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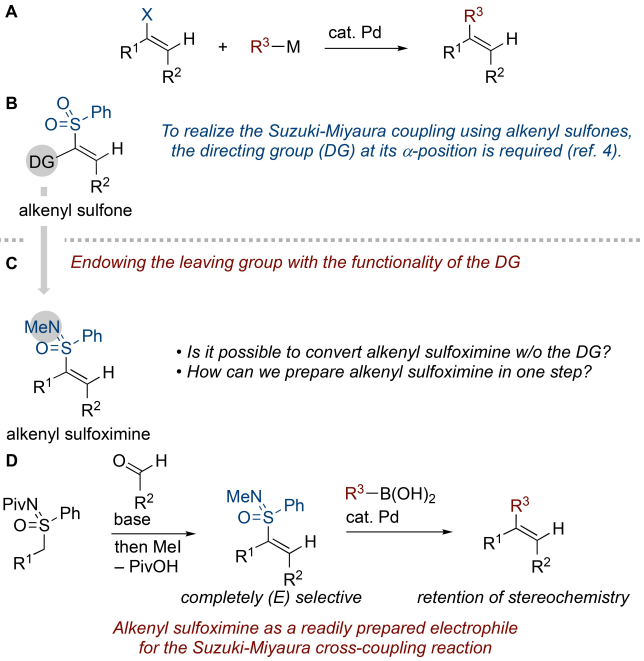
Stereoselective Preparation and Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling of Alkenyl Sulfoximines

Kosuke Yasui, Yuichiro Tomishima, Tomoya Miura, Ken Yamazaki,* and Koji Hirano**

Abstract: Although numerous transition-metal catalyzed cross-coupling reactions of alkenyl electrophiles with a sulfur(VI) leaving group, mainly alkenyl sulfones, have been developed, most rely heavily on highly nucleophilic Grignard reagents, and the use of organoboron reagents remains challenging. We report herein facile preparation and the following Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of alkenyl sulfoximine, a monoaza analog of sulfone. The condensation of alkyl sulfoximine with aldehydes, developed in this study, makes alkenyl sulfoximines more readily available. The resulting alkenes undergo an unprecedented oxidative addition of the C–S bond to the Pd center. This cross-coupling proceeds with retention of its original stereochemistry and provided alkenes bearing three different functionalities in a stereoselective fashion. DFT calculations highlight the critical role of boronic acid and *in situ*-generated boroxines in facilitating this transformation.



Scheme 1. Background and overview of this work.

Transition-metal catalyzed cross-coupling reactions using alkenyl electrophiles and aryl nucleophiles provides valuable alkenes in a stereoselective manner (Scheme 1A).[1] To enhance the accessibility of starting alkenyl electrophiles, it is beneficial to develop new cross-coupling reactions that can convert not only carbon-halogen bonds but also various other bonds. Alkenyl sulfones have emerged as a stable, readily available coupling partner for various cross-coupling reactions.[2] However, most of reported methods using alkenyl sulfone heavily rely on the use of Grignard reagent as nucleophile, significantly decreasing functional group compatibility.[3] Although, exceptionally, Niu reported its cross-coupling with organoboron reagents, the assistance of a directing group (DG) at its α-position is necessary for the reaction to proceed, considerably limiting the structure of products (Scheme 1B).[4] Thus, challenges still remain regarding the scope of nucleophiles applicable to cross-coupling reactions using a sulfur (VI)-based alkenyl electrophiles.

To endow the function of the DG to a leaving group, we turned our attention from sulfone to sulfoximine, the monoaza analog of sulfone, due to its ability as a DG (Scheme 1C).[5] Sulfoximine has emerged as a privileged pharmacophore in pharmaceutical and agrochemical molecules.[6] Accordingly, novel methodologies to functionalize imine moiety[7] and to introduce a point chirality at the sulfur center[8] have been increasingly developed. However,

[*] K. Yasui, Y. Tomishima, K. Hirano
Department of Applied Chemistry
Graduate School of Engineering, Osaka University
Suita, Osaka 565-0871, Japan.
E-mail: k_yasui@chem.eng.osaka-u.ac.jp
k_hirano@chem.eng.osaka-u.ac.jp

K. Yasui, K. Hirano
Innovative Catalysis Science Division
Institute for Open and Transitionary Research Initiative (ICS-OTRI), Osaka University
Suita, Osaka 565-0871, Japan.

K. Yasui
Center for Future Innovation
Graduate School of Engineering, Osaka University
Suita, Osaka 565-0871, Japan.

T. Miura, K. Yamazaki
Division of Applied Chemistry
Okayama University
Tsushimanaka, Okayama 700-8530, Japan
E-mail: k-yamazaki@okayama-u.ac.jp

its use as a leaving group has been largely disregarded; thus, unlike its biological utility, its synthetic utility remains ambiguous. Innovatively, Gais and co-workers explored its reactivity as a leaving group in the Ni-catalyzed cross-coupling reaction with organozinc reagent.[9a] Despite the promising reactivity, the lack of stereoselective methods to prepare multi-substituted alkenyl sulfoximines[10] has hindered the widespread adoption of this catalytic system. Additionally, the scope of nucleophiles should be expanded so that more stable and functional-group-tolerated organoboron reagents can be used instead of organozinc reagents. In this context, we herein report facile, stereoselective preparation and the following Pd-catalyzed Suzuki–Miyaura cross-coupling of alkenyl sulfoximine (Scheme 1D).

