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SYNTHESIS OF UNSYMMETRIC HetAr–X–HetAr’ COMPOUNDS BY RHODIUM-CATALYZED HETEROARYL EXCHANGE REACTIONS

Mieko Arisawa,* Saori Tanii, Takeru Tazawa, and Masahiko Yamaguchi*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba, Sendai, 980-8578, Japan. E-mails: arisawa@m.tohoku.ac.jp, yama@m.tohoku.ac.jp

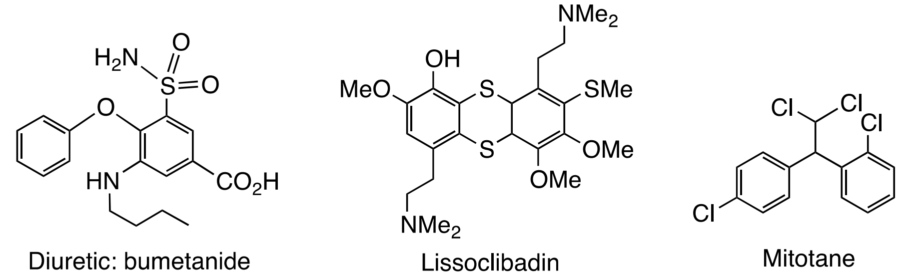
Abstract – Unsymmetric HetAr-X-HetAr’ compounds have flexible and chiral structures, and are expected to exhibit various biological activities by interacting with proteins and nucleic acids. Unsymmetric HetAr-X-HetAr’ compounds were efficiently synthesized by rhodium-catalyzed heteroaryl exchange reactions, which involved equilibrium control by judicious design of organic heteroaryl reagents. By using this method, unsymmetric HetAr–O–HetAr’, HetAr–S–HetAr’, and HetAr–CH_2–HetAr’ compounds as well as HetAr–F compounds were obtained from heteroaryl aryl ethers and various heteroaryl reagents. The rhodium-catalyzed synthesis has a broad applicability, which gives novel unsymmetric HetAr-X-HetAr’ compounds containing five- and six-membered heteroarenes.

CONTENTS

1. INTRODUCTION: UNSYMMETRIC HetAr–X–HetAr' COMPOUNDS

Diaryl Ar–X–Ar' structures with a one-atom linker between two aryl groups are an important scaffold for drugs. Diaryl ethers, sulfides, and methanes are considered privileged structures included in many pharmaceutical products, such as bumetanide, lissoclibadin, and mitotane (Figure 1a).[1] A number of related HetAr–X–Ar compounds, in which an aryl group in an Ar–X–Ar' structure is exchanged with a heteroarene, have also been developed. Examples are sorafenib, XK469, antifolates, AZD4407, trimethoprim, and piritrexim (Figure 1b).[2] It is then a logical extension to consider unsymmetric HetAr–X–HetAr' compounds in which two aryl groups in an Ar–X–Ar' compound are exchanged with two different heteroarenes. They are expected to exhibit various biological activities by taking advantage of the involvement of several heteroatoms capable of interacting with proteins or nucleic acids. Unsymmetrical HetAr–X–HetAr' compounds connected by oxygen, sulfur, and carbon are characterized by structural diversity at their HetAr groups as well as at their linker X groups.

a) Ar–X–Ar' compounds



b) HetAr–X–Ar compounds

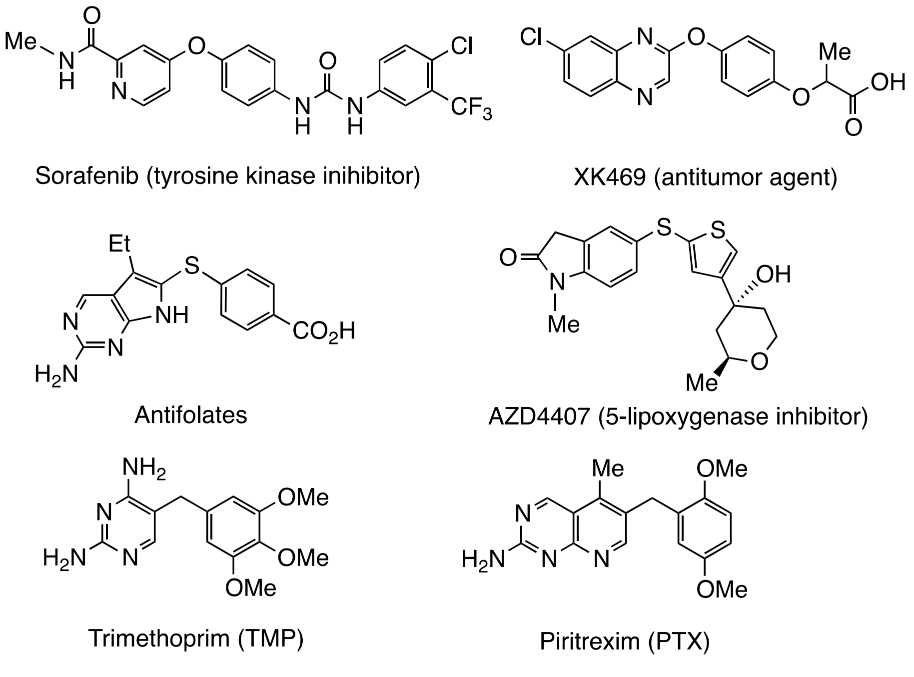


Figure 1. Pharmaceutical products with Ar–X–Ar'/ HetAr–X–Ar structures

Unsymmetric HetAr–X–HetAr' compounds possess rigid heteroaryl structures and two rotating flexible sp^2-C/sp^3-X bonds, which significantly enhance structural diversity in binding to proteins and nucleic acids (Figure 2). Their structures are in contrast to the relatively rigid structures of diaryl Ar–Ar' and di(heteroaryl) HetAr–X–HetAr' compounds lacking a linker atom.

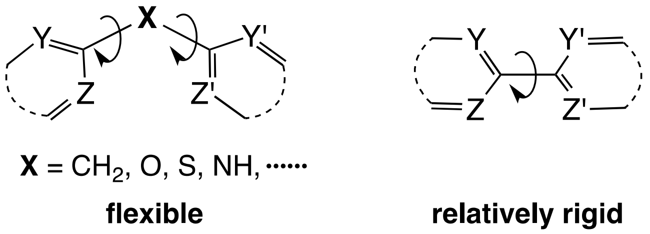


Figure 2. Unsymmetric HetAr–X–HetAr' compounds vs HetAr–HetAr' compounds

To study the conformations of HetAr–X–HetAr' compounds, the Ph–X–Ph structure is discussed as a model. A plane containing the X, C(α), C(α'), C(δ), and C(δ') atoms is considered, where C(α)/C(α') and C(δ)/C(δ') are the *ipso*- and *p*-carbons of two phenyl groups, respectively; the plane is called the horizontal plane (Figure 3). Then, conformations **A** to **F** are conceivable: Conformation **A**, in which a phenyl group containing C(α) and C(δ) and a phenyl group containing C(α') and C(δ') are both on the horizontal plane; conformation **B**, in which a phenyl group containing C(α) and C(δ) and a phenyl group containing C(α') and C(δ') are both vertical to the horizontal plane; conformation **C**, in which one phenyl group containing C(α) and C(δ) is on the horizontal plane and the other phenyl group containing C(α') and C(δ') is vertical to the horizontal plane.

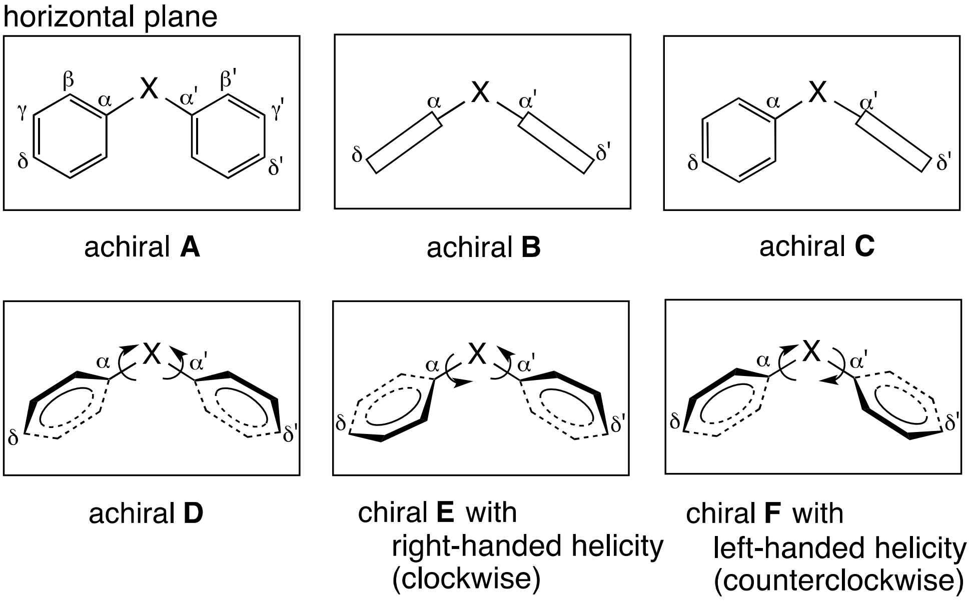
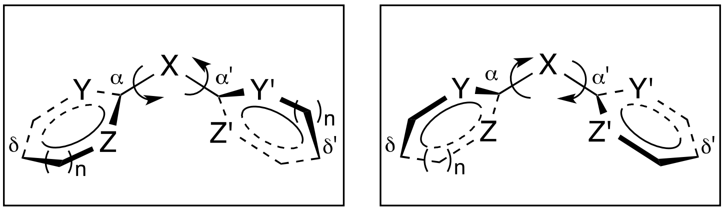


Figure 3. Conformations of diphenyl Ph–X–Ph compound

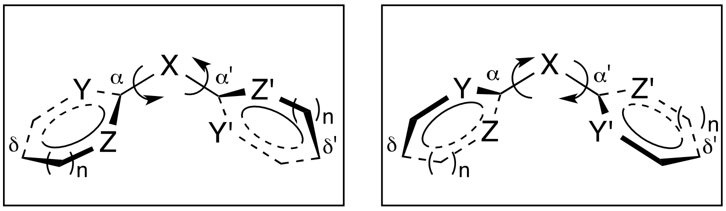
Conformations **A**, **B**, and **C** are achiral. Tilted conformations **D**, **E**, and **F** are also conceivable, in which, to simplify discussion, dihedral angles between the horizontal plane and two phenyl planes are assumed identical. Conformation **D**, in which two phenyl groups containing C(α)/C(δ) and C(α’)/C(δ’) are tilted in the opposite direction with the same dihedral angle, is achiral. Two phenyl groups can be tilted in the same direction either clockwise or counterclockwise. Then, the resulting chiral conformations **E** and **F** are called right-handed pseudohelicity and left-handed pseudohelicity, respectively. Diverse conformations are available for Ph–X–Ph structures.

