Research Article

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, $Na[ZnEt_3]$, by James A. Wanklyn dates back to 1859,[1] and even di-anion type zincate, $Li_2[ZnMe_4]$, 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.
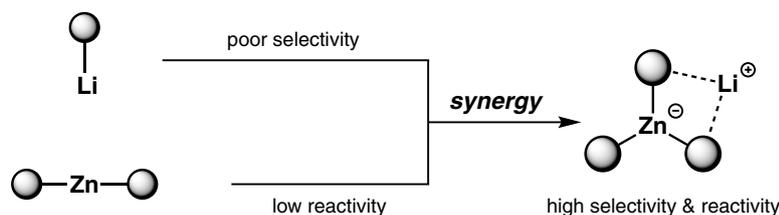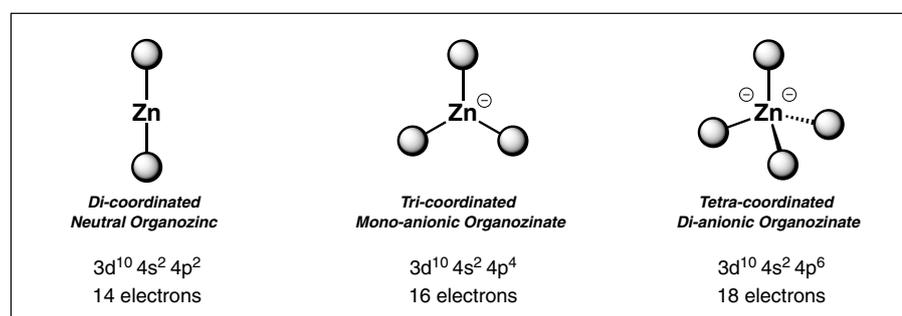

Di-coordinated
Neutral Organozinc

$3d^{10} 4s^2 4p^2$
14 electrons

Tri-coordinated
Mono-anionic Organozinate

$3d^{10} 4s^2 4p^4$
16 electrons

Tetra-coordinated
Di-anionic Organozinate

$3d^{10} 4s^2 4p^6$
18 electrons

poor selectivity

low reactivity

synergy

high selectivity & reactivity

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).
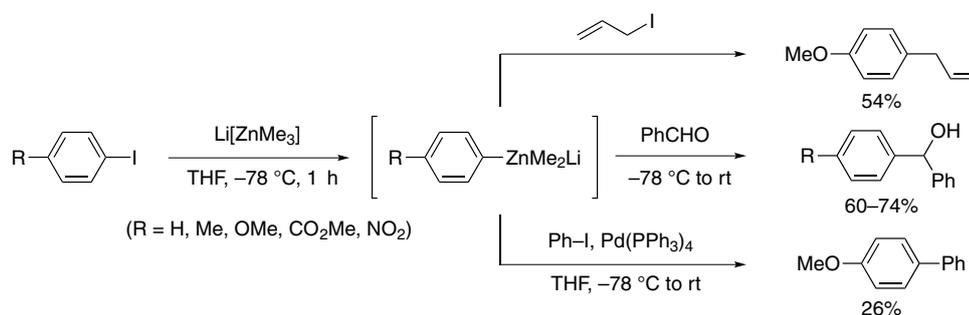
3. Di-anion Type Zincate

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

In 1994, Kondo *et al*. reported that Li[ZnMe₃] undergoes the halogen-metal exchange reaction of various aryl iodides at −78 °C and the generating aryl zincates react with electrophiles (Scheme 1).[3] On the other hand, Li[ZnMe₃] is unreactive to metalate synthetically more desirable aryl bromides.

In 1996, we discovered that di-anion type zincates, Li₂[Zn(X)Me₃] (X = 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, Li₂[ArZnMe₃], exhibit higher reactivity than Li[ArZnMe₂] (Scheme 2). In contrast with the reaction between Li[ZnMe₃] and aryl iodide **1**, ends up only with iodine-zinc exchange, treatment of **1** with Li₂[ZnMe₄] provides the indoline product **2** *via* iodine-zinc exchange followed by intramolecular conjugate addition. Metallation of 2-allyloxyiodobenzene (**3**) with Li₂[ZnMe₄] affords the dihydrobenzofuran **5** *via* carbozincation reaction of the unactivated double bond.[5]

Scheme 1. Halogen-zinc Exchange Reaction with Li[ZnMe₃] by Kondo *et al*.

Table 1. Reactivity of Di-anion Type Zincate: Li₂[Zn(X)Me₃]
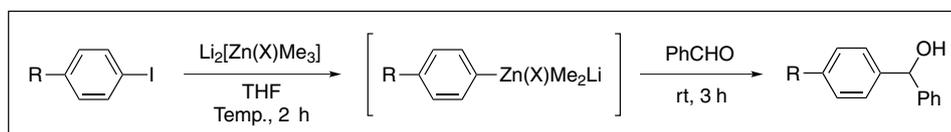
| Entry	R	X	Temp. [°C]	Yield [%]	Entry	R	X	Temp. [°C]	Yield [%]
1	H	Me	0	90	6	MeO	SCN	rt	92
2	H	CN	rt	90	7	CO₂Me	Me	0	trace
3	H	SCN	rt	89	8	CO₂Me	CN	0	trace
4	MeO	Me	0	84	9	CO₂Me	SCN	0	trace
5	MeO	CN	rt	90					

3-2. Highly Bulky Di-anion Type Zincate: Li$_2$[Zn^{t}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, Li$_2$[Zn^{t}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, ^{t}Bu 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 Li$_2$[ArZn^{t}Bu$_3$] was found to deliver the aryl ligand in a highly selective S$_N$2′ fashion to give the corresponding allene product (Table 2).[7]
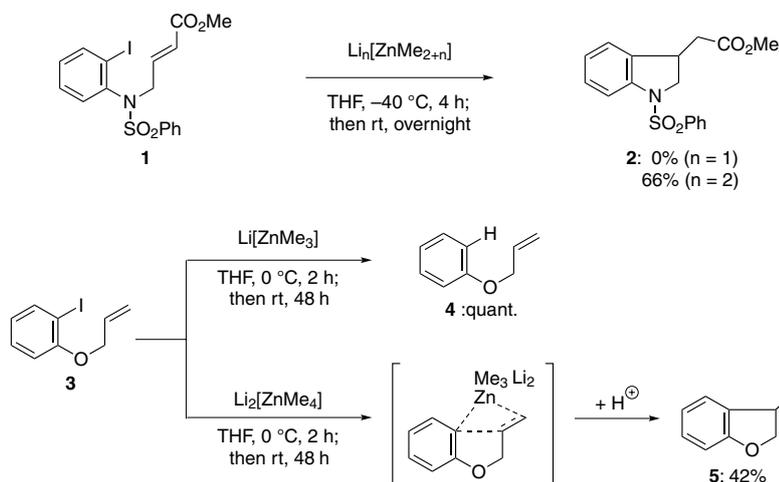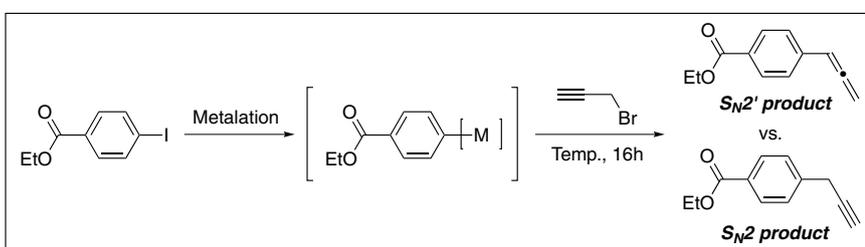
Scheme 2. High Reactivity of Di-anion Type Zincate
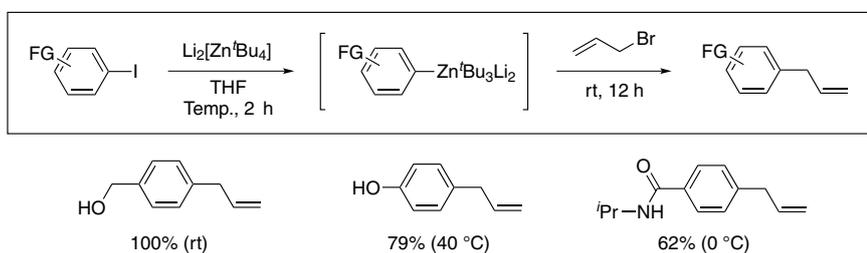
Scheme 3. Chemoselective Zincation of Aryl Halides with Li$_2$[Zn^{t}Bu$_4$]

