

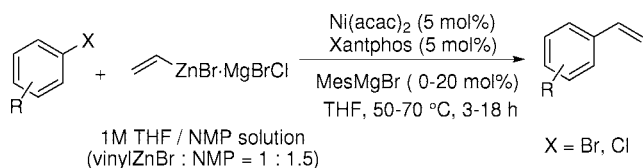
## Nickel-Catalyzed Vinylation of Aryl Chlorides and Bromides with Vinyl ZnBr·MgBrCl

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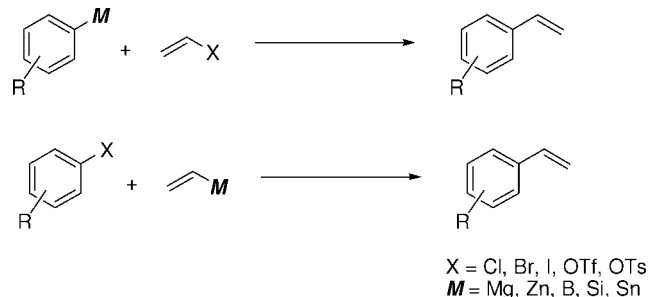
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The Ni-catalyzed cross-coupling of aryl halides and vinylzinc bromide for the synthesis of styrene derivatives was investigated. Of the catalysts surveyed, the combination of Ni(acac)<sub>2</sub> and Xantphos was found to be the most effective for this cross-coupling. This catalyst could be used in reactions with various aryl bromides and chlorides, including electron-rich aryl chlorides such as chloroanisoles.

Styrene derivatives can be transmuted into various functional polymers;<sup>1</sup> they are also often used as key building blocks in fine chemical synthesis and total synthesis.<sup>2</sup> As pointed out by Denmark in a recent review, Pd- and Ni-catalyzed cross-coupling reactions appear to be a versatile means for the synthesis of styrene derivatives.<sup>3</sup> These reactions are classified into two types: one type is the coupling of vinyl electrophiles and aryl metallic reagents, and the other type is the coupling of aryl electrophiles and vinyl metallic reagents (Scheme 1). The only example of the former type of reaction involving vinyl halides<sup>4</sup> is the Ni-catalyzed coupling of aryl magnesium reagents and vinyl chloride.<sup>5</sup> This reaction is currently employed in the industrial manufacture of some styrene derivatives; however, substrates that can be used in this reaction are limited by the tolerance of a substituent for magnesium. In contrast, the latter type of reaction is applicable to a wide range of aryl compounds,

## SCHEME 1. Transition Metal-Catalyzed Synthesis of Styrenes



because various metallic reagents that are compatible with a wide range of substituents can be used in this reaction.

Aryl chlorides are arguably the most useful for cross-coupling reactions because of their cost and availability.<sup>6</sup> Vinylboron,<sup>7</sup> vinylsilicon,<sup>8</sup> vinylzinc,<sup>9</sup> and vinyltin<sup>10</sup> reagents have been used in the Pd-catalyzed vinylation of aryl chlorides. In contrast, only vinyltin reagents are known to be used in the Ni-catalyzed vinylation.<sup>11</sup>

In this study, we investigated Ni-catalyzed cross-coupling of aryl halides and vinylzinc bromide. We found that the combination of Ni(acac)<sub>2</sub> and Xantphos was the most effective catalyst and that it could be successfully used in the synthesis of various styrene derivatives from aryl bromides and chlorides.

Table 1 shows the results of the vinylation of ethyl 4-bromobenzoate (**1a**). Of the Ni complexes and ligands tested, the combination of Ni(acac)<sub>2</sub> or Ni(cod)<sub>2</sub> with Xantphos, which is rarely used in the Ni-catalyzed cross-coupling reaction,<sup>12</sup> resulted in satisfactory yields even at short reaction times (entries 11 and 12).

We found Ni-catalyzed Negishi coupling for vinylation for the first time; therefore, we examined the use of the Ni-Xantphos catalyst in the vinylation of various aryl halides. The results are shown in Table 2. This catalyst also enabled the production of 1-vinylnaphthalene (**2b**) and 4-vinylbiphenyl (**2c**) from **1b** and **1c** in satisfactory yields (entries 1 and 2). It is worth mentioning that **2a** was also obtained from ethyl 4-chlorobenzoate (**3a**) in a moderate yield by using this catalyst (entry 3). We believe that this is the first example of vinylation of aryl chlorides through the cross-coupling reaction using vinylzinc reagents. In contrast, the yield of 1-ethenyl-4-methoxybenzene (**2d**) obtained from 4-bromoanisole (**1d**) was rather low (entries 4 and 5). This result indicates that the Ni-Xantphos catalyst was not suitable for the vinylation of a substrate that possesses an electron-donating substituent, even in the case when the substrate was an aryl bromide.