Accordingly, unsymmetric HetAr–X–HetAr’ compounds, in which two aryl groups of the Ar–X–Ar’ compounds are exchanged with two different heteroaryl groups, can have various conformations including chiral pseudohelical structures. In addition, because of the asymmetry of HetAr groups with regard to the perpendicular plane to heteroaryl groups, more diverse conformations are available (Figure 4). The heteroatoms Y and Y’, for example, can be on either the same side of the horizontal plane or opposite sides, which are noted as the *syn*- and *anti*-conformations, respectively.



chiral **A** with
right-handed helicity
anti-conformation

chiral **B** with
left-handed helicity
anti-conformation



chiral **C** with
right-handed helicity
syn-conformation

chiral **D** with
left-handed helicity
syn-conformation

Figure 4. Conformations of di(heteroaryl) HetAr–X–HetAr’ compound

Chiral pseudohelical structures are observed for unsymmetric HetAr–X–HetAr’ compounds in the solid state, as shown in our studies. For example, the ORTEP views of 6-(4-pyridinylthio)-3-pyridinecarbonitrile showed a chiral pseudohelical structure, in which tilted 3-pyridinecarbonitrile and 4-pyridine groups are in the clockwise and counterclockwise directions, being called right-handed pseudohelicity and left-handed pseudohelicity, respectively (Figures 5a and 5b).[3] 6-Chloro-2-(furylthio)benzoxazole also possesses the chiral pseudohelical structure with a *syn*-conformation with regard to the sulfur atom in thiophene and the nitrogen atom in benzoxazole (Figures 6a and 6b).[3]

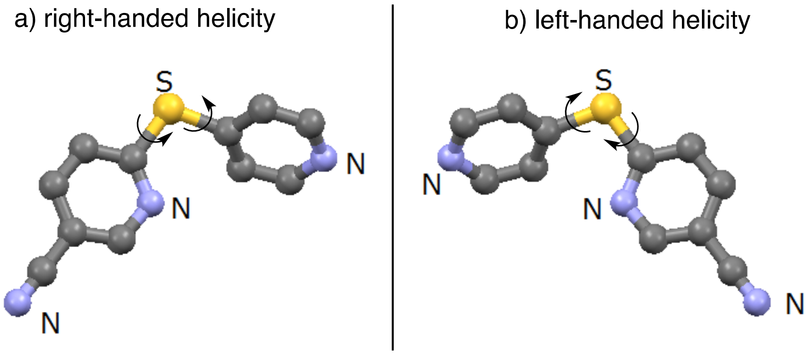


Figure 5. The ORTEP views of 6-(4-pyridinylthio)-3-pyridinecarbonitrile

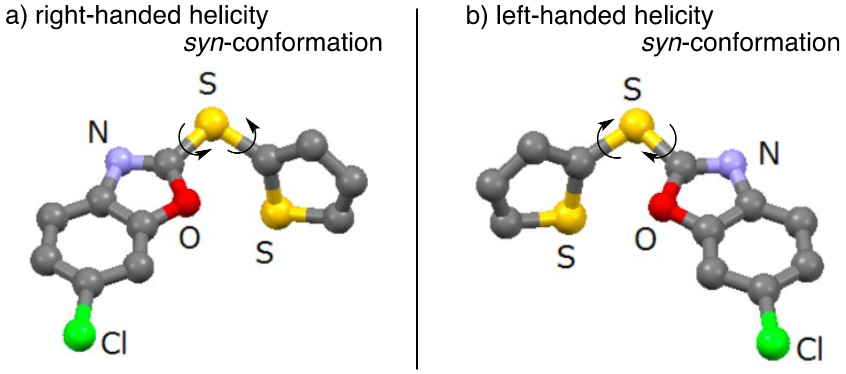


Figure 6. The ORTEP views of 6-chloro-2-(furylthio)benzoxazole

A single unsymmetric HetAr–X–HetAr’ compound can take various conformations involving chiral pseudohelical structures, which can well fit with proteins and nucleic acids, thus, various novel bioactive substances can be developed. Unsymmetric HetAr–X–HetAr’ compounds, however, are rare owing to the lack of efficient and versatile synthetic methods, the development of which is desired.

2. SYNTHETIC METHODOLOGY

Unsymmetric Ar–X–Ar’ and HetAr–X–Ar compounds have been synthesized by the nucleophilic substitution reaction of aryl halides and metalated arylmethyl, arylthio, or aryloxy reagents (Scheme 1).[4] Alternatively, substitution reaction of arylmetal reagents and arylmethyl halides or arylthio chlorides has also been employed.[5]

$$\mathrm{Ar{-}X} + \mathrm{Ar'{-}CH_2M} \longrightarrow \mathrm{Ar{-}CH_2{-}Ar'} + \mathrm{XM}$$

$$\mathrm{Ar{-}X} + \mathrm{Ar'{-}OM} \longrightarrow \mathrm{Ar{-}O{-}Ar'} + \mathrm{XM}$$

$$\mathrm{Ar{-}X} + \mathrm{Ar'{-}SM} \longrightarrow \mathrm{Ar{-}S{-}Ar'} + \mathrm{XM}$$

$$\mathrm{Ar{-}M} + \mathrm{Ar'{-}CH_2X} \longrightarrow \mathrm{Ar{-}CH_2{-}Ar'} + \mathrm{XM}$$

$$\mathrm{Ar{-}M} + \mathrm{Ar'{-}SX} \longrightarrow \mathrm{Ar{-}S{-}Ar'} + \mathrm{XM}$$

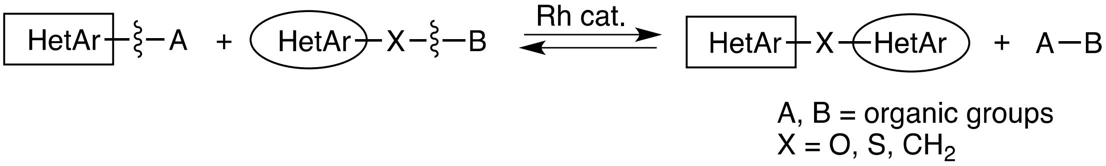
Scheme 1. Synthesis of unsymmetric Ar–X–Ar’ and HetAr–X–Ar compounds

In contrast, only a few examples of synthesized unsymmetric HetAr–X–HetAr’ compounds, in which two different heteroarenes are connected by a one-atom linker, has been reported. The lack of such compounds was ascribed to diverse reactivities of heteroaryl compounds depending on their structure.

The reactivity of heteroaryl halides is significantly affected by their heteroaryl structure. For example, 2- and 4-pyridyl halides are more reactive in substitution reactions than 3-pyridyl halides. Electron-rich heteroarenes such as furyl and thienyl halides are generally less reactive than electron-defficient pyridyl halides.

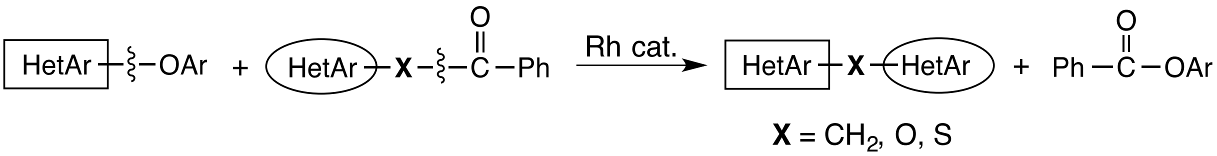
Significant differences in reactivity also appear for metal heteroaryloxide and heteroarylamide reagents depending on their heteroaryl structure. Heteroaryl compounds have diverse acidities, and reaction of their conjugate base should also be diverse, as shown by, for example, the O–H proton of 3-hydroxypyridine (pKa 15.7), and the N–H protons of 2-pyridone (pKa 17.0), 4-pyridone (pKa 14.8), pyrrole (pKa 23.0), diazole derivatives (pKa 18-20), triazole derivatives (pKa 14-15), and indole (pKa 21.0).[6] Reactivity differences depending on the position of heteroatoms in heteroarenes complicate the reaction, and the reaction sites can change depending on the substrate and reaction conditions. For example, metalated 4-hydroxypyridine and 4-pyridone are tautomers, and both their nitrogen and oxygen atoms can react.[7] The availability of heteroaryl components is limited, for example, pyridylmethyl bromide can be stored only as a hydrobromide salt; otherwise, polymerization occurs. The solubility of metal heteroaryloxides and heteroarylamides in organic solvents is generally low and highly depends on the heteroaryl structure, which makes the reaction heterogeneous and complex. Metalated heteroaryl reagents are often not stable. For example, pyridyllithium is unstable above -30 °C and thus is used at -78 °C.[8] Lithium tri(2-oxazolyl)magnasate and lithium tri(2-benzoxazolyl)magnesate rapidly and completely isomerize to lithium 2-(isocyano)enolate and lithium 2-(isocyano)phenolate, respectively.[9] Such difficulties in the synthesis of unsymmetric HetAr–X–HetAr’ compounds are associated with the use of metal reagents and metal bases.

Thus, a synthetic method for unsymmetric HetAr–X–HetAr' compounds utilizing covalent bond exchange involving cleavage and exchange reactions between two organoheteroaryl compounds, which does not use metal reagents or metal bases, is considered attractive (Scheme 2). Such a method is expected to have broad substrate applicabilities, in which reactivities are relatively unaffected by the structures of heteroarenes. The method, however, needs to realize the catalytic cleavage and exchange between two heteroaryl groups, which are not highly reactive. In addition, the relative thermodynamic stabilities of the substrates **S** and products **P** need to be considered in order to obtain a high chemical yield and a reasonable reaction rate. Transition metal catalysis and equilibrium control should also be developed.



Scheme 2. Synthesis of unsymmetric HetAr–X–HetAr' compounds by exchange reaction

As part of our study to develop synthetic methods for organoheteroatom compounds, transition-metal catalysis was developed, which was shown effective for the transformation of organoheteroatom compounds. Various rhodium-catalyzed reactions involving the formation, cleavage, exchange, and rearrangement of C–H, C–S, C–P, C–F, C–N, S–S, P–P, and P–S bonds were developed.[10] These reactions do not require metal reagents or metal bases and can achieve equilibrium, which is controlled by the relative thermodynamic stability of the substrates **S** and products **P**. In this article, rhodium-catalyzed heteroaryl exchange reactions between heteroaryl aryl ethers and heteroaryl reagents were employed for the synthesis of unsymmetric HetAr–X–HetAr' compounds (Scheme 3).[11-13] Various unsymmetric HetAr–X–HetAr' compounds containing five- and six-membered heteroarenes were effectively obtained, using stable and readily available substrates.



Scheme 3. Rhodium-catalyzed heteroaryl exchange for the synthesis of unsymmetric HetAr–X–HetAr' compounds

3. EQUILIBRIUM CONTROL

A catalyst changes the course of a reaction without affecting the relative thermodynamic stability of the substrates **S** and products **P**. The reaction must be exergonic, i.e., an energetically downhill reaction, to obtain a high product yield and a reasonable reaction rate. The synthesis of unsymmetric HetAr–X–HetAr' compounds by the exchange reaction of two heteroaryl compounds often provides an equilibrium mixture, because the relative thermodynamic stabilities of the substrates **S** and products **P** are close (Scheme 2). In order to obtain a product at a high yield, it is necessary to control the equilibrium and develop an exothermic reaction. [See reference 14 for detailed discussions on this subject.]

The development of a judicious combination of the organic co-substrate/organic co-product **S'**/**P'** was considered. The equilibrium between **S** and **P** can be shifted to **P** in the presence of **S'** forming **P'**, when the relative thermodynamic stability of the **P**/**P'** system is higher than that of the **S**/**S'** system (Figure 7). A related concept termed coupled reactions using ATP is employed in biology. The advantage of the organic co-substrate/co-product **S'**/**P'** method is that the reaction can be tuned using various combinations of **S'** and **P'**. In this article, unsymmetric HetAr–X–HetAr' compounds were synthesized using judicious combinations of the substrates **S** and organic co-substrates **S'**: An exothermic reaction is developed, and equilibrium is shifted to the desired product **P**. This is a novel methodology for the catalytic synthesis of unsymmetric HetAr–X–HetAr' compounds in an energy-saving manner. Compared with conventional synthesis involving nucleophilic substitution reactions, reactions are relatively insensitive to heteroarene structures, and the reactions have broad applicability.