Table 2. Reaction of Li$_2$[Zn^{t}Bu$_4$] with Propargyl Bromide: S$_N$2 vs. S$_N$2′

| Entry	Metalation Reagent and Conditions	Temp. [°C]	Yield [%]	Ratio [S$_N$2′/S$_N$2]
1	Li$_2$[Zn^{t}Bu$_4$] (1.1 eq.), THF, 0 °C, 2 h	25	100	98 : 2
2	^{i}PrMgBr (1.1 eq.), THF, –40 °C, 1 h, then CuCN (10 mol%)	–40	76	79 : 21
3	Li$_2$[Cu(CN)Me$_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 $Li_2[Zn^tBu_4]$ 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 $Li_2[ArZnMe_3]$ 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 $Li[ArZnMe_2]$ 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 $Li_2[Zn^tBu_4]$ 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
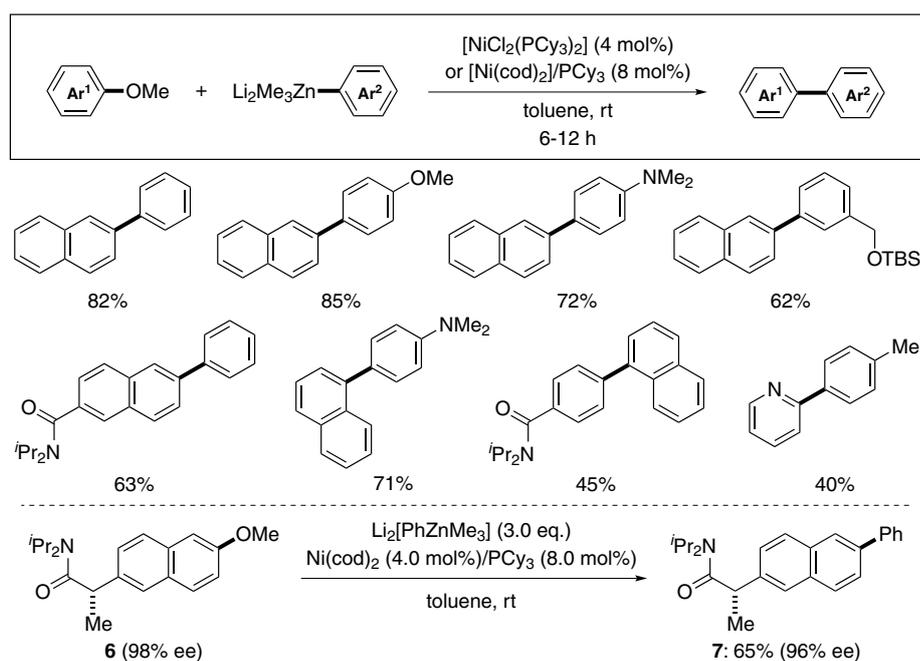
Scheme 4. Negishi Cross-coupling *via* C–O Bond Cleavage

4. Heteroleptic Ate Complexes

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

Deprotonative metalation utilizing ate bases[10] 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^{t}Bu$_2$], prepared from ^{t}Bu$_2$Zn 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 electoron-deficient ones such as pyridines, quinolines, and isoquinolines are smoothly metalated in good yields.

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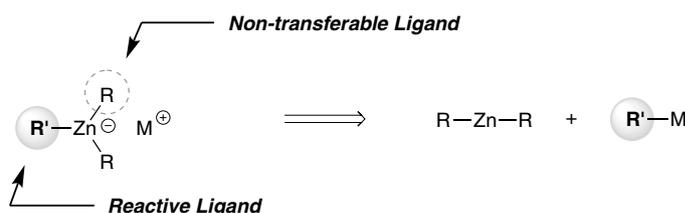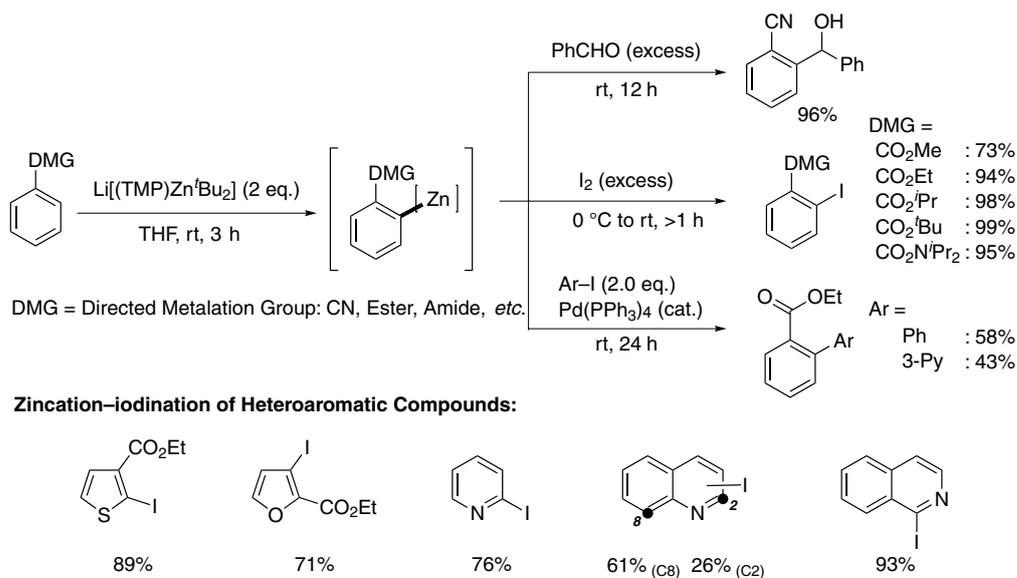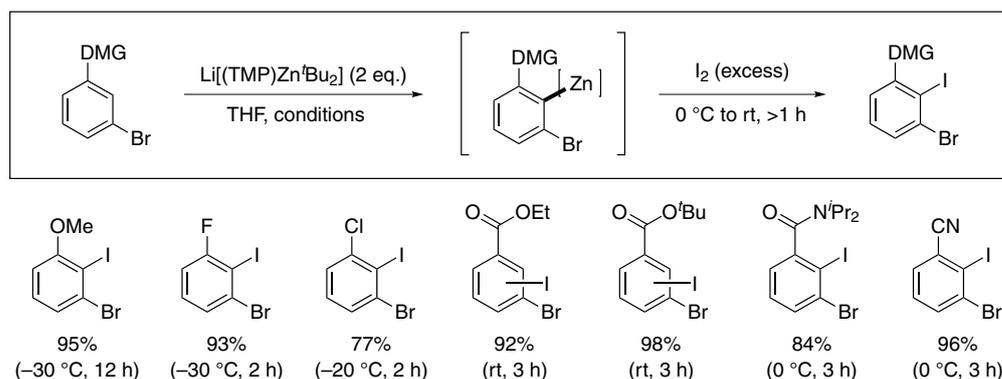

Figure 2. Heteroleptic Zincates

Scheme 5. Highly Regio- and Chemoselective Zincation of Aromatics

**Scheme 6.** *ortho* Iodination of Bromobenzenes

metal bromide salts. Li[(TMP)Zn^{t}Bu$_2$] 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)Zn**Me**$_2$], 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).
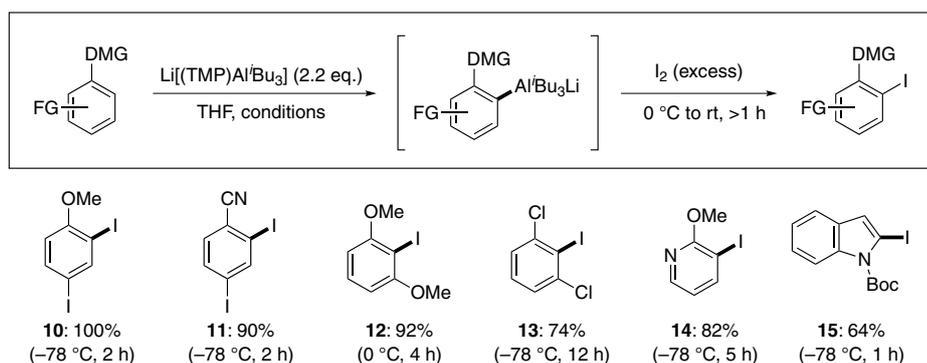
4-1-2. Amidoaluminate Base: Li[(TMP)Al^{i}Bu$_3$]

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^{i}Bu$_3$]. 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)ZnMe$_2$]
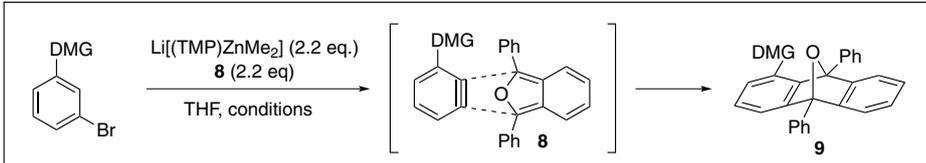
Entry	Substrate	Conditions	Benzyne	Yield [%]	Entry	Substrate	Conditions	Benzyne	Yield [%]
1	OMe, Br	rt, 12 h	OMe	100	5	O OEt, Br	reflux, 3 h	O OEt	55
2	F, Br	60 °C, 15 h	F	71	6	O O^{t}Bu, Br	reflux, 6 h	O O^{t}Bu	88
3	Cl, Br	rt, 48 h	Cl	72	7	O N^{i}Pr$_2$, Br	reflux, 12 h	O N^{i}Pr$_2$	100
4	CF$_3$, Br	rt, 12 h	CF$_3$	100	8	CN, Br	reflux, 12 h	CN	90

10: 100% (–78 °C, 2 h)   **11**: 90% (–78 °C, 2 h)   **12**: 92% (0 °C, 4 h)   **13**: 74% (–78 °C, 12 h)   **14**: 82% (–78 °C, 5 h)   **15**: 64% (–78 °C, 1 h)

Scheme 7. Chemoselective Deprotonative *ortho* Metalation with Li[(TMP)Al^{i}Bu$_3$]

