

TCIMAIL

number **171**



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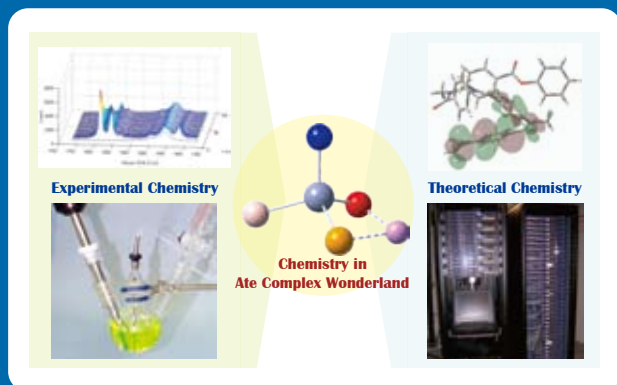
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Development of Novel Methodologies in Organic Synthesis Based on Ate Complex Formation

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Abstract: We have been focusing on development of novel synthetic methodologies based on ate complex formation. By fine-tuning of coordination environments of various main-group metals (Zn, Al, and B) as well as transition metal (Cu), a wide range of carbon-carbon bond and carbon-heteroatom bond (C–I, C–O, C–N, C–H, C–Si, and C–B) formation reactions have been realized in highly regio- and chemoselective manner taking advantage of characteristics of the elements.

Keywords: Ate complex, Halogen-metal exchange, Deprotonative metalation, Chemoselectivity, Regioselectivity

1. Introduction

Ate complexes are known to be anionic organometallic complexes, whose central metals have increased valence by accepting Lewis basic ligands to their vacant orbitals. They are attractive chemical species offering tunable reactivity due to their flexible choices of central metals, counter cations, and coordination environments. We have been working on development of novel methodologies in organic synthesis by designing of various ate complexes including zincates, aluminates, cuprates, and borates. This review article gives an overview of the ate complex chemistry developed in our laboratory.

2. Ate Complexes

Discovery of the first mono-anion type zincate, $\text{Na}[\text{ZnEt}_3]$, by James A. Wanklyn dates back to 1859,¹⁾ and even di-anion type zincate, $\text{Li}_2[\text{ZnMe}_4]$, was already reported by Dallas T. Hurd in 1948.²⁾ Zincates experienced a long blank after these important findings before they started to attract attentions in terms of their unique reactivity and selectivity and enjoy extensive uses in chemical synthesis. Generally, diorganozinc reagents (RZnR) and organozinc halides (RZnX) exhibit low ligand transfer ability, in other words, low reactivity. Reactivity of these species is significantly boosted by adding external ligands, so called ate complex formation.

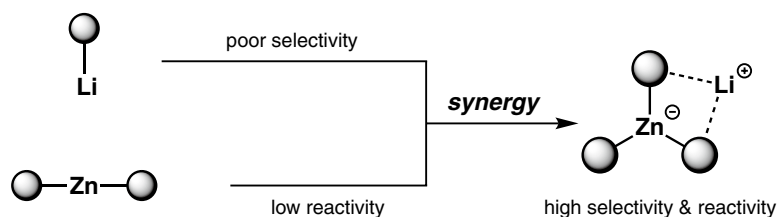
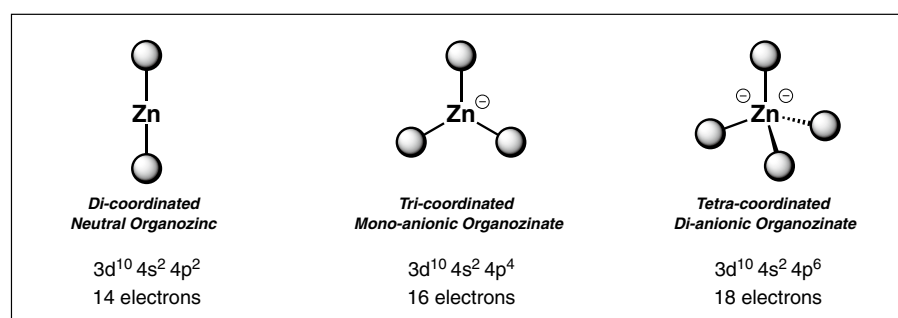


Figure 1. Ate Complexes

The difference in reactivity between a neutral organozinc compound and an ate complex can be understood by their electronic structures in the outer shell of zinc (Figure 1). In neutral organozinc compounds, the outer shell of zinc is 14-electron form. Such an electron-deficient nature makes $RZnX$ or R_2Zn able to act more as a Lewis acid to accept electrons instead of donating the R anion as a nucleophile. Coordination of an additional anionic ligand to the vacant orbital of zinc forms a 16-electron state, which makes the zincate species more stable (enhancing thermodynamic stability and reducing the Lewis acidity). On the other hand, with more anionic ligands, the whole molecule becomes more electronegative, facilitating anion-transfer (promoting kinetic activity).

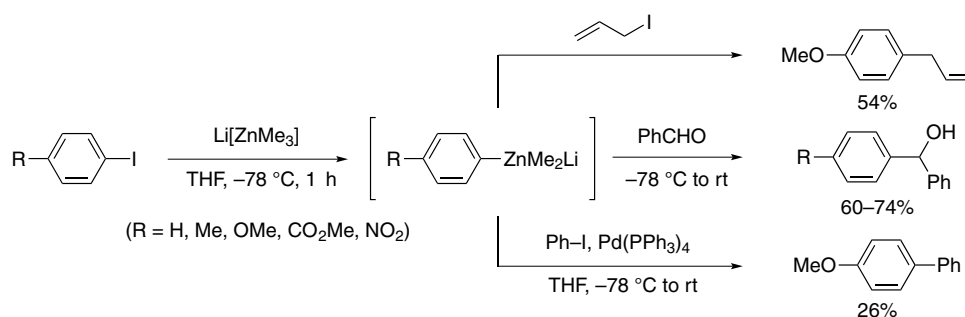
3. Di-anion Type Zincate

3-1. Mono-anion Type Zincates and Di-anion Type Zincates

In 1994, Kondo *et al.* reported that $Li[ZnMe_3]$ undergoes the halogen-metal exchange reaction of various aryl iodides at $-78\text{ }^\circ\text{C}$ and the generated aryl zincates react with electrophiles (Scheme 1).³⁾ On the other hand, $Li[ZnMe_3]$ is unreactive to metalate synthetically more desirable aryl bromides.

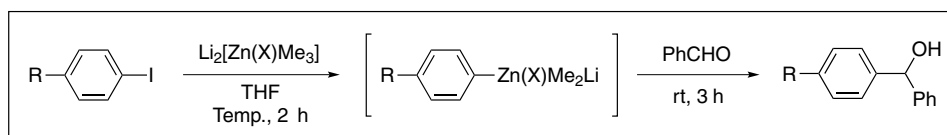
In 1996, we discovered that di-anion type zincates, $Li_2[Zn(X)Me_3]$ ($X = \text{Me, CN, or SCN}$), smoothly react with aryl bromides at ambient temperature and the resultant aryl zincate intermediates are trapped with aldehydes in high yields (Table 1, entries 1-6).⁴⁾ Base-susceptible functionality such as methyl ester is not tolerated due to high reactivity of the zincate to give complex mixture (entries 7-9).

Di-anion type aryl zincates, $Li_2[ArZnMe_3]$, exhibit higher reactivity than $Li[ArZnMe_2]$ (Scheme 2). In contrast with the reaction between $Li[ZnMe_3]$ and aryl iodide **1**, ends up only with iodine-zinc exchange, treatment of **1** with $Li_2[ZnMe_4]$ provides the indoline product **2** via iodine-zinc exchange followed by intramolecular conjugate addition. Metallation of 2-allyloxyiodobenzene (**3**) with $Li_2[ZnMe_4]$ affords the dihydrobenzofuran **5** via carbocation reaction of the unactivated double bond.⁵⁾



Scheme 1. Halogen-zinc Exchange Reaction with $Li[ZnMe_3]$ by Kondo *et al.*

Table 1. Reactivity of Di-anion Type Zincate: $Li_2[Zn(X)Me_3]$



Entry	R	X	Temp. [°C]	Yield [%]	Entry	R	X	Temp. [°C]	Yield [%]
1	H	Me	0	90	6	MeO	SCN	rt	92
2	H	CN	rt	90	7	CO ₂ Me	Me	0	trace
3	H	SCN	rt	89	8	CO ₂ Me	CN	0	trace
4	MeO	Me	0	84	9	CO ₂ Me	SCN	0	trace
5	MeO	CN	rt	90					

3-2. Highly Bulky Di-anion Type Zincate: $\text{Li}_2[\text{Zn}^t\text{Bu}_4]$

3-2-1. Halogen-zinc Exchange in the Presence of Proton Sources

In 2006, we developed a highly chemoselective zincation methodology of aryl bromides and aryl iodides using the newly designed extremely sterically encumbered di-anion type zincate, $\text{Li}_2[\text{Zn}^t\text{Bu}_4]$ (Scheme 3).⁶ This zincate is characterized by unprecedented compatibility with protic functionalities such as alcoholic O–H group as well as even more acidic phenolic

O–H group and N–H group of carboxyamides, and selectively metalates aromatic rings.

Additionally, ^tBu ligands played an important role in controlling the regioselectivity in the substitution reactions of propargyl bromide. In sharp contrast to the Grignard reagent and the cuprate, the $\text{Li}_2[\text{ArZn}^t\text{Bu}_3]$ was found to deliver the aryl ligand in a highly selective $\text{S}_{\text{N}}2'$ fashion to give the corresponding allene product (Table 2).⁷

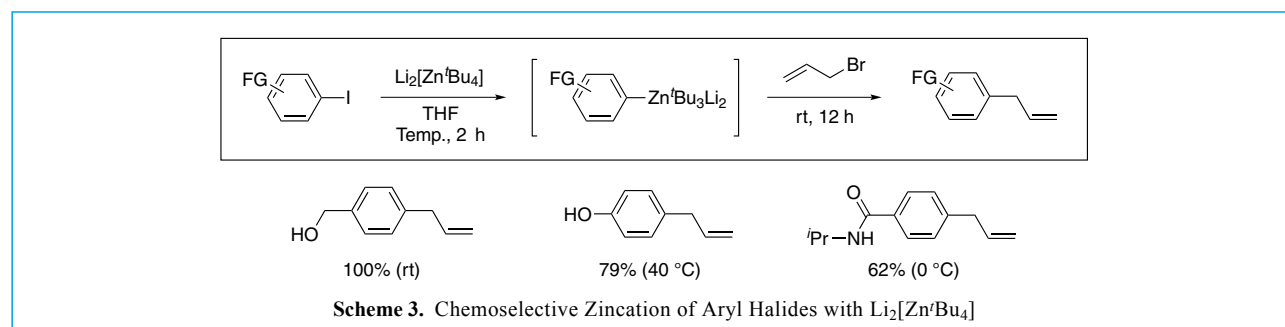
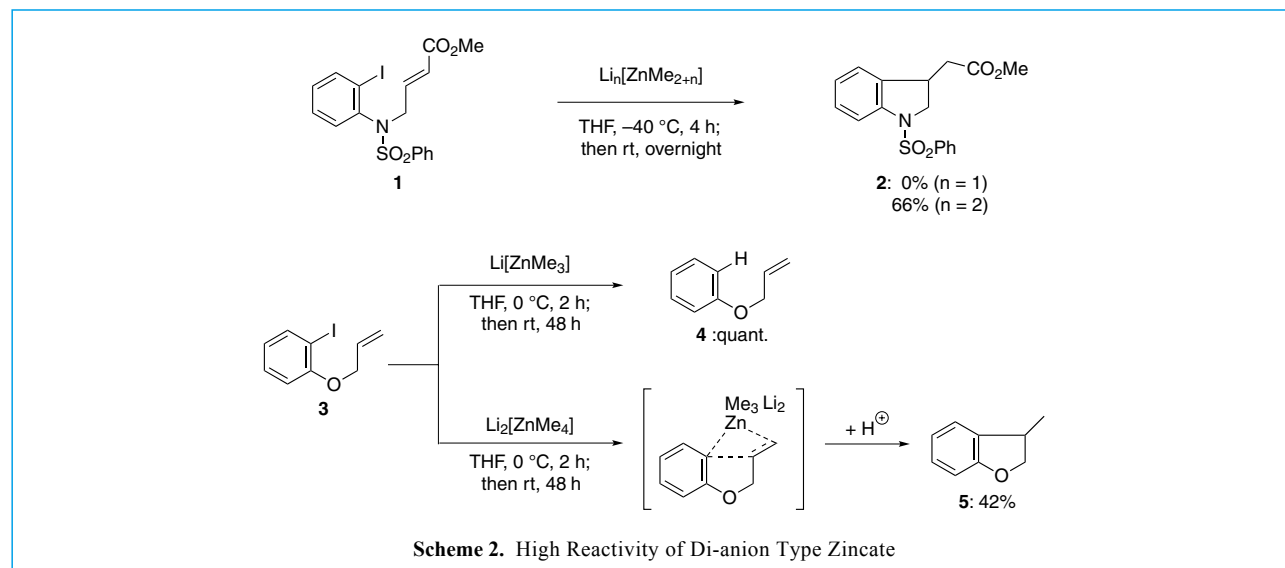
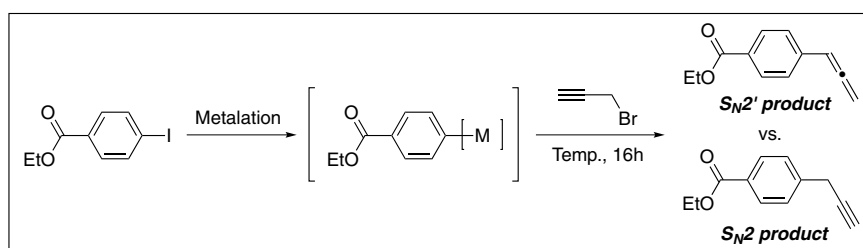


Table 2. Reaction of $\text{Li}_2[\text{Zn}^t\text{Bu}_4]$ with Propargyl Bromide: $\text{S}_{\text{N}}2$ vs. $\text{S}_{\text{N}}2'$



Entry	Metalation Reagent and Conditions	Temp. [°C]	Yield [%]	Ratio [$\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2$]
1	$\text{Li}_2[\text{Zn}^t\text{Bu}_4]$ (1.1 eq.), THF, 0 °C, 2 h	25	100	98 : 2
2	$^t\text{PrMgBr}$ (1.1 eq.), THF, –40 °C, 1 h, then CuCN (10 mol%)	–40	76	79 : 21
3	$\text{Li}_2[\text{Cu}(\text{CN})\text{Me}_2]$ (1.1 eq.), THF, 0 °C, 2 h	25	54	63 : 37

3-2-2. Anionic Polymerization in Water

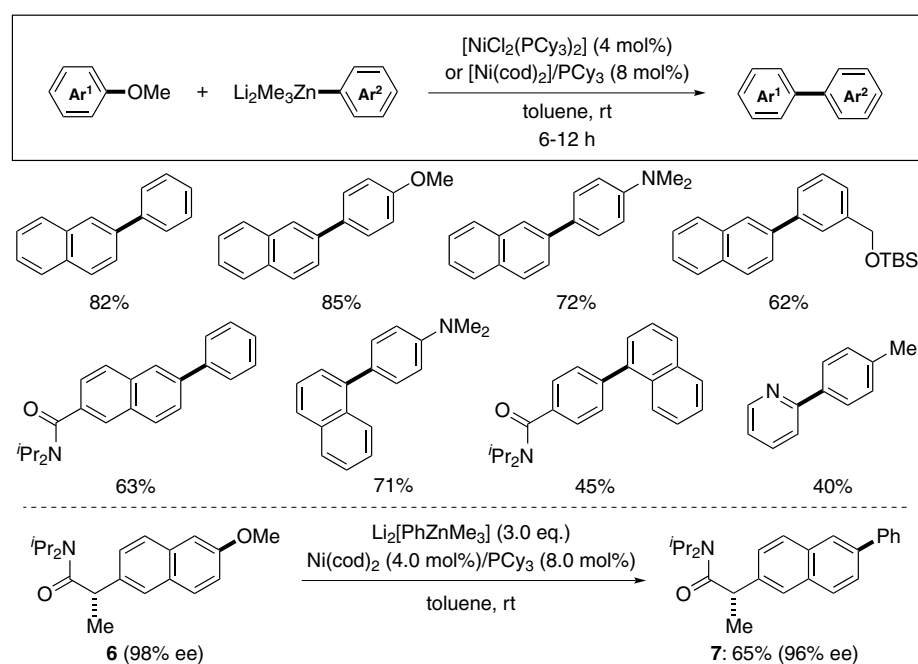
The di-anion type zincate $\text{Li}_2[\text{Zn}^t\text{Bu}_4]$ can be utilized as an initiator of anionic polymerization.⁸⁾ With this organometallic initiator, polymerization of *N*-isopropylacrylamide (NIPAm) proceeds especially rapidly in protic solvents such as MeOH and H_2O to give poly(NIPAm) in high yields (Table 3). It should be emphasized that the reaction completes within 15 minutes in H_2O . This polymerization method is applicable to other acrylic acid-based monomers including *N,N*-dimethylacrylamide, acrylamide, and 2-hydroxyethyl methacrylate.