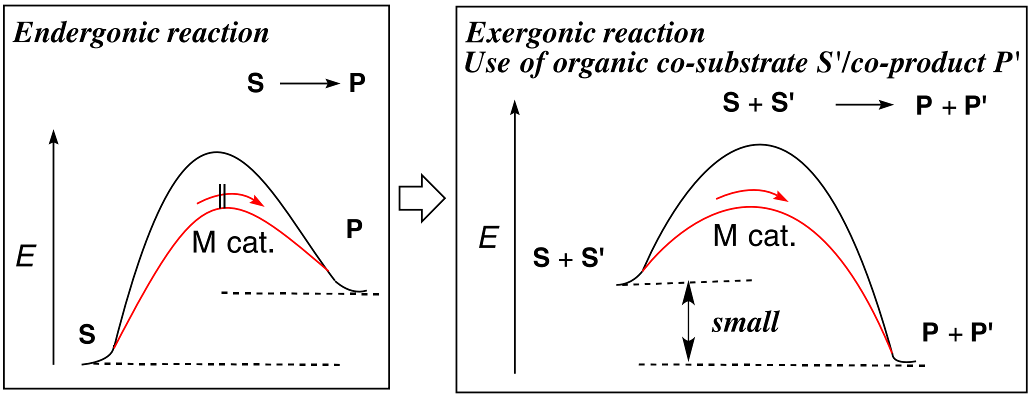


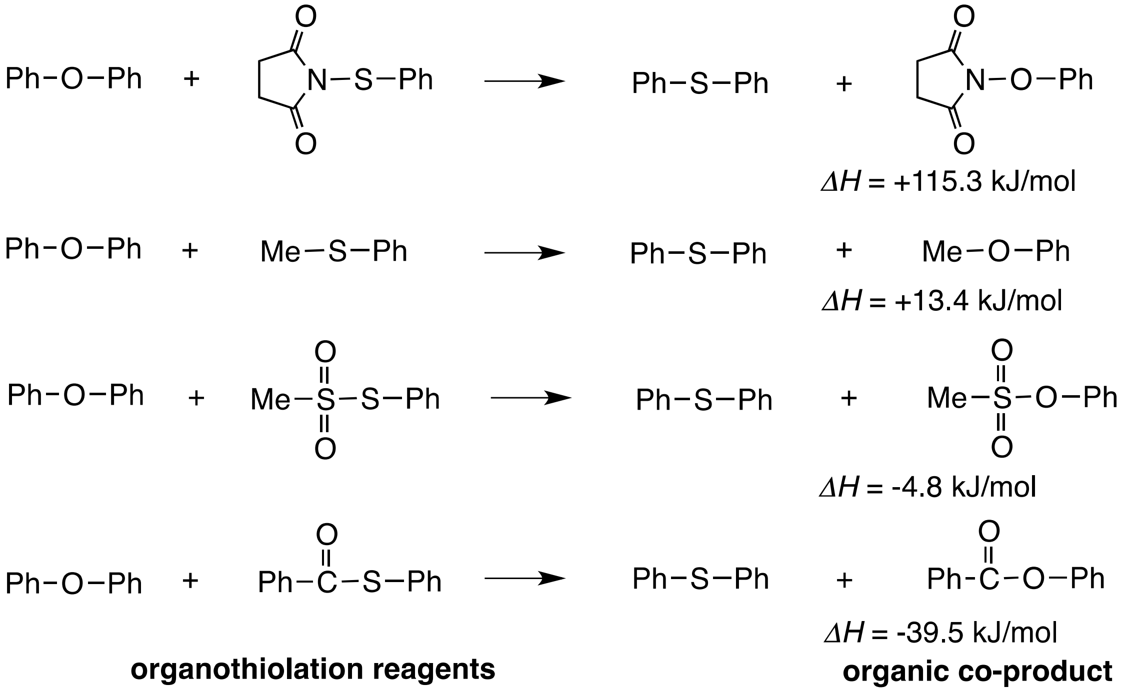
Figure 7. Equilibrium control by use of organic co-substrate **S'**/co-product **P'**

4. SYNTHESIS OF UNSYMMETRIC HetAr–X–HetAr' COMPOUNDS

4-1. SYNTHESIS OF UNSYMMETRIC DI(HETEROARYL) SULFIDES

The reported synthesis of unsymmetric di(heteroayl) sulfides, that is, HetAr–S–HetAr' compounds, has been conducted using heteroaryl halides and heteroarylthiols in the presence of stoichiometric amounts of bases by a classical aromatic nucleophilic substitution reaction[15] or copper- and palladium-catalyzed substitution reactions.[16] In most cases, pyridyl halides and pyridinethiolates have been used, and the synthesized unsymmetric HetAr–S–HetAr' compounds have been limited to pyridyl derivatives.

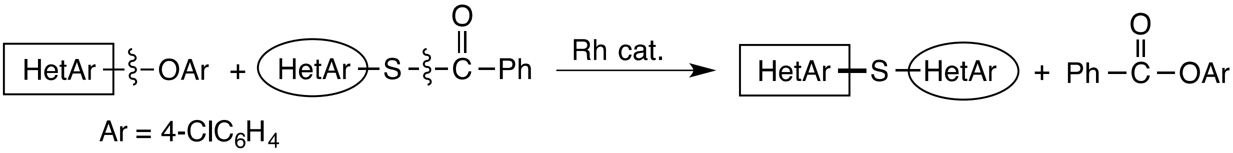
A rhodium-catalyzed heteroaryl exchange reaction for the synthesis of unsymmetric HetAr–S–HetAr' compounds using judicious combinations of substrates and organic co-substrates was developed by our group.[14] The relative thermodynamic stabilities of the substrates and products were tuned, and exothermic reactions were developed to shift the equilibrium to the desired products. The reactions of diphenyl ether and different phenylthiolating reagents are examined as a model by preliminary DFT calculations (Scheme 4). The reaction of diphenyl ether and *S*-phenyl thiobenzoate to form diphenyl sulfide and phenyl benzoate is exothermic (-39.5 kJ/mol),[17] and more exothermic than the reaction of diphenyl ether and *S*-phenyl methanthiosulfonate giving diphenyl sulfide and *O*-phenyl methansulfonate (-4.8 kJ/mol). The reaction of diphenyl ether and thioanisole to give diphenyl sulfide and anisole (+13.4 kJ/mol) and the reaction of diphenyl ether and *N*-(phenylthio)succinimide to give diphenyl sulfide and *N*-(phenoxy)succinimide (+115.3 kJ/mol) are both endothermic. The analysis suggests that unsymmetric HetAr–S–HetAr' compounds could be synthesized without using metal reagents or metal bases by the judicious design of organic substrates.[11]



Scheme 4. Design of organothiolation reagents

Accordingly, unsymmetric HetAr–S–HetAr' compounds are obtained by the rhodium-catalyzed heteroaryl exchange reaction of heteroaryl aryl ethers HetAr–O–Ar and *S*-(heteroaryl) thiobenzoates

PhC(O)–SHetAr' (Scheme 5). The compounds are synthesized using neutral and stable organic substrates, which are applied to various five- and six-membered heteroarenes. Esters are formed as the organic co-products, which can easily be recovered and used for other purposes.

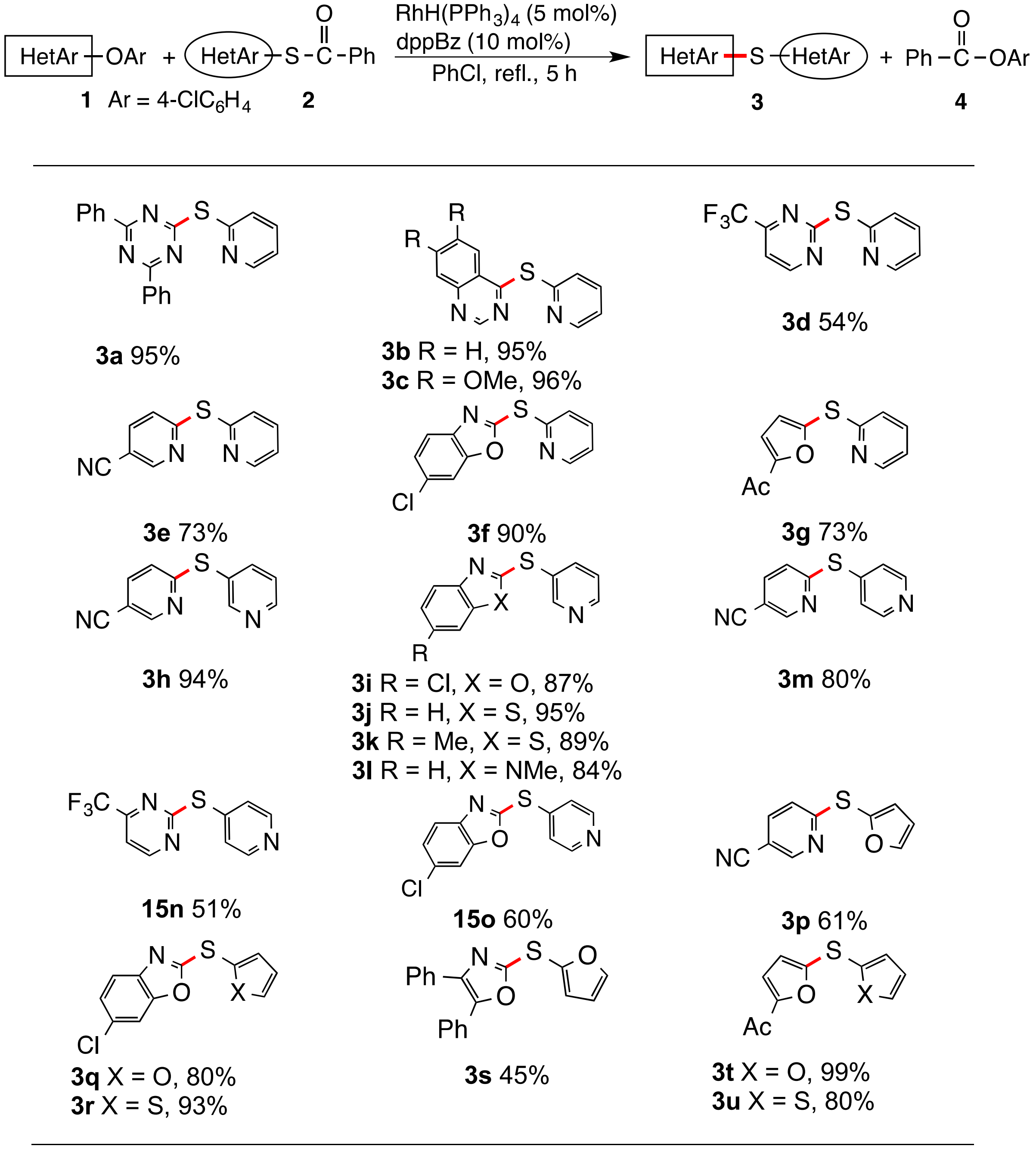


Scheme 5. Rhodium-catalyzed synthesis of unsymmetric HetAr–S–HetAr' compounds

When 4,6-diphenyl-2-(4-chlorophenoxy)triazine **1a** was reacted with *S*-(2-pyridyl) benzothioate **2** (1 equiv.) in the presence of $RhH(PPh_3)_4$ (5 mol%) and dppBz (10 mol%) in refluxing chlorobenzene for 5 h, 2,4-diphenyl-6-(2-pyridinylthio)-1,3,5-triazine **3a** (95%) and 4-chlorophenyl benzoate **4** (98%) were obtained (Table 1, **3a**). The reaction of six-membered heteroaryl aryl ethers and *S*-(heteroaryl) benzothioates proceeded in high yields. The heteroaryl 4-chlorophenyl ethers containing 2-triazyl, 4-quinazolinyl, 2-pyrimidyl, and 2-pyridyl groups reacted with *S*-(2-pyridyl) benzothioate, and the corresponding heteroaryl 2-pyridyl sulfides **3a**–**3e** were obtained in high yields. The reaction of benzoxazolyl and 1-[5-(4-chlorophenoxy)-2-furanyl]ethanone with *S*-(2-pyridyl) benzothioate also gave the corresponding sulfides containing five-membered heteroarenes, **3f** and **3g**. The reaction of *S*-(3-pyridyl) and *S*-(4-pyridyl) benzoates gave the 4-pyridyl and 3-pyridyl derivatives **3h**–**3o**. *S*-(2-Furyl) and *S*-(2-thienyl) benzothioates reacted with heteroaryl 4-chlorophenyl ethers to give the heteroaryl sulfides **3p**–**3u** in high yields. This is a novel catalytic procedure for the synthesis of diverse unsymmetric HetAr–S–HetAr' compounds from readily available heteroaryl aryl ethers. All the unsymmetric HetAr–S–HetAr' compounds shown in Table 1 except **3d** are new compounds.