Before developing the cross-coupling reaction, we explored the single-step preparation of alkenyl sulfoximines from aldehydes and alkyl sulfoximines (Figure S1).[11] Classically, they were prepared in three steps, i.e. carbonyl addition, hydroxyl group activation, and elimination (Figure S2).[12] To make them more available, we pursued conducting these reactions in one process. Given this premise, the sulfoximines protected with a carbonyl group on its nitrogen, such as pivaloyl or acetyl group (**1a** and **1b**), were tested for the condensation with **2a**. Fortunately, upon losing the protecting group during the reaction, **1a** and **1b** reacted with **2a** to form the desired alkene **3a** with complete (*E*)-stereoselectivity in 80 % and 79 %, respectively (Figure 1A and Figure S3). The structure and stereochemistry of **3a** were unambiguously confirmed by X-ray analysis (Figure 1B). The condensation with non-protected sulfoximine **1c**, methylated one **1d**, or sulfone (data not shown), did not proceed at all, suggesting that protection with a carbonyl group is essential for obtaining **3a**. According to these results, a plausible mechanism is shown in Figure 1 C: (1) the addition of deprotonated **1a** to **2a** forms **Int A**, (2) the *N*-to-*O* 1,5-carbonyl migration of **Int A** provides **Int B**, and

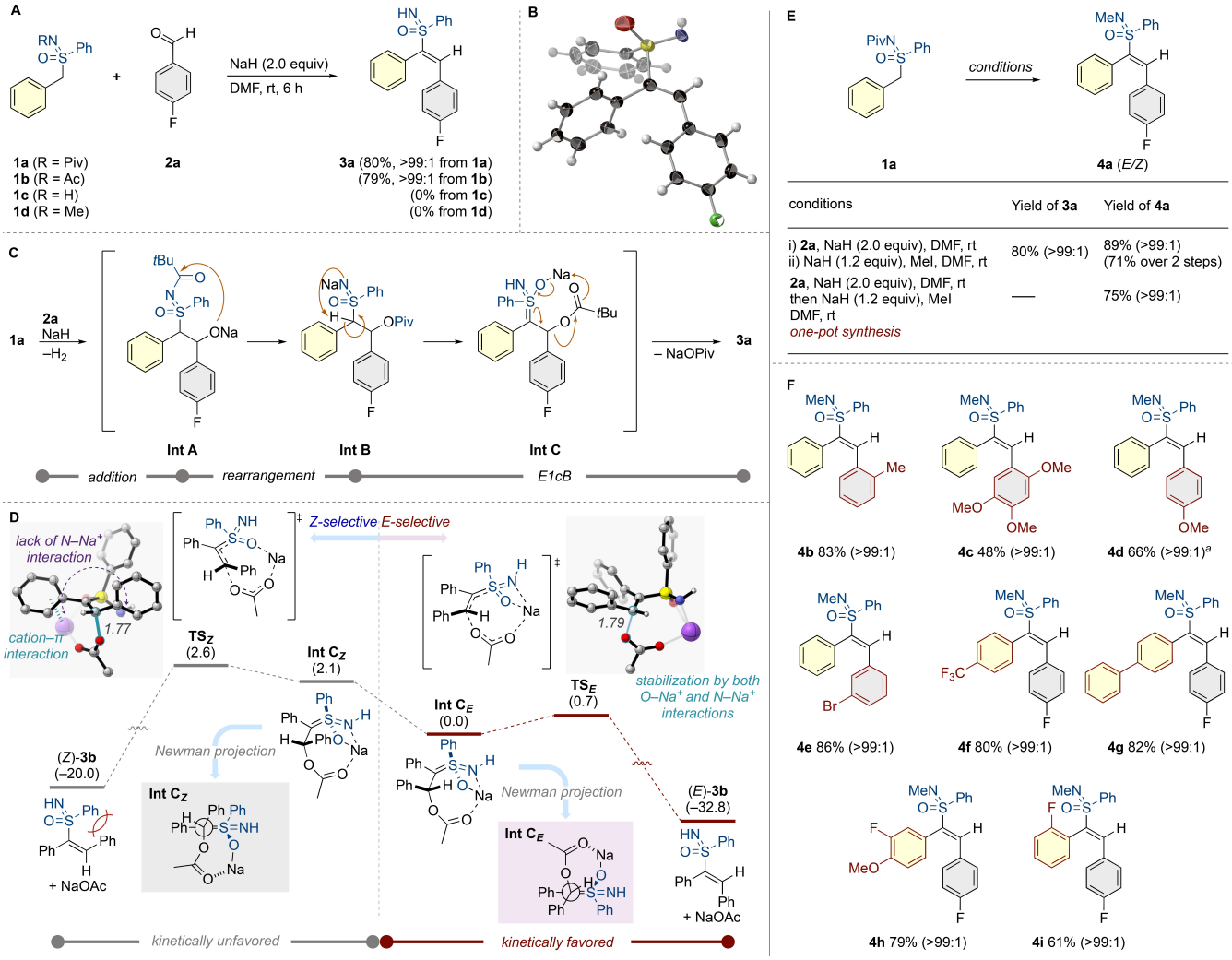
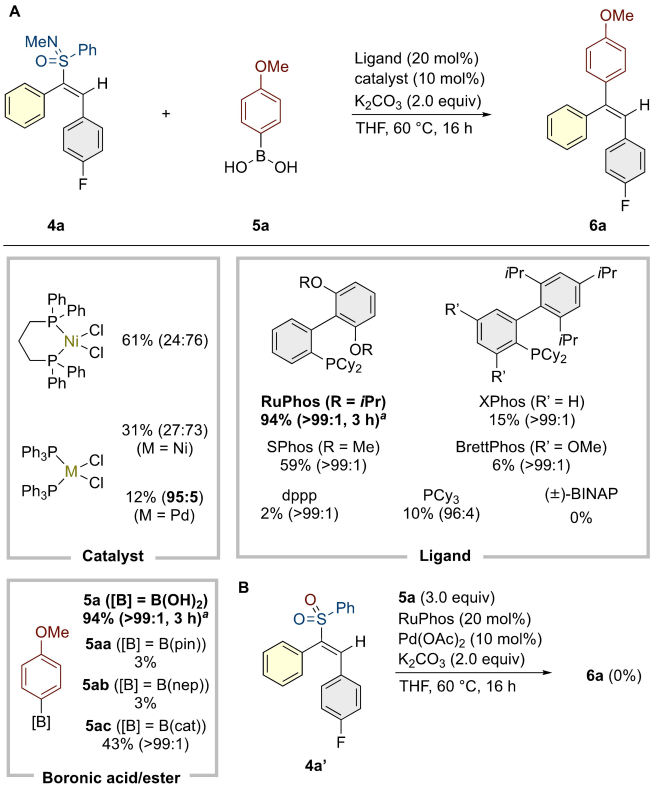