3-3. Cross-coupling Reaction *via* C–O Bond Cleavage

In 2012, we reported the Negishi coupling reaction using aryl ethers as electrophiles (Scheme 4).⁹⁾ With the aid of the nickel catalyst, the cross-coupling reactions between the di-anion type zincates $\text{Li}_2[\text{ArZnMe}_3]$ and aryl ethers uniquely proceed to give biaryl products in good yields at ambient temperature. On the other hand, neutral organozinc reagents (ArZnX or Ar_2Zn) and mono-anion type zincates $\text{Li}[\text{ArZnMe}_2]$ did not lead to biaryl formation. The high chemoselectivity of the zincate as well as the mild reaction conditions of this coupling reaction allow the substitution of methoxy group of (+)-naproxene **6** with phenyl group without loss of optical purity to give **7**. Since aryl ethers are ubiquitously found in natural products and biologically active substances, this cross-coupling reaction is a powerful tool to rapidly fine-tune activity of those compounds by modification of the parent molecular architectures.

Table 3. Polymerization of *N*-Isopropylacrylamide using $\text{Li}_2[\text{Zn}^t\text{Bu}_4]$ as an Initiator

Entry	Solvent	Time [h]	Yield [%]	M_n	PDI	Entry	Solvent	Time [h]	Yield [%]	M_n	PDI
1	THF	24	8	7000	1.50	3	MeOH	3	76	18000	1.65
2	THF	168	33	7000	2.71	4	H_2O	< 1	92	27000	2.72



Scheme 4. Negishi Cross-coupling *via* C–O Bond Cleavage

4. Heteroleptic Ate Complexes

4-1. Deprotonative Metalation of Aromatic C–H Bonds

Deprotonative metalation utilizing ate bases¹⁰ is a highly regio- and chemoselective process to functionalize aromatic rings directly, and thus very efficient synthetic process. Reactivity and selectivity of ate complexes depend on the characteristics of the elements and can be tuned flexibly by changing the central metal. “Heteroleptic” ate complexes are especially fine-tunable by endowing different functions to each ligand (Figure 2).¹¹

4-1-1. Amidozincate Base: Li[(TMP)ZnR₂]

In 1999, we reported the deprotonative zincation reaction by a newly designed amidozincate base, Li[(TMP)Zn^tBu₂], prepared from ^tBu₂Zn and LiTMP (lithium 2,2,6,6-tetramethylpiperidide) (Scheme 5).¹² This ate base enabled directed *ortho* metalation of aromatic rings substituted with ester, amide, and cyano groups without damaging these functionalities. Moreover, π -electron-rich heteroaromatics such as thiophenes and furans as well as electron-deficient ones such as pyridines, quinolines, and isoquinolines are smoothly metalated in good yields.

Generally, *ortho* metalation of bromobenzenes smoothly generates corresponding benzyne *via* facile elimination of

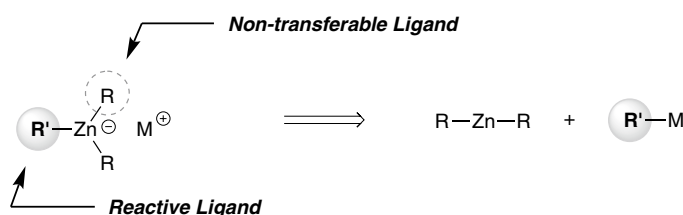
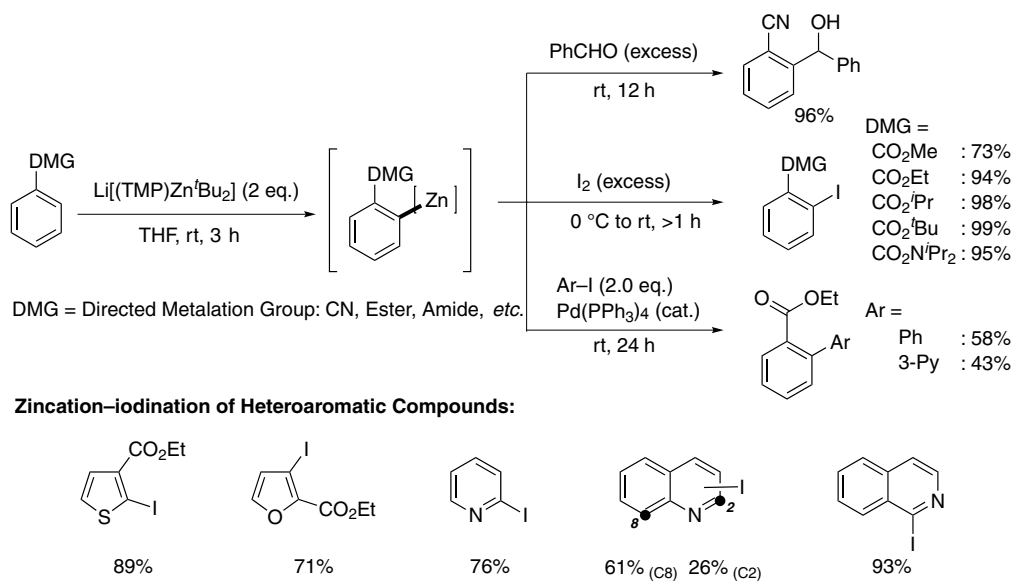
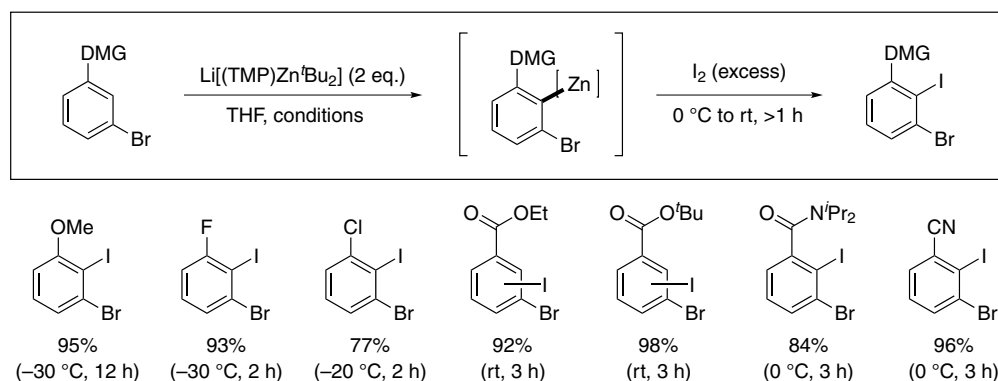


Figure 2. Heteroleptic Zincates



Scheme 5. Highly Regio- and Chemoselective Zincation of Aromatics



Scheme 6. *ortho* Iodination of Bromobenzenes

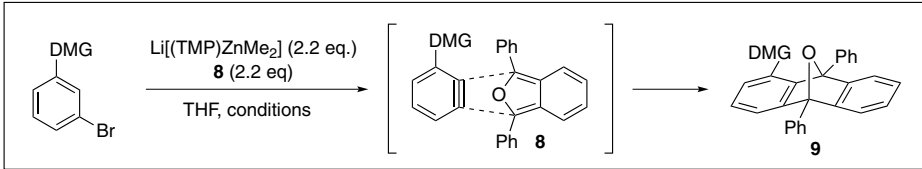
metal bromide salts. Li[(TMP)Zn^tBu₂] deprotonates their *ortho* C–H bond without releasing bromide anion and the resultant aryl zincate can be trapped with various electrophiles in high yields (Scheme 6).¹³

On the contrary, *ortho* metalation with Li[(TMP)ZnMe₂], which has smaller alkyl ligands smoothly generates benzynes. This method enables efficient generation of substituted benzynes taking advantage of highly chemoselective nature of the amidozincate base, and Diels-Alder reactions of benzynes with 1,3-diphenylisobenzofuran (**8**) proceed in high yields (Table 4).

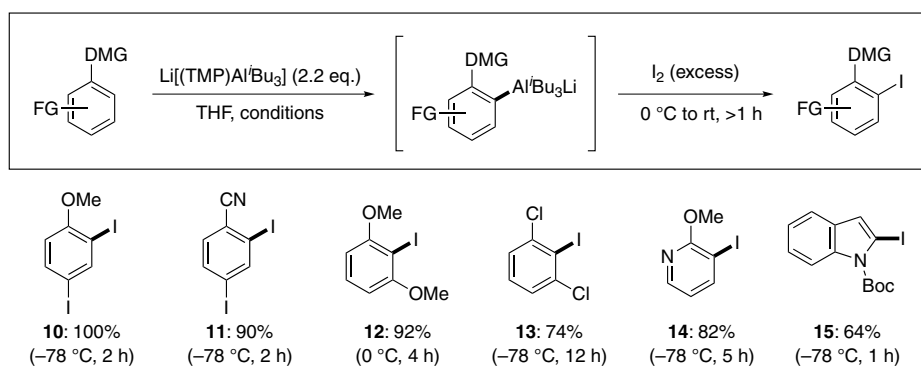
4-1-2. Amidoaluminate Base: Li[(TMP)Al^tBu₃]

Organoaluminum reagents have long been utilized in organic synthesis, but their usage has been limited to mainly aliphatic chemistry. In general, arylaluminum compounds are prepared *via* transmetalation from aryl lithiums and –Grignard reagents to aluminum halides, and this protocol has been confining functional groups on aromatic rings only to robust ones due to too high reactivity of those reagents. We developed a preparative method for functionalized arylaluminums *via* deprotonative metalation with our newly developed amidoaluminate base, Li[(TMP)Al^tBu₃]. A number of functional groups including heteroaromatic rings (**14** and **15**) are tolerated in this metalation reaction (Scheme 7).¹⁴ One of notable features of this aluminate base is its low halogen-metal exchange ability. Taking advantage of this unique reactivity, deprotonative *ortho* metalations of 4-iodoanisole (**10**) and 4-iodobenzonitrile (**11**) proceed chemo- and regioselectively in high yields, while C–I bond at the 4-position remains intact.

Table 4. Regioselective Generation of Substituted Benzynes with Li[(TMP)ZnMe₂]



Entry	Substrate	Conditions	Benzyne	Yield [%]	Entry	Substrate	Conditions	Benzyne	Yield [%]
1		rt, 12 h		100	5		reflux, 3 h		55
2		60 °C, 15 h		71	6		reflux, 6 h		88
3		rt, 48 h		72	7		reflux, 12 h		100
4		rt, 12 h		100	8		reflux, 12 h		90



Scheme 7. Chemoselective Deprotonative *ortho* Metalation with Li[(TMP)Al^tBu₃]

4-1-3. Amidocuprate Base: $\text{Li}_2[(\text{TMP})\text{Cu}(\text{CN})\text{R}]$

Organocuprates are frequently used for various types of C–C bond forming reactions utilizing the redox activity of copper. Envisioning to establish a new method to prepare functionalized arylcopper species *via* deprotonative cupration reactions, we designed a novel Lipshutz-type amidocuprate base, $\text{Li}_2[(\text{TMP})\text{Cu}(\text{CN})\text{R}]$.¹⁵ A series of aromatics with polar functional groups such as methoxy, cyano, and amide groups and heteroaromatics are regioselectively deprotonated with $\text{Li}_2[(\text{TMP})\text{Cu}(\text{CN})\text{Me}]$ (Scheme 8).

