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Carbon(sp^2)-carbon(sp^3) Bond-forming Cross-coupling Reactions Using Sulfur-Modified Au-Supported Nickel Nanoparticle Catalyst

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Abstract. We report a carbon(sp^2)-carbon(sp^3) bond-forming cross-coupling reactions by employing a nano-size nickel catalyst supported on sulfur-modified gold (SANi). This transformation demonstrates an efficient synthesis of functionalized aryl compounds, including heterocycles. Notably, the reactions proceeded in good yields with significantly low leaching of nickel from SANi. Moreover, SANi could be recycled several times without significant loss of catalytic activity.

It is known that the higher the ratio of sp^3 carbon to total carbon in a compound, the more likely it is to be used as a drug.[1] Therefore, the establishment of coupling reactions using organometallic reagents with sp^3 carbon is important for the application of cross-coupling reactions to drug discovery chemistry.[2-4]

In addition, the commonly used homogeneous transition metal catalysts have the following problems:1

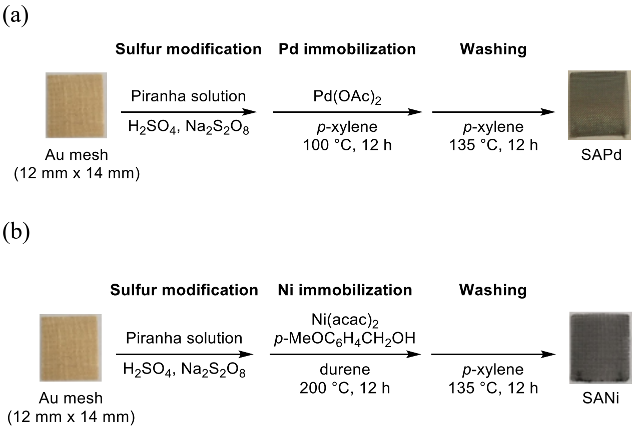
- Transition metal catalysts are generally disposed of after one reaction even though they often use rare elements.[5]
- Ligands and metal catalysts need to be removed from the products. In the synthesis of functional compounds rich in heteroatoms, metals may remain in the reaction system, which is a particular problem in the synthesis of pharmaceuticals.[6] Furthermore, the amount of metal residues in pharmaceuticals is legally regulated.[7, 8]
- In general, ligands are expensive, and many cannot be synthesized easily, although some are commercially available.

To solve these problems, a variety of heterogenous catalysts have been developed.

Metal nanoparticles[9] (NPs) are 1–100 nm diameter particles consisting of tens to thousands of metal atoms that exhibit different properties from bulk metals. As the particle size of the NPs decreases, the specific surface area per volume increases in inverse proportion to the particle size and this particle size effect is known to result in significant differences in optical, catalytic, electrical and magnetic properties compared to bulk metals. To date, metal NP catalysts that take advantage of these NP properties have been used in a variety of fields. Among them, the solid-supported metal NP catalysts are easy to remove from the reaction system, which allows the catalysts to be reused. In addition, the amount of metal remaining in the reaction solution is lower than that of homogeneous metal catalysts, making them useful in pharmaceutical synthesis.

In recent years, the development of reactions using low-cost metal catalysts has become a necessity from an economic and elemental strategic point of view, and the development of inexpensive base metal NP catalysts such as Ni has become more active.[10] In 2017, Hajipour et al. reported the Heck reaction using NiNP catalysts supported on silica.[11] This catalyst was able to be used for six repetitions, and the Ni leakage could be kept below 0.1 ppm. However, NiNP-catalyzed carbon(sp^2)-carbon(sp^3) bond-forming cross-coupling reactions have rarely been reported and are a developing research area. We have successfully developed a Sulfur-modified Au-supported Palladium (SAPd) catalyst with highly active PdNPs on the surface of a sulfur-modified gold mesh (Scheme 1a).[12]

We have also successfully prepared a Sulfur-modified Au-supported Nickel (SANi) catalyst, (Scheme 1b).[13] The key to the preparation of SANi was the addition of 4-methoxybenzyl alcohol as an organic reducing agent during the loading of Ni. In addition, durene (1,2,4,5-tetramethylbenzene) was used as a solvent because a higher temperature was required for the nanoparticulation of Ni.