Diverse unsymmetric HetAr–S–HetAr' compounds containing five- and six-membered heteroarenes were obtained in high yields by a rhodium-catalyzed heteroaryl exchange reaction. The use of a *S*-(heteroaryl)thioester as a heteroarylthiolating reagent enabled the synthesis of unsymmetric HetAr–S–HetAr' compounds by controlling equilibrium. Studies of the biological activities of unsymmetric HetAr–S–HetAr' compounds are under way.

Table 1. Rhodium-catalyzed synthesis of unsymmetric HetAr–S–HetAr' compounds[a]



3a 95%

3b R = H, 95%
3c R = OMe, 96%

3d 54%

3e 73%

3f 90%

3g 73%

3h 94%

3i R = Cl, X = O, 87%
3j R = H, X = S, 95%
3k R = Me, X = S, 89%
3l R = H, X = NMe, 84%

3m 80%

15n 51%

15o 60%

3p 61%

3q X = O, 80%
3r X = S, 93%

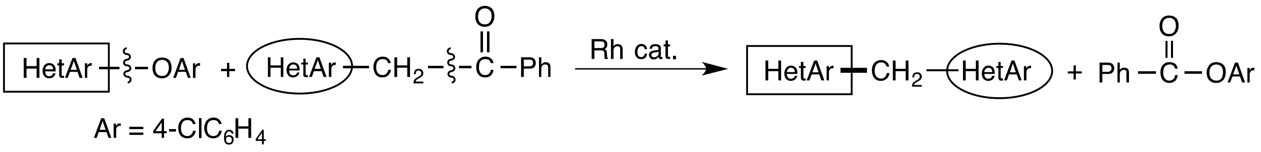
3s 45%

3t X = O, 99%
3u X = S, 80%

[a] The C–S bonds formed by the reaction are shown in red.

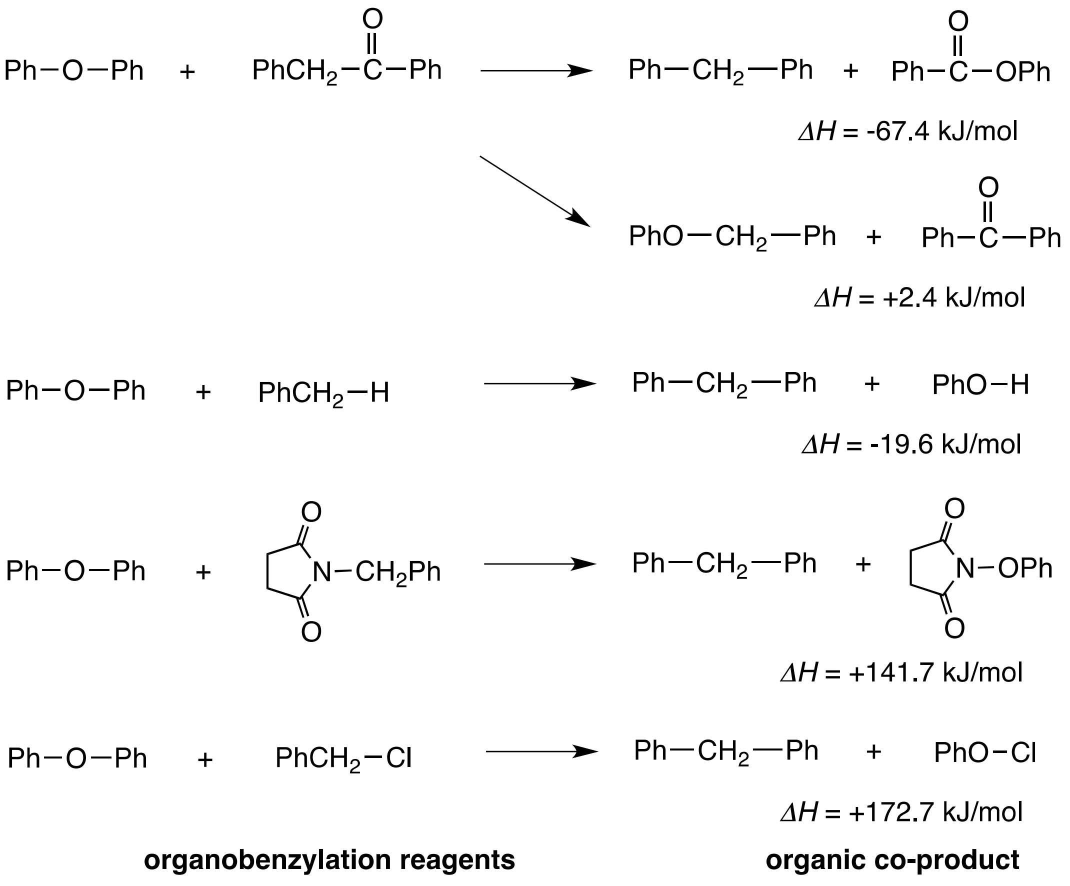
4-2. SYNTHESIS OF UNSYMMETRIC DI(HETEROARYL)METHANES

The reported synthesis of unsymmetric diarylmethanes, i.e., Ar–CH_2–Ar' compounds, involved the reaction of arylmethylmetal reagents and aryl halides, and, alternatively, that of arylmethyl halides and metalated arenes.[18] Both reactions provided HetAr–CH_2–Ar compounds,[19] but only very few unsymmetric HetAr–CH_2–HetAr' compounds.[20] The limited scope is likely due to the limited availability of metalated components.



Scheme 6. Rhodium-catalyzed synthesis of unsymmetric HetAr–CH$_2$–HetAr’ compounds

Unsymmetric HetAr–CH$_2$–HetAr’ compounds were synthesized by a rhodium-catalyzed heteroaryl exchange reaction of heteroaryl aryl ethers and heteroarylmethyl ketones (Scheme 6). In order to design an appropriate combination of substrates and co-substrates, the reactions of diphenyl ether and different benzylating reagents were examined by preliminary DFT calculations.

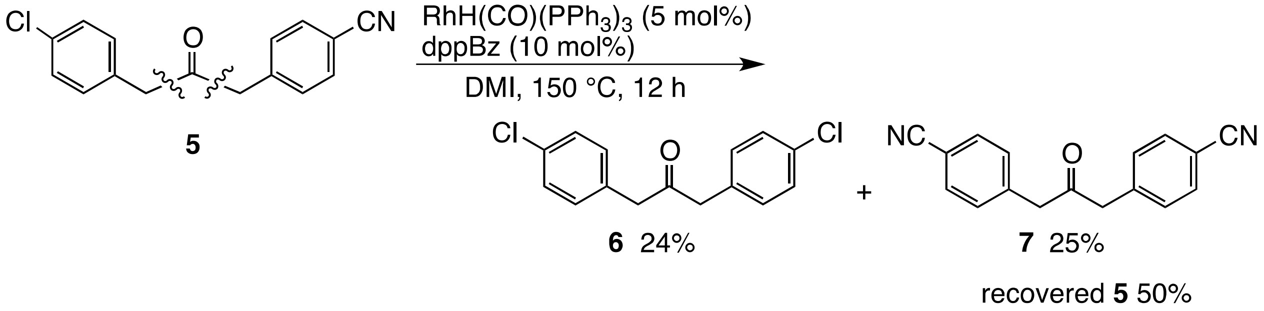


Scheme 7. Design of organomethylation reagents

The reaction of diphenyl ether and phenyl benzyl ketone to form diphenylmethane and phenyl benzoate is considerably exothermic (-67.4 kJ/mol) (Scheme 7).[17] Another reaction to form phenyl benzyl ether and benzophenone is endothermic (+2.4 kJ/mol) and unlikely to occur. The former reaction is more exothermic than the reaction of diphenyl ether and toluene giving diphenyl methane and phenol (-19.6

kJ/mol). The following reactions are endothermic: the reaction of diphenyl ether and *N*-(benzyl)succinimide to give diphenylmethane and *N*-(phenoxy)succinimide (+141.7 kJ/mol); the reaction of diphenyl ether and benzyl chloride to give diphenylmethane and phenoxy chloride (+172.7 kJ/mol). The analysis suggests that diphenylmethane can be synthesized from diphenyl ether and phenyl benzyl ketone. Accordingly, unsymmetric HetAr–CH_2–HetAr' compounds were obtained by the reaction of heteroaryl aryl ethers and phenyl heteroarylmethyl ketones.

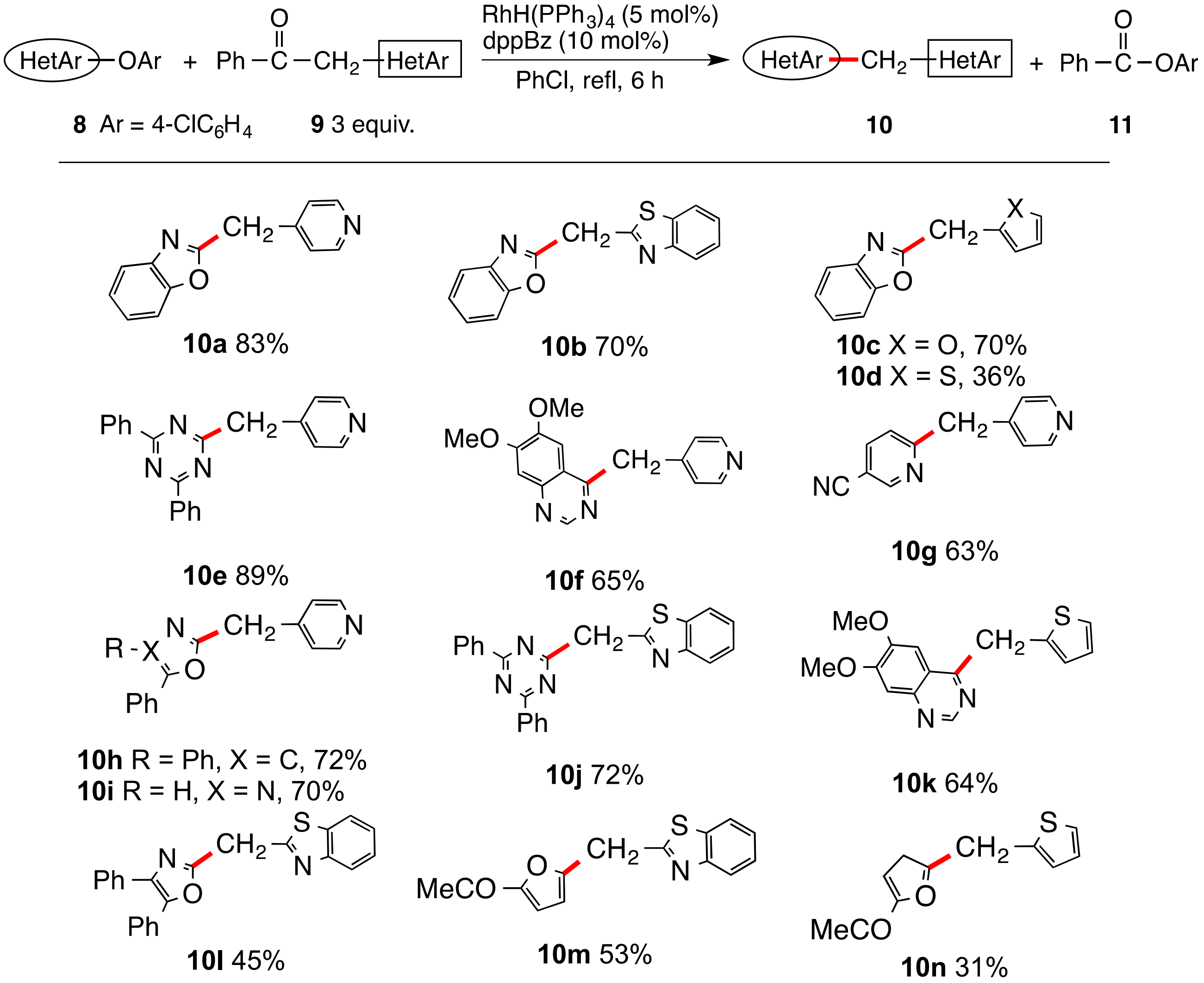
It was initially determined that a rhodium catalyst can cleave the C(O)–C bond of di(benzyl) ketones.[21] When 1-(4-chlorophenyl)-3-(4-cyanophenyl)propane-2-one **5** was reacted in the presence of $RhH(CO)(PPh_3)_3$ (5 mol%) and dppe (10 mol%) in *N,N'*-dimethylimidazolidinone (DMI) for 12 h, 1,3-bis(4-chlorophenyl)propane-2-one **6** (24%) and 1,3-bis(4-cyanophenyl)propane-2-one **7** (25%) were obtained with the recovery of **5** (50%) (Scheme 8). The rhodium complex cleaved the CO–C bond of **5** and transferred the (4-chlorophenyl)acetyl group to another **5** intermolecularly. On the basis of the results of the study, the rhodium-catalyzed synthesis of unsymmetric HetAr–X–HetAr' compounds was developed by the reaction of aryl heteroaryl ethers and heteroarylmethyl ketones.



