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Self-Assembled Multilayer Iron(0) Nanoparticle Catalyst for Ligand-Free Carbon−Carbon/Carbon−Nitrogen Bond-Forming Reactions

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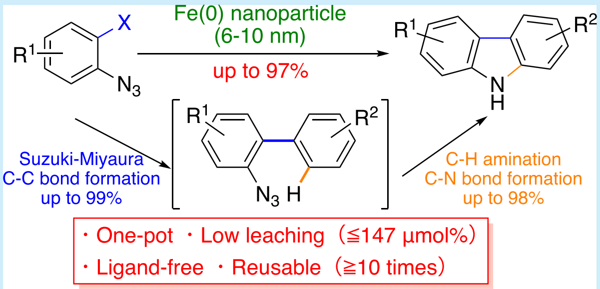
ABSTRACT: Self-assembled multilayer iron(0) nanoparticles (NPs, 6−10 nm), namely, sulfur-modified Au-supported Fe(0) [SAFe(0)], were developed for ligand-free one-pot carbon−carbon/carbon−nitrogen bond-forming reactions. SAFe(0) was successfully prepared using a well-established metal−nanoparticle catalyst preparative protocol by simultaneous *in situ* metal NP and nanospace organization (PSSO) with 1,4-bis(trimethylsilyl)-1,4-dihydropyrazine (*Si*-DHP) as a strong reducing agent. SAFe(0) was easy to handle in air and could be recycled with a low iron-leaching rate in reaction cycles.



Iron has attracted special interest in catalysis for the bond-formation reaction to produce functional molecules, including pharmaceuticals, antibacterial agents, and electroluminescent materials, owing to its natural abundance, relative safety, and low toxicity.[1] There have been several reports of iron-catalyzed bond-forming reactions, such as iron-catalyzed Suzuki−Miyaura coupling[2] and C−H functionalization.[3] However, the development of iron catalysts has been extremely difficult owing to their instability. Moreover, precious ligands are essential for stabilizing and activating these iron catalysts, resulting in a high catalyst loading most of the time. To overcome these disadvantages, we have designed catalysts based on solid-supported metal nanoparticles (NPs), which have high reusability, no ligands, and lower metal contamination in the reaction system.[4] Nevertheless, only a few supported iron(II) or iron(III) NP catalysts have been studied for bond-forming reactions.[5] The only reported recyclable solid-supported iron(0) NP catalyst was limited to the reduction of alkenes (alkynes)[6] because the generation of iron(0) NPs needs a stronger reductant such as Grignard reagents or NaBH$_4$, and these reductants sometimes disturb the target bond-forming reactions, including Suzuki−Miyaura coupling. Accordingly, there is a strong need to immobilize iron(0) NPs on a supporting solid for bond-forming reactions without using any ligands.

We have recently developed a sulfur-modified Au-supported Pd NP catalyst (SAPd) that is usable in Suzuki−Miyaura coupling[7a,b] and C−H functionalization[7c] (Scheme 1a). It was constructed by ∼10 layers of self-assembled Pd(0) NPs (mean size: < 5 nm) supported on a sulfur-modified Au surface. We speculated that the self-assembled Pd NPs, which were encapsulated in a sulfated *p*-xylene polymer matrix,[7d] were formed using *in situ* metal NP and nanospace simultaneous organization (PSSO), as illustrated in Scheme 1b: (i) reduction of a high-valence metal source, (ii) growth of transition-metal NPs, (iii) growth of a matrix with appropriately sized nanopores, and (iv) encapsulation of the metal NPs in these nanopores. To prepare SARu[8] (Scheme 1a), the PSSO method involves the *in situ* reduction of a noble-metal precursor to produce *in situ* ruthenium(0) NPs. Although we also developed SANi[9] and SAFe(II),[10] it remains a challenge to extend the reduction to base metals such as iron. Herein we develop sulfur-modified Au-supported Fe(0) (SAFe(0)) using the combination of *in situ* PSSO and 1,4-bis(trimethylsilyl)-1,4-dihydropyrazine (*Si*-DHP)[11] as a reducing agent for the iron precursor. SAFe(0) was demonstrated as an efficient reservoir of Fe(0) NPs for catalyzing Suzuki−Miyaura coupling and C(sp^2)−H amination under ligand-free conditions. In both types of reactions, this system tolerated a wide range of substrates and was highly recyclable through a simple step.