4-1-3. Amidocuprate Base: Li$_2$[(TMP)Cu(CN)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, Li$_2$[(TMP)Cu(CN)R].[15] A series of aromatics with polar functional groups such as methoxy, cyano, and amide groups and heteroaromatics are regioselectively deprotonated with Li$_2$[(TMP)Cu(CN)Me] (Scheme 8).
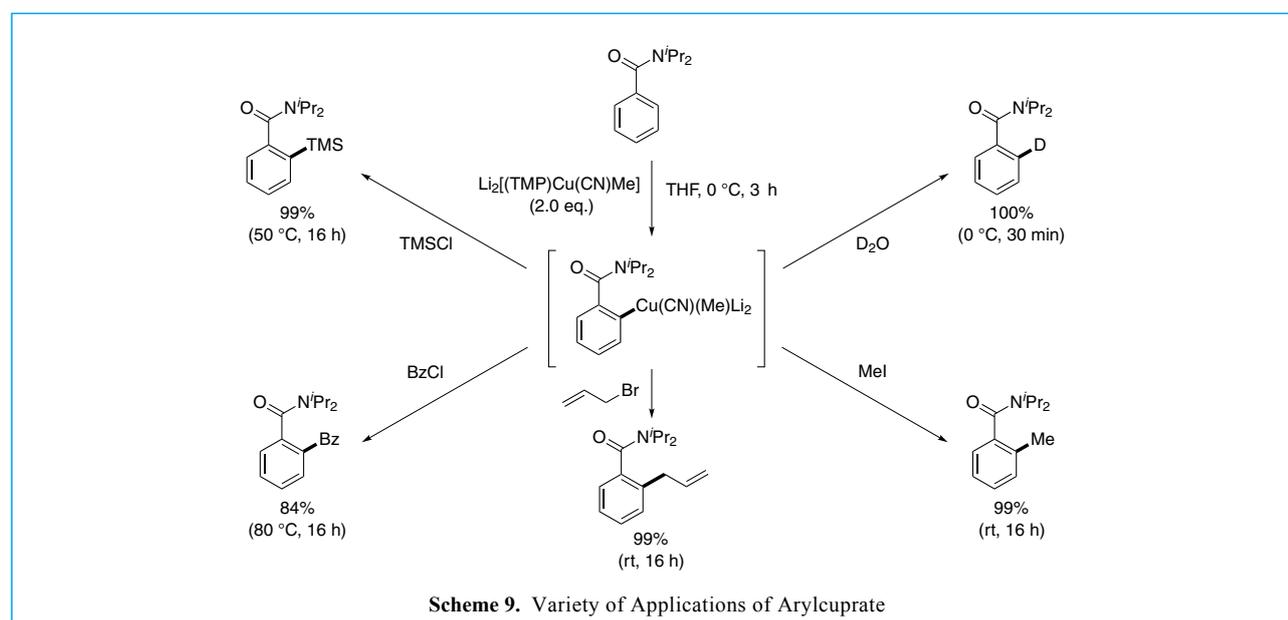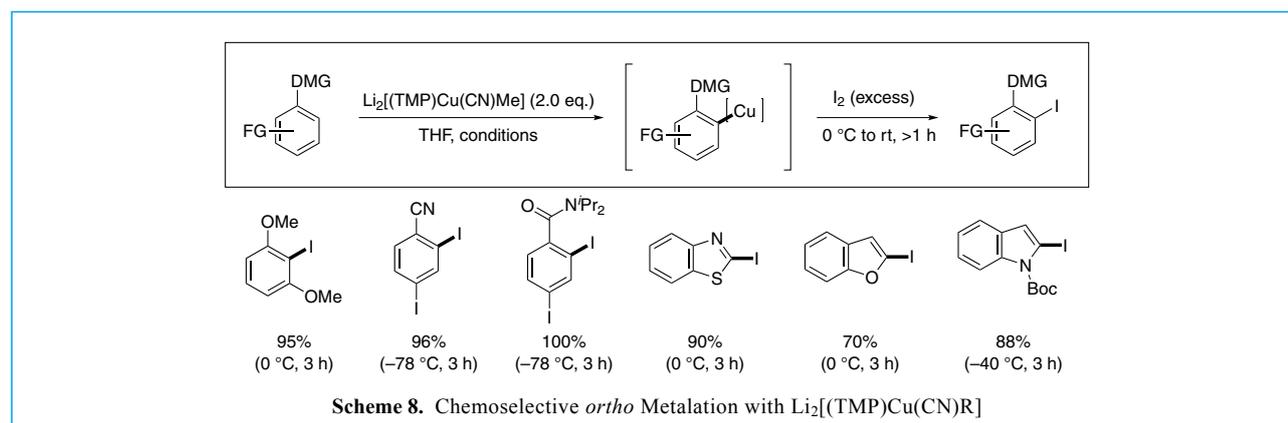
The intermediary arylcuprate reacts with various electrophiles in excellent yields thanks to its high nucleophilicity (Scheme 9).
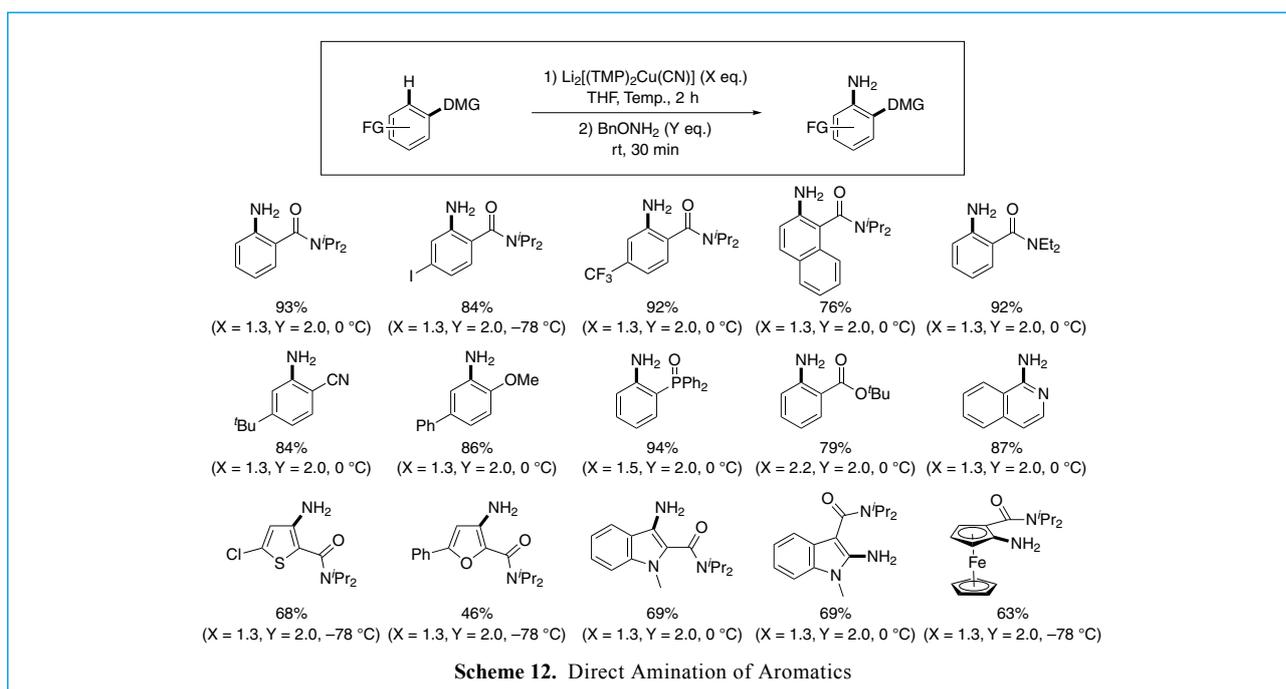
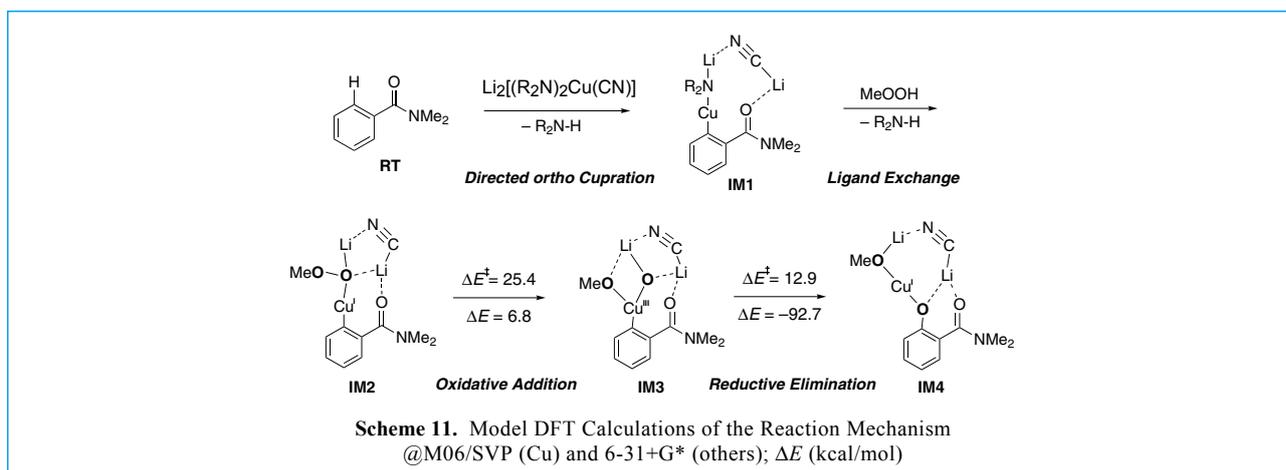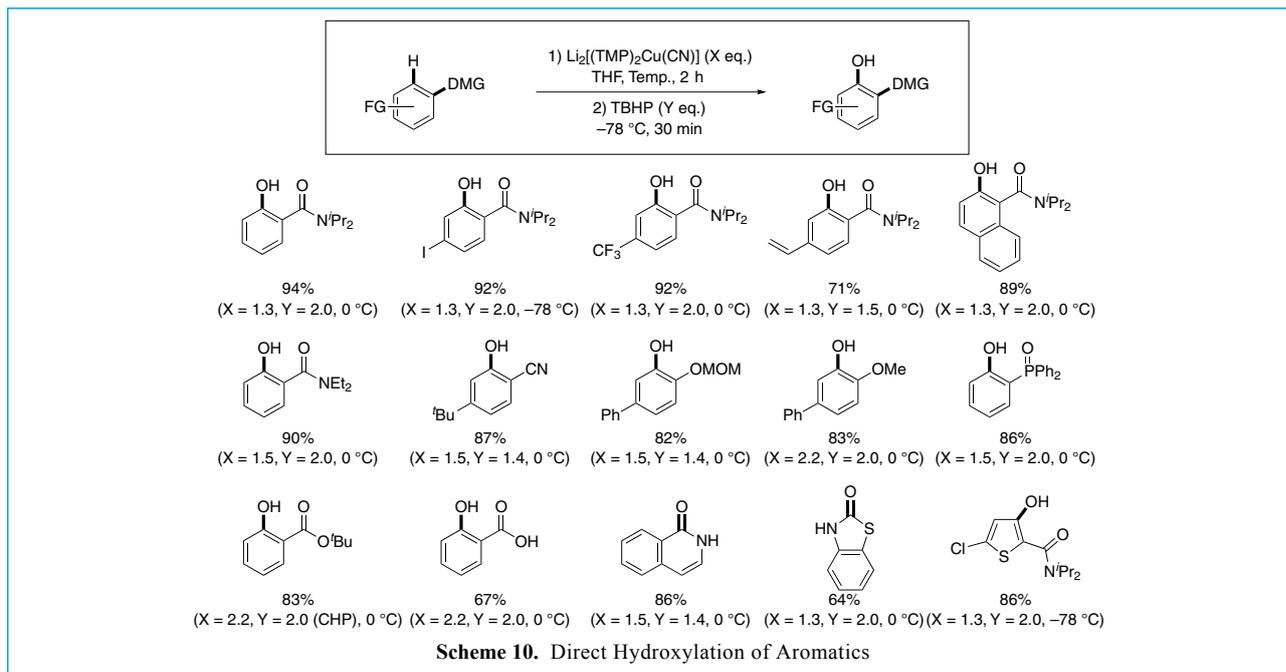We have recently reported that the combination of the arylcuprate intermediate generated by the reaction of Li$_2$[(TMP)$_2$Cu(CN)] with an aromatic compound and hydroperoxide (ROOH) including ^{t}BuOOH (TBHP) and cumene hydroperoxide (CHP) affords the corresponding phenol product in high yield (Scheme 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.