Scheme 8. Rhodium-catalyzed cleavage and exchange reaction of di(benzyl) ketone CO–C bond

When 2-(4-chlorophenoxy)benzoxazole **8a** was reacted with 4-pyridylmethyl phenyl ketone (3 equiv.) in the presence of $RhH(PPh_3)_4$ (10 mol%) and 1,2-bis(diphenylphosphino)benzene (dppBz, 20 mol%) in refluxing chlorobenzene for 6 h, 2-benzoxazolyl-4-pyridylmethane **10a** and 4-chlorophenyl benzoate **11** were obtained in 83% and 78% yields, respectively (Table 2, **10a**). Ether **8a** reacted with benzothiazolylmethyl, furylmethyl, and thienylmethyl phenyl ketones to form unsymmetric HetAr–CH_2–HetAr' compounds **10b**–**10d**. A wide range of electron-deficient/electron-rich five/six-membered heteroaryl ethers **8** such as 2-benzoxazolyl, 2-benzothiazolyl, 2-thiazolyl, 2-oxazolyl, 2-thienyl, 2-furyl, 2-pyridyl, 4-quinazolinyl, and 2-triazyl derivatives were efficiently employed. The broad scope of this reaction is due to the use of stable substrates for both heteroaryl aryl ethers and heteroarylmethyl ketones. The unsymmetric HetAr–CH_2–HetAr' compounds shown in Table 2 except **10a**, **10b**, **10d**, and **10g** are new compounds.

Table 2. Rhodium-catalyzed synthesis of unsymmetric HetAr–CH2–HetAr’ compounds[a]



8 Ar = 4-ClC_6H_4 **9** 3 equiv. **10** **11**

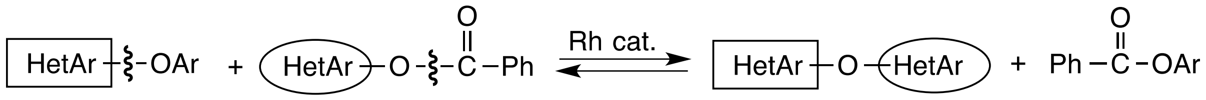
10a 83%
10b 70%
10c X = O, 70%
10d X = S, 36%
10e 89%
10f 65%
10g 63%
10h R = Ph, X = C, 72%
10i R = H, X = N, 70%
10j 72%
10k 64%
10l 45%
10m 53%
10n 31%

[a] The C–C bonds formed by the reaction are shown in red.

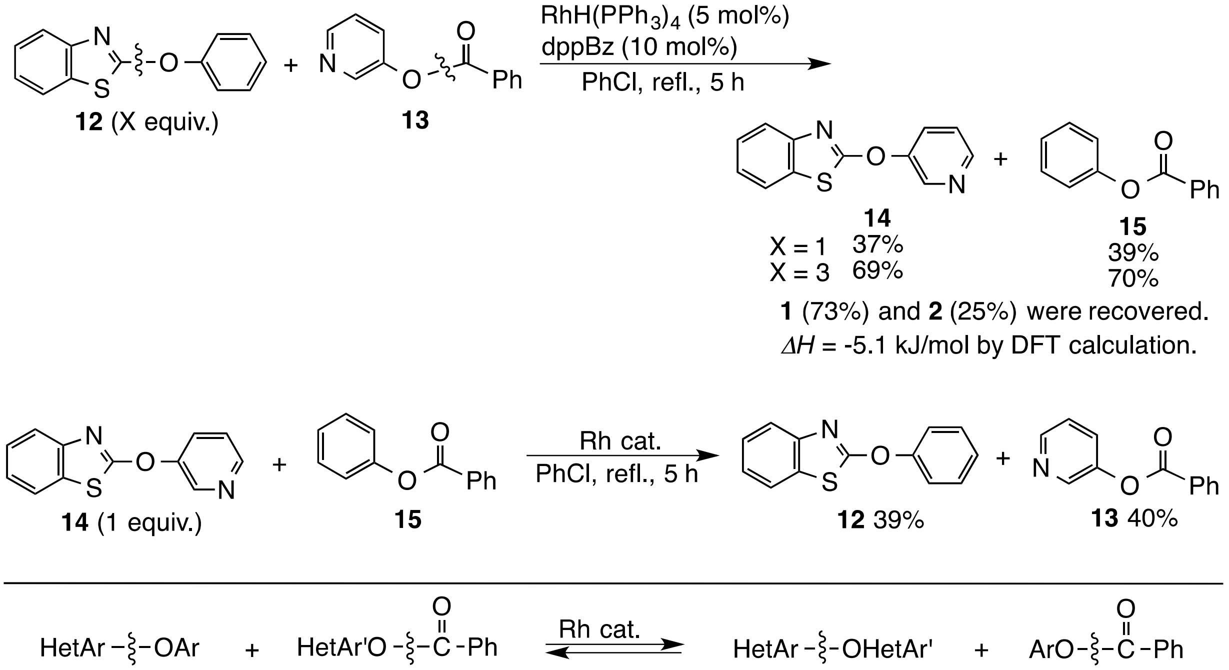
Unsymmetric HetAr–CH2–HetAr’ compounds are synthesized by the rhodium-catalyzed reaction of heteroaryl ethers and heteroarylmethyl ketones, which is applied to various six- and five-membered heteroarenes. Unlike conventional methods, this method allows for the cleavage and formation of the C–C bond without requiring the use of metal reagents or metal bases. The utilization of heteroarylmethyl ketone as a heteroarylation reagent has led to the construction of a system thermodynamically favorable for forming unsymmetric HetAr–CH2–HetAr’ compounds.

4-3. SYNTHESIS OF UNSYMMETRIC DI(HETEROARYL) ETHERS

The reported synthesis of unsymmetric diheteroaryl ethers, i.e., HetAr–O–HetAr’ compounds, has a quite limited scope of the heteroaryl moiety, and only several di(pyridyl) ethers have been synthesized by the classical nucleophilic aromatic substitution of pyridyl halides and hydroxypyridines in the presence of stoichiometric amounts of metal bases,[22] which in some cases employ metal catalysis.[23] On the basis of the results of the synthesis of unsymmetric HetAr–S–HetAr' and HetAr–CH_2–HetAr' compounds described above, unsymmetric HetAr–O–HetAr' compounds were synthesized from heteroaryl aryl ethers and hetroaryl benzoate. The relative thermodynamic stabilities of the substrates and products are comparable in this reaction, and, in order to increase the chemical yield of unsymmetric HetAr–O–HetAr' compounds, an excess amount of a substrate is used in accordance with Le Chatelier's principle (Scheme 9).



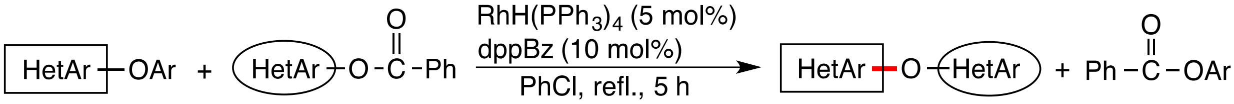
Scheme 9. Rhodium-catalyzed synthesis of unsymmetric HetAr–O–HetAr' compounds



Scheme 10. Rhodium-catalyzed equilibrium etherification

When 2-phenoxybenzothiazole **12** (3 equiv.) was reacted with 3-pyridyl benzoate **13** in the presence of $RhH(PPh_3)_4$ (5 mol%) and dppBz (10 mol%) in refluxing chlorobenzene for 5 h, 2-(3-pyridyloxy)benzothiazole **14** (69%) and phenyl benzoate **15** (70%) were obtained with the recovery of **12** (73%) and **13** (25%) (Scheme 10). When the molar ratio **12**/**13** was changed from 3 to 1, the yields of **14** and **15** decreased to 37% and 39%, respectively. The reverse reaction of **14** and **15** under the same reaction conditions gave **12** and **13** in 39% and 40% yields, respectively, which indicated the equilibrium nature of the reaction. In order to increase the chemical yield of **14**, an excess amount of **12** (3 equiv.) was used. The heteroaryl group of heteroaryl benzoate was transferred to the heteroaryl aryl ethers by rhodium catalysis via the HetArO–COPh bond cleavage.

Table 3. Rhodium-catalyzed synthesis of unsymmetric HetAr–O–HetAr' compounds[a]

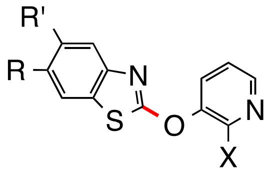


16 3 equiv.
Ar = 4-ClC$_6$H$_4$

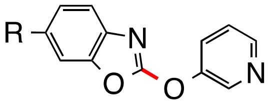
17

18

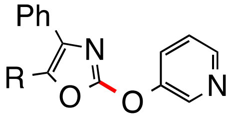
19



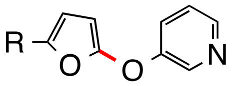
18a R = MeO, R' = X = H, 60%
18b R = R' = MeO, X = H, 64%
18c R = R' = H, X = Cl, 21%



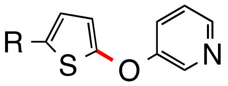
18d R =H, 47%
18e R = Cl, 70%
18f R = Me, 53%



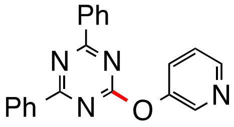
18g R = Ph, 75%
18h R = H, 52%



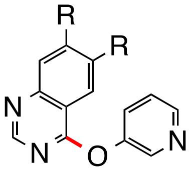
18i R = CN, 58%
18j R = MeCO, 73%



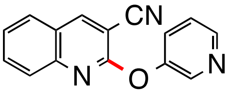
18k R = PhCO, 50%



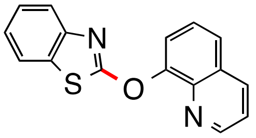
18l 54%[b]



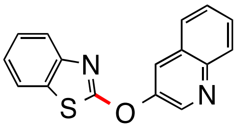
18m R = H, 68%
18n R = MeO, 78%



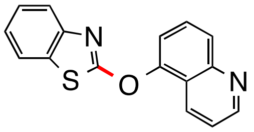
18o 72%[b]



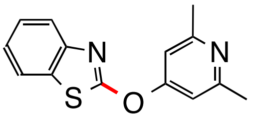
18p 69%



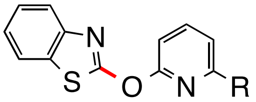
18q 66%



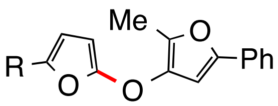
18r 63%



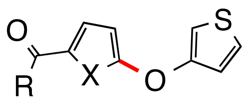
18s 75%



18t R = Ph, 77%
18u R = Cl, 6%, 23%[c]



18v R = MeCO, 72%
18w R = CN, 52%



18x R = Me, X = O, 49%
18y R = Ph, X = S, 43%

[a] The C–O bonds formed by the reaction are shown in red. [b] **16** (1 eq.) and **17** (3 eq.) were reacted.
[c] RhH(PPh$_3$)$_4$ (20 mol%) and dppBz (40 mol%) were used.