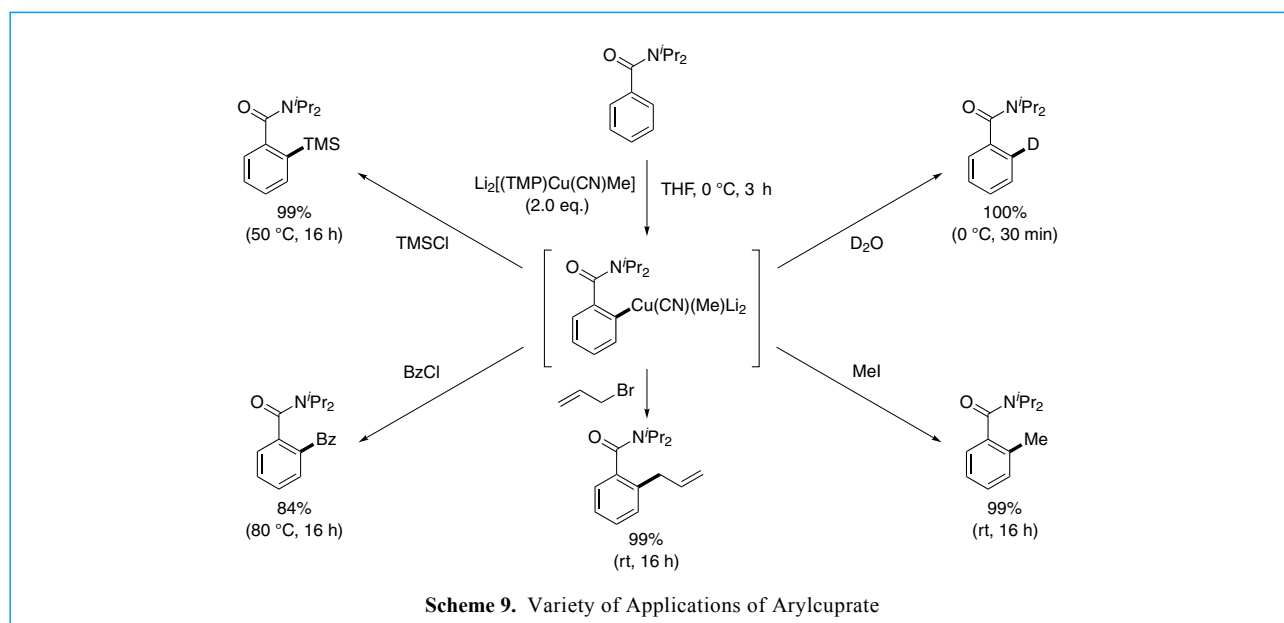
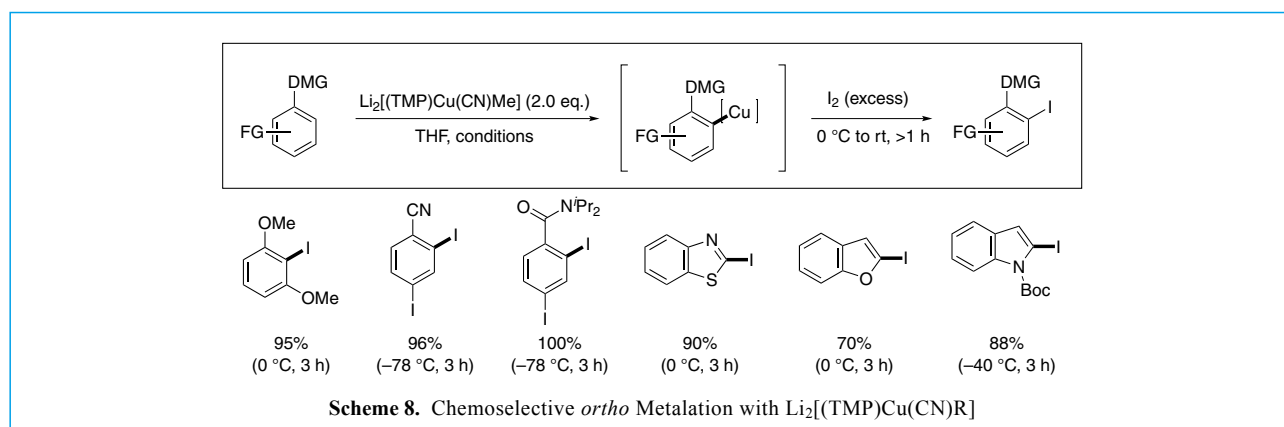
The intermediary arylcuprate reacts with various electrophiles in excellent yields thanks to its high nucleophilicity (Scheme 9).

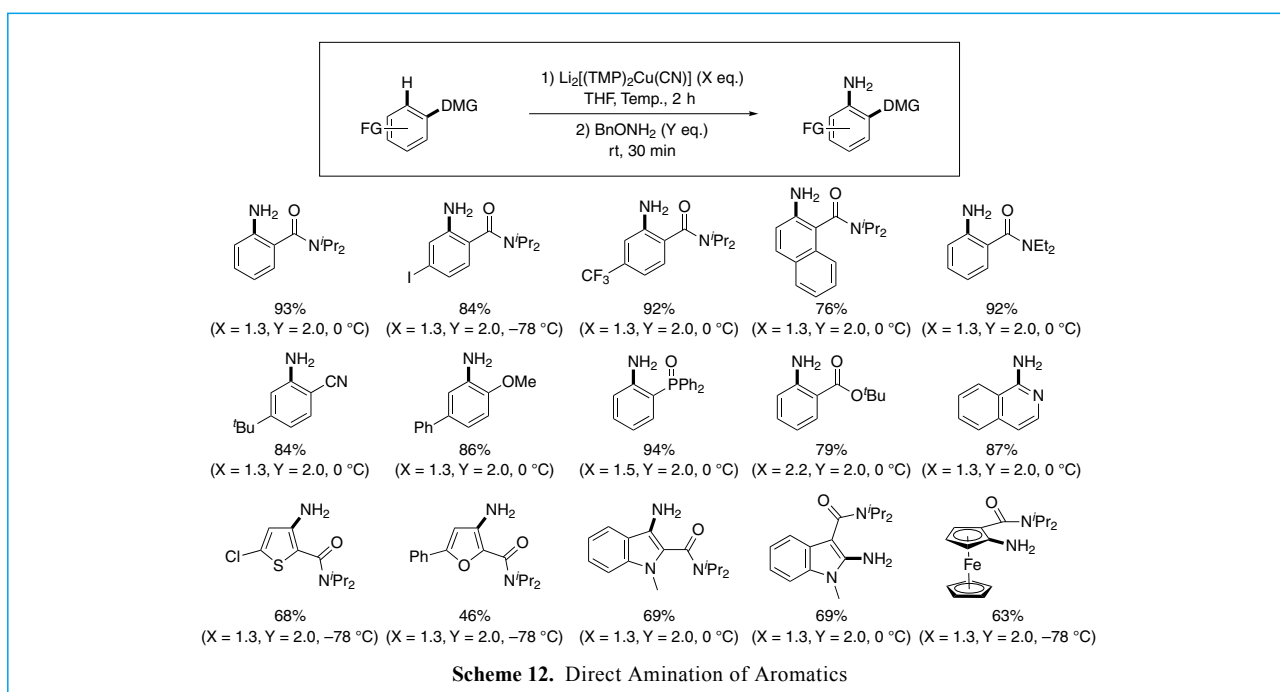
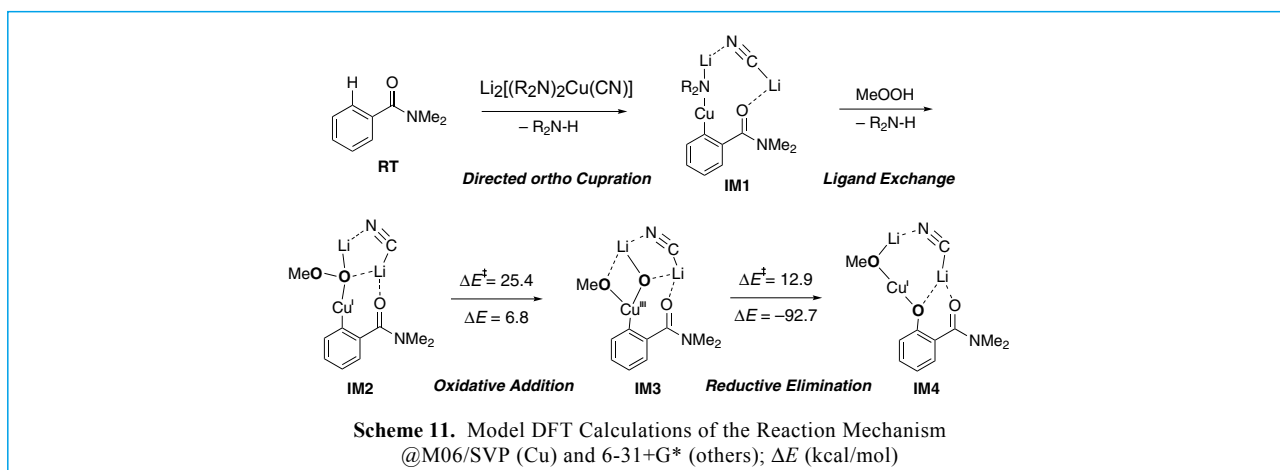
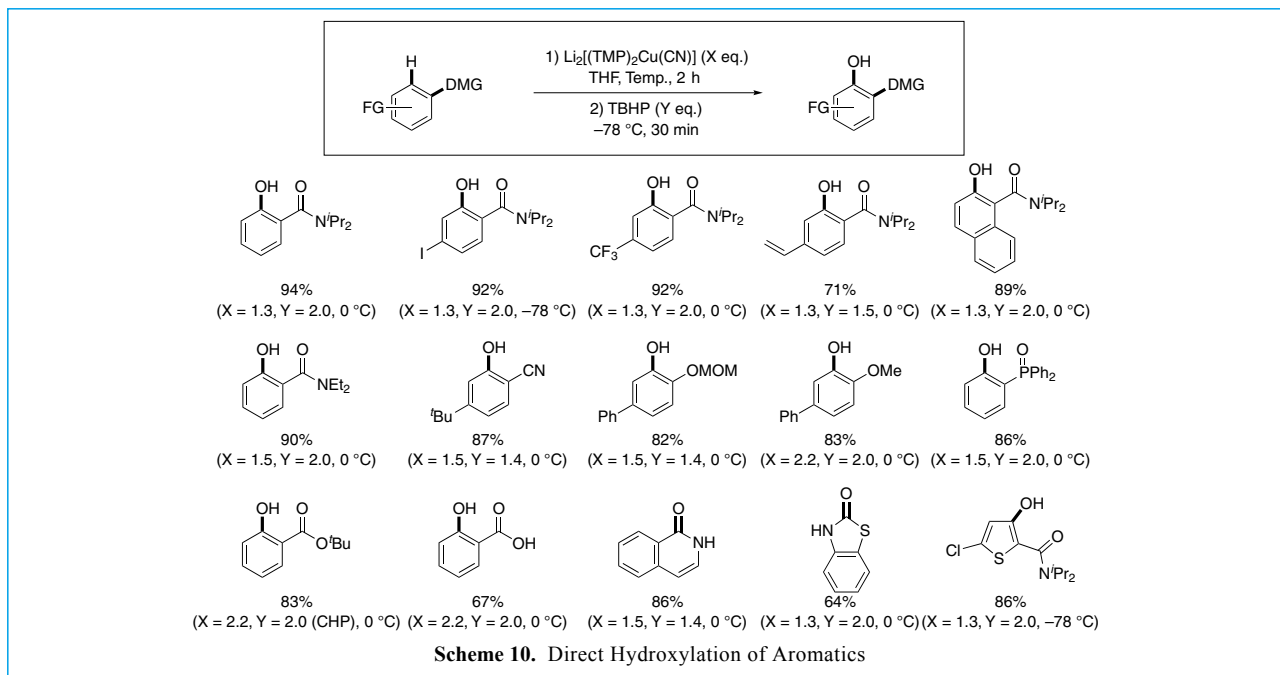
We have recently reported that the combination of the arylcuprate intermediate generated by the reaction of $\text{Li}_2[(\text{TMP})_2\text{Cu}(\text{CN})]$ with an aromatic compound and

hydroperoxide (ROOH) including *t*-BuOOH (TBHP) and cumene hydroperoxide (CHP) affords the corresponding phenol product in high yield (Scheme 10).¹⁶ This approach delivers diverse phenols based on high functional group compatibility of the cuprate base.

DFT calculation suggests that this oxygenation reaction occurs *via* the redox reactions of copper more likely rather than direct nucleophilic attack of arylanion to peroxide (Scheme 11).

Based on the mechanism by DFT calculations, we also achieved the direct amination reaction using BnONH_2 instead of ROOH (Scheme 12). This amination is supposed to proceed in the same way as the hydroxylation, and to the best of our knowledge, this is the first truly efficient and straightforward method to prepare *N*-unsubstituted anilines from their C–H counterparts.



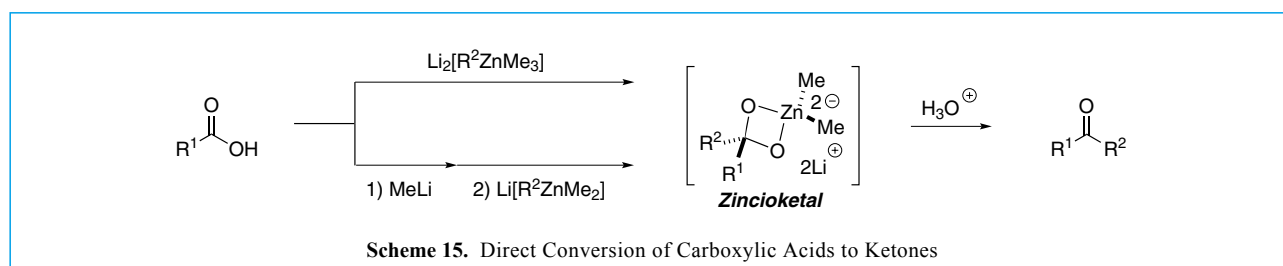
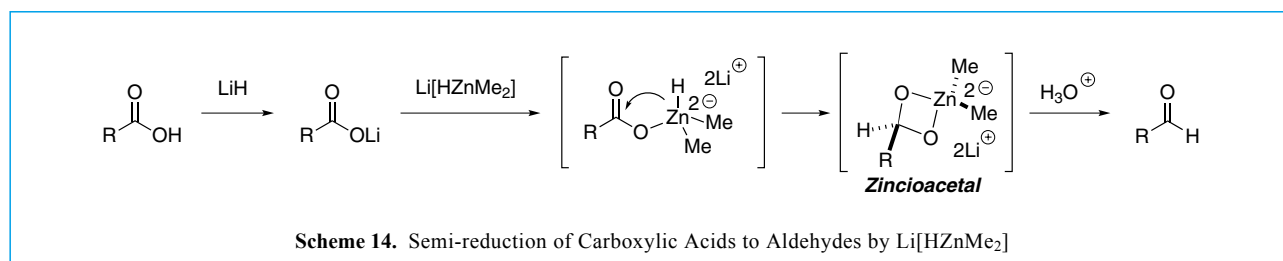
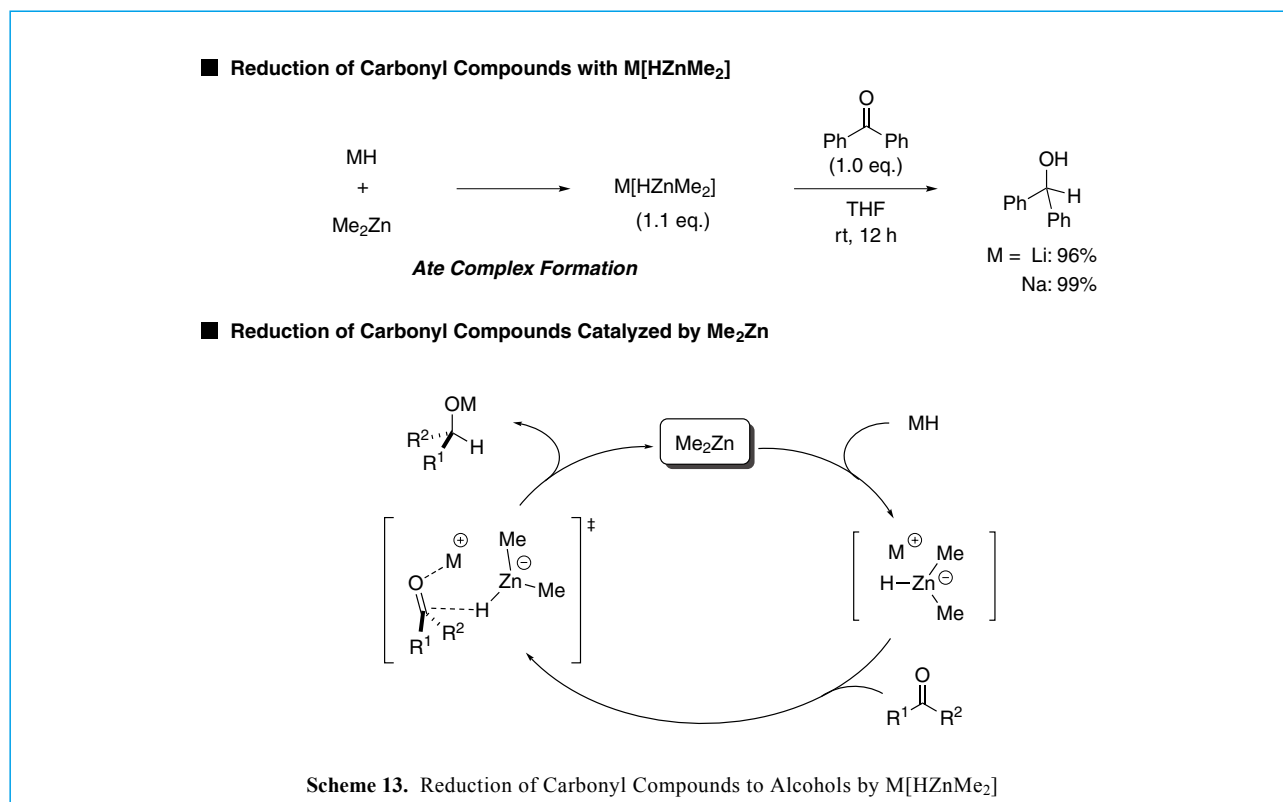


