Ligand-free Reductive Coupling of Aldehyde with 1,3-diene Using Sulfur-Modified Au-Supported Nickel Nanoparticle Catalyst

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Full Paper

Ligand-free Reductive Coupling of Aldehyde with 1,3-diene Using Sulfur-Modified Au-Supported Nickel Nanoparticle Catalyst

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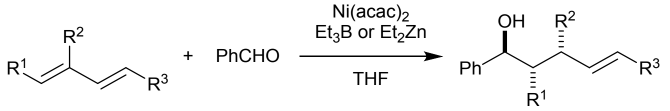
Ligand-free reductive coupling of aldehydes with 1,3-diene was successfully developed using the nickel nanoparticle catalyst SANi, Sulfur-modified Au-supported Nickel. Leakage of nickel species into the reaction solution is minimal. SANi can be used repeatedly and is an environmentally benign reaction.

One attractive strategy for developing carbon-carbon bond forming reactions with conjugated dienes is the transition metal-catalysed reductive coupling of dienes with carbonyls, and several reactions have been developed.[1] For example, the groups of Mori[2], Tamaru[3] and others[4] reported the nickel-catalysed reductive coupling of aldehydes with 1,3-dienes such as isoprene (Scheme 1). The Krische group reported the Ru-catalysed regioselective formation of branched homoallylated alcohols by the allylation of carbonyls with diene under hydrogenation and hydrogen auto-transfer conditions.[5] Asymmetric reactions were also developed.[6] Because the products, homoallylated alcohols, are useful compounds as synthetic raw materials for functional materials, pharmaceuticals, and agrochemicals, as well as intermediates, the development of efficient synthetic methods is desirable.



Scheme 1. Previous report ; nickel-catalysed reductive coupling of aldehydes with 1,3-dienes.[3]

On the other hand, the commonly used homogeneous transition metal catalysts have the following 3 problems.

1. Transition metal catalysts are generally disposed of after one reaction even though they often use rare elements.[7]
2. 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.[8] Furthermore, the amount of metal residues in pharmaceuticals is legally regulated.[9, 10]
3. In general, ligands are expensive, and many cannot be synthesized easily,[11] although some are commercially available.

These problems should be solved from the viewpoint of SDGs, and a variety of heterogenous catalysts have been developed.[12]

Metal nanoparticles[13] (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.[14] In 2017, Hajipour et al. reported the Heck reaction using Ni NP catalysts supported on silica.[15] This catalyst was able to be used for six repetitions, and the Ni leakage could be kept below 0.1 ppm. However, Ni NP-catalysed reductive coupling of aldehydes with 1,3-dienes has rarely been reported

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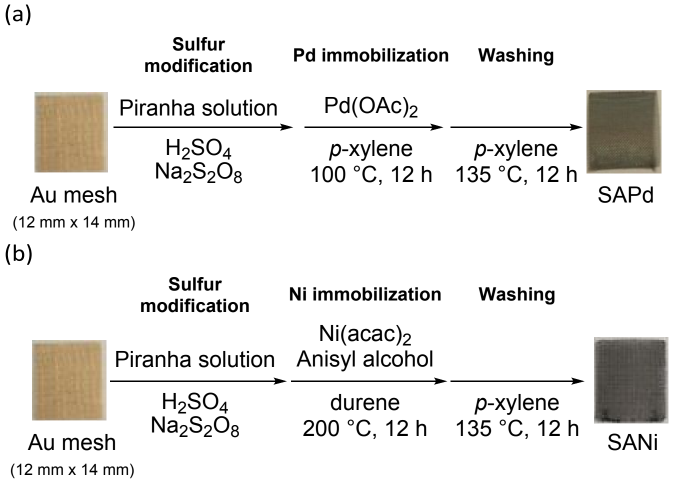
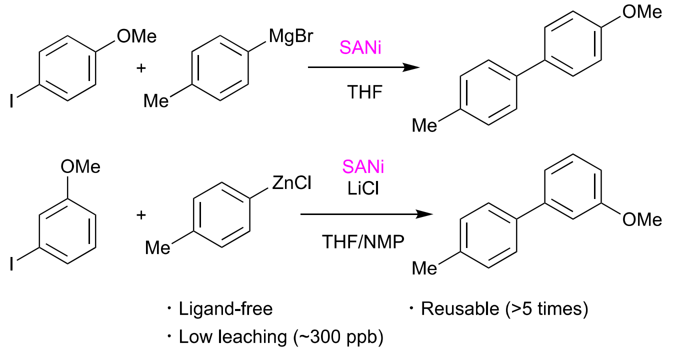
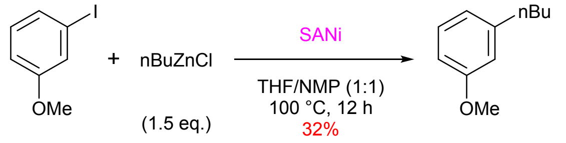


