroxide—generated in situ from the perfluorocarboxylic anhydride (R_f = CF_3, C_2F_5, C_3F_7) and urea•H_2O_2—was reacted with sulfonyl-protected allylamines or pentenylamines in the presence of a catalytic amount of $[Cu(MeCN)_4]PF_6$, affording the desired aziridines or pyrrolidines in up to 95% yields (**Scheme 6**).[25,26] Notably, the amino-trifluoromethylation with trifluoroacetic anhydride (TFAA) showed higher reactivity than that with Togni reagent: the reaction of *N*-tosyl allylamine with TFAA gave the CF_3-containing aziridine in 91% yield at 0 °C after 1 h, whereas only 17% yield was obtained in the reaction with Togni reagent even at 40 °C. Furthermore, we also developed an amino-chlorodifluoromethylation by using chlorodifluoroacetic anhydride (CDFAA).[26] CDFAA is also an inexpensive fluoroalkyl source, and the CF_2Cl-containing products would be useful building blocks for CF_2-containing molecules via substitution of the chlorine atom. However, the relatively unstable diacyl peroxide prepared from CDFAA, in contrast to that containing CF_3, makes it difficult to control the reactivity and selectivity of the reaction with the copper catalyst due to undesired background radical reactions. Finally, we found that the use of $Cu(O_2CCF_3)_2$ as catalyst instead of $[Cu(MeCN)_4]PF_6$ and pyridine as an additive improved the yield of the reaction.

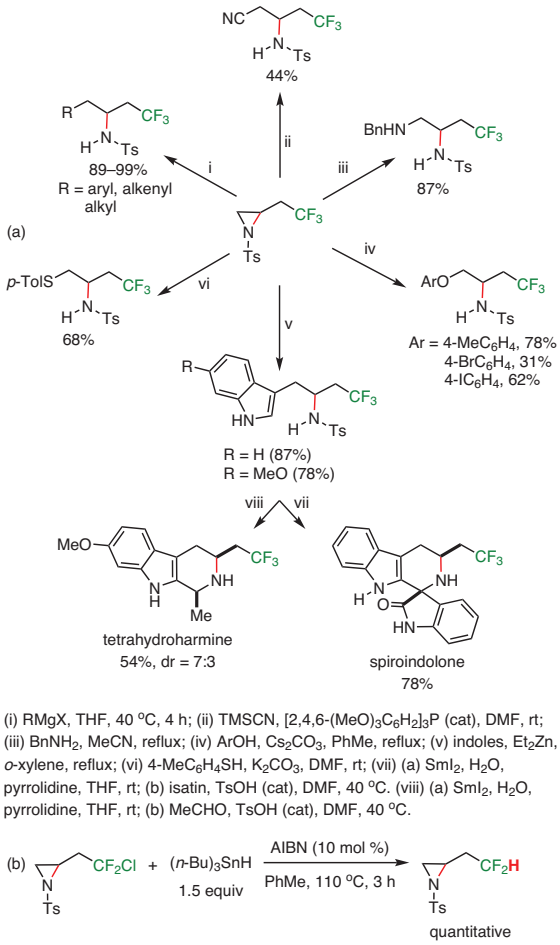
To demonstrate the practical utility of this method, we synthesized bench-stable CF_3-containing *N*-tosyl aziridines on a gram scale and derivatized them to various CF_3-containing amines by means of ring-opening reactions with nucleophiles: (i) RMgX, THF, 40 °C, 4 h; (ii) TMSCN, $[2,4,6\text{-}(MeO)_3C_6H_2]_3P$ (cat), DMF, rt; (iii) $BnNH_2$, MeCN, reflux; (iv) ArOH, Cs_2CO_3, PhMe, reflux; (v) indoles, Et_2Zn, *o*-xylene, reflux; and (vi) 4-MeC_6H_4SH, K_2CO_3, DMF, rt (**Scheme 7**, Part (a)).[25] Among the products, we were particularly interested in the tryptamine derivatives. Trifluoromethylated tetrahydroharmine and



Scheme 5. Intramolecular Difunctionalization-Type Fluoroalkylation Reactions Mediated by Diacyl Peroxide Generated in Situ from Fluorine-Containing Carboxylic Anhydrides. *(Ref. 5b,c)*