Scheme 8. Chemoselective *ortho* Metalation with Li$_2$[(TMP)Cu(CN)R]

Scheme 9. Variety of Applications of Arylcuprate

Scheme 10. Direct Hydroxylation of Aromatics

Scheme 11. Model DFT Calculations of the Reaction Mechanism
@M06/SVP (Cu) and 6-31+G* (others); ΔE (kcal/mol)
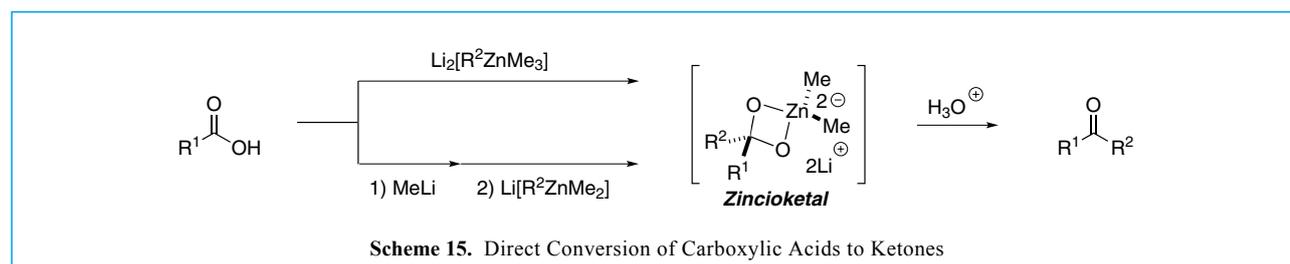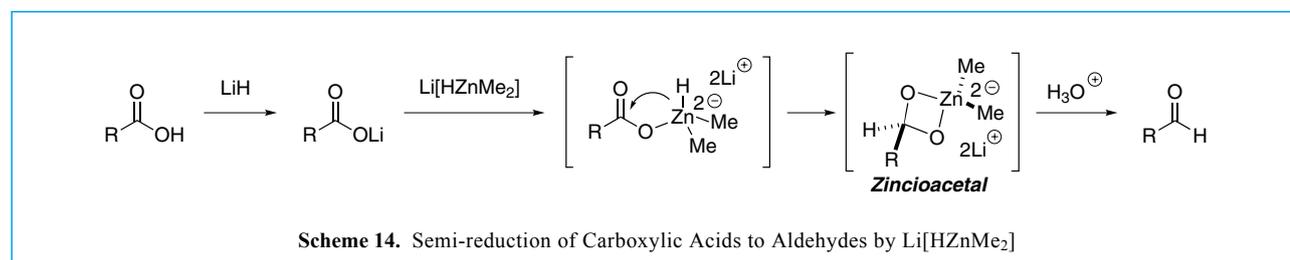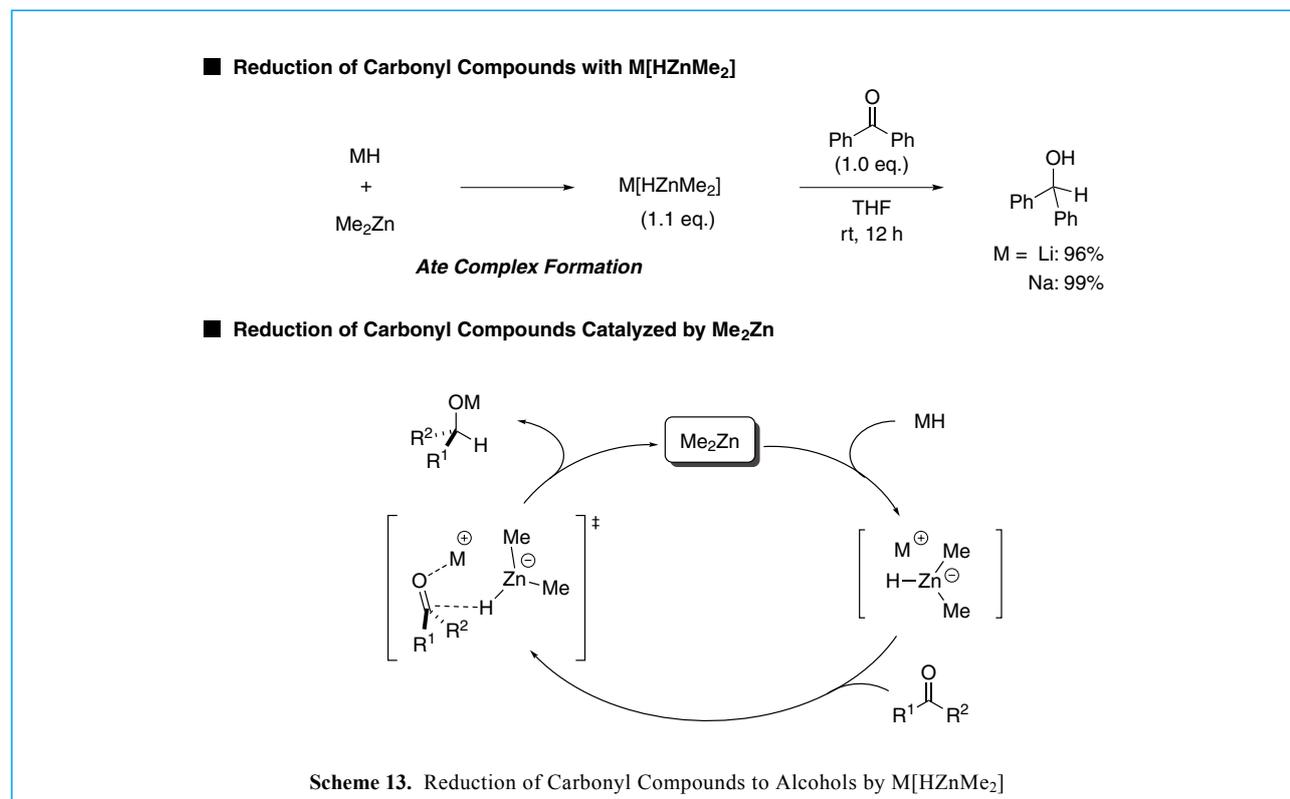