On the basis of our reported approach for SAPd, we developed a three-step method to synthesize catalytically active SAFe(0) that can be repeatedly used for ligand-free Suzuki−Miyaura coupling and C−H amination. The first step in the

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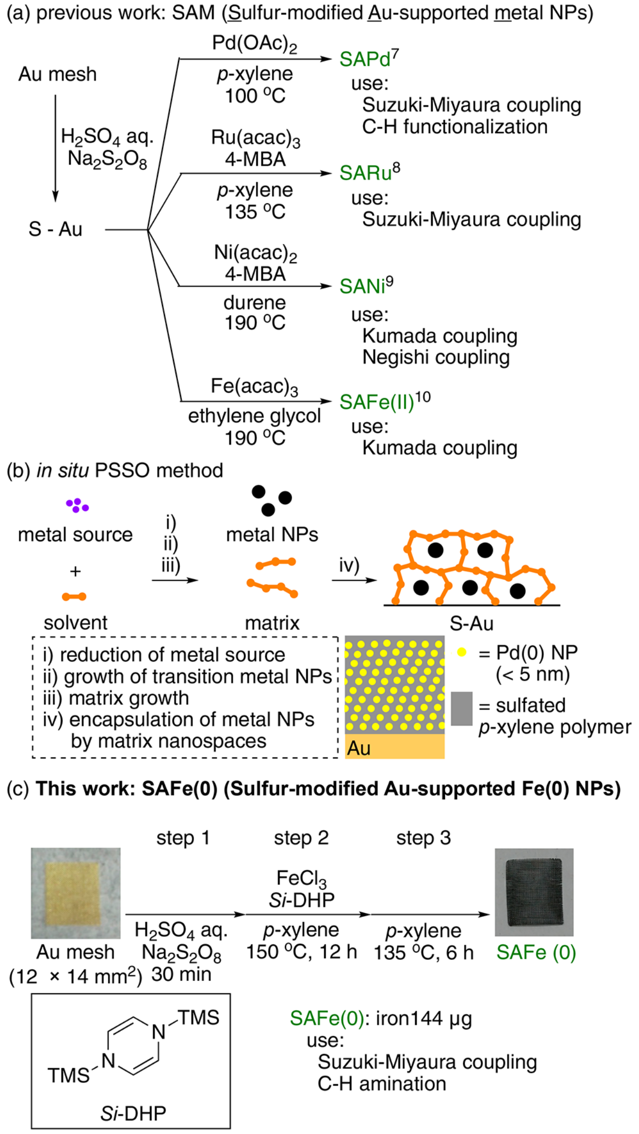
Scheme 1. Preparation of SAM Using Combining *in Situ* PSSO



synthesis was the same as that for SAPd. Namely, sulfur-modified Au (S—Au) was prepared by treating Au mesh (12 mm × 14 mm, 100 mesh) with a piranha solution, that is, H_2SO_4 and $Na_2S_2O_8$ (Scheme 1c, step 1). The second step was the immobilization of iron(0) NPs on S—Au using the *in situ* PSSO method. In our initial attempt, the reaction conditions were similar to those previously reported for the ruthenium(0) precatalyst SARu.[8] However, 4-methoxybenzyl alcohol (4-MBA) used for SARu did not reduce the iron precursor to immobilize iron(0) on S—Au, presumably because of the different oxidation/reduction potentials of Fe and Ru. Therefore, we sought a stronger reductant to produce iron(0) NPs via the chemical reduction of iron(III). We had previously reported that *Si*-DHP[11] could reduce the compounds of some base metals such as iron, cobalt, nickel, and copper to +0 valence under mild conditions without introducing any contamination by salt waste from the reductant. Therefore, *Si*-DHP was tested as a stronger reductant. After identifying suitable conditions, we treated S—Au with a mixture of $FeCl_3$ (15 mg) and *Si*-DHP (3.0 equiv) in *p*-xylene (2.5 mL) at 150 °C for 12 h (Scheme 1c, step 2). The third step consisted of heating and washing the product in *p*-xylene at 135 °C for 6 h (Scheme 1c, step 3). The analysis of SAFe(0) by inductively coupled plasma—mass spectrometry (ICP-MS) showed that the final composite sheet contained 144 ± 44 μg of iron (the mean value over three samples) immobilized on S—Au mesh.[12]

