The Development of Novel C–H Bond Transformations and Their Application to the Synthesis of Organic Functional Molecules

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Abstract: This personal account summarizes our recent progress in the development of C–H transformations. We achieved *ortho*-selective C–H borylation and silylation using Lewis acid–base interaction between two substrates, and *meta*-selective C–H borylation using hydrogen bonding between a hydrogen donor unit of a ligand and a substrate functional group. Regioselective C–H trifluoromethylation and related reactions of 6-membered heteroaromatic compounds were realized at the 2-, 4-, and benzylic-positions of the heteroaromatic rings. In addition, we developed C–H transformations directed towards the synthesis of organic functional materials, such as highly soluble polyimides and π -conjugated molecules containing either heteroatom(s) or a Lewis acid–base interaction.

1. Introduction

Direct C–H bond transformations are one of the most ideal and efficient methods for synthesizing many types of organic molecules.¹ In many such reactions directing groups play important roles, both promoting the desired C–H transformations and controlling the regioselectivity. When starting my academic career in 2003, I decided to develop novel C–H transformations. Since then, our group, as well as other researchers, has investigated especially *basic* C–H transformations. When I was an assistant professor at Okayama University, I developed several novel C–H transformations, mainly using rhenium and manganese catalysts, in collaboration with Prof. Kazuhiko Takai, students, and postdocs.^{1c,2} But, during these investigations I noticed that such directing group methods are not satisfactory for perfectly controlling the regioselectivity, and considered it necessary to develop new methods to achieve this aim. In addition, I came to think that the development of C–H transformations to synthesize useful organic molecules, such as drugs, agrochemicals, and organic functional materials, is also important for the progress of this field. I began such projects in part when I was an assistant professor, and am now investigating these themes as an associate professor at the University of Tokyo, working with Prof. Motomu Kanai, students, and postdocs. In this personal account, I describe the developments of (1) regioselective C–H transformations controlled by non-covalent bond interactions, such as Lewis acid–base interaction and hydrogen bonding; (2) regioselective C–H trifluoromethylation and related reactions of 6-membered heteroaromatic compounds; and (3) C–H transformations directed towards the synthesis of organic functional materials.

2. Regioselective C–H Transformations Controlled by Non-Covalent Bond Interactions

Regiocontrol is a very important issue for obtaining the desired products in C–H transformations because in any given organic molecule there are usually many types of C–H bonds, making it difficult to control the regioselectivity. To solve this problem, directing groups are usually used to achieve regio-

selective C–H transformations. In this case, I am defining a directing group as a coordinating functional group of a substrate, which can coordinate to the metal centers of catalysts and promote the desired reactions regioselectively. Such directing groups are actually powerful promoters of many kinds of C–H transformation, their use limits the range of possible substrates and products. The directing groups must be introduced into substrates before reactions, and if they do not play an important role in the products, they must be then removed from the products after the reactions. In fact, in many cases it is difficult (or impossible) to remove the directing groups from those products. In addition, reactions can generally only be made to occur at the *ortho*-positions in the case of aromatic substrates. Therefore, I considered the following new methods to achieve regioselective C–H transformations without using directing groups as defined above.

2.1 Regioselective C–H Transformations Controlled by Lewis Acid–Base Interaction between Two Substrates^{3,4}

In the case of the directing group-assisted C–H transformations discussed so far, the directing groups coordinate to a transition metal of the catalyst, and thus the metal center is brought close to a reaction site and subsequent C–H activation and successive transformations occur *ortho*-selectively (Scheme 1a). But C–H borylation reactions usually occur at the *meta*- and *para*-positions of aromatic substrates,⁵ and there had been no report on *ortho*-selective C–H borylation when we started to develop this reaction.⁶ I devised a new concept to promote *ortho*-selective C–H borylation (Scheme 1b): (1) the Lewis basic functional group of an aromatic substrate coordinates to a Lewis acidic boron atom of a hydroborane; (2) oxidative addition of a H–B bond to a transition metal occurs; (3) the catalyst comes close to the *ortho*-C–H bond and C–H bond activation occurs at the *ortho*-position regioselectively; and (4) a new C–B bond formation occurs *ortho*-selectively.

Our investigations, demonstrated that palladium(II) acetate promotes *ortho*-selective C–H borylation at room temperature in the reaction between 2-phenylpyridine and 9-BBN, giving the desired *ortho*-borylated 2-phenylpyridine in 87% yield (Scheme 2).^{3a} Judging from the single crystal X-ray structure

Scheme 1. Regiocontrol of C–H transformations: (a) Directing group-controlled *ortho*-selective C–H transformations; and (b) Lewis acid–base interaction-controlled *ortho*-selective C–H transformations.

Scheme 2. *ortho*-Selective C–H borylation of 2-phenylpyridines controlled by Lewis acid–base interaction.

analysis, a Lewis acid–base interaction exists in the product.