Figure 1. Condensation between alkyl sulfoximine and benzaldehyde. (A) The importance of protecting group of alkyl sulfoximines for the condensation. (B) Single crystal X-ray structure of **3a**. (C) Plausible mechanism of the condensation. (D) DFT calculation of the stereoselectivity-determining E1cB elimination step involved in the condensation (ΔG [in kcal mol^{-1}]) computed at SMD(THF)/B3LYP–D3/6–311 + G(d,p)// SMD(THF)/B3LYP–D3/6-31G(d) level of theory. (E) One-pot synthesis of **4a** from **1a**. (F) Selected examples of the condensation reactions. a: The first condensation was conducted at 60 °C in THF, then the methylation with MeI and NaH in THF at rt.

(3) the final elimination of carboxylate[13] proceeds via E1cB mechanism to yield **3a**. That is because the carbanion of **Int C** should be stabilized by the neighboring sulfoximine, and the carboxylate is generally a poor leaving group. These factors suggest that the elimination step proceeds via an E1cB mechanism, which is critical for determining the stereochemistry of **3a**. To gain insight into the mechanism of the elimination, a density functional theory (DFT) calculation was carried out on the model substrate **3b** starting from two conformers **Int** $\mathbf{C}_E$ and **Int** $\mathbf{C}_Z$ (Figure 1D, also see the Supporting Information for more details). The intermediate **Int** $\mathbf{C}_E$ is more stable than **Int** $\mathbf{C}_Z$ by 2.1 kcal mol^{-1}, and the *E*-isomer (*E*)-**3b** is thermodynamically more stable than the other isomer (*Z*)-**3b** (ΔG_{rxn} = –32.8 and –20.0 kcal mol^{-1}, respectively). This energy difference results from steric hindrance between the bulky sulfoximine group and the phenyl group at the *β*-position of the *Z*-isomer. Furthermore, the acetate elimination preferably proceeds through the transition state $\mathbf{TS}_E$ compared to $\mathbf{TS}_Z$ ($\Delta\Delta G^{\ddagger}$ = 1.9 kcal mol^{-1}). The selectivity arises from the lack of cation stabilization by the nitrogen atom in the disfavored transition state $\mathbf{TS}_Z$, since the aromatic ring at the *β*-position restricts free rotation of the sulfoximine group. These observations suggest that the bulkiness of the sulfoximine group leads to the formation of (*E*)-**3b** both kinetically and thermodynamically more favorable, thereby leading to its exclusive formation, aligning with the experimentally observed trend in *E*/*Z* selectivity.