4-2. Hydrido-zincate: M[HZnMe₂]

Although trihydrido-type zincates have been known in the fields of inorganic chemistry and coordination chemistry, reactivities of heteroleptic hydrido-zincates remained unrevealed. We discovered that the hydrido-zincates M[HZnMe₂] (M = Li or Na) deliver the hydrido ligand preferentially to a variety of carbonyl compounds to give the corresponding alcohols (Scheme 13).¹⁷⁾ A noteworthy fact is that no methylation product was obtained in all cases. Therefore, this reduction possibly proceeds catalytically. Indeed, the reduction of carbonyl compounds with NaH/LiH in the presence of catalytic amounts of Me₂Zn proceeded smoothly to give the corresponding alcohols in high yields.

Additionally, Li[HZnMe₂] uniquely semi-reduces carboxylic acids to aldehydes, and no over-reduced alcohol products are obtained (Scheme 14). This is explained by the formation of the zincioacetal intermediate after hydride transfer to the carbonyl group, and this tetrahedral structure is stable in the reaction mixture. Aldehyde is released eventually upon quenching.

This phenomenon can be applied to the direct transformation of carboxylic acids to ketones. Both of the reaction between di-anion type zincate and a carboxylic acid and the reaction between a mono-anion type zincate and a lithium carboxylate form the similar stable zincioacetal intermediate to avoid the formation of an undesired tertiary alcohol by-product (Scheme 15).¹⁸⁾



4-3. Silylzincates

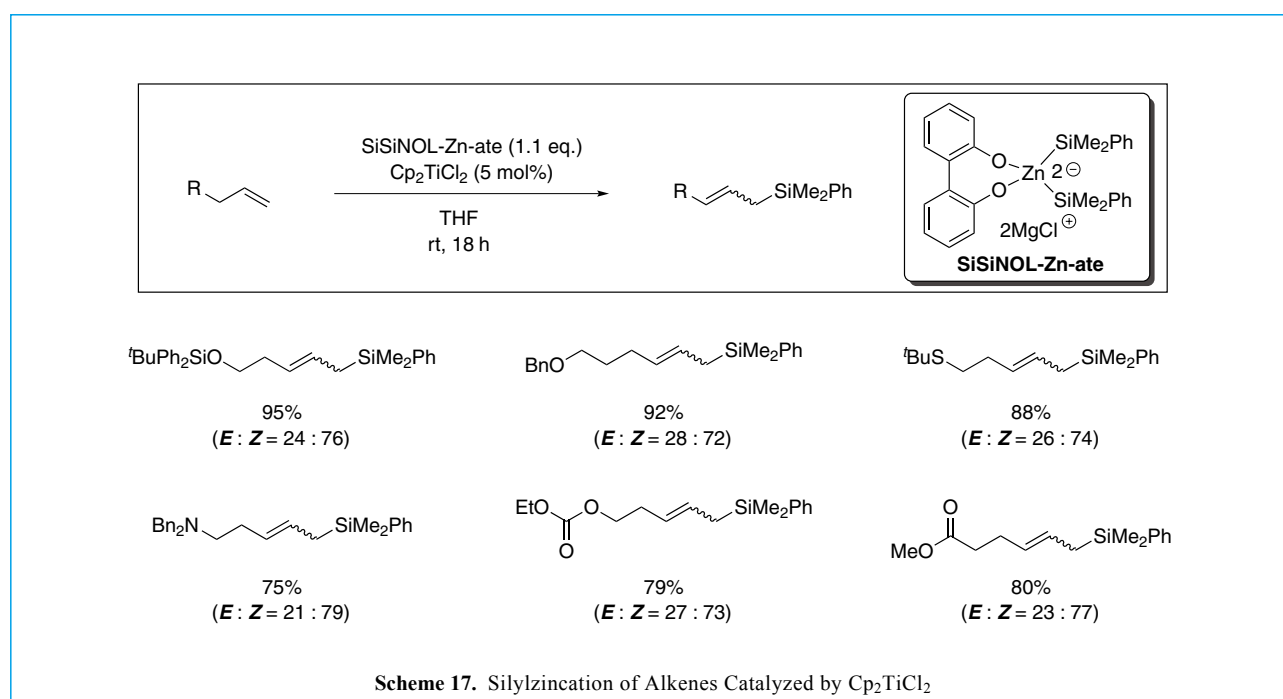
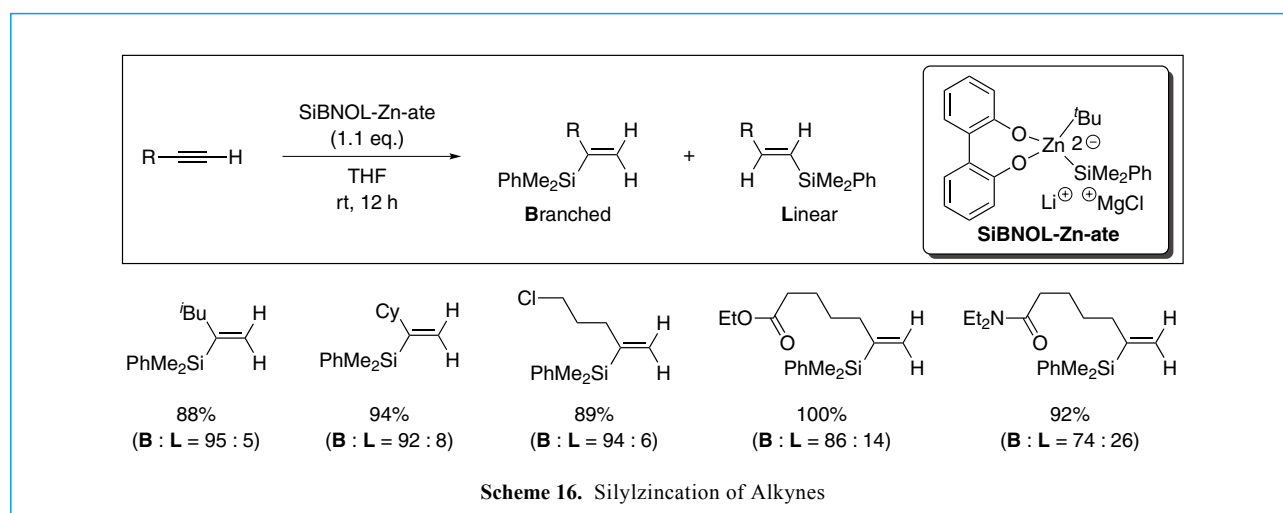
C–C multiple bond is a versatile platform for myriad chemical transformations and addition of organometallic reagents across it is a fundamental and important reaction to increase molecular complexity. We designed various silylzincates and realized regioselective silylzincation reactions of alkynes and alkenes as follows.

4-3-1. Silylzincation of Alkynes

Our di-anion type silyl zincate, SiBNOL-Zn-ate, adds chemoselectively across various terminal alkynes without the aid of transition metal catalysts (Scheme 16).¹⁹ Functionalized branched vinylsilane products are obtained in high yields with high to excellent regioselectivities.

4-3-2. Silylzincation of Alkenes (1): Synthesis of Allylsilanes

Silylzincates by themselves are not reactive towards alkenes. We found that our SiSiNOL-Zn-ate undergoes the silylzincation reaction across terminal alkenes in the presence of a catalytic amount of Cp₂TiCl₂ (Scheme 17).²⁰ Regioselective addition of the SiSiNOL-Zn-ate to alkenes and following β-hydride elimination afford Z-configured allylic silanes in preference to E-isomers. No trace of alkylsilanes nor migration of double bonds is observed.



4-3-3. Silylzincation of Alkenes (1): Synthesis of Alkylsilanes

By using CuCN as a catalyst, silylzincation reaction of alkenes by our SiBNOL-Zn-ate proceeds in high yields (Scheme 18).²¹ In this catalyst system, linear alkylsilanes are obtained as major products without β -hydride elimination. On the other hand, alkenes bearing a highly coordinating unit such as cyano group and phosphine oxide gives the branched isomer with perfect regioselectivities.

4-4. Perfluoroalkylzincate: Li[R_FZnMe₂] & R_FZnR

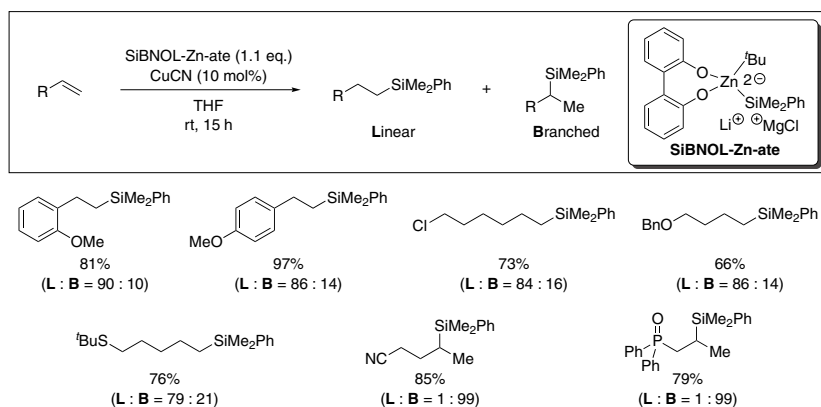
Perfluoroalkyl (R_F) organometallics are known to be thermally unstable and easily decompose *via* α - or β -fluoride elimination. Therefore, generation and use of those species require cryogenic reaction conditions and strict temperature control (Figure 3).²²

We launched the projects on development of novel perfluoroalkylation reactions using zinc as a key element based on relatively stable nature of C–Zn bond. First of all, metalation of C₄F₉–I with various zinc reagents was investigated at 0 °C

and the generating R_F–zinc was trapped at *ambient temperature* (Scheme 19). Ate complexes Li[ZnMe₃] and Li₂[ZnMe₄] did not give the desired adduct **16** under these reaction conditions, whereas **16** was obtained in moderate yields at –78 °C. Contrary to unproductive results using MeZnCl and Me₂Zn, Me₂Zn prepared from ZnCl₂ and 2 equivalents of MeLi successfully gave **16** in 62% yield. Moreover, **16** was obtained by addition of 2 equivalents of LiCl to Me₂Zn and there results imply the perfluoroalkylzincate Li[R_FZn(Me)Cl] is generated from Li[Me₂ZnCl], and this ate complex is “thermally stable” and “highly reactive” at the same time.

R_F–zincates add to various carbonyl compounds with good functional group tolerance, and offer a facile access to Csp³–R_F and Csp³–Ar_F bond formation (Scheme 20).²³

Development of efficient methods for introduction of fluorine-containing functional groups to aromatic rings attracts more and more attention. As an initial attempt, we performed a reaction between Li[R_FZn(Me)Cl] and aryl halide **17** in the presence of CuCl and obtained the desired coupling product **18** in 17% yield (Scheme 21).



Scheme 18. Silylzincation of Alkenes Catalyzed by CuCN

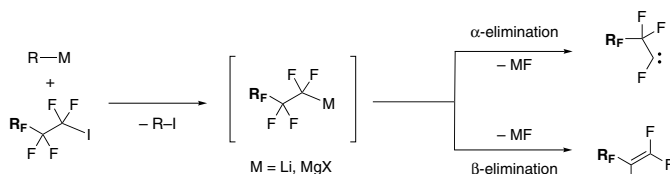
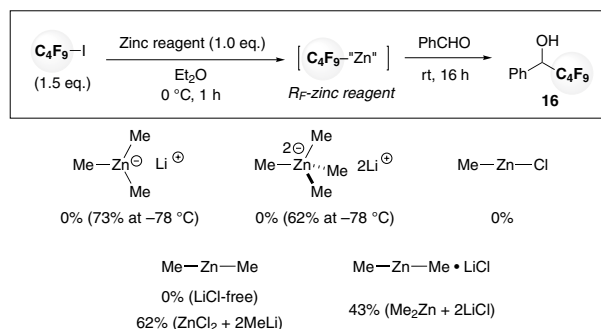
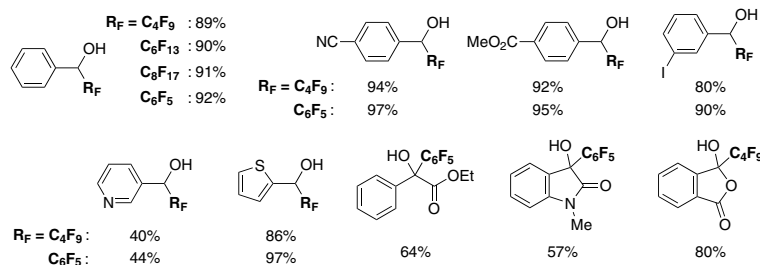
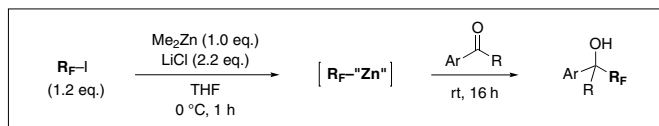


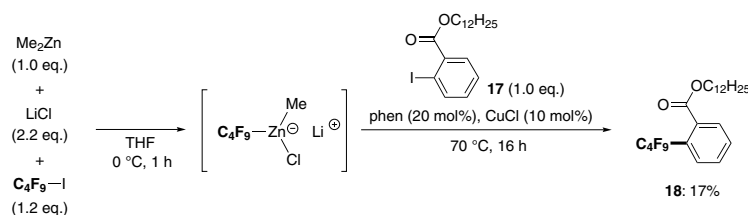
Figure 3. Common Decomposition Pathways of R_F-organometallics