Various unsymmetric HetAr–O–HetAr' compounds were synthesized by the heteroaryl exchange reaction of heteroaryl aryl ethers and heteroaryl benzoates (Table 3). Heteroaryl 4-chlorophenyl ethers containing five-membered heteroarenes such as 1,3-benzothiazolyl, 1,3-benzoxazolyl, 1,3-oxazolyl, 2-furyl, and

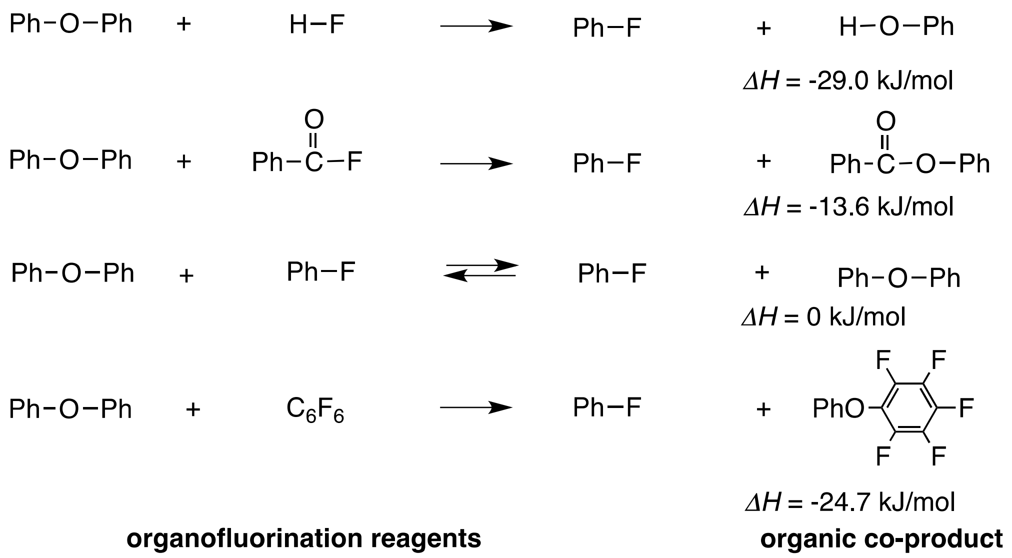
2-thienyl groups reacted with 3-pyridyl benzoate **13**, and the corresponding heteroaryl 3-pyridyl ethers **14** and **18a**–**18k** were obtained. Six-membered heteroaryl 4-chlorophenyl ethers with 2-triazyl, 4-quinazolinyl, and 3-quinolinyl groups were also converted to the HetAr–O–HetAr' compounds **18l**–**18o**. The reaction of 3-quinolinyl, 5-quinolinyl, and 8-quinolinyl benzoates with 2-(4-chlorophenoxy)benzothiazole gave the corresponding benzothiazolyl quinolinyl ethers **18p**–**18r** in high yield. The use of 4-pyridyl and 2-pyridyl benzoate derivatives yielded unsymmetric benzothiazolyl 2- and 4-pyridyl ethers **18s**–**18u** without isomerization to *N*-heteroaryl pyridones.[7] Unsymmetric five-membered HetAr–O–HetAr' compounds containing 2-furyl and 2-thienyl groups **18v**–**18y** were also obtained. All the resulting unsymmetric HetAr–O–HetAr' compounds except **18l** are new compounds.

Unsymmetric HetAr–O–HetAr' compounds were synthesized from heteroaryl aryl ethers and heteroaryl benzoates by a rhodium-catalyzed heteroaryl exchange reaction. Diverse unsymmetric HetAr–O–HetAr' compounds containing five- and six-membered heteroarenes were obtained in high yields. The rhodium-catalyzed heteroaryl exchange reaction has a broad applicability, which is not significantly affected by the reactivities of the heteroaryl moiety.

4-4. SYNTHESIS OF HETEROARYL FLUORIDES

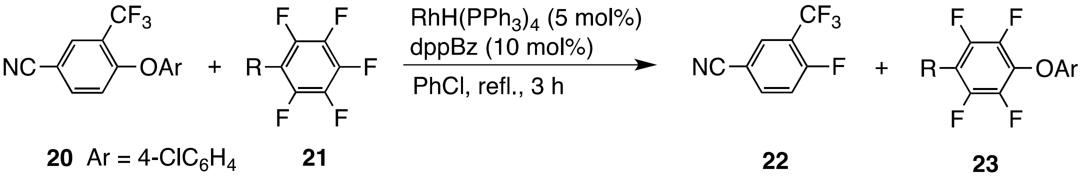
Heteroaryl fluorides, which are HetAr–F compounds, are important as drugs owing to their unique biological activity derived from the unique properties of fluorine.[24] In general, C–F bond formation utilizes nucleophilic metal fluoride reagents[25] or reactive electrophilic fluorinating reagents.[25a,26] In relation to the development of HetAr–X–HetAr' compounds described above, heteroaryl fluorides HetAr–F were synthesized from heteroaryl aryl ethers using a rhodium-catalyzed heteroaryl exchange reaction, which utilized a stable organic fluorinating reagent.[27]

Thermodynamic analysis by preliminary DFT calculations showed that the reaction of diphenyl ether and hydrogen fluoride to form fluorobenzene and phenol is exothermic (-29.0 kJ/mol) (Scheme 11).[17] Hydrogen fluoride, however, is not easy to handle, and organic fluorides were examined as a fluorinating reagent. The reaction of diphenyl ether and benzoyl fluoride to form fluorobenzene and phenyl benzoate is slightly exothermic (-13.6 kJ/mol). Although the reaction of diphenyl ether and fluorobenzene achieves equilibrium (0 kJ/mol), the reaction of diphenyl ether and hexafluorobenzene to give fluorobenzene and phenoxypentafluorobenzene is exothermic (-24.7 kJ/mol). The analysis results suggest that polyfluorobenzenes are efficient organic fluorinating reagents.



Scheme 11. Design of organofluorination reagents

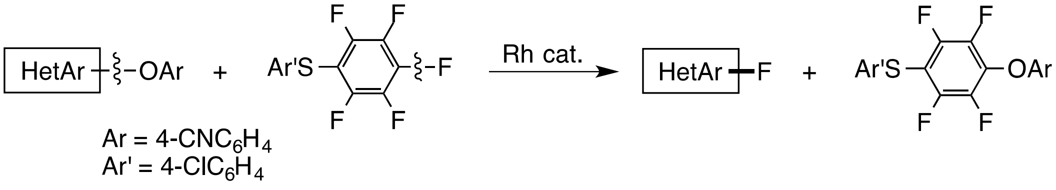
Initially, the fluorination of 4-(4-chlorophenoxy)-2-trifluoromethylbenzonitrile was examined using hexafluorobenzene. When 4-(4-chlorophenoxy)-3-trifluoromethylbenzonitrile **20** was reacted with hexafluorobenzene **21a** (10 equiv.) in the presence of $RhH(PPh_3)_4$ (10 mol%) and dppBz (20 mol%) in refluxing chlorobenzene for 3 h, 4-fluoro-3-trifluoromethylbenzonitrile **22** (47%) and 1,4-bis(4-cyanophenoxy)-2,3,5,6-tetrafluorobenzene **23** (44%) were obtained (Scheme 12). The product yield decreased to 10%, when the amount of **21a** was decreased to 1 equiv, owing to the volatile (bp 81 °C) nature of hexafluorobenzene. Substituted pentafluorobenzenes were used as fluorinating reagents. A higher yield of **22** was obtained when using (4-chlorophenylthio)pentafluorobenzene **21d** (68%) than when using (4-tolyloxy)pentafluorobenzene **21b** (38%) and benzoyl pentafluorobenzene **21c** (42%). On the basis of our results, the reaction of heteroaryl aryl ether and **21d** was employed for the synthesis of heteroaryl fluorides (Scheme 13).



R =	22	23
F (**a**, 10 equiv.)	47%	44%[a]
F (**a**, 1 equiv.)	10%	8%[a]
4-TolO (**b**)	38%	29%[b]
PhCO (**c**)	42%	42%
$4\text{-}ClC_6H_4S$ (**d**, 1 equiv.)	68%	58%
$4\text{-}ClC_6H_4S$ (**d**, 2 equiv.)	84%	83%

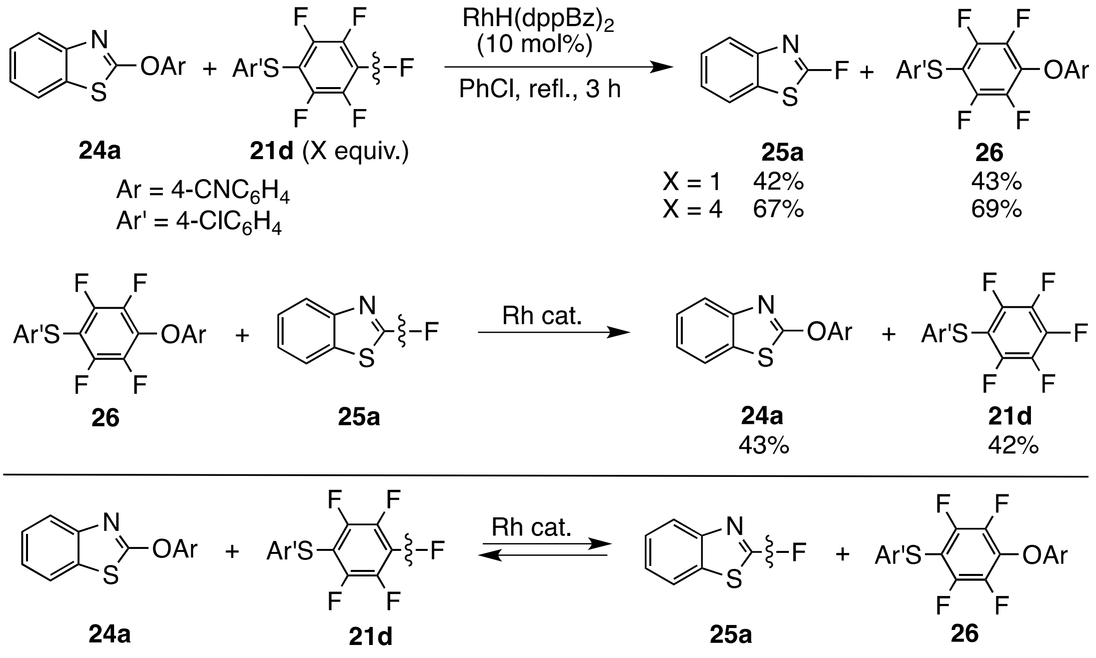
[a] 1,4-bis(4-chlorophenoxy)-2,3,5,6-tetrafluorobenzene was formed.
[b] *p*-isomer:*m*-isomer = 1:5