For using the alkenyl sulfoximine as a coupling partner, *N*-methylation of **3a** was conducted. The methylation of isolated **3a** with methyl iodide and NaH provided **4a** in 89 % yield (Figure 1E). The condensation and *N*-methylation could also be achieved in one pot with comparable efficacy, enhancing their synthetic efficacy. Various *N*-methyl alkenyl sulfoximines could be synthesized by the one-pot operation as shown in Figure 1F. Sterically congested benzaldehydes, including 2-methyl benzaldehyde and 2,3,5-trimethoxy benzaldehyde, could participate in the condensation (**4b** and **4c**). Aldehyde with an electron-donating group underwent the one-pot reaction (**4d**). Alkenyl sulfoximine bearing a bromide group could be prepared without any difficulties (**4e**). Alkyl sulfoximines bearing functional groups on their aromatic rings were also applicable (**4f**–**4i**). These results indicate that the sulfoximine protected with a carbonyl group on its nitrogen simplifies the preparation of the corresponding alkenyl sulfoximine in a stereoselective fashion.

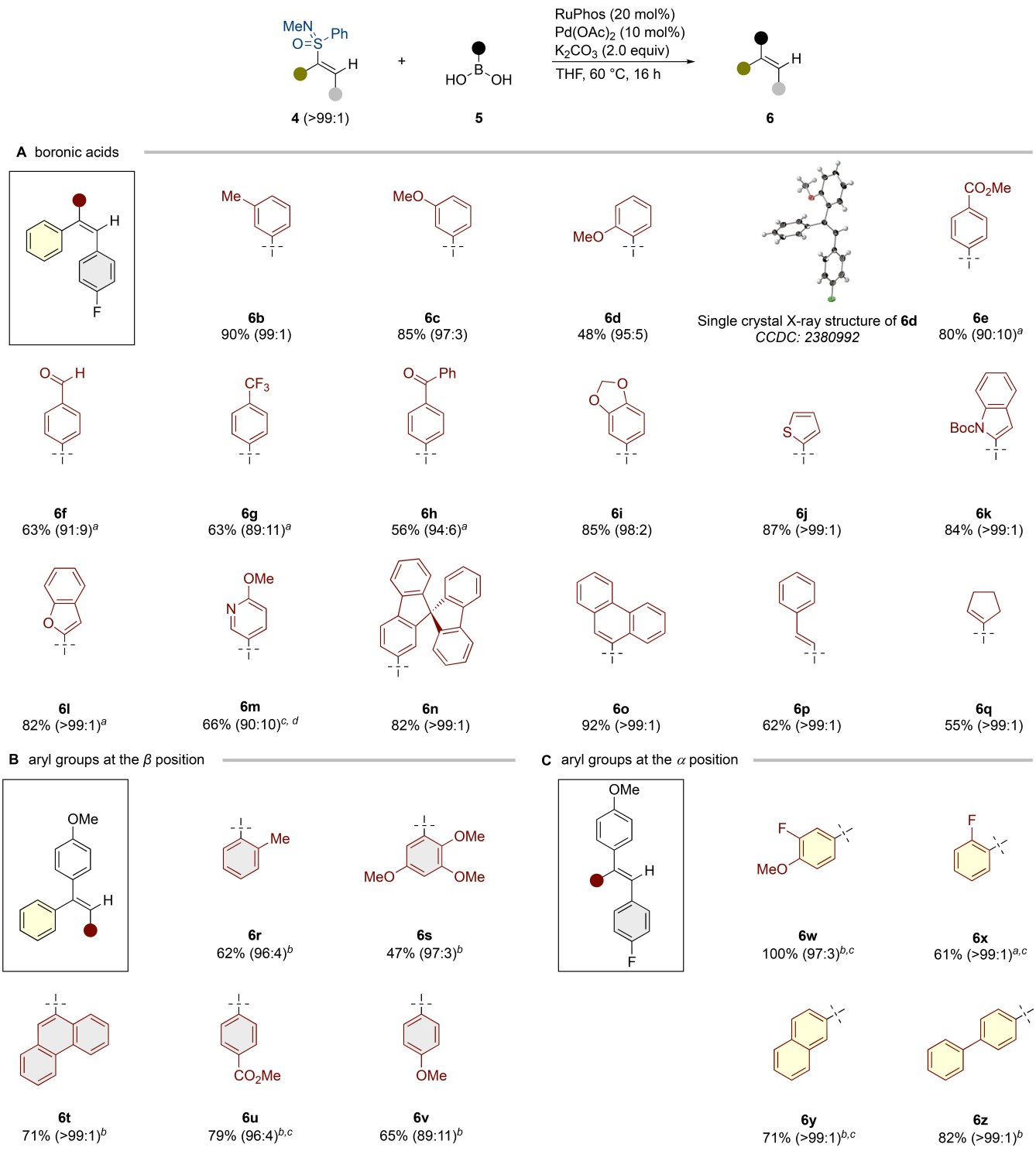
Next, the Suzuki–Miyaura cross-coupling of **4a** with **5a** was examined (Scheme 2A). Initially, we tested $NiCl_2$(dppp) that Gais previously used as a catalyst for the cross-coupling of alkenyl sulfoximine.[9a] The Ni-catalyzed reaction provided the desired coupling product in 61 %, but its stereoselectivity was insufficient. Almost the same stereoselectivity was observed with $NiCl_2(PPh_3)_2$, leading us to conclude that nickel is unsuitable for sufficient stereoselectivity. In stark contrast, gratifyingly $PdCl_2(PPh_3)_2$ catalyst provided the desired product in low yield yet in a highly stereoselective fashion. After exploring suitable phosphine ligands, we found RuPhos, one of the Buchwald phosphine ligands,