Scheme 2. Preparation of SAPd (a) and SANi (b)

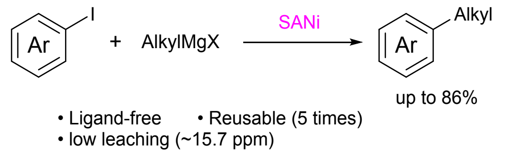
(a) Carbon(sp^2)-carbon(sp^2) bond forming Kumada coupling reaction and Negishi coupling reaction using SANi.



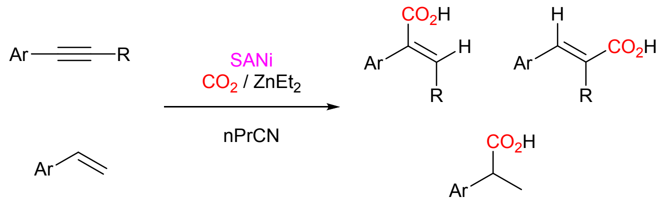
(b) Carbon(sp^2)-carbon(sp^3) bond forming Negishi coupling reaction using SANi.



(c) Carbon(sp^2)-carbon(sp^3) bond forming Kumada coupling reaction using SANi.



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



Scheme 3. Examples of reactions catalysed by SANi

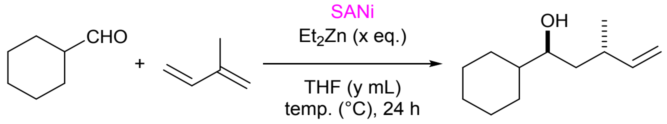
and is a developing research area. We have successfully developed a Sulfur-modified Au-supported Palladium (SAPd) catalyst with highly active Pd NPs on the surface of a sulfur-modified gold, 100 mesh (Scheme 2a).[16] We have also successfully prepared a Sulfur-modified Au-supported Nickel (SANi) catalyst, (Scheme 2b).[17] 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.

The surface structure of SANi was 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. The surface structure of SANi was also analyzed in detail by Transmission Electron Microscopy (TEM). About 3 nm sized Ni NPs are supported and stabilized by the self-assembly of sulfate ions and a durene polymer, similar to SAPd.[18]

Furthermore, SANi shows high catalytic activity in the Kumada and Negishi coupling reactions without the use of ligands and can be used repeatedly for more than five times (Scheme 3a-c).[17] In these reactions, heterogeneous catalyst SANi shows unique characteristics; we speculate that just a tiny amount of Ni(0) NPs leave from the SANi surface and efficiently work as actual active species in these coupling reactions. SANi is likely used as a reservoir to give a minimum amount of Ni(0) NPs for the reaction. It has also been reported that SANi can be applied to the immobilization reaction of carbon dioxide on alkenes and alkynes (Scheme 3d).[19]

Here, we report the unprecedented Ni NP-catalysed reductive coupling of aldehydes with 1,3-dienes. We used SANi as Ni NP.