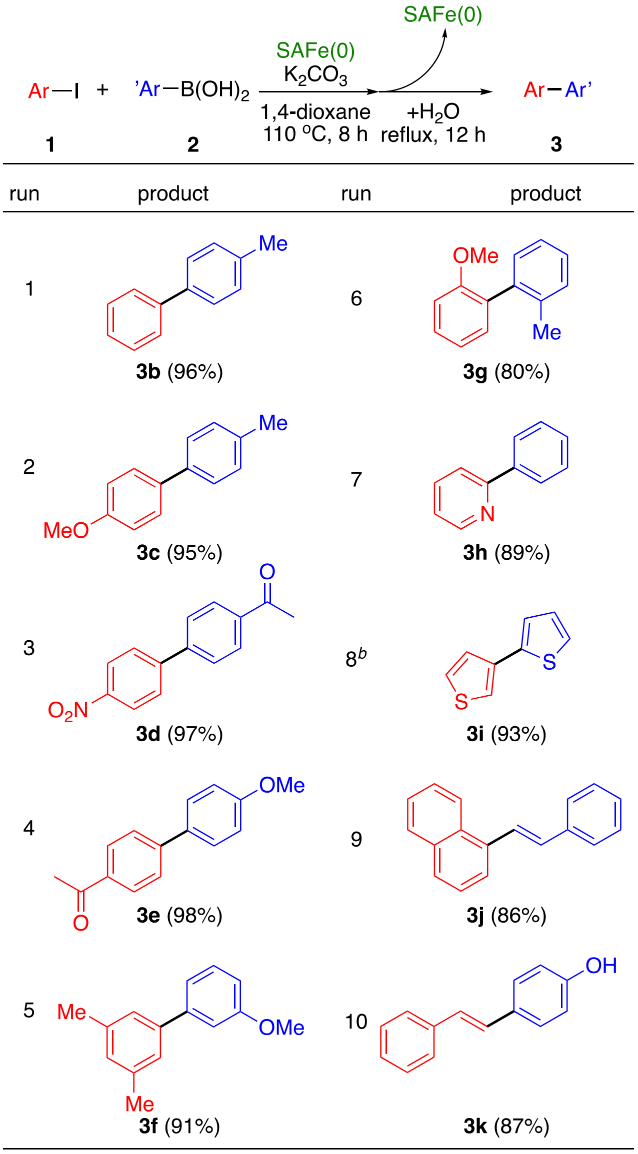
We first considered the formation of a carbon—carbon bond through a ligand-free Suzuki—Miyaura coupling reaction. Under the optimal reaction conditions, a mixed solution of iodobenzene (**1a**), phenylboronic acid (**2a**), K_2CO_3, and SAFe(0) in 1,4-dioxane was heated to 110 °C for 8 h (Table S4, first step). After the removal of SAFe(0), H_2O was added, and the system was refluxed for 12 h (second step). The coupled product **3a** was produced in 99% yield. This methodology was also successful for bromobenzene (**4a**) in place of **1a**, although a longer reaction time (10 h) was needed in the first step.

Next, the same reaction was carried out in cycles. After the first ligand-free Suzuki—Miyaura coupling reaction between **4a** and **2a**, the SAFe(0) sheet was easily removed using tweezers, washed with EtOH, and then reused in the second round of reaction. During the 10 reaction cycles, SAFe(0) retained excellent recyclability with no significant loss of catalytic activity, and the yields of **3a** ranged from 93 to 99% (Table S4). The table also shows that from the ICP-MS analysis of the reaction mixtures in each cycle, SAFe(0) was an efficient reservoir by releasing trace amounts of active iron (Table S4, 0.8—4.1 μg, (29 to 147) × 10^{-6} mol %, TON: (6.74 to 33.9) × 10^5, TOF: (3.06 to 15.4) × 10^4 h^{-1}, referred to **4a**).[13]

We also examined the substrate scope of Suzuki—Miyaura coupling by liquid-phase combinatorial synthesis using the same sheet of SAFe(0) repeatedly. Combinatorial synthesis is a useful technique in medicinal chemistry. The results are summarized in Scheme 2. The reactions of aryl iodides and aryl boronic acids (runs 1—6) provided the corresponding biaryl products **3b**—**3g** in 80—98% yields. The reaction of heteroaryl iodides and (hetero)aryl boronic acids provided the corresponding products **3h** and **3i** in 89 and 93% yields, respectively. The reaction also proceeded in the case of stilbene derivatives (**3j**, **3k**) with high yields. To further evaluate the substrate scope of the Suzuki—Miyaura coupling, we used aryl bromides, which are more commercially available and cheaper than the corresponding iodides. From the results in Table S5, the reactions of various (hetero)aryl bromides with (hetero)aryl boronic acids (runs 1—8) gave the corresponding products (**3b**—**3k**) in 61—98% yields, although a longer reaction time in the first step was necessary due to the relatively slow oxidative addition of aryl bromides. This reaction system[14] was also applicable to natural product derivatives, estrone and quinine, giving the corresponding products in 91 and 67% yields, respectively.[15]