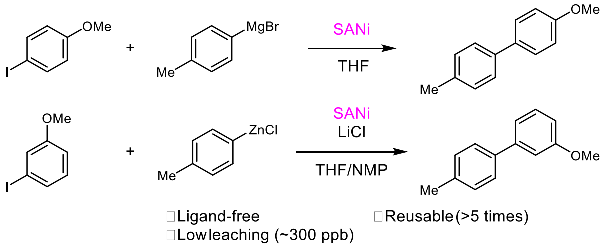
Scheme 1. Preparation of SAPd (a) and SANi (b).

The surface structure of SANi has been analyzed by X-ray Absorption Fine Structure (XAFS), and found to be loaded with Ni(0)NPs with a particle size of about 3 nm. Although the surface structure of SANi was not analyzed in detail by Transmission Electron Microscopy (TEM), it can be inferred that NiNPs are supported and stabilized by the self-assembly of sulfate ions and a xylene polymer, similar to SAPd.[14]

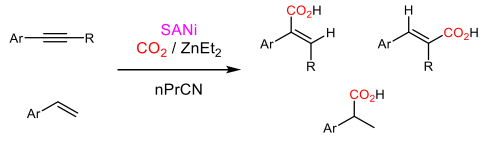
Furthermore, SANi shows high catalytic activity in the Kumada and Negishi coupling reactions of carbon(sp^2)-carbon(sp^2) bond formation without the use of ligands and can be used repeatedly for more than five times (Scheme 2a).[13] It has also been reported that SANi can be applied to the immobilization reaction of carbon dioxide on alkenes and alkynes (Scheme 2b).[15]

As mentioned above, carbon(sp^2)-carbon(sp^2) bond-forming cross-coupling reactions using SAPd and SANi have been achieved, but their application to carbon(sp^2)-carbon(sp^3) bond-forming cross-coupling reactions has been unexplored, except for the example shown in Scheme 2c. Scheme 2c shows an example of Negishi coupling of 3-iodoanisole and *n*-butylzinc chloride using SANi, but the yield was low (only 32%). With this research background, we decided to develop a carbon(sp^2)-carbon(sp^3) bond-forming cross-coupling reaction using SANi.

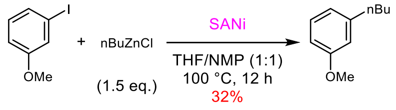
(a) Carbon(sp^2)-carbon(sp^2) bond forming Kumada coupling reaction and Negishi coupling reaction using SANi.



(b) Ligand-free carbon dioxide fixation reaction using SANi.



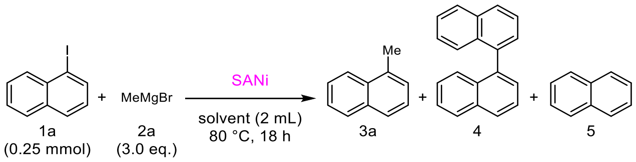
(c) Previous achievement of carbon(sp^2)-carbon(sp^3) bond forming Negishi coupling reaction using SANi.



Scheme 2. Examples of reactions catalyzed by SANi

The Kumada coupling reaction of aryl iodide (**1**) with alkyl Grignard reagents (**2**) to form carbon(sp^2)-carbon(sp^3) bonds using SANi was investigated under various conditions. Table 1 shows the results of the solvent investigation. A solution of 1-iodonaphthalene (**1a**, 0.25 mmol), SANi and methylmagnesium bromide (**2a**, 3.0 eq.) in toluene was heated at 80°C, and the expected product, 1-methylnaphthalene (**3a**), was isolated with 66% yield (Entry 1). When THF – the optimal solvent for the Kumada coupling reaction using SANi to form carbon(sp^2)-carbon(sp^2) bonds – was used, the yield of the desired product decreased to 34% (Entry 2). When DME and 1,4-dioxane were used, the yields were 29% and 47%, respectively (Entries 3 and 4). In an ether solvent, naphthalene (**5**) was obtained as a byproduct because in this solvent halogen-magnesium exchange occurs between **1a** and **2a**, resulting in naphthylmagnesium 1-bromide (iodide), which is thought to be why **5** was formed as a byproduct. From the above results, toluene in Entry 1 was selected as the optimal solvent.[16] Furthermore, it was found that this reaction could not proceed without SANi (Entry 5). When the more reactive methylmagnesium iodide (**2a'**) was used as the Grignard reactant, the yield of the desired product was increased to 81% (Entry 6).[17, 18, 19]