Scheme 6. Copper-Catalyzed Amino-fluoroalkylation Reaction Using Fluorine-Containing Carboxylic Anhydrides. *(Ref. 25,26)*



Scheme 7. (a) Derivatizations of Fluoroalkyl-Group-Containing Aziridines via Ring-Opening Reactions with Nucleophiles. (b) Reduction of CF_2Cl to CF_2H. *(Ref. 25,26)*

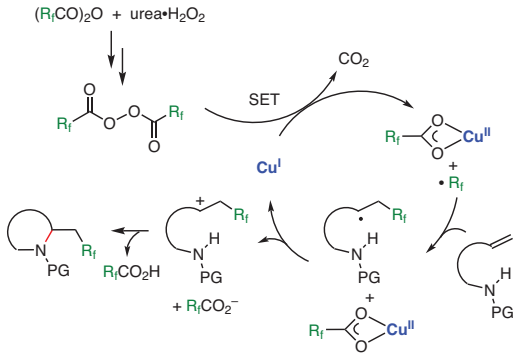
spiroindolone were easily synthesized via the Pictet–Spengler reaction with acetaldehyde and isatin after cleavage of the Ts protecting group in the presence of SmI_2.[25] We also transformed the CF_2Cl-containing aziridine into CF_2H-containing aziridine by reduction with (n-Bu)$_3$SnH/AIBN (Scheme 7, Part (b)).[26]

In the proposed reaction mechanism (**Scheme 8**),[25] single-electron transfer (SET) from Cu(I) to the diacyl peroxide forms the perfluoroalkyl (R_f) radical after decarboxylation. Reaction of the alkene with the perfluoroalkyl (R_f) radical generates an alkyl radical. Oxidation of the alkyl radical with the Cu(II) species affords the corresponding carbocation intermediate and regenerates the Cu(I) species. This oxidation step is considered the most important step for the success of the reaction because, without any treatment, the alkyl radical would give rise to undesired products. The carbocation smoothly produces the desired compound via nucleophilic cyclization.

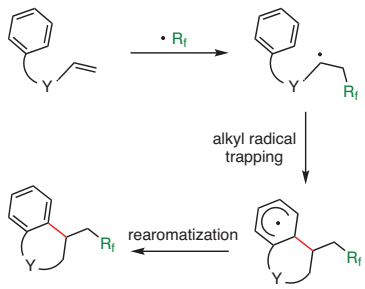
3.3. Transition-Metal-Free Fluoroalkylations

Fluorine-containing diacyl peroxide produces a fluoroalkyl radical upon heating, and reaction of the latter with an alkene readily generates an alkyl radical. In the absence of a transition-metal catalyst, however, the highly reactive alkyl radical affords a complex mixture. We hypothesized that if an aromatic ring were present at an appropriate position on the side chain of the alkene, the alkyl radical would be trapped, and subsequent aromatization would yield the benzo-fused product (**Scheme 9**).[25–27] Gratifyingly, we successfully effected the carbofluoroalkylation reaction of unactivated alkenes bearing a pendant aromatic group by using a fluorine-containing carboxylic anhydride and urea•H_2O_2 without any catalyst or additive (**Scheme 10**).[25–27] By applying this approach, we efficiently constructed various fluoroalkyl-group-containing five-membered-ring and six-membered-ring carbocycles and heterocycles, including oxindoles, benzothiazinane dioxides, indolines and dihydroisoquinolinones. Moreover, addition of a copper catalyst enables carrying out a divergent synthesis by efficiently leading to a different heterocyclic product. For example, the reaction of *N*-tosylallylamine in the presence and absence of a catalytic amount of [Cu(MeCN)$_4$]PF$_6$ selectively afforded CF_3-containing aziridine via amino-trifluoromethylation and benzothiazinane dioxide via carbo-trifluoromethylation, respectively.