Table 1. Reductive coupling of aldehydes with 1,3-dienes using SANi; optimization of reaction conditions.



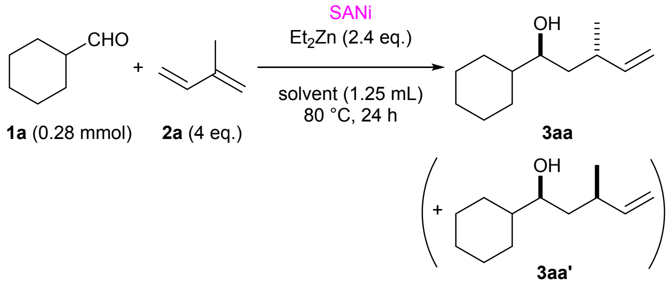
1a (0.28 mmol) **2a** (4.0 eq.) **3aa**

entry	Et_2Zn (x eq.)	THF (y mL)	Temp (℃)	Yield (%)
1	2.4	1.25	80	50
2	2.4	1.25	60	33
3	2.4	1.25	100	49
4	1.2	1.25	80	39
5	3.6	1.25	80	39
6	2.4	2.5	80	50
7	2.4	0.63	80	50
8[a]	2.4	1.25	80	32
9[b]	2.4	1.25	80	<50
10[c]	2.4	0.63	80	66
11[d]	2.4	1.25	80	0

[a] Et_2Zn was added by dropwise manner (5 min.). [b] 8 equivalent of **2a** was used. [c] Half scale (0.14 mmol). [d] Without SANi.

First, SANi was added to a THF solution of 0.28 mmol of aldehyde **1a**, 4 equivalents of isoprene (**2a**), and 2.4 equivalents of Et_2Zn and heated at 80 °C for 24 h. Only the 1,3-anti form of 1-cyclohexyl-3-metyl-4-pentenol (**3aa**) was obtained with a 50% yield. Therefore, in entries 2 and 3, the reaction temperature, in entries 4 and 5, the equivalent amount of Et_2Zn, in entries 6 and 7, the concentration of the reaction, were examined, respectively, and the results were similar to or lower than those of entry 1. Then, in entry 8, the condition of gradually dropping Et_2Zn, in entry 9, the condition of increasing the equivalent amount of **2a** to 8 equivalents, and in entry 10, the condition of reducing the amount of **1a** by half to 0.14 mmol, were examined, respectively. The results showed that in the case of entry 10, the objective **3aa** was obtained with a 66% yield. Entry 11 also confirmed that this reaction does not proceed without SANi. No compounds of note other than the starting materials and products were observed during the above experiment.

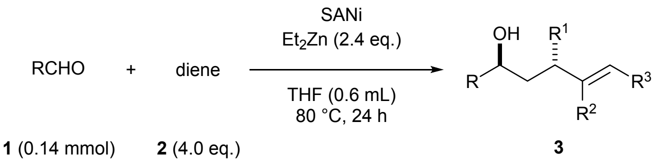
Table 2. Reductive coupling of aldehydes with 1,3- dienes using SANi; solvent effect.

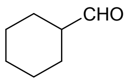
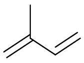
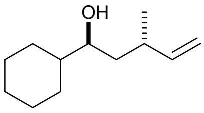
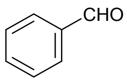
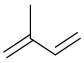
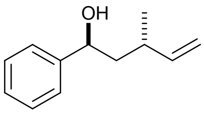
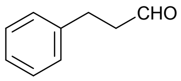
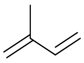
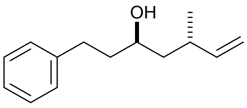
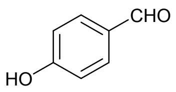
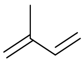
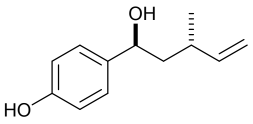
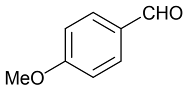
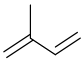
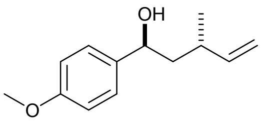
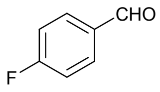
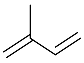
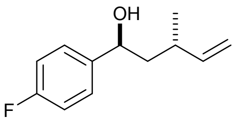
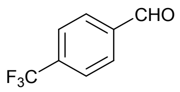
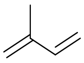
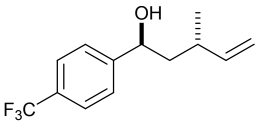
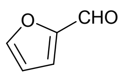
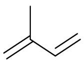
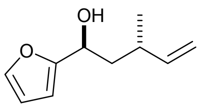