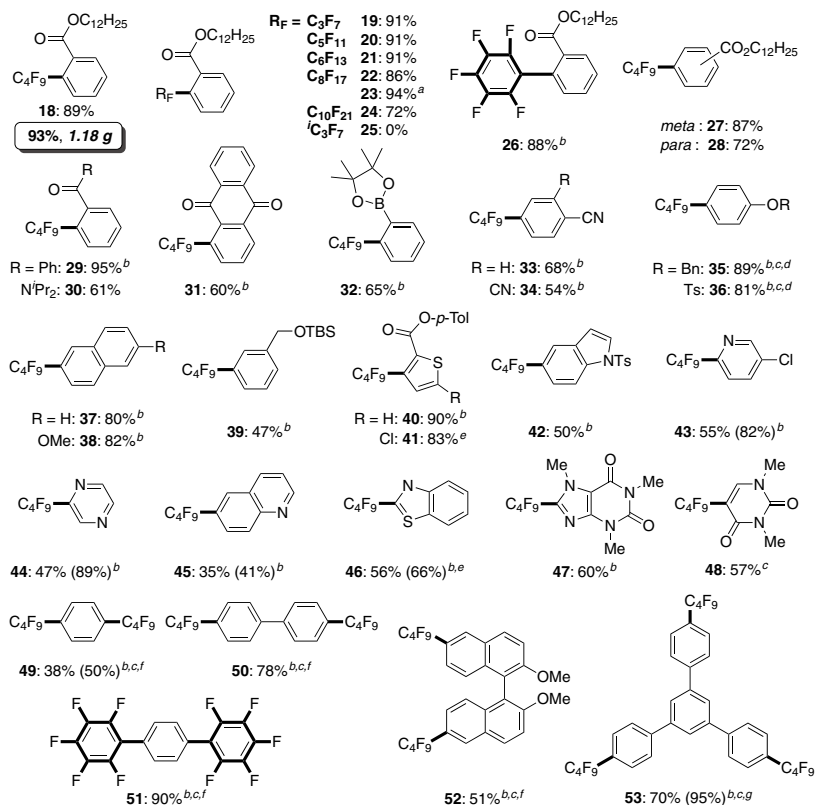
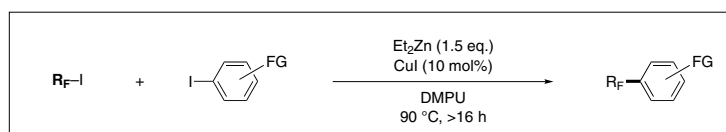
Scheme 19. Zincation of R_F–I



Scheme 20. Perfluoroalkylation and Perfluoroarylation of Carbonyl Compounds



Scheme 21. Initial Attempt on Perfluoroalkylation of Aryl Halide



Scheme 22. Substrate Scope of Aromatic Perfluoroalkylation

Isolated yields. NMR yields are given in parentheses. ^a $C_8F_{17}-Br$ was used. ^b 1,10-Phenanthroline (20 mol%) was added. ^c 120 °C. ^d CuI (20 mol%) was added. ^e Me_2Zn was used instead of Et_2Zn . ^f Amounts of the reagents were doubled. ^g Amounts of the reagents were tripled.

This low yield was attributed to instability of $\text{Li}[\text{C}_4\text{F}_9\text{Zn}(\text{Me})\text{Cl}]$ under heating conditions generally required for cross-coupling reaction by catalytic copper salt. Thus, we systematically screened neutral Lewis basic solvents in order to activate zinc species in an ad-hoc manner, and found *N,N'*-dimethylpropyleneurea (DMPU) to be the best solvent giving **18** in 89% yield. None-coordinating solvents such as toluene and dichloromethane hardly promote the desired reaction. These results indicate that DMPU coordinates the vacant orbitals of zinc²⁴) and this coordination plays important roles to stabilize and activate the R_F -zinc complex. Difference in catalytic activity among cuprous halides was not observed and thus air-stable CuI was chosen as the optimal catalyst.

This perfluoroalkylation reaction displays a wide substrate generality and various R_F groups can be introduced onto aromatic rings (Scheme 22).²⁵) Scaling-up of this reaction is facile and the coupling product **18** is obtained in 93% yield on a gram-scale. Perfluoroaryl group can also be installed with 1,10-phananthroline as a ligand to copper (**26**). This method is applicable to multiple perfluoroalkylations of substrates possessing more than one reactive site (**49-53**), and is expected to contribute in chemical elaboration of functional materials by R_F -groups.

4-5. Design of Borylanion Equivalents and Applications in Synthetic Chemistry

Borylanion is a highly reactive species and an attractive tool to synthesize boron-containing compounds. However, borylanions have been regarded as difficult to generate with a few sophisticated exception such as a finely stabilized borylanion reported by Yamashita and Nozaki²⁶) and the borylcopper complex reported by Sadighi.²⁷) We have been interested in stabilization and control of reactivity of borylanion by ate complex formation and developing novel nucleophilic borylation methodologies.

4-5-1. Borylzincate: $\text{M}[(\text{pinB})\text{ZnEt}_2]$

In the course of our research programs on heteroleptic ate complexes, we got interested in formation and reactivity of borylzincates bearing borylanion as a ligand to zinc. We hypothesized that borylzincate can be generated *via* transmetalation of boryl group from alkoxide-activated diboron to dialkylzinc and performed model DFT calculations (Figure 4). The results implied that the formation of borylzincate is kinetically well feasible process with an activation barrier of 15.8 kcal/mol, and the small stabilization energy for the formation of borylzincate appears to be a hurdle for utilization of this species for chemical synthesis. If this thermodynamically unfavorable energy loss could be compensated by following reactions, borylzincate can be used in borylation reactions as a transient reactive intermediate.

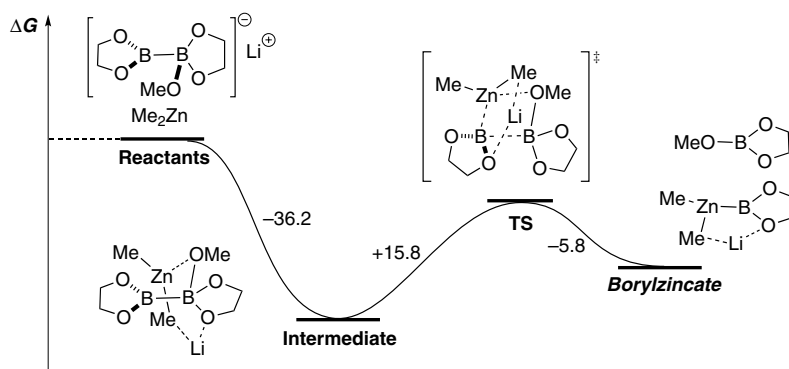


Figure 4. Model DFT Calculation on Borylzincate Formation @M06/SVP (Zn) and 6-31+G* (others); ΔG (kcal/mol)

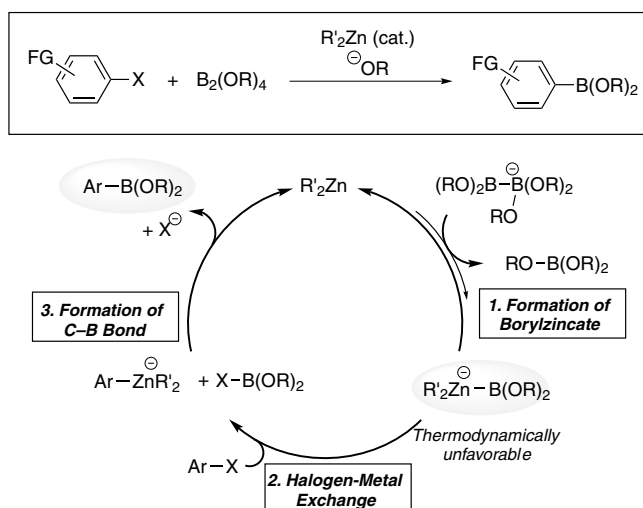
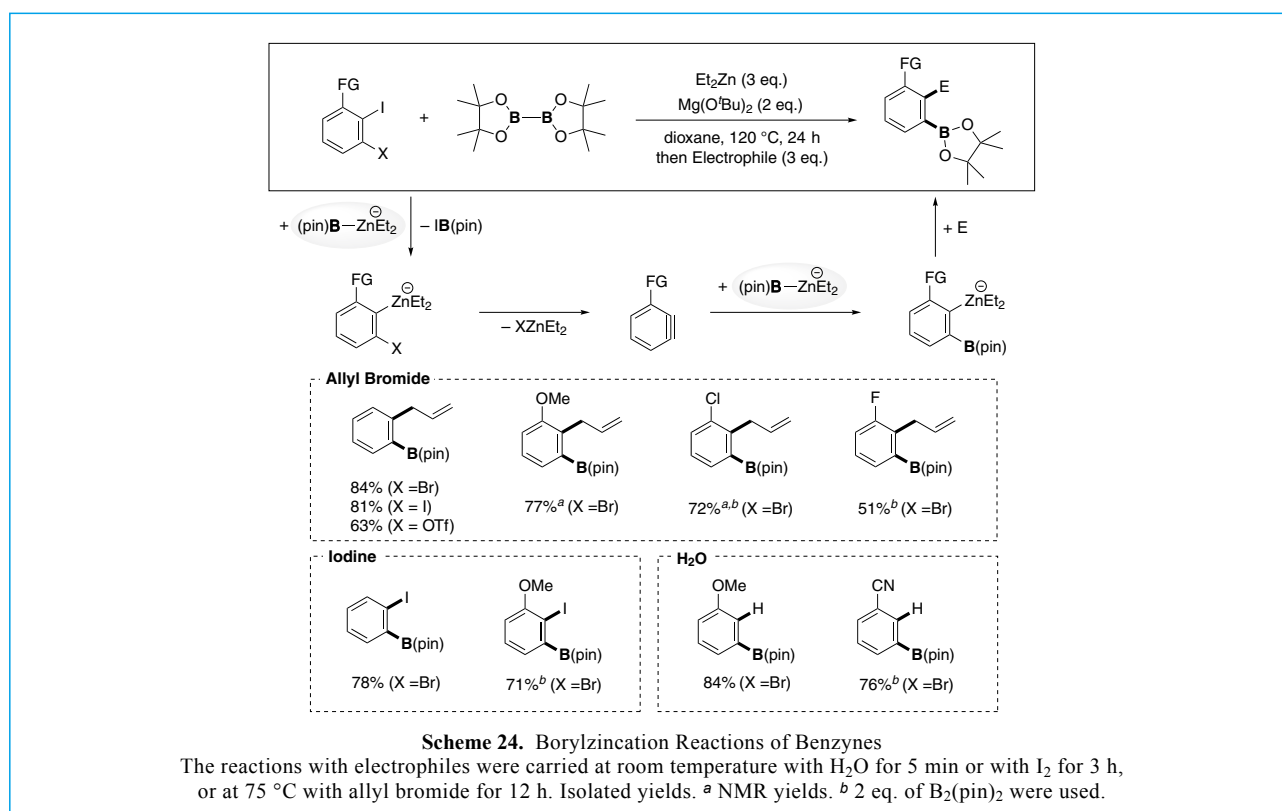
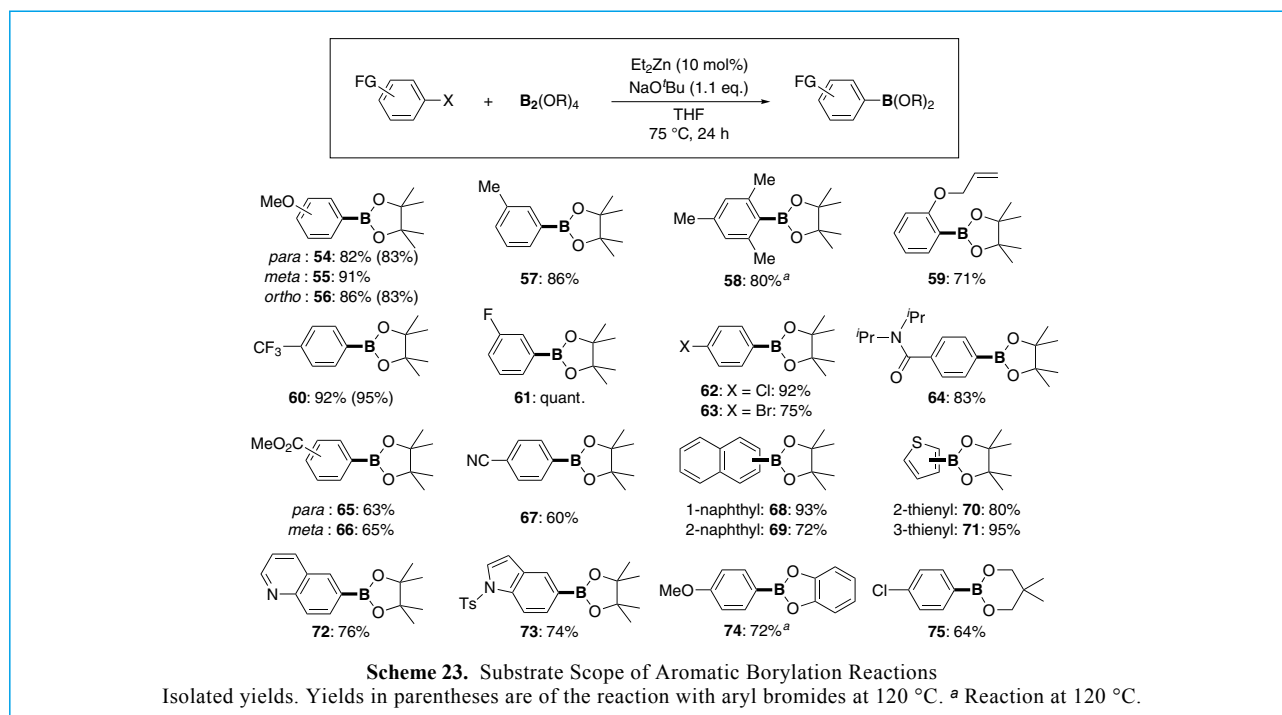


Figure 5. Design of Catalytic Borylation of Aryl Halides

Based on the computation, we envisioned the catalytic borylation of aryl halides *via* a halogen-zinc exchange reaction with borylzincate (Figure 5). In this reaction design, energetically disfavored borylzincate formation is expected to be compensated by stepwise formation of the stable C–Zn and C–B bonds.

After extensive optimization, a set of conditions of Et₂Zn (10 mol%), NaO^tBu (1.1 eq.), and at 75 °C in THF was found

to be optimal to borylate various aryl iodides (Scheme 23).²⁸ It is worth mentioning that sterically hindered mesityl substrate (**58**), aryl iodides containing the transition metal-susceptible allyloxy group (**59**), base-susceptible ester group (**65**, **66**) and cyano group (**67**), and various heteroaromatic substrates (**70–74**) can be employed. Moreover, aryl bromides are also borylated by elevating reaction temperature to 120 °C (**54**, **56**, **60**). Diborons other than bis(pinacolato)diboron can also be applied to this methodology (**74**, **75**).