Based on this result, we next aimed to promote *ortho*-selective C–H silylation using Lewis acid–base interaction. Silicon compounds with electron-withdrawing group(s) have Lewis acidity, and Lewis base(s) can coordinate to the silicon atom to give hypervalent silicon compounds. Therefore, we used hydrosilanes with an electron-withdrawing fluorine atom as Lewis acidic substrates. As a result, the desired *ortho*-selective C–H silylation proceeded when an iridium catalyst was used, even on a gram scale (Scheme 3).⁴

2.2 Regioselective C–H Transformations Controlled by Hydrogen Bonding between Ligand and Substrate⁷

ortho-Selective C–H bond transformations have been

Scheme 3. Iridium-catalyzed *ortho*-selective C–H silylation of aromatic compounds.

achieved using several types of directing groups.^{1,8} However, in these examples it is necessary to introduce and remove the directing group before and after the reactions, and in many cases, it is difficult to remove the directing groups from the products. In addition, the reactions generally occur only at the *ortho*-positions of aromatic compounds, and it is usually difficult to promote C–H transformations at other positions, such as *meta*-positions.

Recently, several pioneering examples of *meta*-selective C–H transformations were reported. The Smith, and the Ishiyama, Miyaura and Hartwig groups independently reported iridium-catalyzed $\text{C}(\text{sp}^2)$ -H borylation in which a mixture of *meta*- and *para*-borylated products were usually formed.⁵ In the case of special substrates, such as 1,3-disubstituted aromatic compounds, only *meta*-borylated products were obtained as this minimizes steric repulsion between the substituents of the substrates and the boryl–iridium catalytic active species. Thus, in these reactions the regioselectivity was controlled by *steric effects*. There have also been several examples of *meta*-selective C–H transformations controlled by *electronic effects*. Yu and co-workers reported palladium-catalyzed oxidative Heck-type *meta*-selective $\text{C}(\text{sp}^2)$ -H alkenylation.⁹ The Frost and Ackermann groups independently reported ruthenium-catalyzed *meta*-selective $\text{C}(\text{sp}^2)$ -H sulfonylation¹⁰ and alkylation.¹¹ The Gaunt group reported copper-catalyzed *meta*-selective C–H arylation of aromatic compounds.¹² In these various reactions, the regioselectivity is controlled by *electronic effects*. Yu and co-workers also recently reported palladium-catalyzed *meta*-selective C–H alkenylation of aromatic compounds with a long-tethered directing group.¹³ Regioselectivity is controlled by this well-designed

directing group. I also designed a similar reaction system, but I did not select this strategy because I thought that we would need to introduce and remove the directing group before and after the reaction, and felt that developing an appropriate and effective directing group would be time-consuming. Therefore, I considered the following, different strategy.

The design of the catalytic system is shown in Scheme 4: a substrate recognition part is introduced into a transition metal catalyst ligand using a suitable linker. This substrate recognition part recognizes a functional group in substrates by hydrogen bonding, and thus the catalytic site is brought close to the *meta*-C-H bond of those substrates. Then the desired reaction occurs at the *meta*-position regioselectively. Because the hydrogen bonding is not so strong, displacement of the product by a substrate molecule occurs easily and the reaction proceeds catalytically.

Scheme 4. Design of hydrogen bond-controlled catalytic system.

We selected bipyridine and urea moieties as the catalytic site and substrate recognition part, respectively (Scheme 5a). We thought that the structure of the linker would be important for controlling the regioselectivity. Therefore, we screened several ligands in the reaction between an aromatic amide and bis(pinacolato)diboron (Scheme 5b). In the case of 4,4'-di-*tert*-butyl bipyridine (dtbpy), the *metapara* ratio was only 0.51 and the *para*-borylated aromatic amide was the major product. On changing the ligand to methylene-bridged urea-bipyridine **1**, the *metapara* ratio slightly increased and *meta*-borylated aromatic amide was the major product. The desired reaction did not proceed using phenylethynylene-bridged ligand **2**. The best result was obtained in the case of phenylene-bridged ligand **3**, when the *metapara* ratio was over 30. The C-H borylation did not proceed using a ligand bearing a thiourea moiety.

The efficiency of hydrogen bonding must depend on solvent polarity. As expected, low polarity solvents, such as cyclohexane and *p*-xylene, gave high *meta*-selectivity. On the other hand, the regioselectivity dramatically decreased when using polar solvents, such as THF and NMP.

We then investigated the substrate scope of the C-H borylation reaction (Scheme 6). This proceeded highly *meta*-selectively using ligand **3** (upper row) whereas the regioselectivity was low in the case of dtbpy (lower row). The borylation reaction exhibited high functional group tolerance with methoxy,

Scheme 5. *meta*-Selective C-H borylation: (a) Ligand design. (b) Results of ligand screening.

^a Ratio of *meta* / *para*.

bromo, trifluoromethyl, and fluoro groups remaining unchanged during the reaction. Because regioselective borylation proceeded from both six- and five-membered (hetero)-aromatic amides, ligand **3** must have some flexibility to accept several types of substrate structures. As well as aromatic amides, several kinds of phosphorus compounds, such as aryl phosphonates, phosphonic diamides, and phosphine oxides, showed excellent *meta*-selectivity.