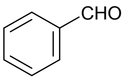
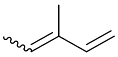
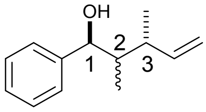
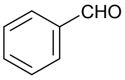
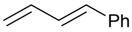
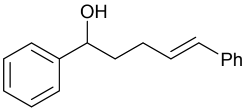
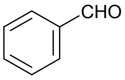
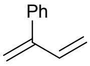
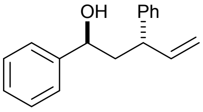
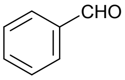
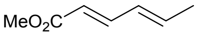
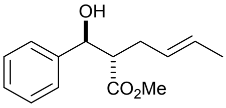
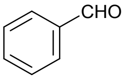
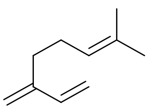
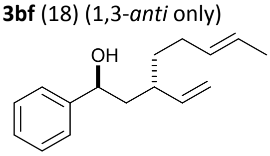
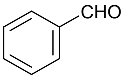
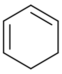
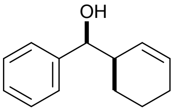
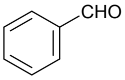
entry	solvent	yield of **3** (%)
1	THF	50 (1,3-*anti* only)
2	MeCN	16 (*anti* : *syn* = 2 : 1)
3	DMA	6 (1,3-*anti* only)
4	PhMe	4 (1,3-*anti* only)
5	CPME	0
6	1,4-dioxane	9 (1,3-*anti* only)

Next, the solvent effect was examined using the conditions of entry 1 in Table 1. All of the solvents shown in Table 2 resulted in lower yields of the product than when THF was used. On the other hand, the 1,3-syn form, (**3aa'**), was obtained in a 2:1 ratio only with acetonitrile, but due to the low yield, we did not study this in any further detail. Based on the above results, THF in entry 1 was selected as the optimal solvent. We then decided to examine the range of substrate adaptations under the conditions of entry 10 in Table 1 (Table 3). First, we examined aldehydes. In Entry 2, using benzaldehyde (**1b**) as the aldehyde, the target compound **3ba** was isolated with a high yield of 76%, both regio- and stereoselectively. In Entry 3, an aliphatic aldehyde **1c**, was converted to **3ca**, albeit with a low yield. In entries 4,5,6,7,8, we used other aromatic aldehydes, which were converted to the corresponding products in 75, 89, 44, 45, and 30 % yields, respectively. We also fixed the aldehyde to **1b** and studied the diene. In entry 9, an isoprene derivative with methyl at the reaction point also gave the target compound with a good yield, but a 1,2-syn stereoisomer was produced. It is possible to use a diene such as **2c**, **2d**, **2e**, **2f** yielding the corresponding products **3bc**, **3bd**, **3be**, **3bf** (entries 10, 11, 12, 13). Entry 14 also showed that cyclic 1,3-diene could be used as a substrate. The results of entry 15 indicate that the structure of 1,3-diene is important. The stereoselectivity of these reactions may also be determined by the electron density of the terminal carbon of the diene.

Table 3. Reductive coupling of aldehydes with 1,3- dienes using SANi; substrate scope.