Scheme 2. (A) Optimization study of Suzuki–Miyaura cross-coupling reaction of alkenyl sulfoximine. (B) The alkenyl sulfone was not suitable for the Suzuki–Miyaura cross-coupling reaction. NMR yields are show otherwise noted. [a] Yield of the isolated product is shown.

particularly effective to obtain **6a** in 94 % yield in a completely stereoselective manner. Additionally, the reaction time was significantly decreased using RuPhos (3 h vs 16 h). Other common phosphine ligands proved unsuitable for the cross-coupling. Evaluation of boronic acid (**5a**) and boronic esters (**5aa**–**5ac**) revealed that boronic acid is indispensable for the cross-coupling. These results suggest that boronic acid significantly promotes the reaction. It should be noted that the corresponding alkenyl sulfone **4a'** did not undergo the cross-coupling reaction at all, probably due to lack of the nitrogen DG (Scheme 2B).[4]

With the optimized reaction conditions in hand, we examined the scope of boronic acids using (*E*)-**4a** as the substrate (Scheme 3A). Boronic acids bearing a methoxy group at *para*, *meta*, or even *ortho* positions could participate in the reaction (**6a**, **6c**, and **6d**), while the *ortho* substituent slightly decreased the yield and stereoselectivity, probably due to its steric hinderance. The retention of stereochemistry of this cross-coupling reaction was confirmed by the X-ray crystal structure of **6d**. Boronic acids with electron-withdrawing groups (**6e**–**6g**) were applicable to the cross-coupling. However, unlike those with electron-donating groups, they required longer reaction time for completion, and their stereoselectivity was somewhat lower. The reduced stereoselectivity can be attributed to the potentially destabilized transmetalation step that competes with the isomerization transition state (*vide intra*). Disub-



Scheme 3. Scope of the Suzuki–Miyaura cross-coupling. [a] 24 h. [b] 48 h. [c] 80 °C. [d] Run with 40 mol% RuPhos and 20 mol% $Pd(OAc)_2$.

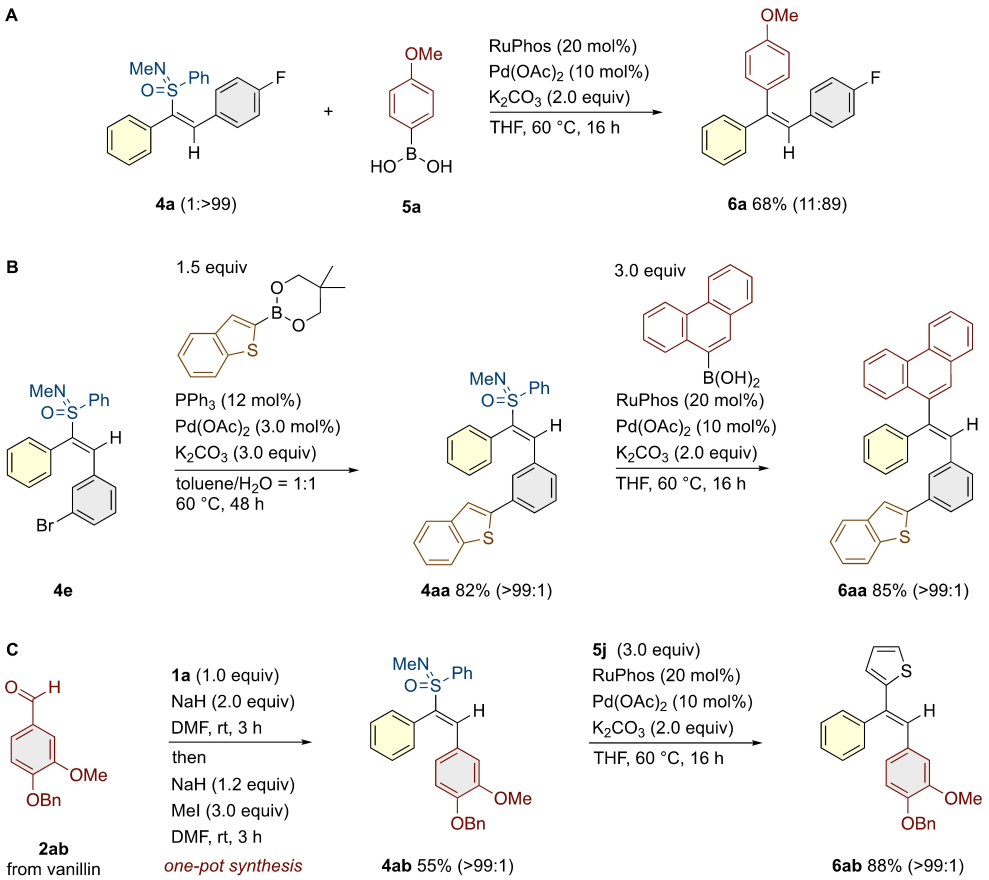
stituted aryl boronic acid with methylenedioxy moiety also reacts to furnish **6i**. Heteroaromatic boronic acids such as thiophene **6j**, *N*-Boc indole **6k**, and benzofuran **6l** are also compatible in this reaction. Increasing the amount of catalyst allowed a six-membered ring heteroaromatic to participate in this cross-coupling (**6m**). Boronic acids bearing π-extended structures, including 9,9'-spirobifluorene and phenanthrene, were also applicable to the cross-coupling, indicating the potential utility for synthesizing π-conjugated systems (**6n** and **6o**). Furthermore, the applicability of styryl boronic acid and 1-cyclopentenyl boronic acid demonstrated the synthetic utility of this reaction to produce conjugated 1,3-dienes stereoselectively (**6p** and **6q**).