To confirm the importance of hydrogen bonding between the substrates and the urea moiety of ligand **3** for the high regioselectivity, we conducted the following experiments. First, significant lower field shifts of the urea N-H protons of ligand **3** were observed by ¹H NMR in the presence of an aromatic amide (substrate). This finding strongly supports the existence of a hydrogen bonding interaction between ligand **3** and these amide substrates. Second, we investigated several control experiments to confirm the importance of hydrogen bonding (Scheme 7). The C-H borylation reaction was carried out using control ligand **3-Me**₂, in which the nitrogen atoms of the urea moiety are blocked by methyl groups. As a result, the *metapara* ratio of the borylated product dramatically decreased compared with that obtained using ligand **3**, and was almost the same as when using the dtbpy ligand. The regioselectivity was also low (*metapara*=1.0) when the reaction was carried out using another control ligand **4**, containing the urea moiety at the *para*-position of the phenylene linker. When a mixture of cyclohexylphenylurea and 2,2'-bipyridine (ligand **5**) was used, the *metapara* ratio was comparable to that when using dtbpy. These results together indicate that suitable posi-

Scheme 6. Substrate scope of *meta*-selective C–H borylation. Upper and lower rows show the results for ligand **3** and dtbpy, respectively.

Scheme 7. Ligands used in, and results obtained for, several control experiments to confirm the importance of hydrogen bonding.

tioning of the bipyridine and urea moieties is important to control the *meta*-selectivity.

3. Trifluoromethylation and Related Transformations of 6-Membered Heteroaromatic Compounds

While developing of *basic* C–H transformations, I gradually came to consider it also important to develop practical C–H transformations to synthesize organic functional molecules,

such as drugs, agrochemicals, and organic functional materials. Many of these compounds contain trifluoromethyl (CF₃) groups, and these CF₃ groups play an important role in their biological and physical properties. Therefore, it is very important to devise useful and efficient trifluoromethylation reactions, and many methods to synthesize organic molecules bearing CF₃ groups, such as building block methods¹⁴ and cross-coupling reactions¹⁵ have recently been developed. However, for the former, examples of CF₃-containing substrates are limited, thus constraining the range of possible products, while for the latter a halogen atom has to be introduced at the desired reaction site before the reaction can proceed. These drawbacks to the alternatives mean that direct C–H trifluoromethylation of aromatic compounds can be considered a more efficient and practical approach.

3.1 2-Position-Selective C–H Trifluoromethylation of 6-Membered Heteroaromatic Compounds¹⁶

The CF₃ anion, cation, and radical are the candidate trifluoromethylation reagents for direct C–H trifluoromethylation, and in many previous cases a highly reactive trifluoromethyl radical has been used as trifluoromethylation reagent. Direct C–H trifluoromethylation of 5-membered heteroaromatic compounds proceeds regioselectively and only single products are obtained.¹⁷ On the other hand, it has been difficult to control the regioselectivity of C–H trifluoromethylation in the case of 6-membered heteroaromatic compounds.¹⁸ With some special substrates, a single product can be obtained, however, in many cases, mixtures of regioisomers are formed. One of the reasons for this low regioselectivity must be the high reactivity of the CF₃ radical.

To achieve regioselective C–H trifluoromethylation of 6-membered heteroaromatic compounds, I selected the less reactive CF₃ anion as trifluoromethylation reagent. As is well known, 2-position-selective nucleophilic reactions of pyridine and quinoline derivatives can be achieved by electrophilically activating heteroaromatic rings via their pyridine and quinoline *N*-oxides or related compounds. As a result, many functional groups, such as amino, alkoxy, thioalkoxy, and cyano groups, and chlorine and bromine atoms, can be regioselectively introduced at the 2-positions of 6-membered heteroaromatics. We therefore investigated trifluoromethylation using quinoline *N*-oxide and its acylated and sulfonylated derivatives as substrates, and a mixture of trifluoromethyltrimethylsilane and fluoride anion as trifluoromethylation reagent. However, the desired trifluoromethylation reaction did not proceed at all. These disappointing results must be due to the low nucleophilicity of the CF₃ anion.

Therefore, I considered that further electrophilic activation of the heteroaromatic rings must be necessary. If we could design molecules with a lower LUMO energy than pyridine and quinoline *N*-oxides and their acylated and sulfonylated derivatives, it might be possible to realize 2-position selective trifluoromethylation even though the CF₃ anion has low nucleophilicity. Theoretical calculations revealed that pyridine *N*-oxide–borane complexes, and especially pyridine *N*-oxide–BF₂CF₃ complex, have lower LUMO energies than pyridine *N*-oxide and other related electrophilically-activated derivatives (Scheme 8). Therefore, I chose this complex as a substrate to investigate 2-position-selective C–H trifluoromethylation.