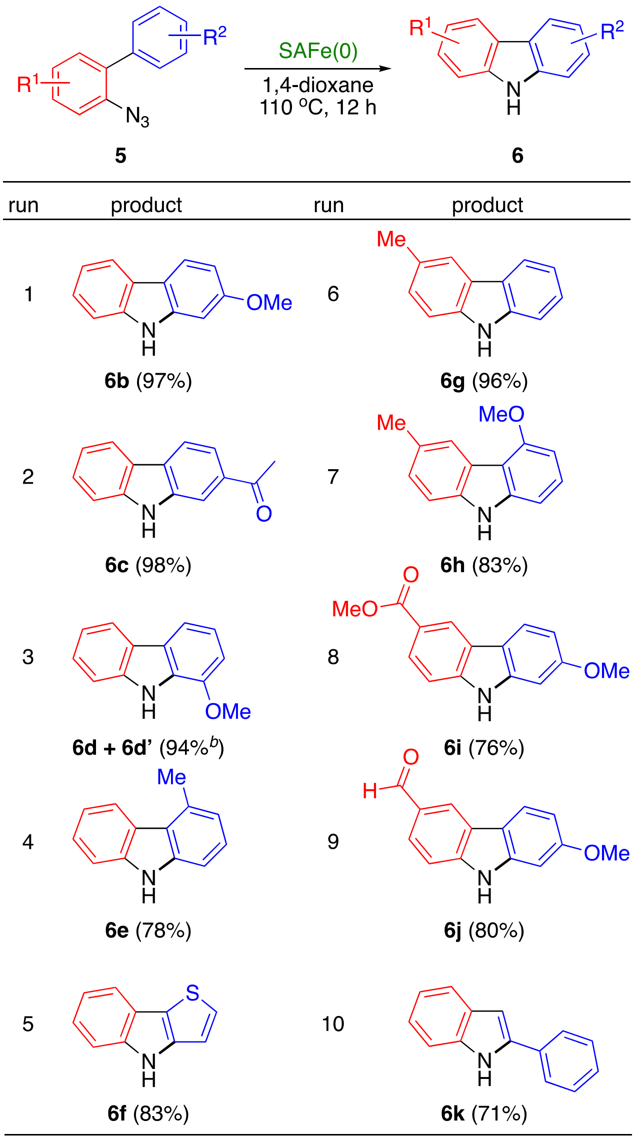
For carbon—nitrogen bond formation, the intramolecular C(sp^2)—H amination of 2-azidebiphenyl (**5a**) proceeded in the presence of SAFe(0), producing an annulated product **6a** under ligand-free conditions (Tables S7 and S8[16]). After this success, we expanded the substrate scope through applying liquid-phase combinatorial synthesis using the same sheet of SAFe(0) repeatedly (Scheme 3). Substrates with substituents in the unsubstituted phenyl ring (blue) of 2-azidobiphenyl (**5b**—**5e**) were examined. The reaction could tolerate phenyl rings substituted with electron-donating groups (EDGs) and electron-withdrawing groups (EWGs). In the presence of a substituent at the meta position of this phenyl ring, a mixture

Scheme 2. Liquid-Phase Combinatorial Synthesis Using SAFe(0) and Aryl Iodides[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 equiv), K_2CO_3 (2.5 equiv), 1,4-dioxane (2.0 mL), H_2O (1.0 mL). [b] Thiophene boronic acid (2.5 equiv) was used.

Scheme 3. Liquid-Phase Combinatorial Synthesis Using SAFe(0) and 2-Azidebiphenyls[a]