Table 1. Carbon(sp^2)-carbon(sp^3) bond forming Kumada coupling reaction catalyzed by SANi: Screening of solvents.



Entry	Solvent	Yield (%)		
		3a	**4**	**5**
1	Toluene	66	18	0
2	THF	34	11	0
3	DME	29	6	36
4	1,4-Dioxane	47	3	9
5[a]	Toluene	No Reaction		
6[b]	Toluene	81	18	0

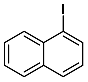
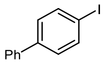
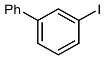
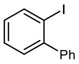
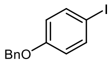
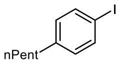
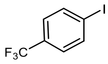
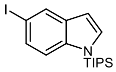
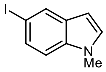
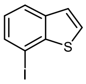
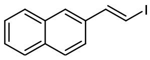
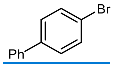
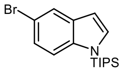
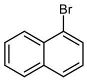
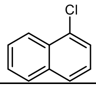
[a] Without SANi; [b] MeMgI was used instead of MeMgBr.

In Table 2, the substrates of aryl halides were examined using the above optimum conditions. The para-substituted **1b** and meta-substituted **1c** gave the desired products in good yields (Entries 2 and 3). For ortho-substituted **1d**, the reaction time was 48 h due to steric hindrance, but the desired product was obtained in good yield (Entry 4). Substrates with electron-donating (**1e**, **1f**) or electron-withdrawing (**1g**) groups substituted on the benzene ring, substrates with heterocycles (**1h**, **1i**, **1j**) and alkenyl iodide (**1k**) gave the desired couplings in good yields (Entries 5–11). When aryl bromide was used, the desired couplings were obtained in moderate yields by setting the reaction temperature to 100°C (Entries 12–14). In the case of aryl chloride, the reaction was carried out at 110°C for a long time, but the desired product was hardly obtained (Entry 15).

When **1a** and other Grignard reagents were employed under optimal conditions (Table 3), the corresponding coupling products were obtained in good yields for alkyl groups without β-hydrogen, a cyclopropyl group and allyl group (Entries 1–5). For alkyl groups with β-hydrogen, such as an ethyl group, the β-hydrogen desorption seems to have progressed and the desired couplings were rarely obtained (Entry 6).

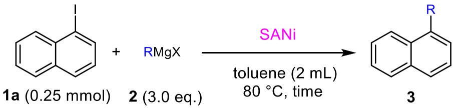
Table 2. Carbon(sp^2)-carbon(sp^3) bond-forming Kumada coupling reaction catalyzed by SANi: Substrate scope

$$\underset{\textbf{1}\text{ (0.25 mmol)}}{\text{Ar-X}} + \underset{\textbf{2a'}\text{ (3.0 eq.)}}{\text{MeMgI}} \xrightarrow[\text{toluene (2 mL)}\atop 80\ ^\circ\text{C, time (h)}]{\text{SANi}} \underset{\textbf{3}}{\text{Ar-Me}}$$

Entry	Ar-X	Time (h)	Yield (%)[a]
1		19	**3a** (81)
2		3	**3b** (78)
3		3	**3c** (72)
4		48	**3d** (78)
5		24	**3e** (57)
6		48	**3f** (61)
7		3	**3g** (63)[b]
8		18	**3h** (86)
9		24	**3i** (66)
10		72	**3j** (64)
11		15	**3k** (62)
12[c]		19	**3b** (28)
13[c]		24	**3h** (48)
14[c]		19	**3a** (51)
15[d]		120	**3a** (trace)

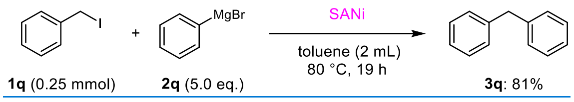
[a] Isolated yield; [b] GC-MS yield; [c] Reaction temperature was 100°C. [d] Reaction temperature was 110°C.

