## Nickel Nanoparticle-catalyzed Carboxylation of Unsaturated Hydrocarbon with CO<sub>2</sub> Using Sulfur-modified Au-supported Nickel Material

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A hydrocarboxylation reaction of alkyne or styrene derivatives with CO<sub>2</sub> proceeded smoothly by using an air-stable nano-sized nickel catalyst supported on sulfur-modified gold (SANi), giving functionalized acrylic acids and phenylpropionic acids including an anti-inflammatory drug, Flurbiprofen. Notably, SANi could be recycled several times without a significant decrease of the yield.

## Keywords: Carboxylation | Carbon dioxide fixation | Nickel nanoparticle

Nanoparticle-supported catalysts have attracted much attention for the synthesis of fine chemicals and pharmaceuticals due to their ideal properties such as recyclability and low-leaching of metal species.<sup>1-3</sup> Recently, we have developed a sulfur-modified Au-supported Pd (SAPd) catalyst that can be easily prepared through an in situ metal nanoparticle and nanospace simultaneous organization (PSSO) method.<sup>4</sup> The SAPd showed remarkable reactivity for Suzuki-Miyaura coupling, Buchwald-Hartwig amination, C-H bond activation, and double carbonylation with low leaching and good recyclability. In this context, we have successfully developed a sulfur-modified Au-supported nickel (SANi) catalyst by a procedure similar to that for SAPd via the in situ PSSO method (Figure 1).<sup>5</sup> Detailed spectroscopic analyses such as EXAFS and XANES revealed that SANi consists of self-assembled multilavers of Ni(0) nanoparticles (NPs) with diameters of ca. 3 nm, and Ni(0) is stable even in air. Furthermore, SANi was found to be an efficient catalyst for Kumada-Tamao-Corriu coupling and Negishi coupling with both a high level of reusability and low-leaching. Based on these results, we investigated the catalytic behavior of SANi for other C-C bond-forming reactions.

Carbon dioxide (CO<sub>2</sub>) is a useful carbon source in organic chemistry because it is abundant, cheap, and relatively nontoxic. It is well known that a zero-valent-nickel complex can activate CO<sub>2</sub>, and various homogeneous zero-valent nickel complexes have been used for carboxylation of carbon-carbon multiple bonds with CO<sub>2</sub>.<sup>6–10</sup> In contrast, carboxylation reaction using CO<sub>2</sub> as a C1 source by heterogeneous Ni catalysts still remains relatively unexplored, although it is known that



Figure 1. Sulfur-modified Au-supported Ni catalyst (SANi).



**Scheme 1.** Plan for carboxylation using SANi. Ar = aromatic ring, R = aryl or alkyl group.

catalysts including Ni NPs can efficiently promote hydrogenation of  $CO_2$  (e.g. Sabatier reaction).<sup>10</sup> Thus, we focused on carboxylation of carbon-carbon multiple bonds with  $CO_2$  using SANi. Recently, Ma and Rovis independently reported Nicatalyzed hydrocarboxylation of alkynes<sup>8</sup> or styrenes<sup>9</sup> with  $CO_2$ using Ni(cod)<sub>2</sub> or Ni(acac)<sub>2</sub> as a catalyst and Et<sub>2</sub>Zn as a reducing reagent. We chose these reaction systems for the evaluation of catalytic behavior of SANi for carboxylation of C-C multiple bonds with  $CO_2$  (Scheme 1).

First, diphenylacetylene (**1a**, 0.25 mmol) was reacted with Et<sub>2</sub>Zn (1 M in toluene, 0.75 mL, 0.75 mmol) and SANi (100 mesh, 12 mm × 14 mm, immobilized Ni: ca.  $509 \mu g$ )<sup>5</sup> in acetonitrile (1 mL) at 60 °C by connection of a CO<sub>2</sub> balloon to the reaction vessel (Table 1, run 1). After acidic workup followed by methylation, the corresponding ester **2a** and **5** were obtained in 59% and 6% yields, respectively. When the reactions were carried out at a higher temperature (100 °C) in *n*-butylonitrile and in DMA instead of in acetonitrile, the yields of **2a** slightly