On treatment of this BF₂CF₃ complex with a mixture of Me₃SiCF₃ and CsF, trifluoromethylation proceeded at the 2-

Scheme 8. LUMO energies of pyridine, pyridine *N*-oxide, related electrophilically-activated compounds, and pyridine *N*-oxide borane complexes (B3LYP/6-31+G* for A, B, C, E, F, and G; B3LYP/LAV3P+* for D).

position regioselectively, and the desired trifluoromethylated product was obtained in 91% yield (Scheme 9). The reaction proceeded with high substrate generality and functional group tolerance. In this reaction other regioisomers were not formed at all, so it is the first example of 2-position selective C-H trifluoromethylation of 6-membered heteroaromatic compounds.

Scheme 9. 2-Position-selective C-H trifluoromethylation of 6-membered heteroaromatic compounds.

The reaction proceeded in excellent yield even on a gram scale, and sequential conversion of a quinoline derivative to the corresponding 2-trifluoromethylquinoline was achieved

without isolation of any intermediates, such as the quinoline *N*-oxide or quinoline *N*-oxide-BF₂CF₃ complex. We also examined the application to late-stage trifluoromethylation of quinine, which is an antimalarial drug. Treatment of quinine *N*-oxide-BF₂CF₃ complex with a mixture of Me₃SiCF₃ and CsF, and then with K₂CO₃ afforded 2-trifluoromethylated quinine in 75% yield (Scheme 10). The regioselectivity was complementary to that reported by Baran and coworkers, in which electrophilic radical trifluoromethylation proceeded at the 7-position of dihydroquinine.^{18a}

Scheme 10. 2-Position-selective C-H trifluoromethylation of quinine.

The proposed mechanism of the present trifluoromethylation is shown in Scheme 11: (1) generation of an activated CF₃ nucleophile from Me₃SiCF₃ and CsF; (2) regioselective nucleophilic attack of the formed CF₃ anion to pyridine or quinoline *N*-oxide-BF₂CF₃ complex to form dearomatized intermediate; and (3) elimination of a borate salt to produce 2-trifluoromethylpyridine and -quinoline derivatives.

Scheme 11. Proposed mechanism for 2-position-selective C-H trifluoromethylation.

3.2 4-Position-Selective C-H Trifluoromethylation of 6-Membered Heteroaromatic Compounds¹⁹

We next investigated 4-position-selective C-H trifluoromethylation of 6-membered heteroaromatic compounds. Similar to the 2-position-selective C-H trifluoromethylation of 6-membered heteroaromatic compounds, prior to this work there had been no reports of 4-position-selective C-H perfluoroalkylation or perfluoroarylation of 6-membered heteroaromatic compounds.

I considered that 4-position-selective C-H trifluoromethy-

lation could be achieved by blocking the 2-position of 6-membered heteroaromatic compounds because the 4-position is next in reactivity to the 2-position towards nucleophilic attack (Scheme 12). Therefore, I designed a new reaction system in which a bulky Lewis acid electronically activates 6-membered heteroaromatic compounds while at the same time sterically protecting the 2-position of the heteroaromatic rings. To achieve this a more bulky Lewis acid $B(C_6F_5)_3$ was used instead of BF_2CF_3 .¹⁶ Unfortunately, quinoline *N*-oxide- $B(C_6F_5)_3$ complex was unstable to silica gel purification, thus the trifluoromethylation reaction had to be conducted without isolation of the complex. Even so, the desired trifluoromethylation did not proceed at all due to decomposition of the complex. Next a stronger Lewis acid $B(C_6F_4-4-CF_3)_3$ was used to stabilize the corresponding quinoline *N*-oxide-borane complex. In this case, quinoline *N*-oxide- $B(C_6F_4-4-CF_3)_3$ complex was stable to silica gel, and the trifluoromethylation was investigated using the isolated complex. As a result, a mixture of trifluoromethylated dihydroquinoline *N*-oxide- $B(C_6F_4-4-CF_3)_3$ complexes was formed with low C4/C2 selectivity. This low regioselectivity must be due to inefficient steric hindrance

Scheme 12. Strategy for 4-position-selective C-H trifluoromethylation of 6-membered heteroaromatic compounds.

Scheme 13. 4-Position-selective C-H trifluoromethylation of 6-membered heteroaromatic compounds.

by the borane moiety as it is relatively distant from the heterocycle because of the intervening oxygen atom. Therefore, we investigated direct activation of quinoline with $B(C_6F_4-4-CF_3)_3$. This resulted in quinoline-tris(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)borane complex giving the desired 4-(trifluoromethyl)quinoline in 86% yield after oxidative rearomatization of an initially formed intermediate **H** (Scheme 13). The 4-position selective C-H trifluoromethylation generally proceeded in good to excellent yields in the case of quinoline derivatives, and with high functional group tolerance, even on a gram scale. The reaction was also applicable to pyridine derivatives, but the yields were slightly lower than those of trifluoromethylquinolines. The trifluoromethylation reaction proceeded regioselectively using other 6-membered heteroaromatic compounds with two or more heteroatoms. Perfluoroalkylation and perfluoroarylation reactions also proceeded well.

The 4-position selective trifluoromethylation could be applied to a late-stage reaction of abiraterone acetate, which is an anti-prostate cancer drug (Scheme 14).²⁰ Treatment of abiraterone acetate- $B(C_6F_4-4-CF_3)_3$ complex with a mixture of Me_3SiCF_3 and TBAT, subsequent oxidation with a hypervalent iodine compound, and elimination of the borane from the product with MeOH gave trifluoromethylated abiraterone acetate in 39% yield.