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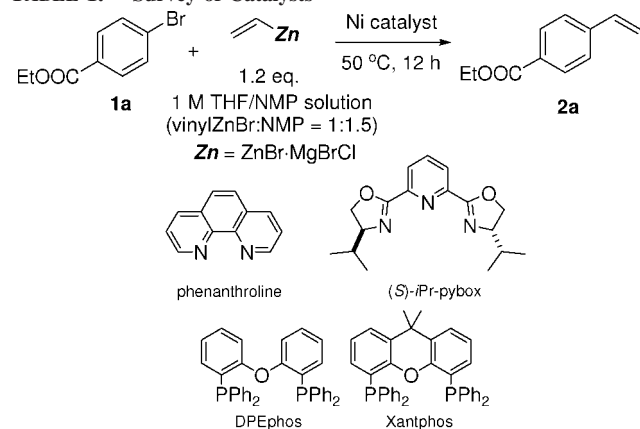
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TABLE 1. Survey of Catalysts



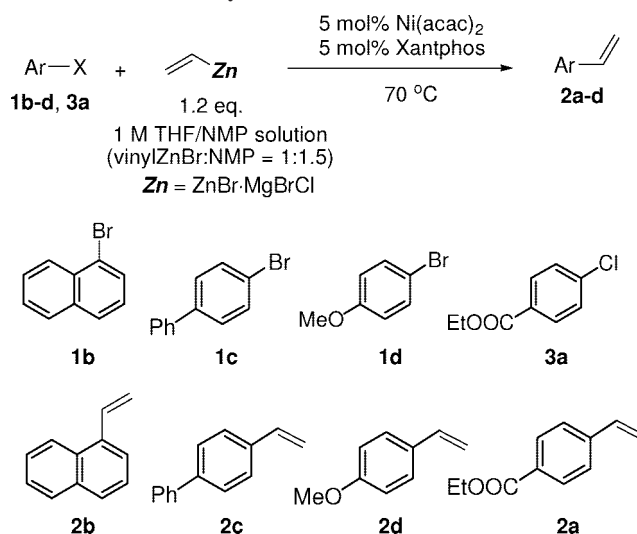
entry	catalyst	yield (%) <sup>a</sup>
1	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	1
2	NiCl <sub>2</sub> (dppm)	1
3	NiCl <sub>2</sub> (dppp)	35
4	NiCl <sub>2</sub> (dppe)	10
5	NiCl <sub>2</sub> (dmpe)	10
6	NiCl <sub>2</sub> (dppp)	10
7	NiCl <sub>2</sub> (dppb)	4
8	NiCl <sub>2</sub> (dppf)	5
9	Ni(acac) <sub>2</sub> + phenanthroline	0
10	Ni(acac) <sub>2</sub> + (S)-iPr-pybox	1
11	Ni(acac) <sub>2</sub> + Dpephos	43
12	Ni(acac) <sub>2</sub> + Xantphos	86 <sup>b</sup>
13	Ni(cod) <sub>2</sub> + Xantphos	74 <sup>b</sup>

<sup>a</sup> Yield based on GC analysis relative to an internal standard.

<sup>b</sup> Reaction time was 6 h.

To overcome this limitation, we changed the manner of addition of the THF solution of vinylzinc bromide, i.e., the solution was charged along with the catalyst and the substrate during the initial surveys: the results of all entries in Table 1 and entries 1–5 in Table 2. It is known that the dropwise addition of a metallic reagent (*slow addition*) frequently improves yield in cross-coupling reactions.<sup>13</sup> Therefore, we added the THF solution of vinylzinc bromide in a dropwise manner to the **1d** reaction mixture at 70 °C for 1–2 h (addition time) and kept the temperature of the mixture for 1 h (reaction time). Consequently, the **2d** yield showed remarkable improvement despite the total reaction time being only 2–3 h (entries 6 and 7). Carrying out this reaction with an addition time of longer than 2 h led to a lower yield (entry 8). *Slow addition* was also efficient in the presence of MesMgBr, which is pre-reductant of Ni(II), providing the highest yield of **2d** (entry 9). In contrast, both the conversion and yield were drastically reduced when *slow addition* was not employed at the same conditions used in entry 9 (entry 10). The detailed effect of *slow addition* is presently unknown and is under investigation.

Since *slow addition* in the presence of MesMgBr produced the highest yield in the reaction with **1d**, it was used for the vinylation of various aryl bromides and chlorides. Table 3 shows the best yields among several reactions carried out at different addition times. Satisfactory yields were obtained in the case of all substrates including halopyridines **1j** and **3j** (entries 16 and 17). It is worth mentioning that the vinylation of electron-rich

TABLE 2. Ni(acac)<sub>2</sub>-Xantphos-Catalyzed Coupling of Vinylzinc Bromide and Various Aryl Halides

entry	aryl halide/ product	addition time (h)/reaction time (h)	conversion (%) <sup>a</sup> / yield (%) <sup>b</sup>
1 <sup>c</sup>	<b>1b/2b</b>	0/4	97/92
2	<b>1c/2c</b>	0/6	97/73
3	<b>3a/2a</b>	0/12	97/62
4 <sup>c</sup>	<b>1d/2d</b>	0/18	29/(6)
5	<b>1d/2d</b>	0/18	30/(19)
6	<b>1d/2d</b>	1/1	70/(62)
7	<b>1d/2d</b>	2/1	82/(74)
8	<b>1d/2d</b>	4/1	92/(67)
9 <sup>d</sup>	<b>1d/2d</b>	2/1	92/81(89)
10 <sup>d</sup>	<b>1d/2d</b>	0/6	25/(3)

<sup>a</sup> Determined by GC used an internal standard method. <sup>b</sup> Isolated yield. The yields in parentheses are GC analysis relative to an internal standard. <sup>c</sup> Reaction temperature was 50 °C. <sup>d</sup> 20 mol % of MesMgBr was added.

aryl chlorides, 4-chloro- (**3d**) and 3-chloroanisole (**3e**), proceeded smoothly (entries 5 and 7). The lower yields obtained in the case of 2-bromoanisole (**1f**) and 2-chloroanisole (**3f**) could be due to steric hindrance (entries 8 and 9).