Table 1. Conditions screening.<sup>a)</sup>

Ph 1a 0.25 m	Ph SANi CO2 3 equi solver 24 h	iv. ZnEt <sub>2</sub>	L) 1 M HCl 2) CH <sub>2</sub> N <sub>2</sub>	CO <sub>2</sub> M Ph Ph 2a	1e Ph	CO J 3a	Et 2Me Ph	$CO_2Me$ Ph $PhPh$ $4Ph$ $PhPh$ $5$
	aalvant	CO <sup>b)</sup>	temp.	yield (%) <sup>c)</sup>				
run	Sorvent	$CO_2^{\circ}$		2a	3a	4	5	SM rec.
1	MeCN	В	60 °C	59	_	_	6	31
2	<sup>n</sup> PrCN	В	100°C	72	4		7	10
3	DMA	В	100°C	69	10	3	7	
4	<sup>n</sup> PrCN	S	100 °C	88 <sup>d)</sup>	3		_	2
5	DMA	S	100°C	63	3	4	3	27
6	dioxane	S	100°C	19	8	8		73
7	toluene	S	100°C	9		3		88

 $^{a)}SANi$  (100 mesh, 12 mm  $\times$  14 mm, immobilized Ni: ca. 509  $\mu g)$  was used.  $^{b)}B$ : balloon, S: sealed tube.  $^{c)}NMR$  yield.  $^{d)}Isolated$  yield.



<sup>a)</sup> SANi (100 mesh, 12 mm  $\times$  14 mm, immobilized Ni: ca. 509 µg) was used.

increased to 72% and 69%, respectively (runs 2 and 3). When the reaction was carried out in a sealed tube under an atmosphere of CO<sub>2</sub>, the yield of **2a** greatly improved up to 88%, while the formation of a hydrogenated product **5** was suppressed (run 4). The use of other solvents including DMA, 1,4-dioxane and toluene was found to be not effective in this reaction (runs 5–7).

With the optimal reaction conditions in hand, we next examined the substrate scope of this SANi-catalyzed carboxylation of alkynes (Table 2). The reaction of symmetrical dialkyl substituted alkynes such as 4-octyne only gave a trace amount of the desired carboxylated product. On the other hand, the reaction of symmetrical diaryl alkynes proceeded, giving the corresponding carboxylated methyl esters in moderate to high yields with high *cis* selectivity (**2b–2g**). In the reaction of **1h** (R = 2-naphthyl), the corresponding carboxylated product **2h** was obtained in 83% yield along with *trans*-isomer **3h** in 10% yield.

When the reaction of aryl-phenethyl-substituted alkyne **1i** as an unsymmetrical alkyne was carried out, 60% of the carboxylated product was obtained as a 1/1.2 regioisomer mixture (Scheme 2, eq 1). On the other hand, in the reaction of substrates having an oxygen functionality in the tether, it was found that regioselective carboxylation occurred. Thus, the reaction of **1j** under optimal conditions gave products of **2ja** and **2jb** in a total yield of 88% in a ratio of 3.2/1. Also, the reaction of **1k** showed the same tendency, producing **2ka** and **2kb** in a total yield of 91% in a ratio of 9.1/1. It is noteworthy that the major isomers in both reactions of **1j** and **1k** are always produced via carboxylation at the carbon near the oxygen functionality in



Scheme 2. Carboxylation of unsymmetrical alkynes. The optimized conditions shown in Table 2 were applied followed by HCl and  $CH_2N_2$  workup.

the alkyne, suggesting that the benzyloxy moiety serves as a directing group to affect the regioselectivity.

Next, we investigated SANi-catalyzed carboxylation of styrenes, and the results are summarized in Table 3. It was found that the reaction of electron-deficient styrene derivatives **6a** and **6b** under slightly modified conditions from those of the abovementioned reaction of alkynes proceeded smoothly to give the corresponding 2-arylpropionic acid derivatives **7a** and **7b** in 98% and 68% yields, respectively. Carboxylation of a styrene carrying C–OTs (Ts = Tosyl) bond, which are usually labile in the presence of low-valent group 10 metal complexes, interestingly gave the desired product **7c** in a good yield. It is noteworthy that the anti-inflammatory drug Flurbiprofen (**7d**) was easily accessible by carboxylation of the corresponding styrenes with CO<sub>2</sub> and Et<sub>2</sub>Zn.