Next, we designed another strategy to gain a large stabilization energy of the system by the reaction of borylzincate with benzyne. Benzyne are highly unstable intermediate and form stable benzene rings after the reaction with nucleophiles. Highly nucleophilic borylzincate undergoes an iodine-zinc exchange reaction followed by concomitant elimination of an *ortho* leaving group to give a benzyne (Scheme 24). Addition of another borylzincate across the benzyne generates functionalized arylzincate, which is trapped by various electrophiles to give multiply substituted benzenes with high regioselectivities.²⁸⁾

4-5-2. *trans*-Diborylation of Alkynes via *pseudo*-Intramolecular Reaction

Vinylboronates are important and useful synthetic precursors in organic synthesis of pharmaceuticals and functional molecules. In general, those compounds are prepared through hydroboration, haloboration, and diborylation of alkynes. These types of reactions normally utilize the interaction between triple bond and the vacant p-orbital of boron or transition metal-boron bond for the C–B bond formation so that *cis*-configured alkene products are generally obtained (Figure 6). We expected that addition of borylanion (equivalent) to a triple bond would lead to unprecedented *trans*-selective diborylation reaction.

Initially, exhaustive efforts were devoted to the reactions between internal alkynes and diborons activated by Lewis bases (intermolecular approach),²⁹⁾ but no desired diborylated product was obtained (Scheme 25). Model DFT calculation computed the activation barrier for the initial C–B bond formation to be more than 50 kcal/mol and entirely insurmountable, which is well consistent with the experimental results.

Thus, we designed “*pseudo*-intramolecular reaction”³⁰⁾ by using alkynes possessing a Lewis basic site within the molecule in order to facilitate a C–B bond forming event in terms of enthalpy and entropy (Figure 7).

The reaction of bis(pinacolato)diboron with the propargylic alkoxide afforded the desired diborylated product **76** in 77% yields (Scheme 26).³¹⁾ This diborylation reaction can be easily operated on a gram-scale and has a broad substrate scope. Triple bonds proximal to the alkoxide group react preferentially over the distal multiple bonds in the cases of enyne and diyne substrates (**91** and **92**). Applicable substrate is not limited to tertiary alcohols and a range of secondary alcohols is converted to the oxaborole products in high yields (**92-98**). On the other hand, primary alcohols and homopropargylic alcohols do not participate in this type of diborylation reaction.

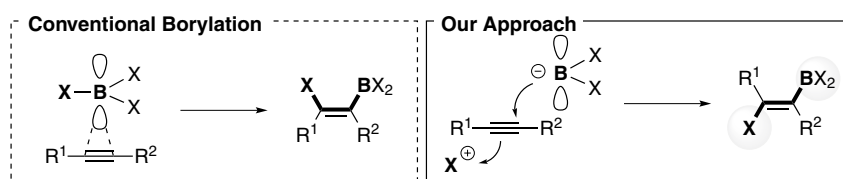
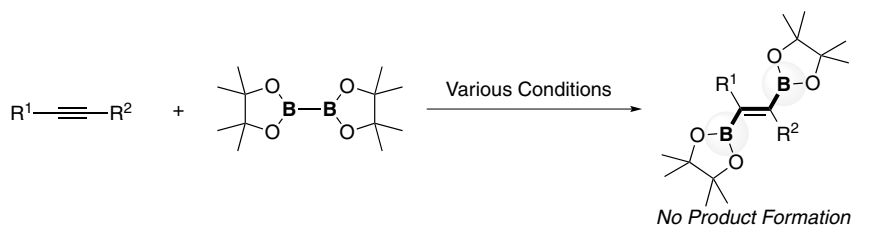
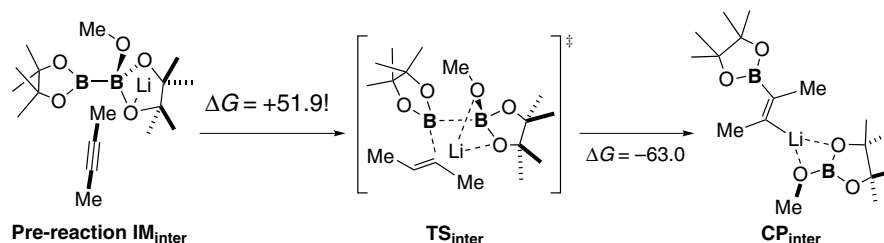


Figure 6. Concepts of Borylation of Triple Bonds



■ DFT Calculation@B3LYP/6-31+G*(kcal/mol)



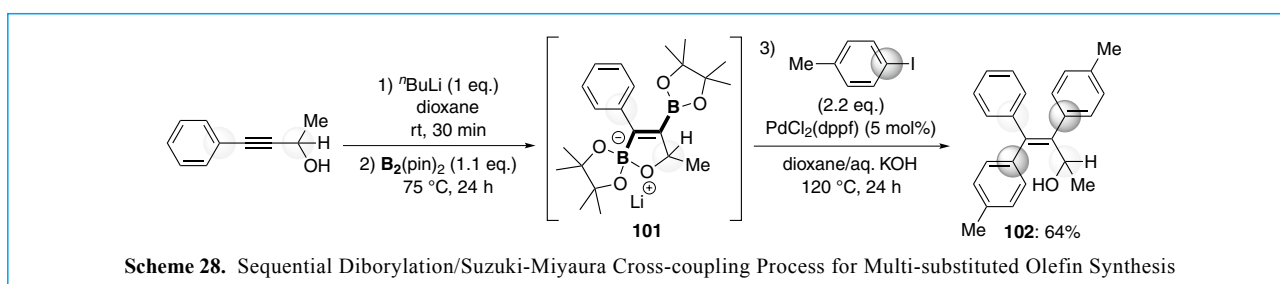
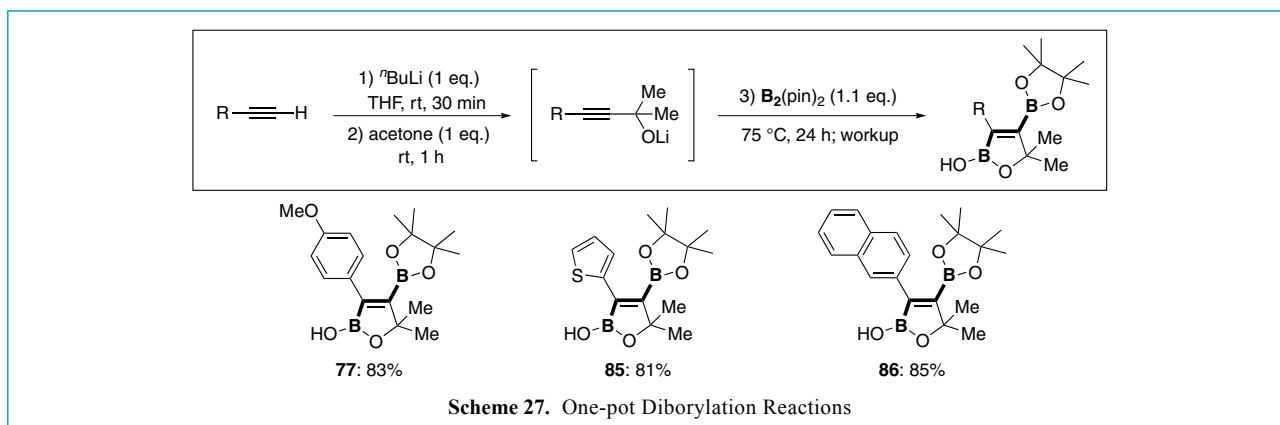
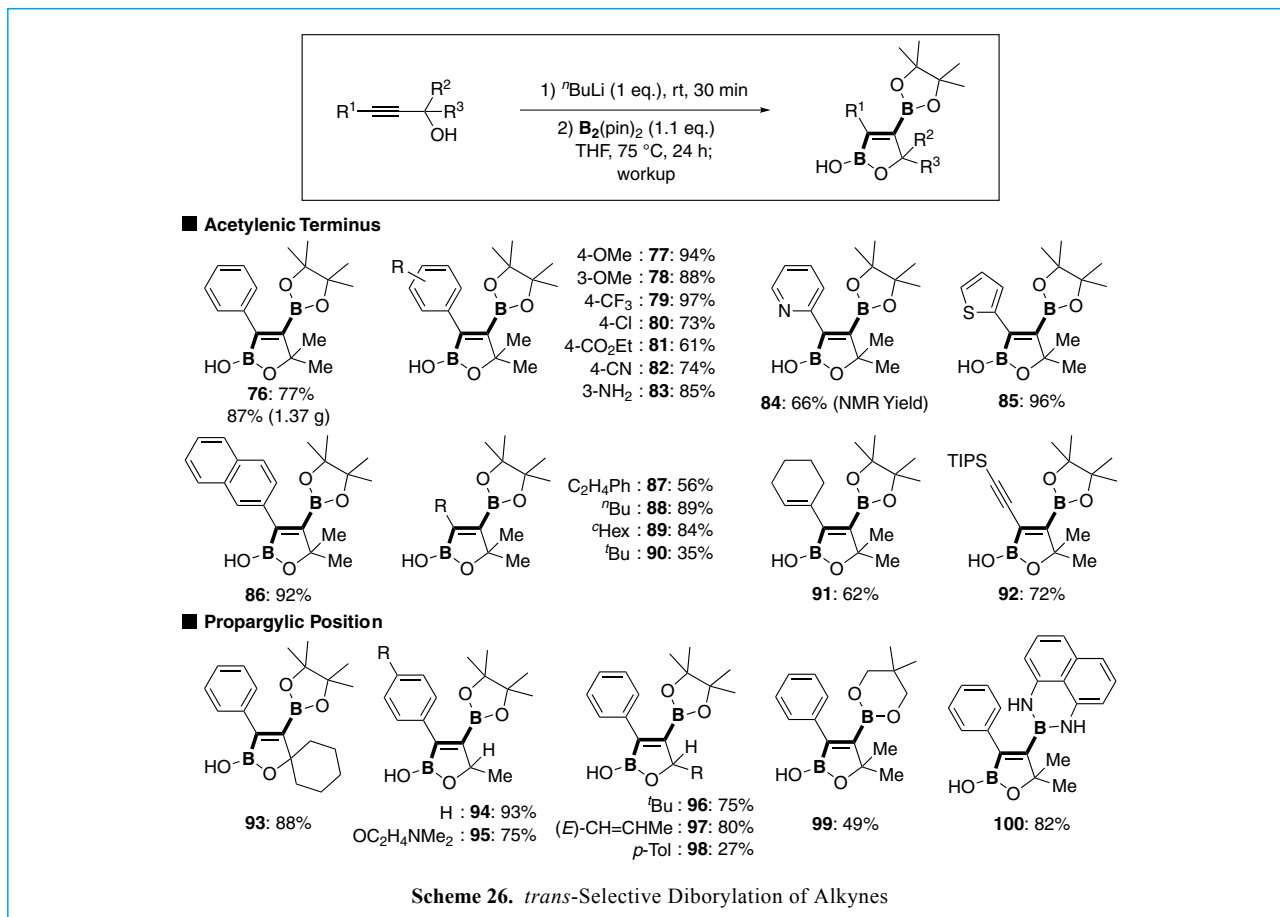
Scheme 25. Attempts on Intermolecular Diborylation of Alkynes



Figure 7. *pseudo*-Intramolecular Activation of Diborons

The diborylation reaction can be performed in one-pot starting with terminal alkynes (Scheme 27). Lithium alkoxides generated *in situ* by the reaction of a corresponding lithium acetylide with acetone react with diboron smoothly to give *trans*-diborylated products **77**, **85** and **86** with high efficacy.

Furthermore, the fully substituted olefin **102** is synthesized through a sequential diborylation/Suzuki-Miyaura cross-coupling reaction in one-pot without isolating the borate intermediate **101** (Scheme 28). This tandem process offers a rapid and versatile access to fully substituted olefins in a regioselective manner and should surely contribute to exploration of novel biologically active compounds.



5. Conclusion

This article outlined the design of functional ate complexes and their applications in synthetic organic chemistry developed by our research group. By combining “element chemistry” which understands and utilizes characteristics of elements with “ate complex formation” which brings out potential of elements, we realized unprecedented reactivities and chemo-, regio-, and stereoselectivities. In concrete, we have developed “chemoselective metalation of aryl halides”, “development of novel ate bases and deprotonative metalation of aromatics”, “silylzincation reactions of unsaturated C–C bonds”, “chemo- and regioselective generation of substituted benzyne”, “anionic polymerization reactions in water”, “Ni-catalyzed Negishi cross-coupling reaction using aryl ethers as electrophiles”, “perfluoroalkylation reactions using thermally stable but reactive perfluoroalkylzincs”. Recently, we also focus on utilization of borylanions. By designing novel reaction intermediates and mode of reaction, we achieved “aromatic borylation reaction with borylzincate” and “the first *trans*-selective diborylation of alkynes *via pseudo*-intramolecular activation of diborons”.

As reviewed in this article, ate complex formation is a powerful and attractive strategy to create/bring out unprecedented reactivities and functions of organometallic reagents, and believed to continue pioneering the frontiers of synthetic organic chemistry and materials sciences.

Acknowledgements

Our research works have been done at Graduate School of Pharmaceutical Sciences of Tohoku University, Graduate School of Pharmaceutical Sciences of The University of Tokyo, and RIKEN. We are grateful to these institutions and generous financial supports by the Ministry of Education, Culture, Sports, Science and Technology, Japan Society for the Promotion of Science, and Japan Science and Technology Agency. Magnificent contributions by our co-workers are gratefully acknowledged.