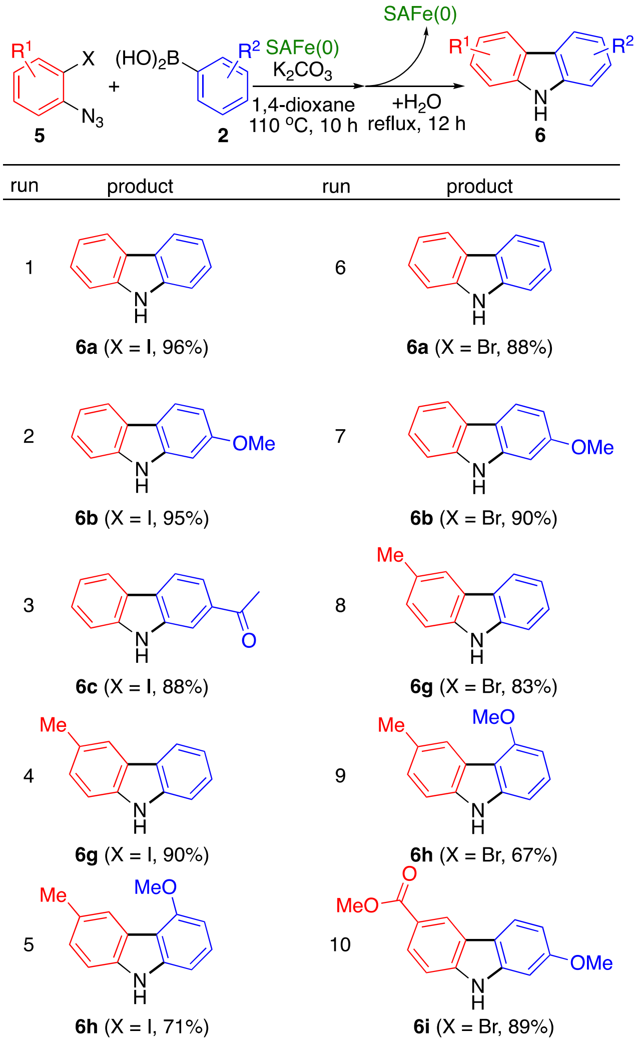
[a] Reaction conditions: **5** (0.40 mmol), 1,4-dioxane (4.0 mL). [b] Regioisomers were obtained (**6d**: 1-methoxycarbazole, **6d′**: 3-methoxycarbazole, **6d**/**6d′** = 1.10).

of products **6d**/**6d′** was obtained in good yield but with low regioselectivity. These observations are consistent with previous reports[3a] on the metal-catalyzed processes. 1-Azide-2-heteroaryl-benzene was tolerated under the optimized conditions to produce **6f**, showing applicability to the synthesis of heteroarene-fused carbazoles such as 4*H*-thieno[3,2-*b*]-indole. Next, various substrates with a substituent in the azidephenyl ring (red) were examined. Substrates with either EDG substituents (**5g**, **5h**) or EWG substituents (**5i**, **5j**) reacted smoothly under the optimized conditions, giving the desired carbazoles in high yields. In addition, 2-azidestilbene (**5k**) was tolerated in the reaction system, giving 2-phenylindole (**6k**, 71%).

Because both the Suzuki–Miyaura coupling (C–C) and C(sp^2)–H amination (C–N) proceeded ligand-free, we hypothesized that these reactions could be carried out in one pot using SAFe(0). After the optimization of the reaction conditions, we found that SAFe(0) could work for the one-pot C–C/C–N bond formation reaction of 1-azide-2-iodobenzene (**5l**) and phenylboronic acid (**2a**), giving the carbazole (**6a**) in 96% yield. We next investigated the substrate scope of this one-pot reaction by using the same SAFe(0) repeatedly (Scheme 4). The reaction of 1-azide-2-iodo (bromo) benzene derivatives and phenylboronic acid derivatives proceeded and gave moderate to high yields (67–95%).

X-ray photoelectron spectroscopy (XPS) experiments were conducted to investigate the structure and chemical composition of the SAFe(0) precatalyst. The spectra are shown in Figure S1. For SAFe(0) samples before and after use in the Suzuki– Miyaura coupling of **1a** and **2a** in Table S4, the strongest peak was located at the binding energy (BE) of 707.0 eV, and there was a weaker one at BE = 709.6 eV, etching the surface of SAFe(0) (Figure S1).[17] This correlates with the BE values of 707.0 and 709.6 eV reported for the Fe $2p_{3/2}$ regions

Scheme 4. Liquid-Phase Combinatorial Synthesis of the One-Pot C−C Bond-Forming Reaction[a]



[a]Reaction conditions: **5** (0.5 mmol), **2** (1.5 equiv), K_2CO_3 (2.5 equiv), 1,4-dioxane (2.0 mL), H_2O (1.0 mL).

of iron(0) and iron(II), respectively. This result suggests that the particles consisted of iron(0) with some iron oxide layer on the surface.