<sup>a)</sup> SANi (100 mesh, 12 mm  $\times$  14 mm, immobilized Ni: ca. 509 µg) was used. <sup>b)</sup> Isolated after methylation with CH<sub>2</sub>N<sub>2</sub>.

Table 4. Reusability of SANi for carboxylation of alkyne

	<b>a</b> , 0.25 mmol	SANi CO <sub>2</sub> (Se 3 equiv "PrCN, 24 h	aled)	<sub>2</sub> н 8
cycle	yield (%	) <sup>a),b)</sup>	amount of Ni (μmol) <sup>c)</sup>	conc. of Ni (ppm)
1st	74		0.11	3.8
2nd	79		0.063	2.1
3rd	75		0.073	2.5
average of 3 cycles	76		0.083	2.8

<sup>a)</sup>Yields were determined by HPLC analysis. <sup>b)</sup>The yield of each cycle was calculated by the average of three reactions under the same conditions. <sup>c)</sup>The amount of Ni was determined by ICP-MS.

We turned our attention to the reusability of SANi in the reaction of diphenylacetylene. After the first reaction of diphenylacetylene under optimal conditions, SANi was removed from the reaction mixture and reused in the next reaction. As a result, it was found that SANi could be used three times without a significant decrease of yield. On the basis of the results of ICP-MS analysis of each cycle of the reaction mixture shown in Table 4, it was revealed that the amount of Ni leached was 0.07–0.11 µmol, which is approximately 1% of the total amount of Ni on SANi, and that the concentration of Ni in the reaction mixture was 2.1–3.8 ppm.<sup>11</sup>

We also checked reusability of SANi for carboxylation of styrene derivatives. After carboxylation of 6a was performed with SANi, which delivered desired product in 98%, the SANi was removed before workup. When this SANi was reused as catalyst for carboxylation of **6a**, the yield dropped to 25%. We thought that under carboxylation conditions for styrenes using highly polar solvent DMA, the amount of leaching Ni would be too large to withstand repetitious usage.<sup>12</sup> Thus, we assumed that removal of SANi from the reaction mixture after leaching Ni NPs precludes SANi from full consumption of active Ni. To a reaction vessel was charged SANi, styrene 6a and DMA and the mixture was heated at 80 °C for 4 h to complete leaching (Figure 2). After quick removal of SANi, the vessel was attached to CO2 balloon and ZnEt2 was added. After 24 h stirring, 95% of 7a was obtained. Repeating the same sequence delivered 7a in 84%. Finally, SANi was used as catalyst without removal for 24h to give the carboxylated product in 60%. Although further investigation to find optimized condition for repetitious use is required, we successfully demonstrated reusability of SANi for carboxylation of styrenes.

In summary, we investigated the reactivity of SANi toward chemical  $CO_2$  fixation to alkynes and styrenes. It was found that SANi-catalyzed hydrocarboxylation reaction proceeded efficiently under mild conditions, and alkyne and styrene derivatives were smoothly converted to the corresponding carboxylated products. Also, SANi can be reused at least three times with low leaching of Ni. To the best of our knowledge, this is the first example of Ni NP-catalyzed carboxylation reaction with  $CO_2$  as a C1 source, which would be a new entry to show the



Figure 2. Reusability of SANi for carboxylation of styrene.

potential activity of Ni NPs for C-C bond formation reactions beyond cross-coupling reaction systems.<sup>13</sup> It is thought that these SANi-catalyzed hydrocarboxylations proceed via a hydrozincation process which had been reported by Ma<sup>8</sup> and Rovis<sup>9</sup> by using a conventional nickel complex. Further studies using SANi as a platform of Ni NPs including mechanistic studies are in progress.

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