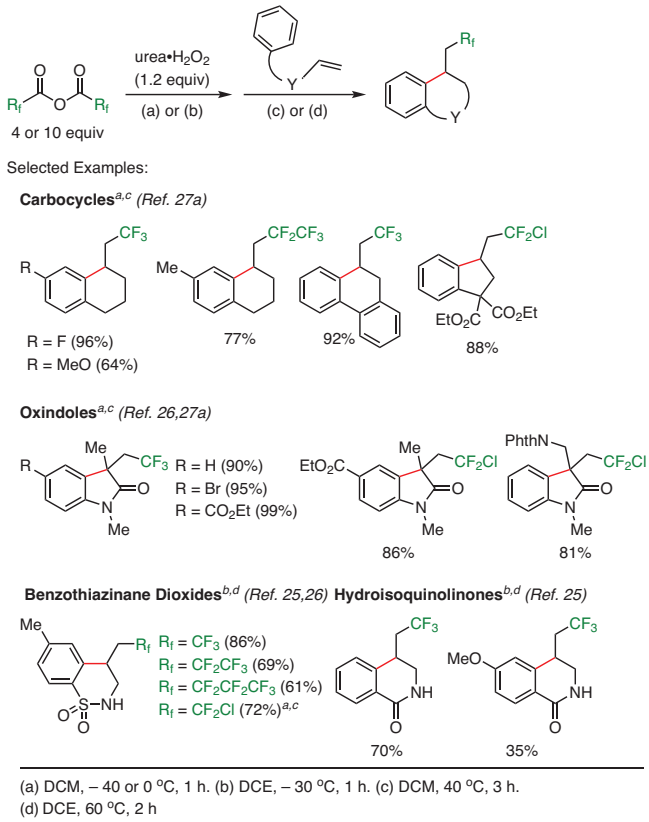
Furthermore, as another approach to the transition-metal-free reaction, the intramolecular aminoperfluoroalkylation was achieved by taking advantage of the unique redox activity of styrenes (**Scheme 11**).[28] The transition-metal-free amino-fluoroalkylation is extremely rare[29] because of the difficulty



Scheme 8. Proposed Mechanism of the Amino-fluoroalkylation with Fluorine-Containing Carboxylic Anhydrides. *(Ref. 25)*



Scheme 9. Conceptual Metal-Free Carbo-fluoroalkylation Reaction with Fluorine-Containing Carboxylic Anhydrides. *(Ref. 25–27)*

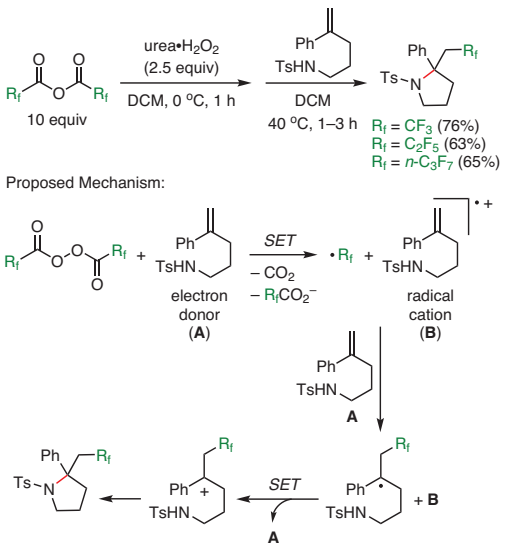


Scheme 10. Scope of the Metal-Free Carbo-fluoroalkylation Reaction with Fluorine-Containing Carboxylic Anhydrides. *(Ref. 25–27)*

of effecting the conversion of the fluoroalkyl-containing alkyl radical intermediate to the desired product in the absence of a catalyst. Nevertheless, we found that the reaction of styrenes bearing a pendant amino group with perfluorocarboxylic anhydrides and urea•H_2O_2 proceeded well, affording perfluoroalkyl-containing pyrrolidine derivatives in good yields. Based on mechanistic investigations, we concluded that the reaction begins with SET between in situ generated diacyl peroxide and styrene to produce the perfluoroalkyl radical and the radical cation of styrene. Then, the perfluoroalkyl radical reacts with another styrene molecule rather than the electron-deficient radical cation, forming a benzyl radical. The benzyl radical is oxidized by the radical cation species as the strongest oxidant in the reaction mixture and generates the key carbocation intermediate. Finally, nucleophilic cyclization gives the desired pyrrolidine product.