Table 3. Carbon(sp^2)-carbon(sp^3) bond-forming Kumada coupling reaction catalyzed by SANi: Scope of Grignard reagent



Entry	RMgX	Time (h)	Yield (%)$^{a)}$
1	MeMgI	19	**3a** (81)
2	BnMgCl	19	**3l** (74)
3	TMSCH$_2$MgCl	30	**3m** (84)
4	*c*PrMgBr	42	**3n** (42)
5	allylMgBr$^{b)}$	19	**3o** (25)
6	EtMgBr	19	**3p** (trace)

$^{a)}$ Isolated yield; $^{b)}$ 5.0 eq.

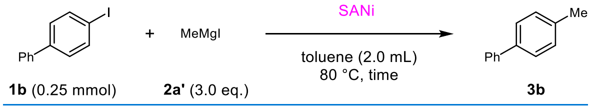


Scheme 3. Carbon(sp^3)-carbon(sp^2) bond forming Kumada coupling reaction catalyzed by SANi: Coupling reaction of an aromatic Grignard reagent (PhMgBr) with an alkylhalide (benzyl iodide).

This methodology applies to the Carbon(sp^3)-carbon(sp^2) bond-forming Kumada coupling reaction between an aromatic Grignard reagent (PhMgBr) and an alkyl halide (benzyl iodide) (Scheme 3).

Using the optimum conditions, three sheets of SANi were subjected to the Kumada coupling reaction shown in Table 4 five times and the desired couplings were obtained in high yields in all cases, although longer reaction times were required as the number of repeated uses increased. The amount of Ni remaining in the reaction solutions was measured by inductively coupled plasma mass spectrometry (ICP-MS). It was revealed that the leaching amount of Ni was 2–30 μg, which is 0.3–5% of the total amount of Ni on SANi,[13, 20] and the concentration of Ni in the reaction mixture was 1.2–15.7 ppm.

Table 4. Kumada coupling reaction of **1b** and **2a** with SANi (repeated use) and the Ni leakage in the reaction solution



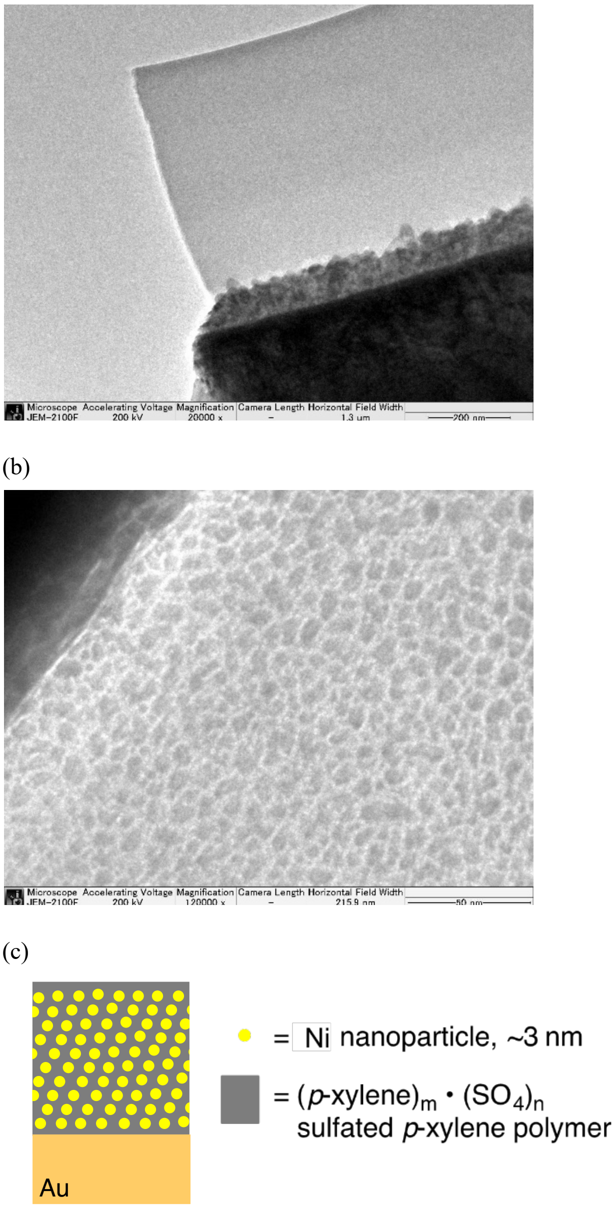
Run	Time (h)$^{a)}$	Yield of **3b** (%)$^{a, b)}$	Released Ni (μg)$^{a)}$	ppm$^{a)}$
1st	3	90	12	6.5
2nd	22	98	13	6.9
3rd	40	90	14	7.6
4th	64	95	4	1.9
5th	64	76	4	2.0
Total			47	