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TCI Related Products

B3534	NiCl ₂ (PCy ₃) ₂ [= Bis(tricyclohexylphosphine)nickel(II) Dichloride]		1g	5g
B3095	Ni(cod) ₂ [= Bis(1,5-cyclooctadiene)nickel(0)]			5g
T1165	PCy ₃ [= Tricyclohexylphosphine (contains Tricyclohexylphosphine Oxide) (ca. 18% in Toluene, ca. 0.60mol/L)]			25mL
B3153	TBHP [= <i>tert</i> -Butyl Hydroperoxide (70% in Water)]			100g
C2223	CHP [= Cumene Hydroperoxide (contains ca. 20% Aromatic Hydrocarbon)]			100g
T0616	Cp ₂ TiCl ₂ [= Titanocene Dichloride]		5g	25g
C1952	CuCN [= Copper(I) Cyanide]		25g	300g
N0499	C ₄ F ₉ -I (= Nonafluorobutyl Iodide)	25g	100g	500g
T1098	C ₆ F ₁₃ -I (= Tridecafluorohexyl Iodide)		5g	25g
P1084	C ₈ F ₁₇ -I (= Heptadecafluoro- <i>n</i> -octyl Iodide)			25g
H0844	C ₁₀ F ₂₁ -I (= Heneicosfluorodecyl Iodide)		5g	25g
P1188	C ₆ F ₅ -I (= Pentafluoroiodobenzene)		5g	25g
H0629	ⁱ C ₃ F ₇ -I (= Heptafluoroisopropyl Iodide)		25g	100g
D2014	DMPU (= <i>N,N</i> -Dimethylpropyleneurea)	25g	100g	500g
D3214	Et ₂ Zn [= Diethylzinc (ca. 17% in Hexane, ca. 1mol/L)]		100mL	500mL
D3902	Et ₂ Zn [= Diethylzinc (ca. 15% in Toluene, ca. 1mol/L)]			100mL
B1964	B ₂ (pin) ₂ [= Bis(pinacolato)diboron]	1g	5g	25g
B2254	Bis(neopentyl Glycolato)diboron		1g	5g
B3757	Bis(catecholato)diboron		1g	5g
S0450	NaO ^t Bu (= Sodium <i>tert</i> -Butoxide)	25g	100g	500g
B0396	ⁿ BuLi [= Butyllithium (ca. 15% in Hexane, ca. 1.6mol/L)]		100mL	500mL
B4697	ⁿ BuLi [= Butyllithium (ca. 20% in Cyclohexane, ca. 2.3mol/L)]		100mL	500mL

Furan Photo-Oxidation Based Click Reactions: Labeling, Crosslinking and Conjugation of Peptides and Oligonucleotides under Physiological Conditions

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Keywords: Furan oxidation, Photosensitizer, Oligonucleotides, DNA to Protein Crosslinking, Peptide Labeling

Site-specific chemical modification of proteins and nucleic acids is crucial for understanding protein and nucleic acid structure and interactions as well as providing insights into cellular events. We here report on a simple, efficient and versatile procedure for furan-oxidation mediated modification of biomolecules. Furan derivatives are commercially available under a variety of forms thus allowing straightforward incorporation of the furan moiety during solid phase synthesis.^[1] Once incorporated into a peptide or nucleic acid, furan can be considered a caged electrophile which can be uncovered by selective activation through oxidation (Figure 1).

Furan-containing peptides and oligonucleotides can be subjected to mild oxidative conditions (NBS or air/light/photosensitiser) so that the reactive electrophilic species are generated. These reactive intermediates can be intercepted by various nucleophiles to form stable conjugates.

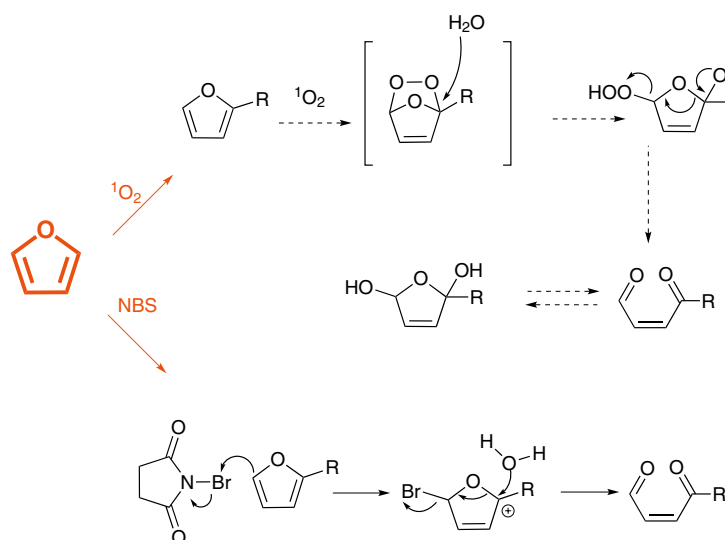


Figure 1. Furan oxidation by NBS or singlet oxygen treatment

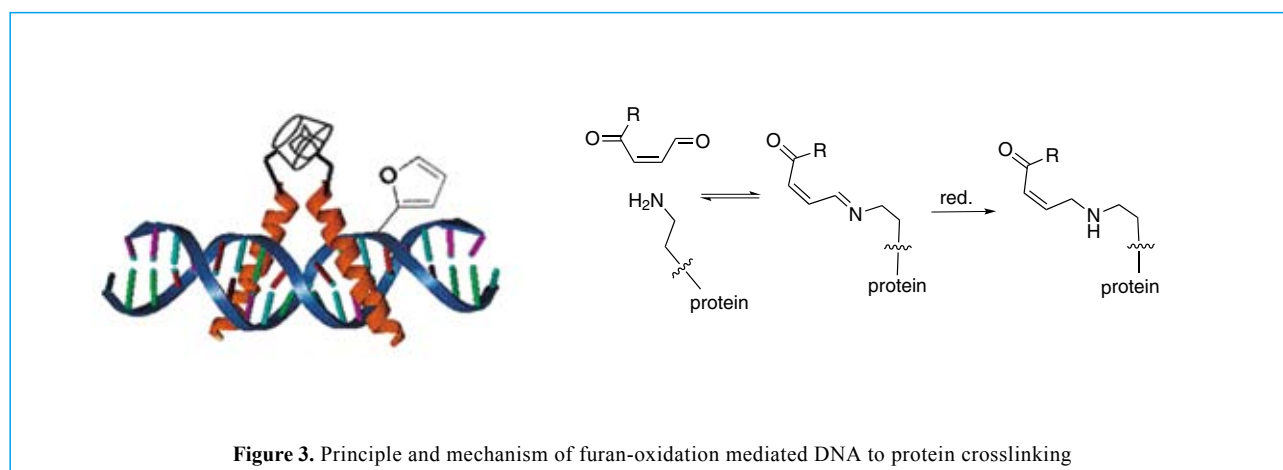
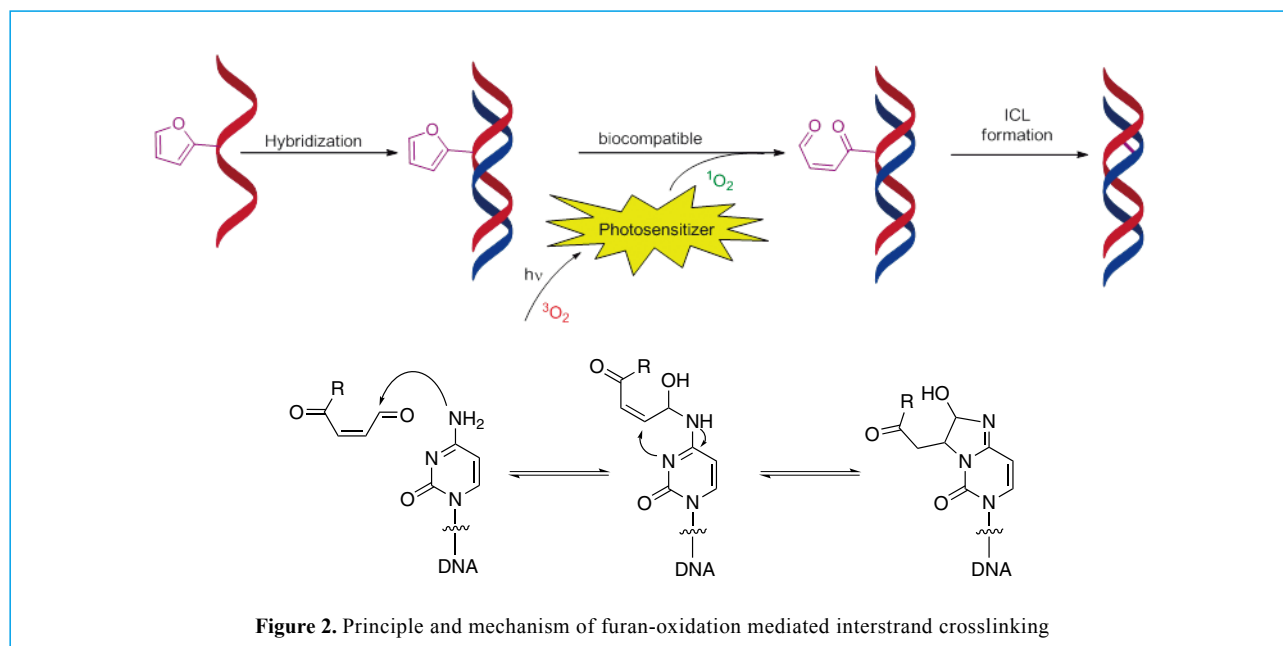
Scope:

I. Furan-mediated Nucleic Acid Interstrand Crosslinking^[2]

Easily accessible furan modified nucleosides, a commercially available photosensitizer, and visible light irradiation constitute the necessary tools to achieve selective duplex interstrand cross-linking of furan modified oligonucleotides. The crosslink mechanism involves formation of a covalent link through reaction with exocyclic amino functionalities at the corresponding position in the complementary strand (Figure 2). Both DNA^[3] as well as RNA targets^[4] can be covalently trapped in this way using furan-modified oligonucleotide probes.

II. DNA to Protein Crosslinking

The methodology has also been further extended for its bidirectional use in protein – nucleic acid cross-linking, modifying protein or nucleic acid respectively to react with the unmodified counterpart as target (Figure 3).^[5] As the cross-link reaction is highly distance dependent, mapping of interaction surfaces is within reach. Understanding the remarkable selectivity and affinity of nucleic acid binding proteins for their targets (DNA and RNA) in the complex cellular environment, which is central in the regulation and execution of biological processes, is a major challenge driven by the ambition to design novel drugs that can compete in such interactions.

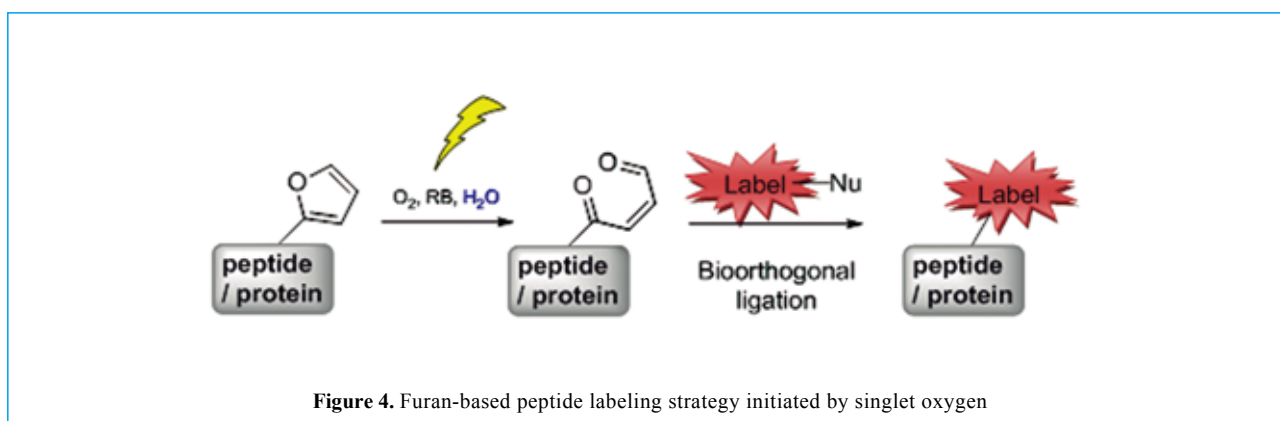


III. Solid Phase-based Peptide Labeling

Furan-oxidation was also used as a method for the labeling of solid-phase bound peptides by generation of a reactive aldehyde in the sequence. Hereby, the non-natural *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-3-(2-furyl)-L-alanine can be incorporated into a peptide and subsequently converted into a 4-oxo-enal moiety by selective oxidation of the furan moiety. Next, a simple reductive amination allows introducing the desired fluorophore.^[6] The incorporated furan moiety further enables another orthogonal strategy for highly selective labeling. The furan diene has shown to be a useful partner in Diels–Alder reactions with commercially available maleimides as dienophile. The more recently described 1,2,4-triazole-3,5-diones present an excellent alternative.^[7]

IV. Singlet Oxygen ($^1\text{O}_2$) Mediated Furan-based Peptide Labeling in Physiological Aqueous Solutions

Completely deprotected furan-containing peptides, following selective furan-oxidation in aqueous solution can also be intercepted by α -effect nucleophiles (such as hydrazine / hydrazine derivatives of dyes or fluorescent labels) to form stable conjugates (Figure 4). Incorporation of nucleophilic fluorophores through a cascade reaction sequence, leads to the efficient construction of site-selectively labeled fluorescent peptides.^[8] This reaction can be used for the site specific labeling of peptides and proteins and can be carried out in aqueous solution.



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Introduction of the author:

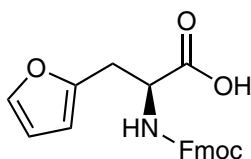


Annemieke Madder,
Prof. Dr.

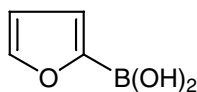
Organic and Biomimetic Chemistry Research Group, Department of Organic and Macromolecular Chemistry, Ghent University

Annemieke Madder started chemistry studies at Ghent University in 1988. After undergraduate thesis work at the University of Santiago de Compostela in Spain, she graduated in June 1992. In February 1997, she obtained her Ph.D. in organic chemistry from Ghent University. After postdoctoral stays in the laboratory of Prof. Dr. C. Gennari at the University of Milan and in the research group of Prof. Dr. R. Strömberg at the Karolinska Institute in Stockholm, she returned to Ghent and obtained a position as a Lecturer in 2002. In 2014, she was promoted to a Full Professor at the Department of Organic and Macromolecular Chemistry. Currently she is heading the Organic and Biomimetic Chemistry Research Group specialized in the design and synthesis of modified peptides and nucleic acids and methods for their conjugation and labeling.

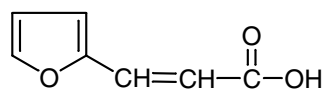
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New Allotropes of Main Group Elements (2)

Kentaro Sato

Continuing from the previous time, let us take a look at some of the recently discovered allotropes of main group elements.

Silicon

Silicon, having Clarke number 25.8, is the second most abundant element in the Earth's crust next to oxygen. Its most famous allotrope is one in which silicon atoms are bonded in a diamond-like network and it is a gray, hard but weak solid. This material is essential to our contemporary society as it is used everywhere to make semiconductors.

Another allotrope of silicon that is stable under ambient pressure is amorphous silicon. It consists of a random three dimensional reticular network of silicon atoms and appears as a brown powdery solid. Because it has a larger energy gap than crystalline silicon and is easier to be processed into a film, it is used for thin-film transistors and solar batteries. In a strict sense, though, amorphous silicon is not an allotrope since it is thought to contain hydrogen atoms attached to the silicon skeleton.

Other than these two, it is known that crystalline silicon undergoes pressure-induced phase transition into other structures such as β -tin form. The application of these new crystalline forms is yet to be explored.

New Three Dimensional Cage

Recently, the synthesis of a new three dimensional reticular allotrope of silicon was reported (*Nat. Mater.* **2015**, *14*, 169.). Timothy Strobel and his coworkers at Carnegie Institution of Washington treated silicon with sodium

under high thermal and pressure conditions and obtained a compound with the composition NaSi_6 , in which sodium atoms were trapped in silicon-based cages. Then, it was found that by heating it to 400 K in a vacuum, the sodium atoms were gradually removed, leaving the caged structure intact.