Scheme 14. 4-Position-selective C-H trifluoromethylation of abiraterone acetate.

3.3 Benzyl Position-Selective C-H Trifluoromethylation of 6-Membered Heteroaromatic Compounds²¹

Next, we investigated benzylic C-H trifluoromethylation of 6-membered heteroaromatic compounds. At the time examples of $C(sp^3)-CF_3$ bond formation reactions via $C(sp^3)-H$ trifluoromethylation were rare, and there was only a few reports on benzylic $C(sp^3)-H$ trifluoromethylation.²² Furthermore the products were obtained in low to moderate yields as mixtures of desired and undesired products.

Based on our 2-position selective C-H trifluoromethylation of 6-membered heteroaromatic compounds,¹⁶ I considered that benzylic trifluoromethylated product **K** could be obtained by nucleophilic attack of a CF_3 anion on an enamine-type intermediate **J** derived from 2-alkylpyridine or quinoline derivatives (Scheme 15). This intermediate **J** should be formed from 2-alkylpyridine or 2-alkylquinoline-*N*-oxide- BF_2CF_3 complex **I** by deprotonation (Scheme 15).

Treatment of 2-methylquinoline *N*-oxide- BF_2CF_3 com-

Scheme 15. 2-Position-selective C–H trifluoromethylation of 6-membered heteroaromatic compounds.

plex with a mixture of Me_3SiCF_3 and TMAF in several solvents, such as ethyl acetate, acetonitrile, and dichloromethane, gave the desired trifluoromethylated product (Scheme 16). Interestingly, the trifluoromethylation reaction also proceeded without the use of added Me_3SiCF_3 , giving the desired trifluoromethylated product. This finding indicated that the BF_2CF_3 group acted as both a Lewis acid and a trifluoromethylation reagent.

Scheme 16. Benzylic position-selective C–H trifluoromethylation of 2-methylquinoline.

solvent	yield (%) ^a	solvent	yield (%) ^a
AcOEt	39	DMF	<1
THF	8	CH_2Cl_2	38
CH_3CN	77	CH_2Cl_2	30 ^b

^a ^{19}F NMR yield. ^b Without addition of Me_3SiCF_3 .

Next we investigated in more detail trifluoromethylation with no added Me_3SiCF_3 . Under these conditions the benzylic position-selective trifluoromethylated product was produced in 80% yield on reaction at 25 °C for 11 h (Scheme 17). The reaction also proceeded at 65 °C within 10 min, in which case and the desired product was obtained in 85% yield. The trifluoromethylation reaction proceeded in moderate to excellent yields using other quinoline substrates without affecting their functional groups, and also occurred at internal benzylic positions. Interestingly, the trifluoromethylation reaction also proceeded at the 4-methyl group of quinoline *N*-oxide- BF_2CF_3 complex, and produced the corresponding trifluoromethylated product without generating any C2 trifluoromethylated product. On the other hand, the yields of trifluoromethylated products were relatively lower using pyridine substrates. Trifluoromethylated products were also obtained using other heteroaromatic substrates, such as isoquinoline and quinazoline derivatives. Pentafluoroethylated and heptafluoropropylated products were obtained in good yields.

The reaction proceeded in excellent yield even on a gram scale, and the trifluoromethylated product could be obtained from 2-methylquinoline by sequential reactions without isolating the quinoline *N*-oxide or quinoline *N*-oxide- BF_2CF_3 complex. In addition the method was applied to benzylic trifluoromethylation of papaverine, which is an antispasmodic drug (Scheme 18).²³ This result demonstrates that the present

Scheme 17. Benzylic position-selective C–H trifluoromethylation of 6-membered heteroaromatic compounds.

Scheme 18. Benzylic position-selective trifluoromethylation of papaverine.

reaction enables late-stage trifluoromethylation of bioactive molecules containing *N*-heteroaromatic ring(s) and functional groups. This reaction is the first example of a benzylic position-selective *practical* C–H trifluoromethylation and related reactions of 6-membered heteroaromatic compounds.

4. C–H Transformations Leading to the Synthesis of Organic Functional Materials

As described in the Introduction of Section 3, I thought that devising *practical* C–H transformations directed towards the synthesis of organic functional materials must be important for the further development of C–H transformation chemistry. Recently, some such reactions have been reported, and there have been several reviews,²⁴ including our own,²⁵ of

such topics. In this section, I focus on the synthesis of π -conjugated molecules bearing heteroatom(s) or a Lewis acid–base interaction and on polymers. Incidentally, we have also reported the synthesis of pentacene²⁶ and silylindene²⁷ derivatives by transition metal-catalyzed C–H transformations, but the details are not described in this account due to limitations of space.