The scope of alkenyl sulfoximines was also evaluated (Scheme 3B and 3 C). Although steric hindrance of the β-substituents slightly affected the efficacy of the cross-coupling, the desired products could still be synthesized (**6r** and **6s**). **6t**, bearing phenanthrene at the β-position, was obtained in 71 % yield with complete stereoselectivity. These three results suggest that the conjugation of the double bond with β-substituents affects the efficacy of the cross-coupling reaction. Next, we examined the electronic effect of the aryl ring at the β-position on the efficacy of the cross-coupling. An alkenyl sulfoximine bearing an electron-deficient aryl group at the β-position was convertible into the corresponding triaryl alkenes in a stereoselective manner (**6u**). In contrast, **6v**, bearing an electron-rich aryl group, was obtained with lower stereoselectivity than that of **6u**. On the other hand, the steric and electronic nature of substituent at the α-position gave little impact on the reaction. Alkenyl sulfoximines bearing the electron-deficient, electron-rich, and π-extended aryl groups all were successfully converted into the corresponding **6w**–**6z** in synthetically acceptable yields and stereoselectivity. Although alkenyl sulfoximine bearing an alkyl group at α- and β-position could be prepared by the condensation reaction, these substrates did not undergo the cross-coupling reaction (See SI).

The stereospecificity of the cross-coupling reaction was examined using (*Z*)-**4a**, prepared by the photoirradiation (See SI) to the solution of (*E*)-**4a** (Scheme 4A). The cross-coupling reaction provided **6a** in 68 % yield with slight erosion of original stereochemistry (*E*/*Z* = 11 : 89). This result indicated that the cross-coupling proceeds with retention of stereochemistry.

The reactivity of alkenyl sulfoximine with aryl bromide moiety was also evaluated by sequential Suzuki–Miyaura cross-coupling (Scheme 4B). Arylation of the C–Br bond of **4e**, readily available by the condensation, was achieved by the conventional Suzuki–Miyaura cross-coupling reaction to provide **4aa** in 82 % without any loss of the sulfoximine group and the stereochemistry of the double bond. The subsequent C–S bond arylation by presently developed Pd/RuPhos-catalyzed cross-coupling reaction yielded **6aa** in 85 % with complete retention of the stereochemistry. These results suggest that specific reactivity of sulfoximine allows sequential cross-coupling.

Vanillin, a natural product with a formyl group, could be applied to this method for structural diversification (Scheme 4C). Condensation of benzyl protected vanillin **2ab** with **1a** produced the coupling partner **4ab** according to the one-pot synthesis. The following cross-coupling reaction with **5j** provided the triaryl alkene **6ab** bearing a thiophene ring and a protected vanillyl group in 88 % with complete retention



Scheme 4. (A) Stereospecificity of the Suzuki–Miyaura cross-coupling reaction. (B) Sequential Suzuki–Miyaura Cross-coupling (C) Transformation of vanillin.

of stereochemistry. The triaryl alkene is a promising candidate for antiproliferative agents, inhibitors of tubulin polymerization, and inhibitors of colchicine binding to tubulin,[14] suggesting potential synthetic utility of this method.

To elucidate the reaction mechanism and understand the role of boronic acids for the stereoretentive cross-coupling reaction of sulfoximines, DFT study was performed (Figure 2).[15] The catalytic cycle begins with a complexation of the substrate **SM** and the Pd(0) active species to generate the thermodynamically stable complex **Int1** ($\Delta G = -27.3$ kcal mol^{-1}) (Figure 2A). The initial oxidative addition of C(alkenyl)–S bond to the Pd center from the intermediate **Int1** requires the energy barrier of 23.2 kcal mol^{-1} through the transition state **TS1**. An alternative oxidative addition of C(aryl)–S bond requires much higher energy barrier through the transition state **TS1'** ($\Delta G^{\ddagger} = 30.2$ kcal mol^{-1}). The favored bond cleavage of C(alkenyl)–S bond over C(aryl)–S bond likely originates from the stabilization of the transition state by the adjacent C=C double bond ($\Delta\Delta G^{\ddagger} = 7.0$ kcal mol^{-1}) (Figure 2B). In addition, the oxidative addition of C-(alkenyl)–S bond is further accelerated by the coordination of the *in situ*-generated boroxine $(PhBO)_3$ (**TS2**: $\Delta G^{\ddagger} = 19.5$ kcal mol^{-1}) or the boronic acid $PhB(OH)_2$ (**TS3**: $\Delta G^{\ddagger} = 17.4$ kcal mol^{-1}) to give the vinyl Pd(II) species **Int2**.[16] The relatively low activation energy barrier with the almost