Scheme 12. Direct Amination of Aromatics

4-2. Hydridozincate: M[HZnMe₂]

Although trihydrido-type zincates have been known in the fields of inorganic chemistry and coordination chemistry, reactivities of heteroleptic hydridozincates remained unrevealed. We discovered that the hydrodozincates 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 zincioketal intermediate to avoid the formation of an undesired tertiary alcohol by-product (Scheme 15).[18]

Scheme 13. Reduction of Carbonyl Compounds to Alcohols by M[HZnMe₂]

Scheme 14. Semi-reduction of Carboxylic Acids to Aldehydes by Li[HZnMe₂]

Scheme 15. Direct Conversion of Carboxylic Acids to Ketones
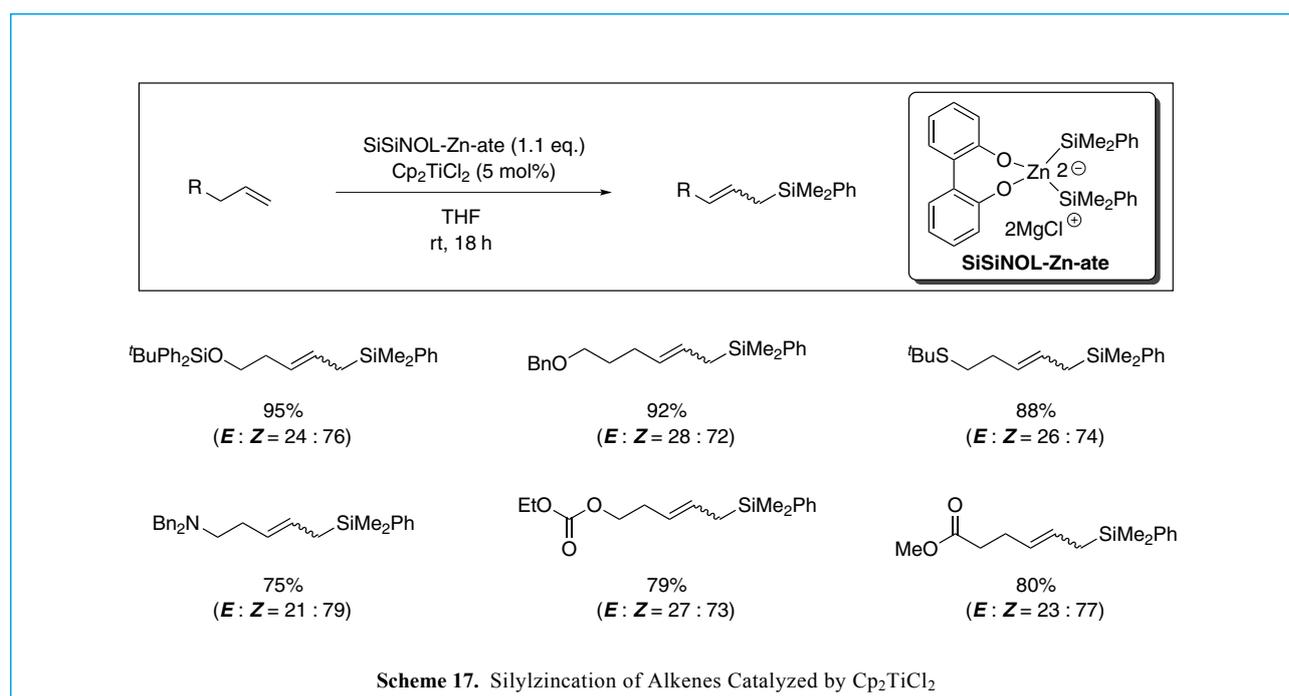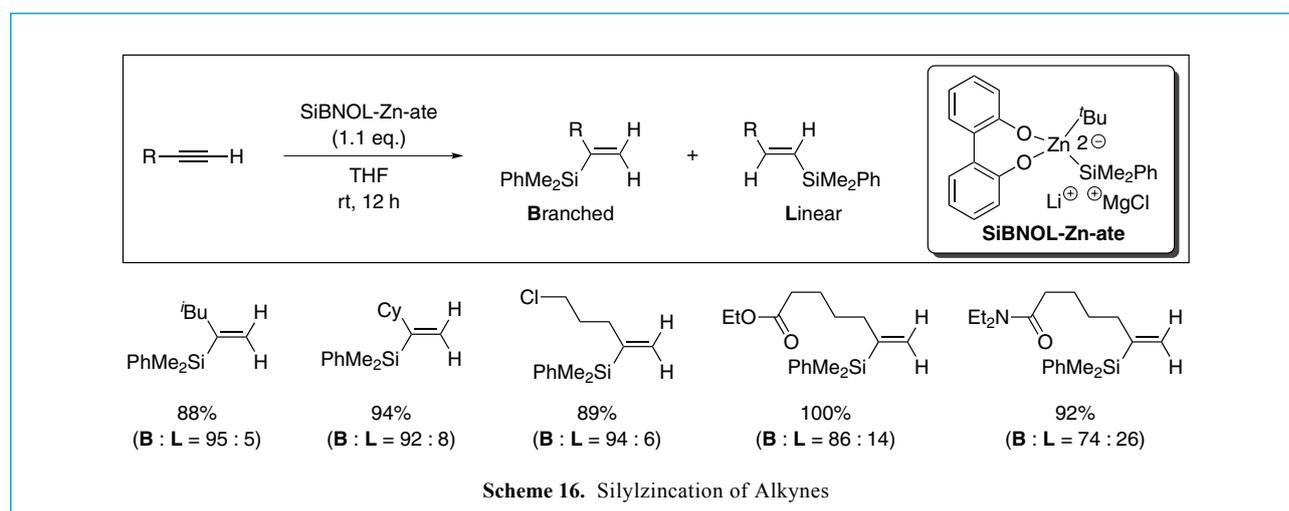
4-3. Silylzincates

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 Cp_2TiCl_2 (Scheme 17).[20] Regioselective addition of the SiSiNOL-Zn-ate to alkenes and following β-hydride elimination afford Z-configurated allylic silanes in preference to E-isomers. No trace of alkylsilanes nor migration of double bonds is observed.

Scheme 16. Silylzincation of Alkynes

Scheme 17. Silylzincation of Alkenes Catalyzed by Cp_2TiCl_2

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_FZnMe_2] & 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 C_4F_9–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[$ZnMe_3$] and Li$_2$[$ZnMe_4$] 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 Me$_2$Zn, Me$_2$Zn prepared from ZnCl$_2$ and 2 equivalents of MeLi successfully gave **16** in 62% yield. Moreover, **16** was obtained by addition of 2 equivalents of LiCl to Me$_2$Zn and there results imply the perfluoroalkylzincate Li[$R_FZn(Me)Cl$] is generated from Li[Me$_2$ZnCl], 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 Csp^3–R_F and Csp^3–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).
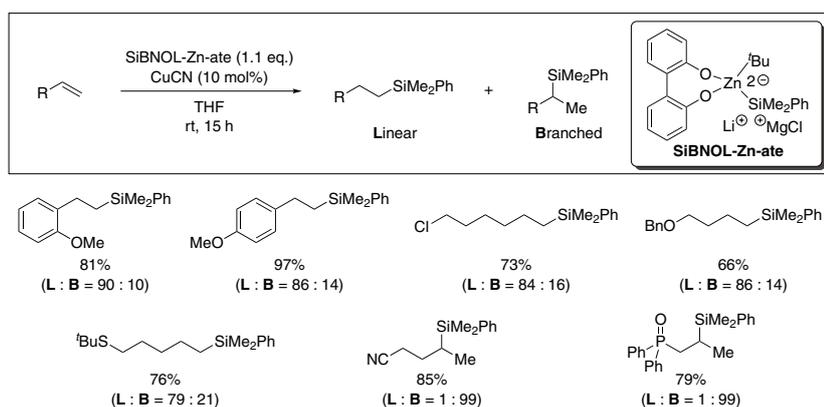
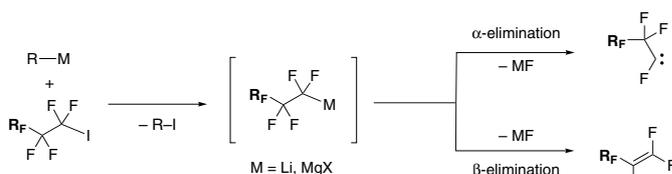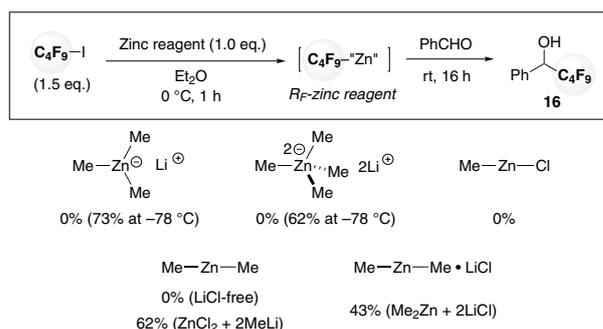**Scheme 18.** Silylzincation of Alkenes Catalyzed by CuCN

Figure 3. Common Decomposition Pathways of R_F-organometallics

Scheme 19. Zincation of R_F–I

Scheme 20. Perfluoroalkylation and Perfluoroarylation of Carbonyl Compounds

R_F–I (1.2 eq.) — Me$_2$Zn (1.0 eq.), LiCl (2.2 eq.), THF, 0 °C, 1 h — [R_F–"Zn"] — Ar–CO–R, rt, 16 h