4.1 Heteroatom-Containing π -Conjugated Molecules^{28–31}

π -Conjugated molecules containing heteroatom(s), such as silafluorene derivatives, have important uses as organic functional materials such as fluorophores, and in solar cell devices. We have reported the synthesis of silafluorene derivatives^{28,29} and phosphafluorene oxides³⁰ by intramolecular C–H/heteroatom–H coupling reactions. Another strategy for the synthesis of heteroatom-containing π -conjugated molecules is C–H/C–H coupling reaction of heteroatom-bridged biaryl compounds (Scheme 19).^{31,32} This reaction provided a variety of π -conjugated molecules bearing heteroatoms, such as nitrogen, oxygen, phosphorus, and sulfur atoms, and in some cases also a carbonyl group. The π -conjugated molecules were synthesized efficiently, even on a gram scale, and larger π -conjugated molecules could also be obtained by a double C–H/C–H cross-coupling reaction and subsequent oxidative cycloaromatization (Scheme 19, bottom row).

Scheme 19. Synthesis of ladder-type π -conjugated molecules from heteroatom- or carbonyl-bridged biaryl compounds.

The proposed reaction mechanism for the formation of heteroatom-containing ladder-type π -conjugated molecules is shown in Scheme 20: (1) C–H bond activation of a heteroaromatic ring to give a heteroaryl–palladium species by a concerted metalation–deprotonation mechanism via the elimina-

tion of pivalic acid; (2) C–H bond activation of an aromatic ring to give a palladacyclic intermediate by a concerted metalation–deprotonation mechanism via the elimination of pivalic acid; and (3) AgOPiv-mediated oxidative reductive elimination to give π -conjugated molecule and regenerate the palladium catalyst Pd(OPiv)₂.

Scheme 20. Proposed mechanism for the formation of ladder-type π -conjugated molecules.

4.2 π -Conjugated Molecules Containing a Lewis Acid–Base Interaction³³

In general π -conjugated molecules contain only covalent bonds, and examples of π -conjugated molecules containing a Lewis acid–base interaction are still rare.^{3a,34} It is expected that such molecules would show characteristic properties different from those of standard π -conjugated molecules, and due to the flatness of the molecules and a decrease in their LUMO energies.

As described in Section 2.1, we reported the synthesis of borafluorene and silafluorene equivalents bearing a Lewis acid–base interaction via C–H bond activation.^{3a,4} We also achieved palladium-catalyzed synthesis of silafluorene equivalents containing a Lewis acid–base interaction by C–H fluorosilylation of 2-phenylpyridine derivatives (Scheme 21).³³ The fluorosilylated 2-phenylpyridines were fluorescent and the fluorescent quantum yield was 0.50 (Scheme 21). For expression of the fluorescence, the Lewis acid–base interaction between silicon and nitrogen atoms is indispensable. In fact, the quantum yields of two compounds without a fluorine or nitrogen

Scheme 21. Synthesis of 2-fluorosilylated product and comparison of fluorescent quantum yields in THF.

atom were quite low ($\Phi_F=0.01$ and 0.02) (Scheme 21). Interestingly, the quantum yield of the product was much higher than that of the corresponding silafluorene ($\Phi_F=0.06$). The same product can be synthesized using another reaction, as described in Scheme 3.⁴

The proposed mechanism for the fluorosilylation is shown in Scheme 22: (1) formation of an *ortho*-palladated intermediate **L** (C–H bond activation); (2) formation of a fluorosilyl-palladium intermediate **N** from intermediate **L** and **M**; (3) reductive elimination of **N** to give the fluorosilylated product and palladium(0) species; and (4) oxidation of the palladium(0) species by $K_2S_2O_8$ to regenerate the palladium(II) catalyst. The intermediate **M** would be formed by (5) the formation of silicate **O** from a silylation reagent and KF ; and (6) elimination of Et_2N -Bpin from **O**.

Scheme 22. Proposed mechanism for *ortho*-selective C–H fluorosilylation.

4.3 Soluble Polyimide Derivatives³⁵

Polyimides are rigid polymers with high strength intensity, heat-resisting properties, and electric non-conductance, and are useful and important in the fields of aerospace engineering³⁶ and electronic materials.³⁷ For example, polyimides are used as the “gold film” of artificial satellites. However, polyimides have quite low solubility in organic solvents, and therefore it is difficult to fabricate them into the desired shapes. If highly soluble polyimide derivatives with rigid structures and high thermal stability can be synthesized, they would have great practical use. I considered that the low solubility could be improved by changing some of the carbonyl groups (C=O double bond) of polyimides to imino groups (C=N double bond) with long alkyl chains on the nitrogen atoms. One of the possible methods that can be considered for synthesizing such polyimide analogues is condensation of polyimides and amines, but unfortunately this reaction did not proceed at all.

To introduce imino groups into polyimide skeletons, I designed a new method incorporating a leaving group into the directing group of substrates (Scheme 23). My retrosynthetic strategy is shown in Scheme 23: (1) iminoisoindolinone **P**, which is the partial structure of a polyimide derivative, is constructed by the elimination of methanol from intermediate **Q**; (2) intermediate **Q** is generated from intermediate **R** by intramolecular nucleophilic cyclization; and (3) intermediate **R** is

formed by insertion of isocyanate **T** into an *ortho*-C–H bond of aromatic imide **S**. Based on this strategy, we successfully synthesized iminoisoindolinones via C–H bond activation without loss of the imino functional groups.