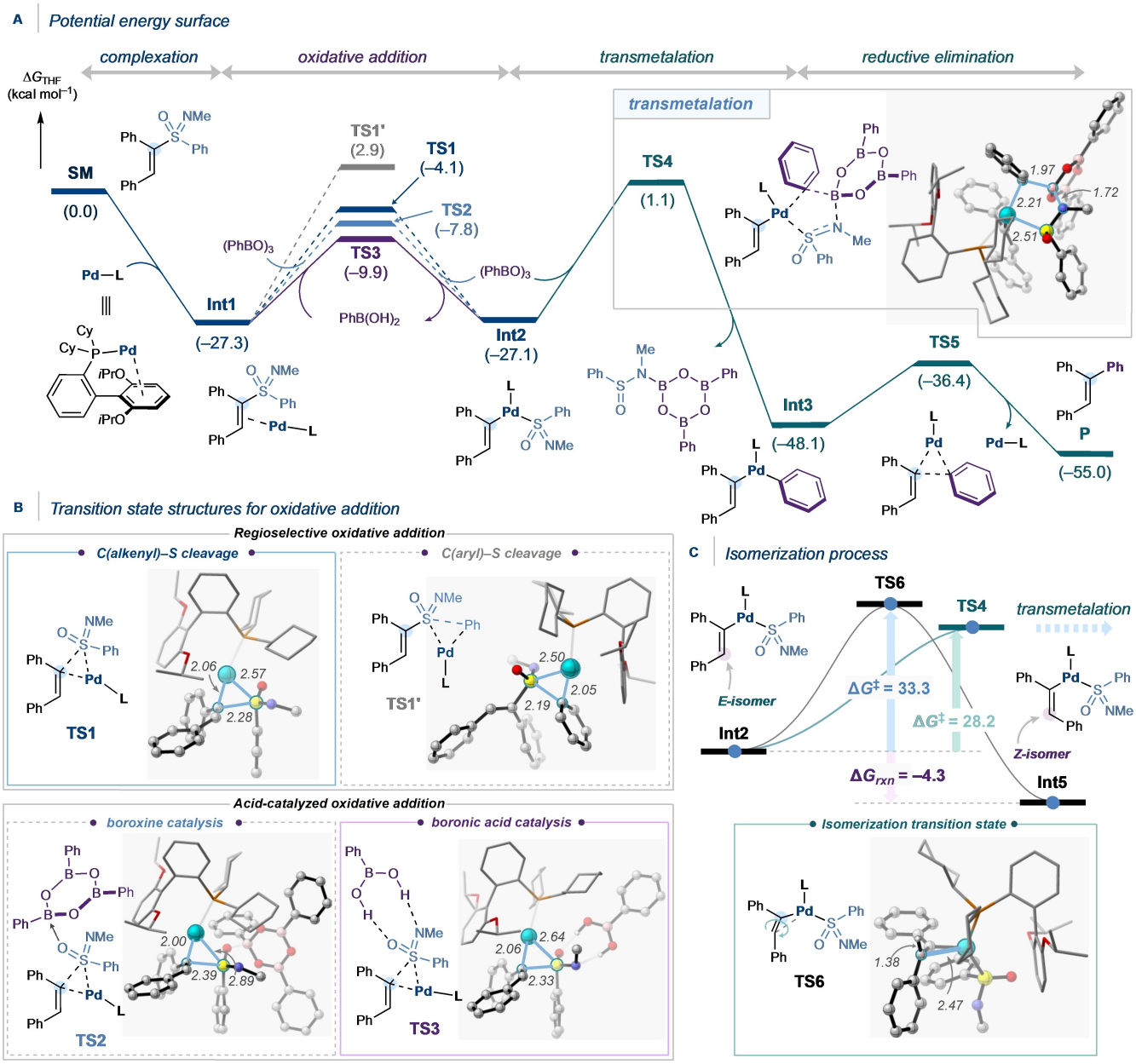


Figure 2. DFT calculations. (A) Potential energy surface of the proposed mechanism (ΔG [in kcal mol^{-1}]) computed at SMD(THF)/B3LYP–D3/SDD(Pd)-6–311+G(d,p)//SMD(THF)/B3LYP- D3/Lanl2dz(Pd)-6-31G(d) level of theory. (B) Transition state structures for oxidative addition step. (C) Isomerization of palladium vinyl species. Energies (kcal mol^{-1}) and forming bond lengths (Å) of TS geometries are provided in the insert.