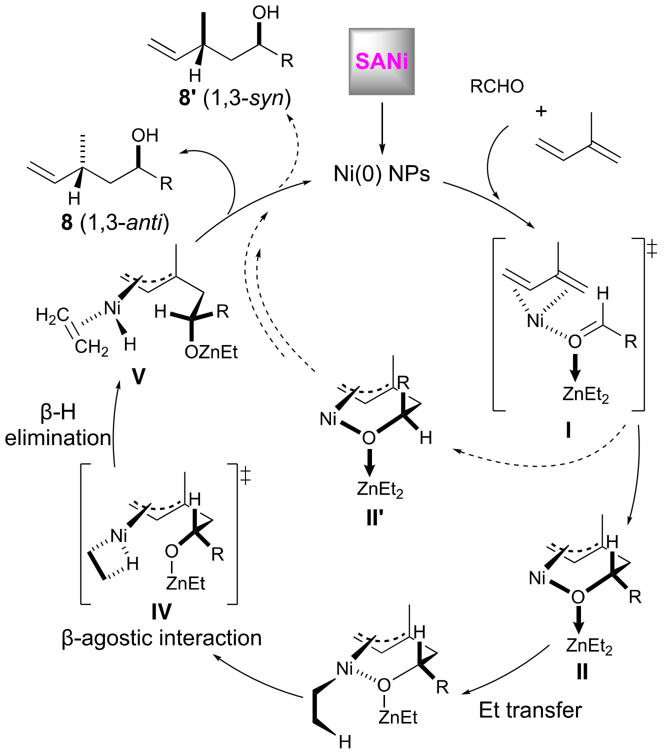
entry	**1** (R =)	**2**	yield of **3** (%)^a
1	**1a**  	**2a** 	**3aa** (66) (1,3-*anti* only) 
2	**1b**  	**2a** 	**3ba** (76) (1,3-*anti* only) 
3	**1c**  	**2a** 	**3ca** (29) (1,3-*anti* only) 
4	**1d**  	**2a** 	**3da** (75) (1,3-*anti* only) 
5	**1e**  	**2a** 	**3ea** (89) (1,3-*anti* only) 
6	**1f**  	**2a** 	**3fa** (44) (1,3-*anti* only) 
7	**1g**  	**2a** 	**3ga** (45) (1,3-*anti* only) 
8	**1h**  	**2a** 	**3ha** (30) (1,3-*anti* : *syn* = 5 : 1) 
9	**1b**	**2b** (*cis*:*trans* = 1:2)	**3bb** (63) (1,3-*anti* only, 1,2-*anti* : *syn* = 3 : 1)

			
10	**1b** 	**2c** 	**3bc** (25) 
11	**1b** 	**2d** 	**3bd** (27) (1,3-*anti* only) 
12	**1b** 	**2e** 	**3be** (20) (1,3-*anti* only) 
13	**1b** 	**2f** 	**3bf** (18) (1,3-*anti* only) 
14	**1b** 	**2g** 	**3bg** (30) (1,2-*anti* : *syn* = 10 : 3) 
15	**1b** 	**2h** 	**3bh** (0)

[a] Isolated yield. [b] *cis* : *trans* = 1 : 2.

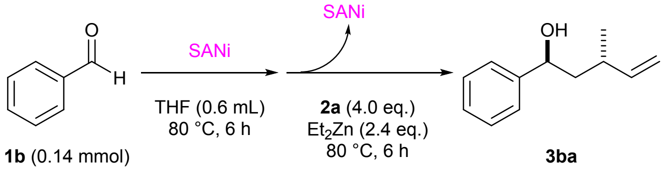
Next, the reaction mechanism is discussed. From the substrate generality, we assume that the reaction is basically the same as when using homogeneous Ni catalysts.[3f] That is, oxidative cyclization proceeds via transition state I, which consists of an aldehyde with the Et$_2$Zn coordination, a diene, and Ni(0) NPs. The diene pushes electrons to the aldehyde on the one hand and receives electrons from Ni on the other. These two actions may be the reason why both electron-rich and electron-poor dienes are allowed in this reaction. In addition, the structure of the π-allyl complex in intermediate II may make it difficult to allow dienes that are sterically crowded with methyl groups. The ethyl group then rearranges to form intermediate **III**, the β-agostic interaction forms transition state IV, and β-hydrogen elimination forms intermediate V, after which the target product **3** is formed.