The newly obtained silicon allotrope consists of a network based on 5, 6, and 8-membered rings and contains 24 silicon atoms per unit cell. It is stable in air up to around 750 K and has a band gap of 1.3 eV, which are desirable characteristics as a material for solar batteries. And importantly, the synthetic methodology used by the Strobel group has a potential to yield even more silicon allotropes, and therefore further development is expected.

Silicene

Can't we synthesize silicon-based nanomaterials that correspond to those nanocarbon materials? When it comes to Si_{60} , the silicon analogue of fullerene, it has been evaluated by theoretical calculations but has yet to be synthesized. The relative weakness of π -conjugation among silicon atoms is considered to be the obstacle. The silicon equivalent of graphite has not been known either.

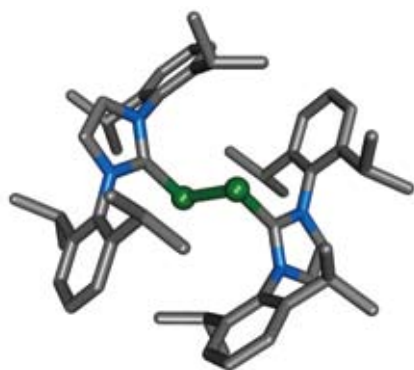
On the other hand, in recent years, the silicon version of graphene called silicene has been drawing an attention. Similar to graphene, it has a honeycomb structure. Although silicene had long been the subject of theoretical research, its first synthesis was achieved in 2010 by vapor deposition of silicon onto silver surface (*Appl. Phys. Lett.* **2010**, *97*, 223109.).

Since sp^2 hybridization of silicon is not as stable as that of carbon, silicene is not completely planar and has a rippled surface, and it is also unstable to air. However, expectations are high because it can have functions that are not possible with graphene. In 2015, a transistor using silicene was already introduced. It is a new exciting material toward the realization of ultrafast computers.

Holding Si(0) with NHC

In 2008, Gregory Robinson and his coworkers at University of Georgia reported the synthesis of carbene-stabilized diatomic Si(0) compounds. (*Science* **2008**, 321, 1069.). The reduction of $SiCl_4$ -NHC (NHC=*N*-heterocyclic carbene) complex with KC_8 led to the formation of stable compounds containing a Si=Si bond. Interestingly, the bond angle of C-Si-Si is almost perpendicular (about 93 degrees).

Diatomic silicon species had hitherto been detected only spectroscopically at ultralow temperature, but now, it can be isolated as a crystalline solid in carbene-stabilized form. Since the carbene is merely a ligand, the central Si_2 unit can be regarded as a new allotrope of silicon. This is recognized as a landmark achievement in main group chemistry.



Si_2 (the green atoms in the center) stabilized by the coordination of two NHC ligands

Complex Allotropes of Phosphorus

The allotrope of phosphorus includes yellow phosphorous and red phosphorous, according to high school textbooks. It is explained that yellow phosphorus exists as P_4 and a flammable pale yellow solid, and red phosphorus is a less reactive powder used in matches.

However, the more recent understanding is that there is no such pure substance as yellow phosphorus and it is actually white phosphorus that contains impurities including red phosphorous. Similarly, even though there are other phosphorus “allotropes” such as black, violet, and scarlet phosphorous according to some literature, it has become clear that these do not qualify as true allotropes either. Scarlet phosphorus, for example, is considered to be fine crystals of red phosphorus. The world of phosphorus allotropes is rather complex.

One dimensional polymeric form of phosphorus allotrope was discovered after the turn of the 21st century. The research team led by Pfitzner and Eckert in Germany obtained a reddish brown solid composed purely of phosphorus, when they treated the adduct of red phosphorous and copper(I) iodide with aqueous solution of potassium cyanide, which removed copper. The analysis revealed that it was a polymer with a unit structure composed of 12 phosphorus atoms connected in tubular fashion (*Angew. Chem. Int. Ed.* **2004**, 43, 4228.). One of them is shown below. By exploring the variation of synthetic conditions, there seems to be a good possibility for the discovery of more new allotropes.

Stabilization by NHC

Nitrogen sits above phosphorus in the periodic table and is most stable in diatomic N_2 form. As one might wonder, the diatomic form of phosphorus (P_2) is also known. The phosphorus atoms are triply bonded to each other and the bond length is 189.5 pm, which is significantly shorter than ordinary P-P single bond (roughly 220 pm). This “diphosphorus” is formed when white phosphorus is heated



One dimensional polymer composed of phosphorus atoms

to 1100 K, but is also extremely unstable and difficult to be handled. It has been found recently that it undergoes hetero-Diels-Alder reaction with dienes, which could be developed into an effective synthetic strategy for phosphorus-containing compounds.

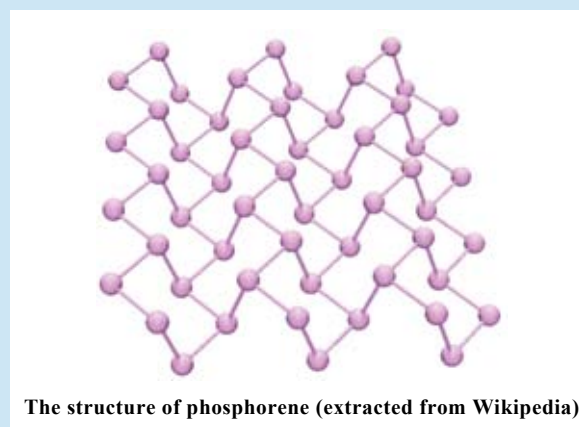
Then, can the diatomic phosphorus be stabilized by the coordination of NHC just like the aforementioned diatomic silicon? In fact, the Robinson group has already synthesized a stabilized diatomic phosphorus molecule by the almost same approach they employed for silicon (*J. Am. Chem. Soc.* **2008**, *130*, 14970.). These are truly the significant impacts that NHC ligands have had in the world of chemical science.

Sheet of Phosphorus

Black phosphorus is one of the allotropes known for a long time and it forms when white phosphorus is heated under 12,000 atm. It consists of stacked sheets of phosphorus-based honeycomb structure and resembles carbon-based graphite.

Graphene, the popular substance in materials science today, was first created by peeling a single layer of sheet off of graphite. Then, could we do the same for black phosphorus and obtain a phosphorus analogue having unique properties? This question was answered by Peide Ye of Purdue University and his coworkers in 2014 and the answer was yes (*ACS Nano* **2014**, *8*, 4033.).

The new two dimensional material, named phosphorene, has a wave-like structure unlike flat graphene. And interestingly, while graphene is a good electric conductor, phosphorene behaves as a semiconductor. It is already drawing a major attention and the initial report has been referenced more than 800 times in just a couple of years. Phosphorene has a potential to be developed into high-performance electronic devices and it can be prepared from inexpensive phosphorus. Therefore, it is counted as one of the promising materials for future application.



Silicon and phosphorus, the two elements so familiar to us, still offer this many opportunities for new discovery. This serves as a great reminder of the vast possibility of chemistry.

Introduction of the author :

Kentaro Sato

[Brief career history] He was born in Ibaraki, Japan, in 1970. 1995 M. Sc. Graduate School of Science and Engineering, Tokyo Institute of Technology. 1995-2007 Researcher in a pharmaceutical company. 2008-Present Freelance science writer. 2009-2012 Project assistant professor of the graduate school of Science, the University of Tokyo. 2014-present Publicist for π -system figuration, scientific research on innovative areas.

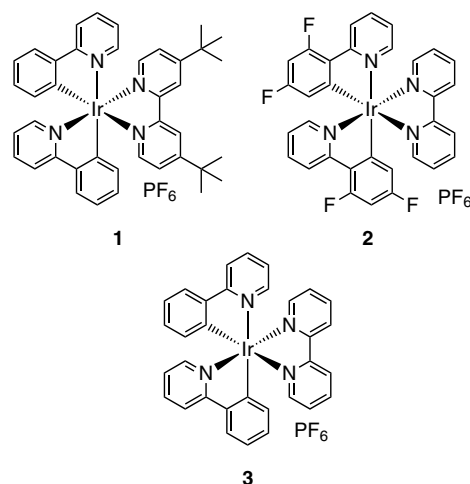
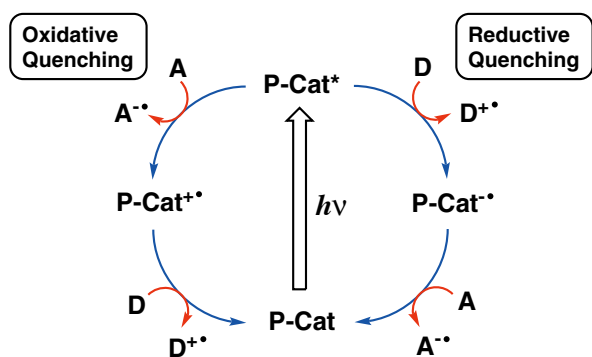
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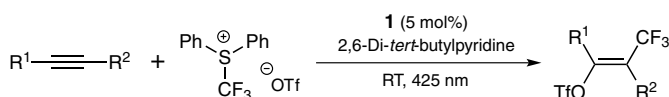
Visible Light Photoredox Catalysts

D4887	(4,4'-Di- <i>tert</i> -butyl-2,2'-bipyridine)bis[(2-pyridinyl)phenyl]iridium(III) Hexafluorophosphate	200mg
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B4944	(2,2'-Bipyridine)bis[2-(2,4-difluorophenyl)pyridine]iridium(III) Hexafluorophosphate	200mg
(2)		
B4893	(2,2'-Bipyridine)bis(2-phenylpyridinato)iridium(III) Hexafluorophosphate	200mg
(3)		

A photocatalyst working for both one-electron oxidation and reduction under visible light irradiation, the so-called "visible light photoredox catalyst", receives much attention, because there is the possibility for use as a solar energy source.¹⁾ A reaction mediated by a photoredox catalyst particularly works simply, whereas a thermal reaction under coexistence of oxidizing and reducing reagents is normally hard to make work. The reaction cycle using a photoredox catalyst involves both oxidative and reductive pathways, thus it shows a 'redox-neutral' mechanism overall.



Visible light induced trifluoromethylation



Some iridium(III) phenylpyridyl complexes (1, 2 and 3) and ruthenium(II) polypyridyl complexes work as photoredox catalysts under irradiation of visible light.^{2,3)} These transition metal complexes are useful photocatalysts, because they can form a long-lived triplet-excited state under photoirradiation. A chemical modification of the coordinating ligands controls the redox potentials of the transition metal complexes.⁴⁾

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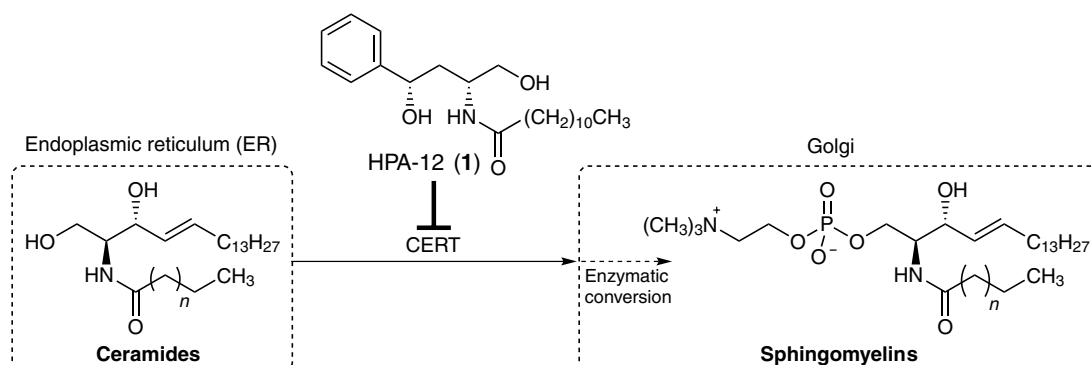
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A Ceramide-Trafficking Protein (CERT) Inhibitor

H1553 HPA-12 (1)

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Scheme. CERT-mediated transport to Golgi for further processing to sphingomyelins

HPA-12 (1) is a ceramide(Cer)-trafficking inhibitor that was first discovered and synthesized by Hanada and Kobayashi *et al.*^{1,2)} Ceramide is synthesized in the endoplasmic reticulum (ER) and is transported to the Golgi apparatus,^{3,4)} where it is converted to sphingomyelin, by means of the ceramide transport protein (CERT).⁵⁾ 1 inhibits the CERT, and has been used as a CERT inhibitor in various biological science studies.⁶⁾ For example, 1 possesses antiviral and antibacterial properties against the growth of hepatitis C virus (HCV) and the obligate intracellular bacteria *Chlamydiae* in cultured human cells.^{6a,d,e)} In addition, the CERT inhibition results in resensitization of cancer cells to chemotherapeutic agents such as paclitaxel.^{6b)} Therefore, the inhibition of CERT may represent medical strategies, such as anti-infective and anticancer chemotherapy.

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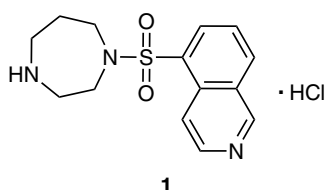
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Protein Kinase Inhibitor

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Isoquinolinesulfonamide derivatives have been developed as protein kinase inhibitors.¹⁾ Fasudil hydrochloride (1) is one of the derivatives and inhibits various protein kinases (an example; Table 1).¹⁻³⁾

Human embryonic stem (hES) cells are vulnerable to apoptosis upon cellular detachment or dissociation and the cloning efficiency of dissociated hES cells is generally low, for example 0.24~0.83%⁴⁾ and 0.4%.⁵⁾ Treatment of hES cells with 1 diminishes the cell-dissociation-induced apoptosis, resulting in the promotion of colony formation by undifferentiated cells (Table 2).⁶⁾

Table 1. K_i values of Fasudil for serine/threonine protein kinases²⁾

Protein kinase	K_i (μ M)
Rho kinase	0.40 \pm 0.03*
Protein kinase N	1.10
cAMP-dependent protein kinase	1.6
cGMP-dependent protein kinase	1.6
Protein kinase C	3.5 \pm 0.2**
Myosin light chain kinase	32

* Means \pm S.E. (n=3), ** Means \pm S.E. (n=5)

Table 2. Colony formation of undifferentiated hES cells with Fasudil⁶⁾

Treatment	Cloning efficiency (%)
With Fasudil	25.1 \pm 1.6
Without Fasudil	1.3 \pm 0.8

P < 0.001, (n=3)

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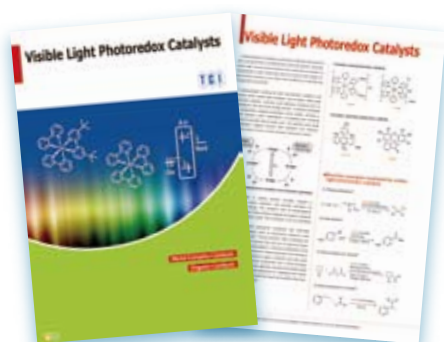
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