Scheme 23. Retrosynthetic analysis for polyimide derivative containing long alkyl chains.

As a result of optimizing the reaction conditions, we found that the reaction of an aromatic imide with *p*-tolyl isocyanate in the presence of a rhenium catalyst proceeded smoothly

Scheme 24. Synthesis of iminoisoindolinone and polyimide derivatives containing *N*-alkyl groups.

and gave an iminoisoindolinone quantitatively (Scheme 24a). Based on this, I thought that polyimide derivatives would be formed from diimides and diisocyanates. In fact, treatment of a diimide with a diisocyanate did lead to alternating copolymerization and a polyimide derivative was obtained (Scheme 24b). This is the first example of the synthesis of a polyimide derivative containing imino groups. The thermal stability of these polyimide analogues was lower than that of the related polyimide. However, interestingly, this polymer is highly soluble in organic solvents such as toluene, THF, dichloromethane, and chloroform.

5. Conclusions

We succeeded in the establishment of new concepts to control the regioselectivity of C–H transformations using noncovalent bonds, such as Lewis acid–base interaction and hydrogen bonding. As a result, *ortho*-selective C–H borylation and silylation, and *meta*-selective C–H borylation were achieved. In addition, we also developed practical C–H transformations directed towards the synthesis of organic functional molecules, such as drugs, agrochemicals, and organic functional materials. As a result, 2-, 4-, and benzylic-position-selective C–H trifluoromethylation and related reactions were realized for the first time, and it was shown that these reactions can be utilized for the late-stage introduction of fluorinated functional groups. Highly soluble polyimides, heteroatom-containing π -conjugated molecules, and π -conjugated molecules with a Lewis acid–base interaction were efficiently synthesized via C–H bond activation.

By expanding this novel conceptual realization of regiocontrol, we will be able to control regioselectivities in many synthetic organic reactions including C–H transformations. If regioselective C–H trifluoromethylations and similar related reactions at many other positions could be developed, such transformations will surely contribute to the development of pharmaceuticals, agrochemicals, and organic functional materials because compound libraries could then be constructed using a series of such transformations. From the viewpoint of practicability, we have already been able to contribute to C–H bond activation chemistry through the development of new synthetic methods for polymers and π -conjugated molecules via C–H activation.

I believe that our and other groups' ceaseless efforts to develop novel C–H transformations and concepts will lead to a time when direct C–H transformations can become a main player in *practical* synthetic organic reactions, and hopefully replace many traditional organic transformations in the near future.

Acknowledgment

I would like to thank Prof. Motomu Kanai and Prof. Kazuhiko Takai for fruitful discussions and warm support. I also appreciate all my collaborators, including students, postdocs, and other co-authors for their great efforts. I am also grateful for financial support by Grant-in-Aid for Scientific Research (B) and Grant-in-Aid for Challenging Exploratory Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, CREST and ERATO from Japan Science and Technology Agency (JST), Astellas Foundation for Research on Metabolic Disorders, and Yakugaku Shinkoukai.

References

- For several recent reviews of C–H transformations, see: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) McMurray, L.; O'Hara, F.; Gaunt, M. *J. Chem. Soc. Rev.* **2011**, *40*, 1885. (c) Kuninobu, Y.; Takai, K. *Chem. Rev.* **2011**, *111*, 1938. (d) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (e) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (g) Engle, K. M.; Nei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (h) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (i) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (j) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. (k) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. (l) Wencel-Delord, J.; Glorius, F. *Nature Chem.* **2013**, *5*, 369. (m) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. (n) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29. (o) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74. (p) Tani, T.; Uehara, T. N.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2014**, *5*, 123. (q) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci.* **2014**, *5*, 2146. (r) Valyaev, D. A.; Lavigne, G.; Lugan, N. *Coord. Chem. Rev.* **2016**, *308*, 191.
- For accounts, see: (a) Kuninobu, Y.; Takai, K. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 656. (b) Kuninobu, Y. *J. Synth. Org. Chem., Jpn.* **2013**, *71*, 425.
- (a) Kuninobu, Y.; Iwanaga, T.; Omura, T.; Takai, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4431. (b) Murai, M.; Omura, T.; Kuninobu, Y.; Takai, K. *Chem. Commun.* **2015**, *51*, 4583.
- Wakaki, T.; Kanai, M.; Kuninobu, Y. *Org. Lett.* **2015**, *17*, 1758.
- (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka Jr., R. E.; Smith III, M. R. *Science* **2002**, *295*, 305. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390.
- During our investigation, Sawamura and co-workers reported the first example of *ortho*-selective C–H borylation, see: Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 19310.
- Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nature Chem.* **2015**, *7*, 712.
- Chatani, N. *J. Synth. Org. Chem., Jpn.* **2013**, *71*, 406.
- Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072.
- Kociok-Köhne, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011**, *133*, 19298.
- Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877.
- (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (b) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 463.
- (a) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518. (b) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215.
- For several recent reviews, see: (a) Usachev, B. I. *J. Fluorine Chem.* **2015**, *175*, 36. (b) Meyer, F. *Chem. Commun.* **2016**, *52*, 3077.
- (a) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909. (b) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.
- Nishida, T.; Ida, H.; Kuninobu, Y.; Kanai, M. *Nat. Commun.* **2014**, *5*, 3387.
- (a) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (b) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298.
- (a) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411. (b) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.
- Nagase, M.; Kuninobu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2016**, *138*, 6103.
- Attard, G.; Reid, M. A. H.; Yap, T. A.; Raynaud, F.; Dowsett, M.; Settattree, S.; Barrett, M.; Parker, C.; Martins, V.; Folkard, E.; Clark, J.; Cooper, C. S.; Kaye, S. B.; Dearnaley, D.; Lee, G.; de Bono, J. S. *J. Clin. Oncol.* **2008**, *26*, 4563.
- Kuninobu, Y.; Nagase, M.; Kanai, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 10263.
- (a) Binkley, R. W.; Ambrose, M. G. *J. Org. Chem.* **1983**, *48*, 1776. (b) Chu, L.; Qing, F.-L. *Chem. Commun.* **2010**, 6285. (c) Mitsudera, H.; Li, C.-J. *Tetrahedron Lett.* **2011**, *52*, 1898.
- Papaverin shows smooth muscle-relaxing activity. (a) Gross, E. G.;