R_F = C$_4$F$_9$: 89%
C$_6$F$_{13}$: 90%
C$_8$F$_{17}$: 91%
C$_6$F$_5$: 92%

R_F = C$_4$F$_9$: 94%
C$_6$F$_5$: 97%

92%
95%

80%
90%

R_F = C$_4$F$_9$: 40%
C$_6$F$_5$: 44%

86%
97%

64%

57%

80%

Scheme 21. Initial Attempt on Perfluoroalkylation of Aryl Halide

Me$_2$Zn (1.0 eq.) + LiCl (2.2 eq.) + C$_4$F$_9$–I (1.2 eq.) — THF, 0 °C, 1 h — [C$_4$F$_9$–Zn(Me)(Cl) Li$^+$] — 17 (1.0 eq.), phen (20 mol%), CuCl (10 mol%), 70 °C, 16 h — 18: 17%

Scheme 22. Substrate Scope of Aromatic Perfluoroalkylation

R_F–I + I–C$_6$H$_4$–FG — Et$_2$Zn (1.5 eq.), CuI (10 mol%), DMPU, 90 °C, >16 h — R_F–C$_6$H$_4$–FG

18: 89%
93%, *1.18 g*

R_F = C$_3$F$_7$ 19: 91%
C$_5$F$_{11}$ 20: 91%
C$_6$F$_{13}$ 21: 91%
C$_8$F$_{17}$ 22: 86%
23: 94%[a]
C$_{10}$F$_{21}$ 24: 72%
^{i}C$_3$F$_7$ 25: 0%

26: 88%[b]

meta : 27: 87%
para : 28: 72%

R = Ph: 29: 95%[b]
N^{i}Pr$_2$: 30: 61%

31: 60%[b]

32: 65%[b]

R = H: 33: 68%[b]
CN: 34: 54%[b]

R = Bn: 35: 89%[b,c,d]
Ts: 36: 81%[b,c,d]

R = H: 37: 80%[b]
OMe: 38: 82%[b]

39: 47%[b]

R = H: 40: 90%[b]
Cl: 41: 83%[e]

42: 50%[b]

43: 55% (82%)[b]

44: 47% (89%)[b]

45: 35% (41%)[b]

46: 56% (66%)[b,e]

47: 60%[b]

48: 57%[c]

49: 38% (50%)[b,c,f]

50: 78%[b,c,f]

51: 90%[b,c,f]

52: 51%[b,c,f]

53: 70% (95%)[b,c,g]

Isolated yields. NMR yields are given in parentheses. [a] C$_8$F$_{17}$–Br was used. [b] 1,10-Phenanthroline (20 mol%) was added. [c] 120 °C. [d] CuI (20 mol%) was added. [e] Me$_2$Zn was used instead of Et$_2$Zn. [f] Amounts of the reagents were doubled. [g] Amounts of the reagents were tripled.

This low yield was attributed to instability of Li[C$_4$F$_9$Zn(Me)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 zinc[24] 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 Nozaki[26] 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: M[(pinB)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.
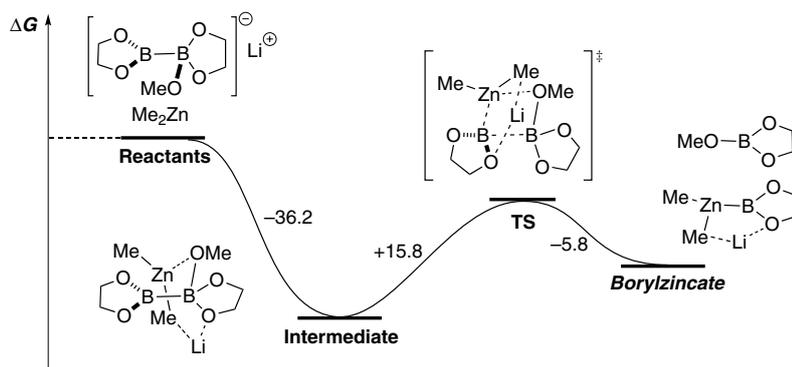

Figure 4. Model DFT Calculation on Borylzincate Formation @M06/SVP (Zn) and 6-31+G* (others); ΔG (kcal/mol)
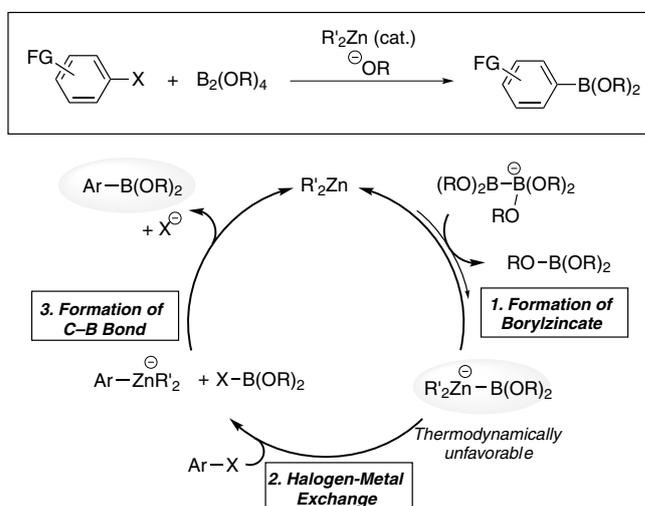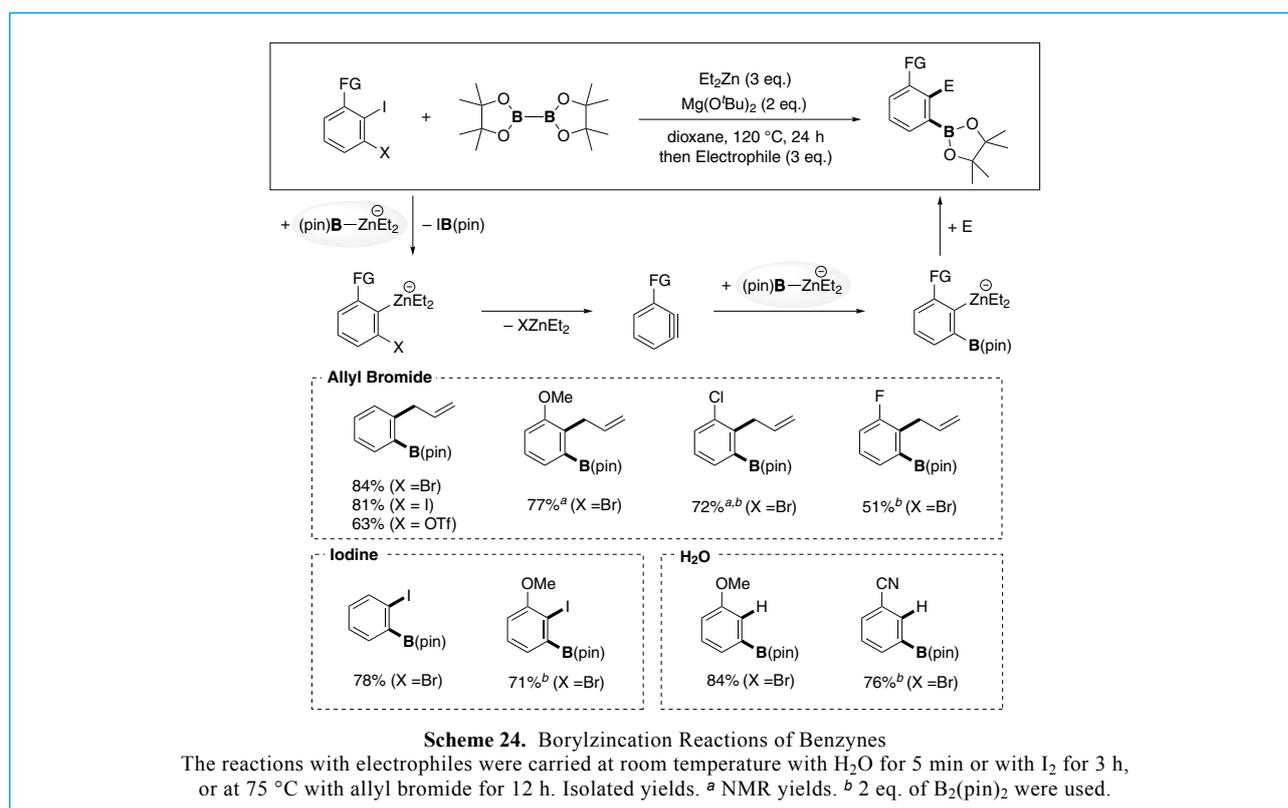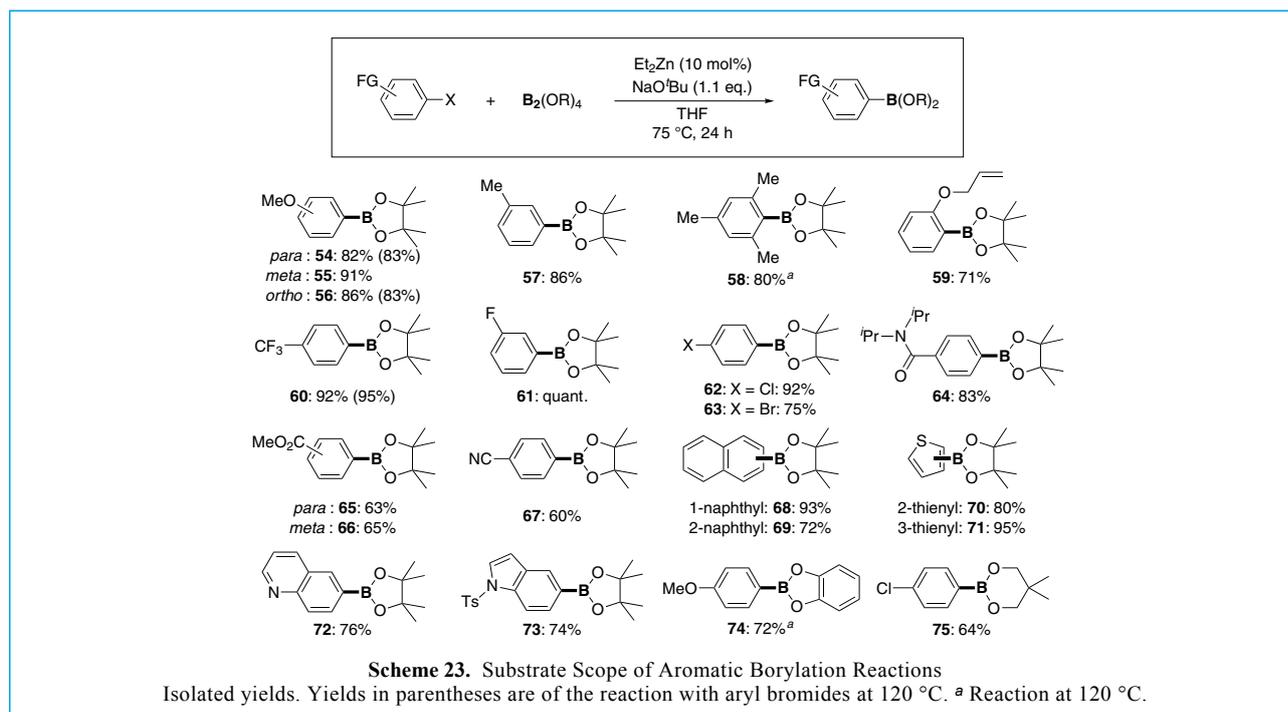