identical energies of **Int1** and **Int2** through the boronic acid-catalyzed oxidative addition indicates that this C–S bond cleavage process is a reversible pathway. The following transmetalation goes through the rate-determining transition state **TS4** to furnish the stable Pd(II)-phenyl vinyl species **Int3** ($\Delta G^{\ddagger}$ = 28.2 kcal mol^{-1}). This process is constituted of Pd–C and B–N bonds formation as well as Pd–S and C–B bonds cleavage through the five-membered transition state **TS4**. It is noteworthy that we were not able to locate the transmetalation transition state with boronic acid due to its preference as a hydrogen bond donor rather than behaving as a Lewis acid. Finally, the reductive elimination proceeds smoothly through the transition state **TS5** to furnish the coupling product **P** along with the regenerated active catalyst. The computational investigation of the catalytic cycle with sulfone substrate revealed that the rate-determining transmetalation step is thermodynamically preferred in the presence of a nitrogen atom that may arises from the breakage of an inherently unstable S=N double bond to S–N single bond to promote the process (see Figure S9 in the Supporting Information).

Based on the above computational studies along with the experimental observations, we propose the following complete catalytic cycle for our coupling reaction between alkenyl sulfoximines and boronic acids. Initially, the Pd(0) active species coordinates to the substrate. The following oxidative addition of C–S bond is accelerated by boronic acid. During this process, the C(alkenyl)–S bond primarily cleaves over the C(aryl)–S bond due to the existence of an adjacent electron donating stabilization from the C=C bond. Then, a transmetalation event occurs between the Pd(II) intermediate and an *in situ*-generated boroxine. The formation of boroxines from boronic acids is energetically favorable (ΔG_{rxn} = –4.5 kcal mol^{-1}), and the Lewis acidity of this species is essential for the transmetalation. Furthermore, the origin of a partial erosion of *E/Z* selectivity can be described by the isomerization process that may occur before the rate-determining transmetalation (Figure 2C). In fact, the product **6f** (*E*/*Z* = 90:10) did not undergo isomerization under catalytic reaction conditions at all, suggesting that the isomerization occurs only within the catalytic cycle (Figure S5). A representative isomerization transition state structure **TS6** contains a perpendicular C=C bond moiety with a higher activation barrier from **Int2** ($\Delta G^{\ddagger}$ = 33.3 kcal mol^{-1}) towards a more energetically stable isomerized intermediate **Int5** (ΔG = –4.3 kcal mol^{-1}).[17] The origin of stereochemistry erosion in the presence of EDG at the β-position can be attributed to the potentially minimized energy difference between **TS4** and **TS6**, leading to the faster isomerization process that ultimately determines the *E/Z* selectivity of products.

In summary, we developed facile preparation of alkenyl sulfoximines and the following Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of them. The key to realizing the condensation is the use of sulfoximine bearing a carbonyl group on its nitrogen, which renders the alkenyl sulfoximine much more readily available. The resulting sulfoximine exhibited markedly different reactivity, enabling Suzuki–Miyaura coupling that could not be achieved with the corresponding sulfone. Besides, the use of boronic acids is also critical for the cross-coupling reaction; promotion of the oxidative addition of C–S bond and generation of boroxine suitable for the transmetalation. Further exploration of nontrivial synthetic strategies based on the use of sulfoximine as a leaving group is ongoing in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Sulfoximines · Condensation · Cross-coupling · Trisubstituted alkenes · Stereoselectivity

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[18] Deposition Numbers 2380991 (for **3a**) and 2380992 (for **6d**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the jointCambridge Crystallographic Data Centre and Fachinforma-tionszentrum Karlsruhe Access Structures service.

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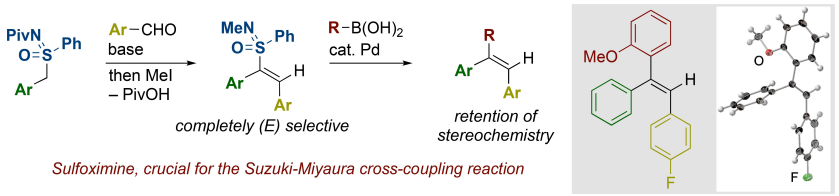
Communication

Homogeneous Catalysis

K. Yasui,* Y. Tomishima, T. Miura,
K. Yamazaki,* K. Hirano* — **e202420949**

Stereoselective Preparation and Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling of Alkenyl Sulfoximines



Sulfoximine, crucial for the Suzuki-Miyaura cross-coupling reaction

The facile preparation of alkenyl sulfoximines, monoaza analogues of sulfones, by condensation of alkyl sulfoximines with aldehydes and their palladium-catalyzed Suzuki–Miyaura cross-coupling are reported. These alkenyl electrophiles underwent unique oxidative addition of the C–S bond to Pd to provide alkenes with three substituents. DFT calculations revealed the crucial role of the boronic acid in the transformation.