Scheme 12. Rhodium-catalyzed fluorination of diaryl ether



Scheme 13. Rhodium-catalyzed synthesis of HetAr–F compounds

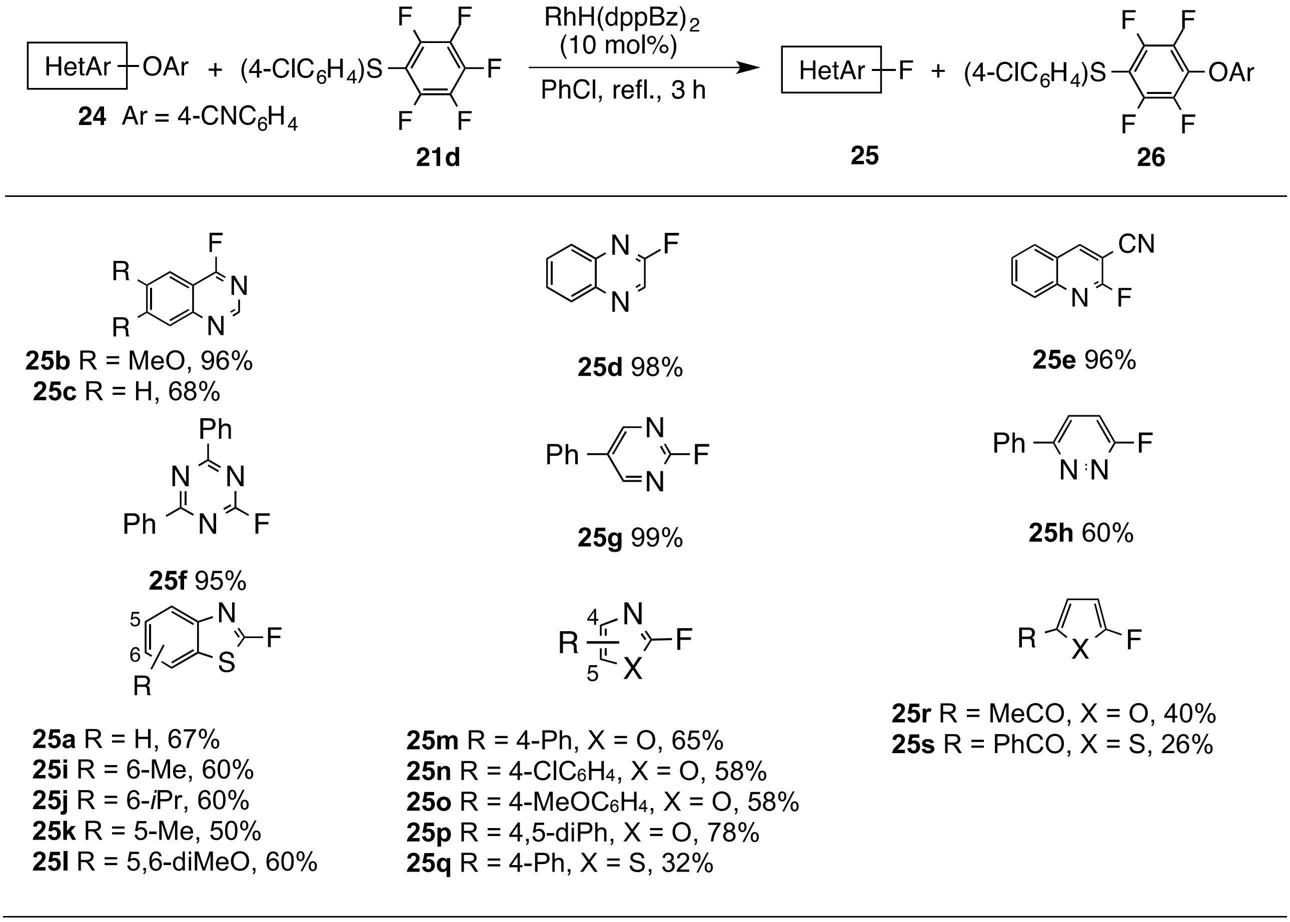
When 4-(2-benzothiazolyloxy)benzointrile **24a** was reacted with **21d** (1 equiv.) in the presence of RhH(dppBz)$_2$ (10 mol%, dppBz = 1,2-bis(diphenylphosphino)benzene) in refluxing chlorobenzene for 3 h, 2-fluorobenzothiazole **25a** (42%) and 1-(4-chlorophenylthio)-4-(4-cyanophenoxy)-2,3,5,6-tetrafluorobenzene **26** (43%) were obtained with recovery yields of **24a** (40%) and **21d** (42%) (Scheme 14). The reverse reaction of **25a** and **26** under the same conditions gave **24a** and **21d** in 43% and 42% yields, respectively. When the molar ratio of **21d** to **24a** was changed from 1 to 4, the yield of **25a** increased to 67%, which was consistent with the reaction being in equilibrium. Although the above calculations suggested a somewhat exothermic nature of the fluorination reaction using hexafluorobenzene, the experimental results indicated the equilibrium nature of the reaction.



Scheme 14. Rhodium-catalyzed equilibrium fluorination

The fluorination of six-membered heteroaryl aryl ethers using **21d** (2 equiv.) proceeded in high yields. Heteroaryl 4-cyanophenoxy ethers containing 4-quinazolinyl, 2-quinoxalinyl, 2-quinolinyl, 2-triazyl, 2-pyrimidyl, and 3-pyridazyl groups reacted with **2**, and the corresponding heteroaryl fluorides **25b**–**25h** were obtained in quantitative yields. The fluorination of various five-membered heteroaryl aryl ethers containing benzothiazolyl, oxazolyl, thiazolyl, furyl, and thienyl ethers **25a**, **25i**–**25s** occurred using **21d** (4 equiv.) (Table 4).

Table 4. Rhodium-catalyzed synthesis of HetAr–F compounds



25b R = MeO, 96%
25c R = H, 68%

25d 98%

25e 96%

25f 95%

25g 99%

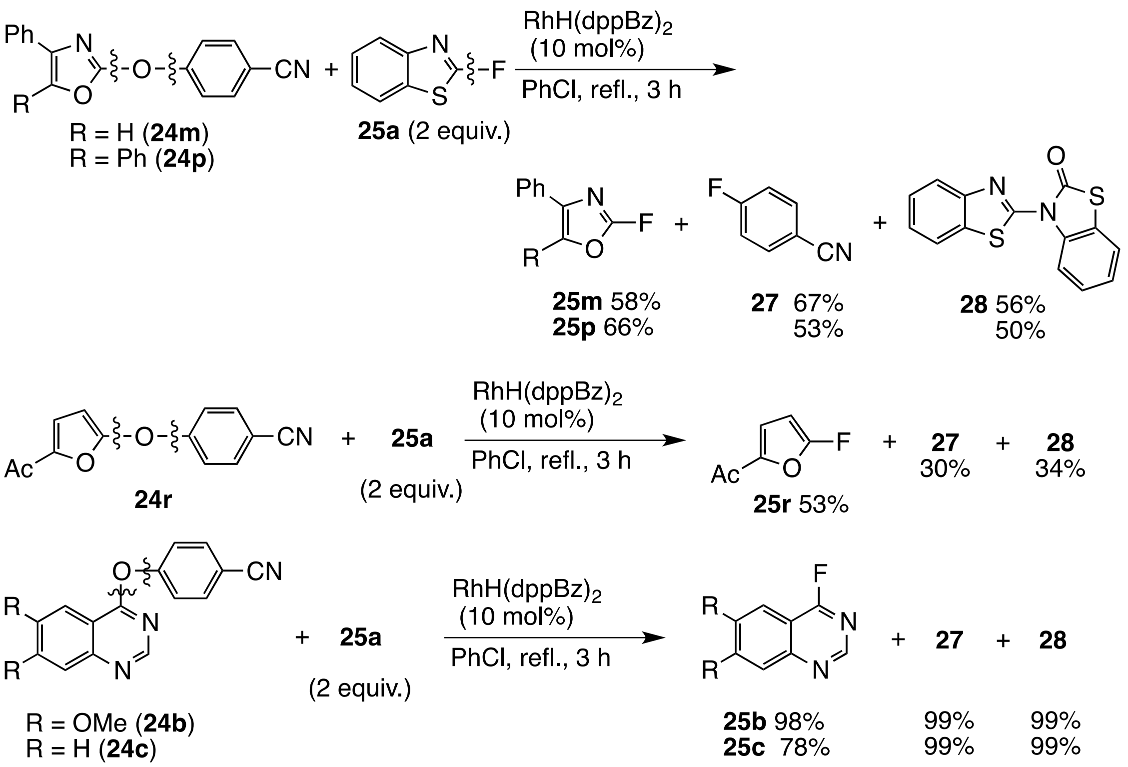
25h 60%

25a R = H, 67%
25i R = 6-Me, 60%
25j R = 6-*i*Pr, 60%
25k R = 5-Me, 50%
25l R = 5,6-diMeO, 60%

25m R = 4-Ph, X = O, 65%
25n R = 4-ClC$_6$H$_4$, X = O, 58%
25o R = 4-MeOC$_6$H$_4$, X = O, 58%
25p R = 4,5-diPh, X = O, 78%
25q R = 4-Ph, X = S, 32%

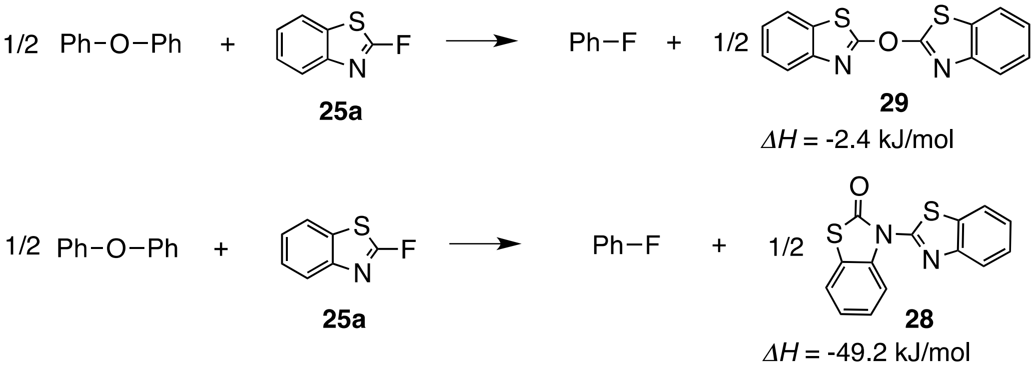
25r R = MeCO, X = O, 40%
25s R = PhCO, X = S, 26%

Notably, both heteroaryl and aryl C–O bonds in heteroaryl aryl ether **24m** were converted to C–F bonds, when 2-fluorobenzothiazole **25a** was employed as the organic fluorinating reagent (Scheme 15). The reaction of **25a** (2 equiv.) and **24m** gave 2-fluoro-4-phenyloxazole **25m** (58%) and 4-fluorobenzonitrile **27** (67%), which was accompanied by [2,3'(2'*H*)-benzothiazol]-2'-one **28** (56%).[28] Note that two C–O bonds of **24m** were converted into two C–F bonds, and the oxygen atom of **24m** was captured by **25a**, which resulted in the formation of the dimeric compound **28**. The reverse reaction did not occur, which indicated an exothermic nature of the reaction. The heteroaryl C–O bond of **24m** should initially be converted into the C–F bond, which would then be followed by the fluorination of the aryl C–O bond. 4-[(5-Acetyl-2-furanyl)oxy]benzonitrile **24r**, 4-quinazolinyl 4-cyanophenyl ethers **24b**, and **24c** also reacted with **25a** and were fluorinated.