Figure 5. Design of Catalytic Borylation of Aryl Halides

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 Et$_2$Zn (10 mol%), NaO^{t}Bu (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**).

Scheme 23. Substrate Scope of Aromatic Borylation Reactions
Isolated yields. Yields in parentheses are of the reaction with aryl bromides at 120 °C. [a] Reaction at 120 °C.

Scheme 24. Borylzincation Reactions of Benzynes
The reactions with electrophiles were carried at room temperature with H$_2$O for 5 min or with I$_2$ for 3 h, or at 75 °C with allyl bromide for 12 h. Isolated yields. [a] NMR yields. [b] 2 eq. of B$_2$(pin)$_2$ were used.

Next, we designed another strategy to gain a large stabilization energy of the system by the reaction of borylzincate with benzyne. Benzynes 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.
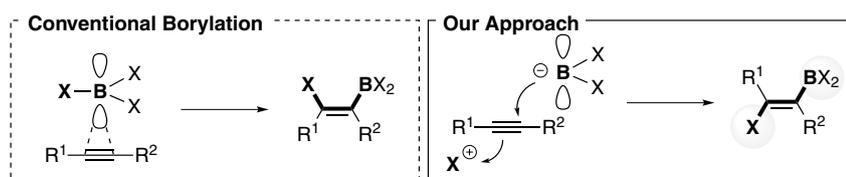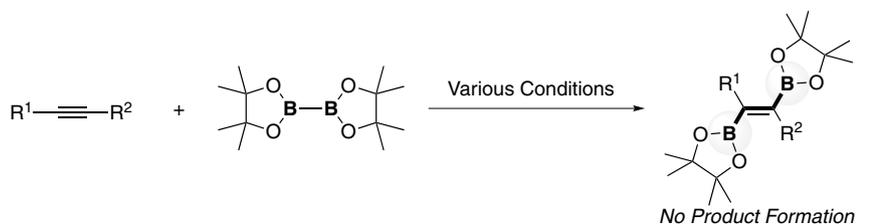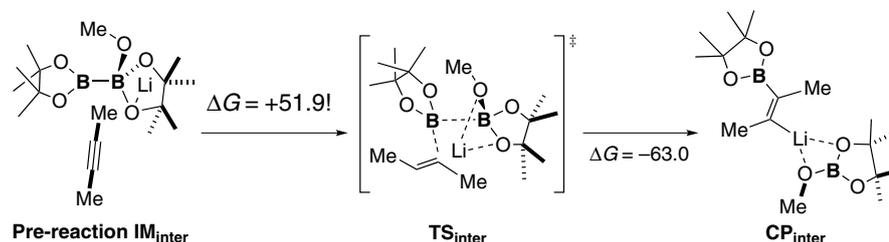

Figure 6. Concepts of Borylation of Triple Bonds

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

$\Delta G = +51.9!$

$\Delta G = -63.0$

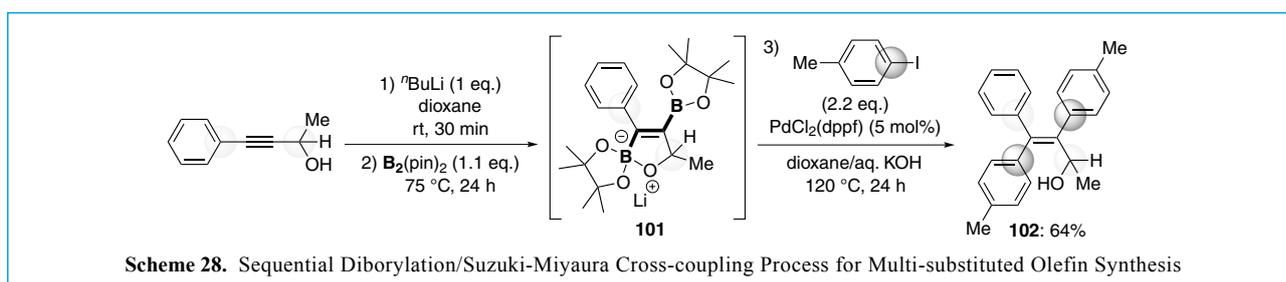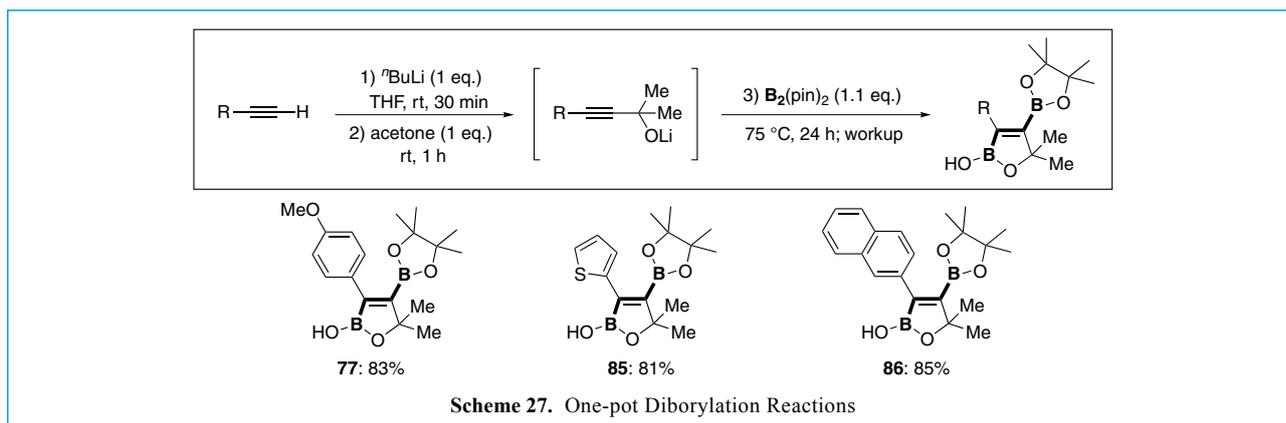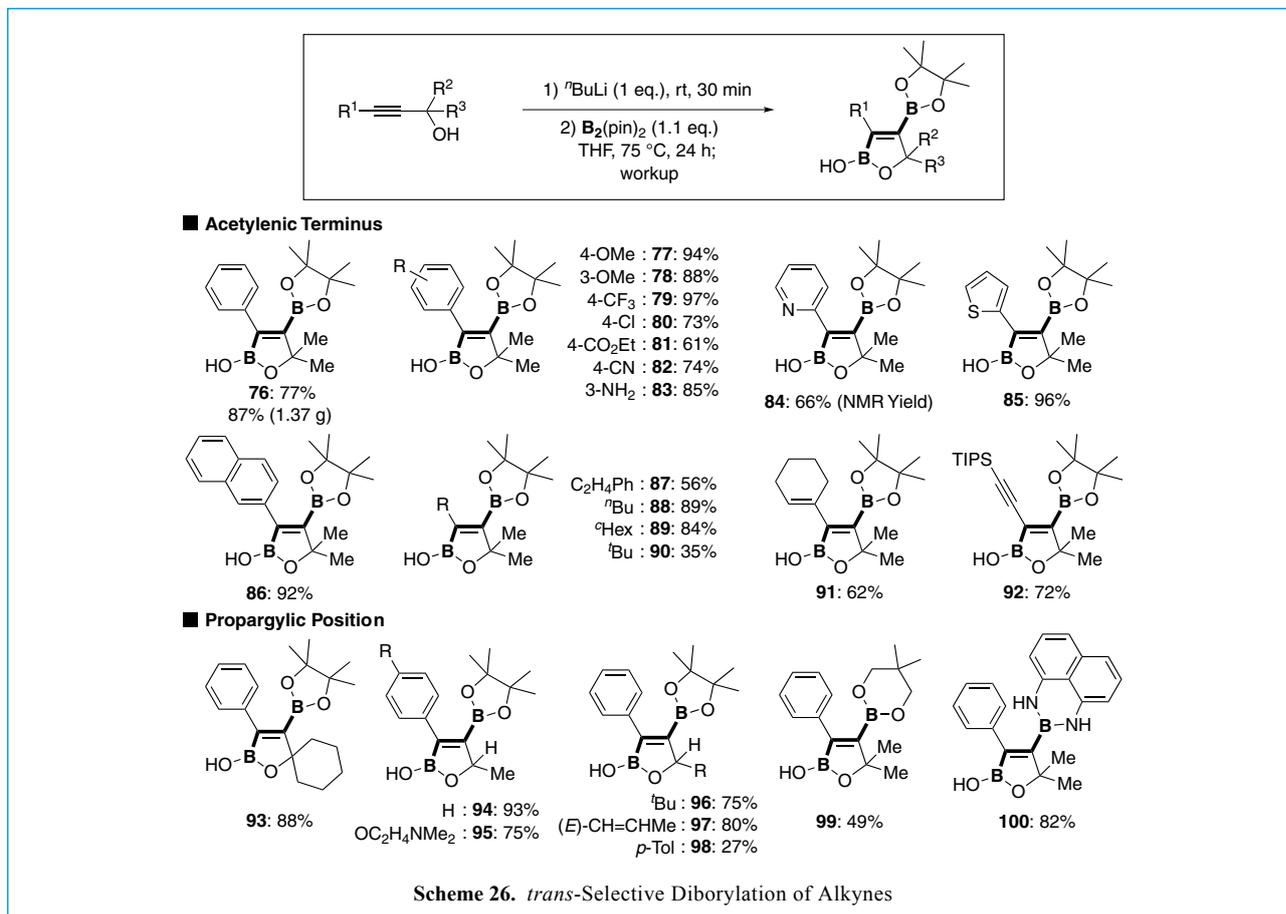**Pre-reaction IM**inter **TS**inter **CP**inter