Using the optimum conditions, three sheets of SANi were subjected to the reductive coupling of **1b** with **2a** shown in Table 4 five times and the desired couplings were obtained with high yields in all cases. SANi was added to a THF solution of 0.14mmol of aldehyde **1b** and the whole was heated at 80 °C for 6 h, After SANi was removed from the solution, 4 equivalents of isoprene (**2a**), and 2.4 equivalents of Et$_2$Zn were added to to the solution, and the whole was heated at 80 °C for 6 h. 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 5-23 µg, which is 0.7-3% of the total amount of Ni on SANi,[17, 20, 21] and the concentration of Ni in the reaction mixture was 6.01-29.5 ppm. These indicate that just a few mmol% of Ni species surprisingly catalyzed this reaction, while a few mol% of Ni species are usually employed in homogeneous reactions. We speculate that the actual active Ni species in this reaction could be the tiny amount of leached soluble Ni(0), ~3 nm, species from SANi.[22, 23, 24, 25] It should be noted that SANi is handled in the air without any loss in catalytic activities, while homogeneous Ni catalysts are usually unstable and should be handled in inert conditions.[26]



Scheme 4. Proposed reaction mechanism.

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



Run	yield of **3ba** (%)[a,b]	released Ni (µg)[a]	mmol%[a]	ppm[a]
1st	74	23±6.9	2.87	29.5
2nd	62	13±1.2	1.61	16.5
3rd	64	13±10.1	1.61	16.6
4th	65	10±4	1.27	13.1
5th	56	5±1.5	0.58	6.01

[a] The average of three sets of reaction. [b] GC-MS yield.

In summary, we developed a regio- and stereoselective homoallylation reaction of aldehydes with 1,3-dienes using a Ni NP catalyst, SANi, prepared by our original method. The reaction proceeded ligand-free and afforded homoallylated alcohols in a regioselective and 1,3-anti selective manner. SANi can be used repeatedly, and the amount of Ni leakage in the reaction solution was minimal. These results provide valuable information for considering the structure and fabrication of metal NP catalysts.

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Conflicts of interest

There are no conflicts to declare.

Author Contributions

Ryosuke Ohta: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Yasunori Shio:** Data curation, Formal analysis, Investigation, Methodology. **Mitsuhiro Arisawa:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing. All author contributed to Data curation, Formal analysis, Investigation.

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This study was partially supported by JST, CREST Grant Number JP JPMJCR20R1, Japan, by a Grant-in-Aid from JSPS KAKENHI (Grant No. JP 15KT0063), by Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number JP22ama121054, by Cooperative Research Program of "Network Joint Research Center for Materials and Devices" from the Ministry of Edu- cation, Culture, Sports, Science and Technology (MEXT).

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20 ICP-MS analysis showed that 716 μg and 684 μg (the average of three samples) of Ni were immobilized on SANi, before and after the reaction (5 times).

21 Au mesh is recyclable. Once used SANi is washed with HCl, we can use it as normal Au mesh.

22 Valence of the leached Ni spaces in the reaction mixture was analysed by XAFS. However, we could not get any information, because the amount of Ni was too trace.

23 The yield decreases when the catalyst is recycled. Some Ni leaches more easily whilst some is more difficult.

24 The leaching decreases when the catalyst is recycled. A plausible explanation is that SANi contains a wide array of Ni NP environments and some are more likely to leach than others.

25 There is no direct quantitative link between yield and leaching. See notes 23 and 24.

26 Recently, air stable Ni catalysts are reported. See reference 4e.