- Slaugfiter, D. H. *J. Pharmacol.* **1931**, *43*, 551. (b) Klotz, U.; Vapaatalo, H. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1974**, *284*, 373. (c) Hayashi, S.; Toda, N. *Br. J. Pharmacol.* **1977**, *60*, 35.
- 24) (a) Wencel-Delord, J.; Glorius, F. *Nature Chem.* **2013**, *5*, 369. (b) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 66.
- 25) Kuninobu, Y.; Sueki, S. *Synthesis* **2015**, *47*, 3823.
- 26) Kuninobu, Y.; Seiki, T.; Kanamaru, S.; Nishina, Y.; Takai, K. *Org. Lett.* **2010**, *12*, 5287.
- 27) Sueki, S.; Kuninobu, Y. *Chem. Commun.* **2015**, *51*, 7685.
- 28) Ureshino, T.; Yoshida, T.; Kuninobu, Y.; Takai, K. *J. Am. Chem. Soc.* **2010**, *132*, 14324.
- 29) Kuninobu, Y.; Yamauchi, K.; Tamura, N.; Seiki, T.; Takai, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 1520.
- 30) Kuninobu, Y.; Yoshida, T.; Takai, K. *J. Org. Chem.* **2011**, *76*, 7370.
- 31) Saito, K.; Chikkade, P. K.; Kanai, M.; Kuninobu, Y. *Chem. Eur. J.* **2015**, *21*, 8365.
- 32) Just after our report, a similar reaction was described: Okada, T.; Unoh, Y.; Satoh, T.; Miura, M. *Chem. Lett.* **2015**, *44*, 1598.
- 33) Xiao, Q.; Meng, X.; Kanai, M.; Kuninobu, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 3168.
- 34) (a) Ishida, N.; Narumi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 1279. (b) Ishida, N.; Moriya, T.; Goya, T.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 8709. (c) Ishida, N.; Ikemoto, W.; Narumi, M.; Murakami, M. *Org. Lett.* **2011**, *13*, 3008. (d) Ishida, N.; Narumi, M.; Murakami, M. *Helv. Chim. Acta* **2012**, *95*, 2474. (e) Hudson, Z.; Ko, S.-B.; Yamaguchi, S.; Wang, S. *Org. Lett.* **2012**, *14*, 5610. (f) Tokoro, Y.; Yeo, H.; Tanaka, K.; Chujo, Y. *Chem. Commun.* **2012**, *48*, 8541. (g) Tokoro, Y.; Tanaka, K.; Chujo, Y. *Org. Lett.* **2013**, *15*, 2366.
- 35) Sueki, S.; Guo, Y.; Kanai, M.; Kuninobu, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 11879.
- 36) (a) Russell, D. A.; Connell, J. W.; Fogdall, L. B. *J. Spacecraft Rockets* **2002**, *39*, 833. (b) Dever, J. A.; Miller, S. K.; Sechkar, E. A.; Wittberg, T. N. *High Perform. Polym.* **2008**, *20*, 371.

- 37) (a) Nishikawa, M.; Reznikov, Y.; West, J. L. *Liq. Cryst.* **1999**, *26*, 575. (b) Ling, Q.-D.; Chang, F.-C.; Song, Y.; Zhu, C.-X.; Liaw, D.-J.; Chan, D. S.-H.; Kang, E.-T.; Neoh, K.-G. *J. Am. Chem. Soc.* **2006**, *128*, 8732. (c) You, N.-H.; Suzuki, Y.; Yorifuji, D.; Ando, S.; Ueda, M. *Macromolecules* **2008**, *41*, 6361.

PROFILE

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