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.

Scheme 26. *trans*-Selective Diborylation of Alkynes

Scheme 27. One-pot Diborylation Reactions

Scheme 28. Sequential Diborylation/Suzuki-Miyaura Cross-coupling Process for Multi-substituted Olefin Synthesis

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 benzynes", "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.

References

1) J. A. Wanklyn, *Liebigs Ann.* **1858**, *108*, 67.
2) D. T. Hurd, *J. Org. Chem.* **1948**, *13*, 711.
3) Y. Kondo, N. Takazawa, C. Yamazaki, T. Sakamoto, *J. Org. Chem.* **1994**, *59*, 4717.
4) M. Uchiyama, M. Koike, M. Kameda, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1996**, *118*, 8733.
5) M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1998**, *120*, 4934.
6) M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto, K. Tanaka, *J. Am. Chem. Soc.* **2006**, *128*, 8404.
7) T. Furuyama, M. Yonehara, S. Arimoto, M. Kobayashi, Y. Matsumoto, M. Uchiyama, *Chem. Eur. J.* **2008**, *14*, 10348.
8) M. Kobayashi, Y. Matsumoto, M. Uchiyama, T. Ohwada, *Macromolecules* **2004**, *37*, 4339.
9) C. Wang, T. Ozaki, R. Takita, M. Uchiyama, *Chem. Eur. J.* **2012**, *18*, 3482.
10) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802.
11) W. Tückmantel, K. Oshima, H. Nozaki, *Chem. Ber.* **1986**, *119*, 1581.
12) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539.
13) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514. See also: M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Y. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc.* **2008**, *130*, 472.
14) M. Uchiyama, H. Naka, Y. Matsumoto, T. Ohwada, *J. Am. Chem. Soc.* **2004**, *126*, 10526. See also: H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatley, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc.* **2007**, *129*, 1921.
15) S. Usui, Y. Hashimoto, J. V. Morey, A. E. H. Wheatley, M. Uchiyama, *J. Am. Chem. Soc.* **2007**, *129*, 15102. See also: S. Komagawa, S. Usui, J. Haywood, P. J. Harford, A. E. H. Wheatley, Y. Matsumoto, K. Hirano, R. Takita, M. Uchiyama, *Angew. Chem. Int. Ed.* **2012**, *51*, 12081.
16) N. Tezuka, K. Shimojo, K. Hirano, S. Komagawa, K. Yoshida, C. Wang, K. Miyamoto, T. Saito, R. Takita, M. Uchiyama, *J. Am. Chem. Soc.* **2016**, *138*, 9166.
17) M. Uchiyama, S. Furumoto, M. Saito, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1997**, *119*, 11425. For mechanistic studies by DFT calculations, see: M. Uchiyama, S. Nakamura, T. Ohwada, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 10897.
18) R. Murata, K. Hirano, M. Uchiyama, *Chem. Asian J.* **2015**, *10*, 1286.
19) S. Nakamura, M. Uchiyama, T. Ohwada, *J. Am. Chem. Soc.* **2004**, *126*, 11146.
20) S. Nakamura, M. Uchiyama, T. Ohwada, *J. Am. Chem. Soc.* **2005**, *127*, 13116.
21) S. Nakamura, M. Uchiyama, *J. Am. Chem. Soc.* **2007**, *129*, 28.
22) For a comprehensive review on R_F–organometallics, see: D. J. Burton, Z.-Y. Yang, *Tetrahedron* **1992**, *48*, 189.
23) X. Wang, K. Hirano, D. Kurauchi, H. Kato, N. Toriumi, R. Takita, M. Uchiyama, *Chem. Eur. J.* **2015**, *21*, 10993.
24) I. Popov, S. Lindeman, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 9286. See also: K. Aikawa, Y. Nakamura, Y. Yokota, W. Toya, K. Mikami, *Chem. Eur. J.* **2015**, *21*, 96.
25) H. Kato, K. Hirano, D. Kurauchi, N. Toriumi, M. Uchiyama, *Chem. Eur. J.* **2015**, *21*, 3895.
26) Y. Segawa, M. Yamashita, K. Nozaki, *Science* **2006**, *314*, 113.
27) D. S. Laitar, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2005**, *127*, 17196.
28) Y. Nagashima, R. Takita, K. Yoshida, K. Hirano, M. Uchiyama, *J. Am. Chem. Soc.* **2013**, *135*, 18730.
29) For inspiring work on addition of Lewis base activated diborons to nonactivated olefins, see: A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás, E. Fernández, *Angew. Chem. Int. Ed.* **2011**, *50*, 7158.
30) Y. Yamamoto, J.-I. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 9625.
31) Y. Nagashima, K. Hirano, R. Takita, M. Uchiyama, *J. Am. Chem. Soc.* **2014**, *136*, 8532.

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TCI Related Products

Code	Product				
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 [= tert-Butyl Hydroperoxide (70% in Water)]				100g
C2223	CHP [= Cumene Hydroperoxide (contains ca. 20% Aromatic Hydrocarbon)]				100g
T0616	Cp_2TiCl_2 (= Titanocene Dichloride)			5g	25g
C1952	CuCN [= Copper(I) Cyanide]			25g	300g
N0499	$C_4F_9–I$ (= Nonafluorobutyl Iodide)		25g	100g	500g
T1098	$C_6F_{13}–I$ (= Tridecafluorohexyl Iodide)			5g	25g
P1084	$C_8F_{17}–I$ (= Heptadecafluoro-n-octyl Iodide)				25g
H0844	$C_{10}F_{21}–I$ (= Heneicosafluorodecyl Iodide)			5g	25g
P1188	$C_6F_5–I$ (= Pentafluoroiodobenzene)			5g	25g
H0629	$^iC_3F_7–I$ (= Heptafluoroisopropyl Iodide)			25g	100g
D2014	DMPU (= N,N-Dimethylpropyleneurea)		25g	100g	500g
D3214	Et_2Zn [= Diethylzinc (ca. 17% in Hexane, ca. 1mol/L)]			100mL	500mL
D3902	Et_2Zn [= Diethylzinc (ca. 15% in Toluene, ca. 1mol/L)]				100mL
B1964	$B_2(pin)_2$ [= Bis(pinacolato)diboron]	1g	5g	25g	100g
B2254	Bis(neopentyl Glycolato)diboron		1g	5g	25g
B3757	Bis(catecholato)diboron			1g	5g
S0450	NaO^tBu (= Sodium tert-Butoxide)		25g	100g	500g
B0396	^nBuLi [= Butyllithium (ca. 15% in Hexane, ca. 1.6mol/L)]			100mL	500mL
B4697	^nBuLi [= Butyllithium (ca. 20% in Cyclohexane, ca. 2.3mol/L)]			100mL	500mL