Scheme 15. Rhodium-catalyzed fluorination of heteroaryl and aryl C–O bonds in heteroaryl aryl ethers

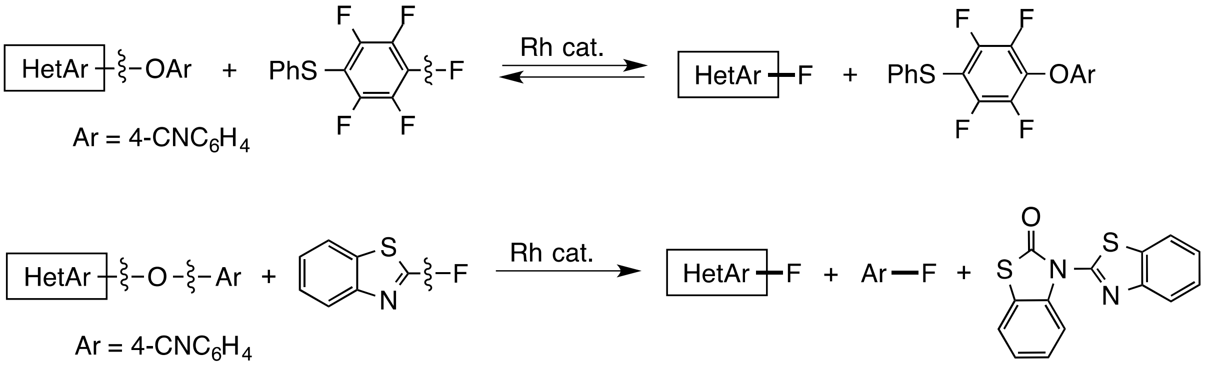
The formation of the dimer **28** from two molecules of **25a** shifted the equilibrium to form heteroaryl fluorides and aryl fluorides, which was supported by DFT calculation. The reaction of diphenyl ether and **25a** to form fluorobenzene and [2,3'(2'H)-bibenzothiazol]-2'-one **28** (-49.2 kJ/mol) is more exothermic than the formation of fluorobenzene and di(2-benzothiazyl) ether **29** (-2.4 kJ/mol) (Scheme 16).[17]



Scheme 16. Equilibrium control of fluorination using 2-fluorobenzothiazole

Heteroaryl fluorides, i.e., HetAr–F compounds, were synthesized by the reaction of heteroaryl aryl ethers and phenyl thiopentafluorobenzene under equilibrium. The fluorination of various five- and six-membered heteroaryl aryl ethers proceeded in high yields. When 2-fluorobenzothiazole was used, two

C–O bonds of heteroaryl aryl ethers were both fluorinated to give heteroaryl fluorides and aryl fluorides. This reaction converts stable heteroaryl aryl ethers into heteroaryl fluorides with stable organic fluorinating reagents (Scheme 17).



Scheme 17. Rhodium-catalyzed fluorination using organic fluorinating reagents

5. CONCLUSIONS

Unsymmetric HetAr–X–HetAr' compounds have flexible and chiral pseudohelical structures, and are expected to exhibit various biological activities by interacting with proteins and nucleic acids. Rhodium-catalyzed heteroaryl exchange reactions are a novel and efficient method of synthesizing unsymmetric HetAr-X-HetAr' compounds, and unsymmetric HetAr–O–HetAr', HetAr–S–HetAr', and HetAr–CH_2–HetAr' compounds were obtained from heteroaryl aryl ethers and various heteroaryl reagents (Figure 8). This method involving these reactions can also be used to synthesize HetAr–F compounds.

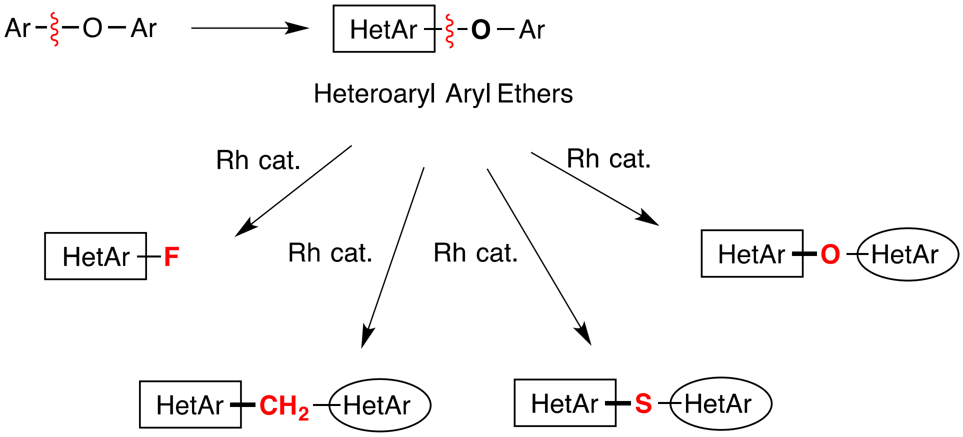
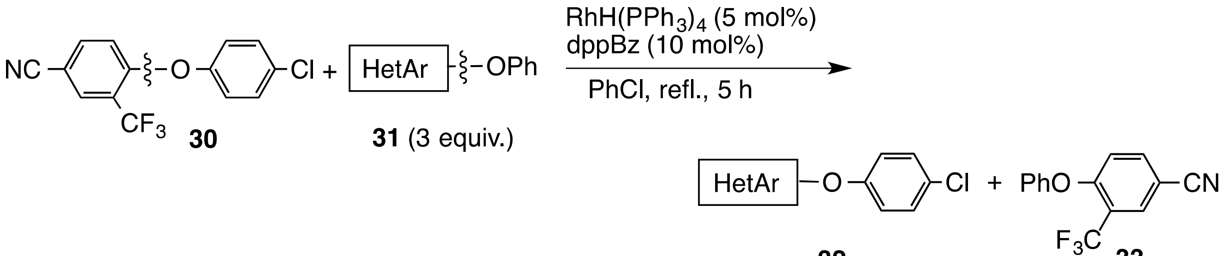


Figure 8. Rhodium-catalyzed synthesis of HetAr–X–HetAr' compounds

This method involves equilibrium control of the relative thermodynamic stability of starting materials and products. Then, the structure of organic heteroaryl reagents can be tuned, and an energetically downhill reaction system can be designed. Metal reagents and metal bases are not required; accordingly, the rhodium-catalyzed heteroaryl exchange reaction is not significantly affected by the structures of heteroarenes, being applied to the synthesis of novel compounds including five- and six-membered heteroarenes.

The catalytic method employs stable and readily available heteroaryl aryl ethers. It was shown in our study that heteroaryl aryl ethers used as starting materials can be synthesized by a heteroaryl exchange reaction from diaryl ether. For example, heteroaryl aryl ethers containing five- and six-membered heteroarenes **32a**–**32d** can be synthesized from 4-(4-chlorophenoxy)-3-trifluoromethylbenzonitrile **30** under rhodium-catalyzed conditions (Scheme 18).[11] The rhodium complex catalyzes the aryl–O bonds cleavage and heteroaryl exchange of the activated diaryl ether. A simple diphenyl ether, in principle, can be used as a starting material to synthesize various unsymmetric HetAr–X–HetAr' compounds. The development of such a method is a subject of future studies.



HetAr =	32	33
benzothiazolyl (**a**)	74%	74%
6-Cl-benzoxazolyl (**b**)	74%	71%
6,7-di(MeO)-2-quinazolyl (**c**)	72%	69%
4-CN-2-pyridyl (**d**)	66%	70%

Scheme 18. Rhodium-catalyzed exchange reaction using diaryl ethers

ACKNOWLEDGEMENT

The research reviewed in this paper was possible only through the enthusiasm and creativity of all co-workers, whose names are acknowledged on the publications from our laboratory cited here. This research was supported by the Platform Project for Supporting Drug Discovery and Life Science Research funded by Japan Agency for Medical Research and Development (AMED), JSPS KAKENHI Grant Numbers 17K19112, 15H00911, Tohoku University Center for Gender Equality Promotion (TUMUG), and Morinomiyako Project for Empowering Women in Research.

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17. The energies for DFT calculations by Jaguar 9.0, B3LYP_6-31G**//B3LYP_6-311G** were used. Also see supporting information.

Total Free Energies (at 298.15 K) of compounds including vibrational frequencies

Diphenyl ether, E = -538.496873 a.u.

Diphenyl sulfide, E = -861.479903 a.u.

S-Phenyl thiobenzoate, E = -974.841529 a.u.

Phenyl benzoate, E = -651.873551 a.u.

S-Phenymethansulfonic acid, E = -1218.386188 a.u.

Methansulfonic acid phenyl ester, E = -895.404972 a.u.

Thioanisole, E = -669.748303 a.u.

Anisole, E = -346.760172 a.u.

N-(Phenylthio)succinimide, E = -989.932671 a.u.

N-(Phenoxy)succinimide, E = -666.905728 a.u.

1,2-Diphenylethanone, E = -615.917356 a.u.

Diphenylmethane, E = -502.566358 a.u.

Benzyl phenyl ether, E = -577.792982 a.u.

Benzophenone, E = -576.620318 a.u.

Toluene, E = -271.538254 a.u.

Phenol, E = -307.476246 a.u.

N-(Benzyl)succinimide, E = -631.029188 a.u.

Benzyl chloride, E = -731.169926 a.u.

Phenyl hypochloride, E = -767.034653 a.u.

Hydrogen fluoride, E = -100.476901 a.u.

Benzoyl fluoride, E = -444.880072 a.u.

Fluorobenzene, E = -331.508593 a.u.

Hexafluorobenzene, E = -827.819294 a.u.

1,2,3,4,5-Pentafluoro-6-phenoxybenzene, E = -1034.817000 a.u.

2-Fluorobenzothiazole, E = -821.996240 a.u.

Di(2-benzothiazolyl) ether, E = -1519.474007 a.u.

[2,3'(2*H*')-Bibenzothiazol]-2'-one, E = -1519.509650 a.u.

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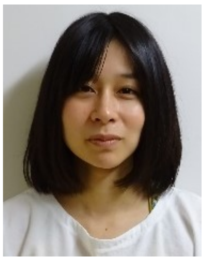
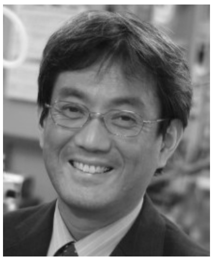
Mieko Arisawa is an associate professor at Tohoku University. She was born in Yamagata in 1974, and received her BSc (1996) and PhD degrees (2001) from the Tohoku University under the guidance of Professor Masahiko Yamaguchi. In 1998, she was appointed as a research associate at Tohoku University, and was promoted to an assistant professor in 2001 and a lecturer in 2010. Since 2013, she is an associate professor at Tohoku University. She received the Sankyo Chemical Co., LTD. Award in Synthetic Organic Chemistry, Japan in 2001, Banyu Young Chemist Award in 2002, the Incentive Award in Synthetic Organic Chemistry Japan in 2010, and Thieme Chemistry Journals Award in 2011. Her research interests are the development of transition-metal-catalyzed efficient synthetic methodology/reactions of organoheteroatom compounds.



Saori Tanii is a research associate at Tohoku University. She was born in Toyama in 1990, and received her BSc (2013) from Kanazawa University under the guidance of Professor Yutaka Ukaji. In 2013, she joined Professor Masahiko Yamaguchi's group at Tohoku University as a PhD student. She had opportunity to work under the direction of Professor Byeang Hyean Kim at Pohang University of Science and Technology for 1 month in 2015. In 2016, she was appointed as a research associate at Tohoku University. Her research interest is the development of metal-catalyzed transformation of inert bonds such as C-C or C-O bonds.

Takeru Tazawa is a student of Tohoku University (MC2). He was born in Aomori in 1992, and received his BSc (2016) from Tohoku University under the guidance of Professor Kohji Fukunaga. In 2016, he joined Professor Masahiko Yamaguchi’s group at Tohoku University as a master course student. His research interests are the development of synthesis of heteroaryl compounds by rhodium-catalyzed reactions.



Masahiko Yamaguchi is a professor at Tohoku University. He was born in Fukuoka in 1954, and received his BSc (1977) and PhD degrees (1982) from the University of Tokyo under the guidance of Professor Teruaki Mukaiyama. He joined the Department of Industrial Chemistry, Kyushu Institute of Technology, in 1982 as assistant professor and was promoted to associate professor in 1985. He became associate professor of the Department of Chemistry at Tohoku University in 1991. From 1987 to 1988 he worked as a post doctoral fellow at Yale University with Professor S. Danishefsky. In 1997, he was appointed as a professor in the Faculty of Pharmaceutical Sciences of Tohoku University. He was Professor of Graduate School of Pharmaceutical Sciences and Graduate School of Science of the same university in 2006-2013, and PI of WPI-AIMR in 2007-2013. During 2007-2013, he was group leader of GCOE program for chemistry in Tohoku University. Since 2013, he is Professor of Graduate School of Pharmaceutical Sciences. He received the Chemical Society of Japan Award for Young Chemists in 1986 and the Synthetic Organic Chemistry Award, Japan in 2007. His research interests are in the area of synthetic methodology and synthesis/function of helical compounds.