4. Conclusion and Outlook

We have briefly summarized the difunctionalization-type fluoroalkylations of alkenes via carbo/heterocycle formation with Togni reagent and fluorine-containing carboxylic anhydrides, focusing mainly on our work. The reactions using Togni reagent provide access to a wide variety of CF_3-containing carbo- and heterocycles by activation with copper or Brønsted acid catalysts or electron-donating additives, including metal iodides. The reactions using fluorine-containing carboxylic anhydrides provide broad access to carbo- and heterocycles containing not only CF_3 but also other fluoroalkyl groups, such as C_2F_5, C_3F_7, and CF_2Cl. In addition to the reactions described here, a great variety of reaction conditions have been reported to date, enabling the synthesis of a diverse array of fluoroalkyl-group-containing molecules. We believe that these fluoroalkylation methods will contribute to the expansion of organofluorine-based compound libraries for pharmaceutical and agrochemical research.



Scheme 11. Metal-Free Amino-perfluoroalkylation Reactions of Styrenes. *(Ref. 28)*

5. Acknowledgments

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About the Authors

Subrata Mukherjee was born in 1991 in Burdwan, India. He completed his B.Sc. (Honors) degree in chemistry at Calcutta University in 2011, and his M.Sc. degree at the Indian Institute of Technology (IIT), Madras, in 2014. He received his Ph.D. degree in 2019 from the National Chemical Laboratory, Pune, under the supervision of Prof. A. T. Biju. Currently, he is working as a postdoctoral researcher in Prof. Sodeoka's research group at RIKEN.

Shintaro Kawamura received his B.Eng. degree in 2007 from Doshisha University. He received his M.Eng. and Ph.D. degrees from Kyoto University. Since 2012, he has worked in Prof. Sodeoka's group at RIKEN. He was promoted from a postdoctoral researcher to a Research Scientist in 2017 and to a Senior Research Scientist in 2021.

Mikiko Sodeoka received her B.S., M.S., and Ph.D. degrees from Chiba University. After working at the Sagami Chemical Research Center, Hokkaido University, Harvard University, and the University of Tokyo, she became a Group Leader at the Sagami Chemical Research Center in 1996. She moved to the University of Tokyo as an Associate Professor and then to Tohoku University as a Full Professor in 2000. Since 2004, she has been a Chief Scientist at RIKEN.

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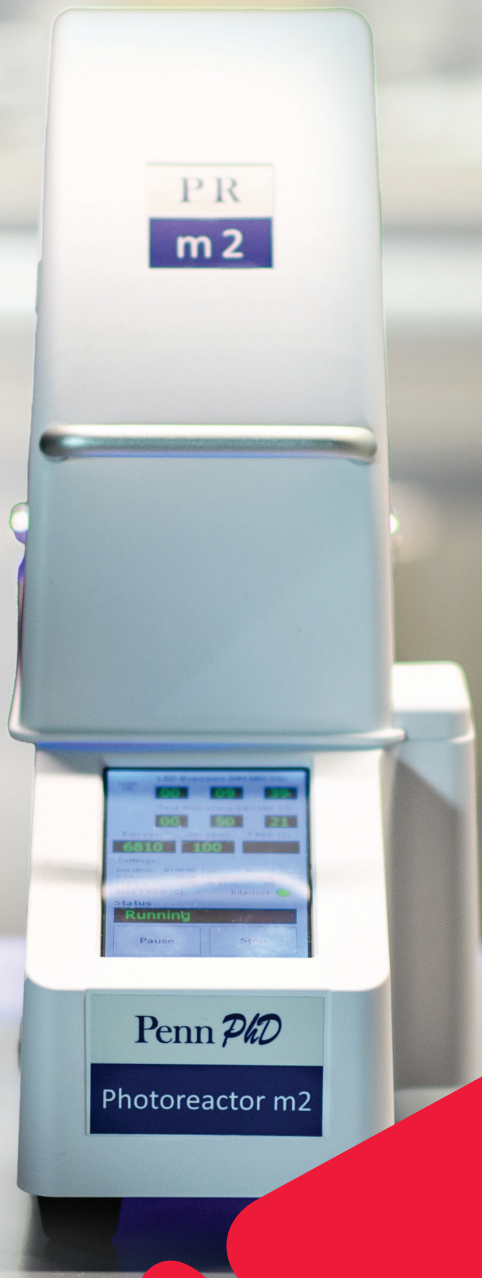

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