Figure S2 presents the iron K-edge X-ray absorption near-edge structure (XANES) spectra of SAFe(0) in the pristine state (black) and after 10 cycles of use in the Suzuki−Miyaura coupling of **1a** and **1b** (red) in Table S4. The spectra of Fe foil, $FeSO_4$, Fe_3O_4, and $FeCl_3$ standard samples are also shown for reference. The spectra of SAFe(0) before and after the reaction both resemble that of Fe foil most closely, whereas the other three references ($FeSO_4$, Fe_3O_4, and $FeCl_3$) showed more significant difference in their chemical shifts. These data led us to conclude that the iron component in SAFe(0) was mostly iron(0).

To examine the sulfur component in SAFe(0), the sulfur K-edge XANES spectra before and after 10 cycles of the same reaction are displayed in Figure S3, together with the spectra of four standards (Na_2SO_3, $Na_2S_2O_8$, Na_2SO_4, and SAPd). Both before and after the Suzuki−Miyaura coupling, the SAFe(0) sample displayed a clear resonance at 2481.6 eV. A comparison with the standard references suggests that the sulfur in SAFe(0) is strongly oxidized into SO_4^{2-}, with a chemical shift similar to that previously reported for SAPd.

In the scanning electron microscopy (SEM, JSM-7400) observation of SAFe(0), the more prominent morphology was the many layers that uniformly accumulated on the gold mesh as a supporting solid (Figure S4a,b). A further investigation of the layers was conducted using transmission electron microscopy (TEM, JEM-2100F). For surface protection, a carbon coating layer was deposited by an SEM focused ion beam (FIB, JIB-4600F). The TEM sample was prepared by sputtering with a gallium ion beam. The sectional images revealed that the layers on the gold mesh had a total thickness of 90 to 140 nm and consisted of iron NPs approximately 6−10 nm in size (Figures S4c and S5). These data indicated that the iron(0) NPs ca. 10 nm or less in size were encapsulated in xylene polymer derivatives and uniformly deposited on the gold mesh to generated the multilayers.

On the basis of the above observations, we conclude that SAFe(0) consisted of iron(0) NPs in a matrix formed by the complexation of SO_4^{2-} and *p*-xylene as the solvent and that the iron(0) NPs were self-assembled into multilayers (Figure S4d).

In summary, we successfully developed a sulfur-modified Au-supported reservoir of iron(0) NPs, SAFe(0), for ligand-free Suzuki−Miyaura coupling and C(sp^2)−H amination with low leaching and high recyclability. SAFe(0) was easily prepared using our *in situ* PSSO method and a stronger reductant, *Si*-DHP. As representative one-pot C−C/C−N bond-forming reactions, Suzuki−Miyaura coupling and C−H amination were successfully demonstrated with SAFe(0) to give carbazole derivatives. Detailed spectroscopic analyses showed that the iron(0) NPs with a size of 6−10 nm, which tend to be easily oxidized to iron(III), were stable in air when immobilized in SAFe(0) with self-assembled multilayers. These results suggest that the *in situ* PSSO method could be a versatile technique for immobilizing metal NPs. Further studies are in progress to extend it to other metals and to use it to prepare catalysts for organic synthesis.[18]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02574.

Experimental procedures (preparation of SAFe(0) and coupling reaction experiments), SAFe(0) characterization data, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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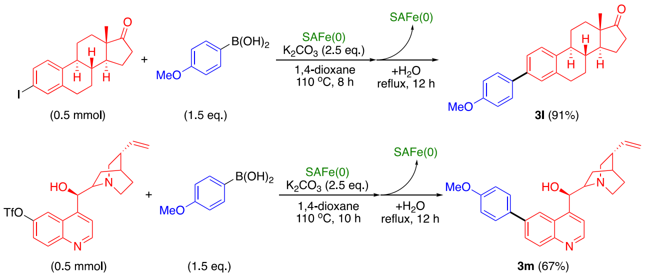
(12) Palladium contaminants were not detected from SAFe(0) by ICP-MS (LOD (limit of detection): 0.01 mg/L).

(13) Our methodology works well with the addition of a tiny amount of active iron(0) species, which has been recognized an efficient method, but it is difficult.

(14) This reaction system was applicable to a 1 mmol scale reaction. See Table S6.

(15)



(16) This reaction system was applicable to a 1 mmol scale reaction.

(17) Etching time (10 s and 110 s) were examined. See the Supporting Information.

(18) Even though there is a possibility that a ligand might allow these reactions to proceed under much milder conditions, it is difficult to add so little ligand.