$^{a)}$ The average of three sets of reaction; $^{b)}$ GC-MS yield.

Investigation of the layers was conducted using TEM (JEM-2100F). For surface protection, a carbon coating layer was deposited. It was scattered by focused ion beam (FIB, JIB-4600F), observing by Scanning Electron Microscopy (SEM). 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 about 80 nm and consisted of NiNPs approximately 3 nm in size (Scheme 4a, b). These data indicated that Ni(0)NPs of ca. 3 nm or less in size, were encapsulated in durene polymer derivatives and uniformly deposited on the gold mesh to generate the multilayers. Taking these TEM images and previously reported informationinto account,[13] we can draw a structual diagram of SANi(0) (Scheme 4c).

In summary, we investigated the reactivity of SANi toward carbon(sp^2)-carbon(sp^3) bond-forming cross-coupling reactions. It was found that the SANi-catalyzed carbon(sp^2)-carbon(sp^3) bond-forming cross-coupling reactions proceeded efficiently under mild conditions. Aryl halides, including heterocycles, were smoothly converted to the corresponding alkylated products. Also, SANi can be easily reused at least five times, with low leaching of Ni. In this report, we have also succeeded in investigating the surface structure of SANi using TEM.

(a)



Scheme 4. Surface structure of SANi: (a,b) TEM images; (c) structural diagram.

Experimental section

General procedure for the synthesis of **3a**

In a test tube (15 Φ), a mixture of 1-iodonaphthalene **1a** (64.5 mg, 0.254 mmol) was dissolved in toluene (2 mL) in the presence of SANi under an argon atmosphere. MeMgI **2a'** (3 M Et_2O solution, 0.25 mL, 0.75 mmol) was added into the reaction mixture and heated at 80 °C for 19 h without stirring. After the reaction mixture had been cooled to room temperature, the SANi was removed from the reaction mixture and rinsed several times with EtOH. Then, sat. NH_4Cl aq. (5 mL) was added into the reaction mixture, and the reaction mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residual crude product was purified by flash silica gel column chromatography (100% *n*-hexane) to afford 1-methylnaphthalene **3a** (29.2 mg, 0.205 mmol, 81%) as a colorless oil.

Acknowledgements

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Keywords

catalyst recycling; cross coupling nanostructure; C(sp^2)-C(sp^3) coupling; nickel

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[19] A control experiment with SAPd yielded the product **3a** in 13% yield.

[20] ICP-MS analysis showed that 509 mg (the average of three samples) of Ni were immobilized on SANi. See reference 17.

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Carbon(sp^2)-carbon(sp^3) Bond-forming Cross-coupling Reactions Using Sulfur-Modified Au-Supported Nickel Nanoparticle Catalyst

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