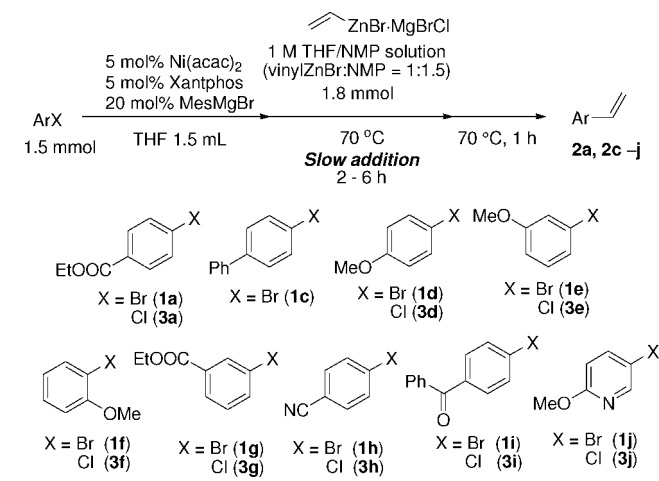
In conclusion, we report that the combination of Ni(acac)<sub>2</sub> and Xantphos is an efficient catalyst for the vinylation of various aryl halides with vinylzinc bromide. *Slow addition* of vinylzinc bromide is the key to obtaining a high yield. This reaction appears to be a versatile means for the synthesis of styrene derivatives with various substituents, not only from aryl bromides but also from aryl chlorides.

## Experimental Section

**General Procedure for Ni-Catalyzed Vinylation of Aryl Halides (all entries in Table 1 and entries 1–5 in Table 2).** In a 10 mL test tube sealed with a rubber septum, Ni catalyst (0.075 mmol) was dissolved in dry THF (2.0 mL) by stirring with a magnetic stirring bar under an Ar atmosphere. An aryl halide (1.5 mmol) and 1.8 mL of a 1.0 mol/L THF solution of vinylzinc bromide (1.8 mmol) were then added to the solution at room temperature. The reaction mixture was stirred at 50 or 70 °C for 4–18 h. After the reaction mixture was cooled to room temperature, a saturated aqueous solution of NH<sub>4</sub>Cl (3.0 mL) was added. An aliquot of the organic layer of the reaction mixture was diluted with hexane (7.0 mL) and the solution was subjected to quantitative analysis by GC. The desired product was extracted into hexane (2 × 7.0 mL) and then into AcOEt (7.0 mL). The organic layers were

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TABLE 3. Vinylation of Various Aryl Chlorides and Bromides



entry	aryl halide/product	addition time (h)	conversion (%) <sup>a</sup> /yield (%) <sup>b</sup>
1	1a/2a	2	91/79
2	3a/2a	6	91/70
3	1c/2c	2	99/84
4	1d/2d	2	89/81
5	3d/2d	5	87/81
6	1e/2e	2	100/78
7	3e/2e	5	93/70
8	1f/2f	2	98/71
9	3f/2f	6	81/62
10	1g/2g	2	99/89
11	3g/2g	4	97/79
12	1h/2h	2	100/77
13	3h/2h	4	96/68
14	1i/2i	2	99/86
15	3i/2i	3	100/76
16	1j/2j	2	100/76
17	3j/2j	4	100/71

<sup>a</sup> Yield based on GC analysis relative to an internal standard.

<sup>b</sup> Reaction time was 6 h.

combined and concentrated in vacuo. The obtained crude residue was purified by passing it through a silica gel column with a hexane/ethyl acetate (100:0 to 100:1) eluent.

**1-Ethenyl-naphthalene<sup>14</sup> (2b).** To a solution of Ni(acac)<sub>2</sub> (19.3 mg, 0.075 mmol), Xantphos (43.4 mg, 0.075 mmol), and 1-bromonaphthalene (311 mg, 1.5 mmol) in dry THF (2 mL) was added 1.8 mL of a 1.0 mol/L THF solution of vinylzinc bromide (1.8 mmol) under Ar atmosphere. The mixture was stirred for 4 h at 50 °C; after it was cooled to room temperature, a saturated aqueous solution of NH<sub>4</sub>Cl (3.0 mL) was added. An aliquot of the organic layer of the reaction mixture was diluted with hexane (7.0 mL) and the solution was subjected to quantitative analysis by GC. The desired product was extracted into hexane (2 × 7.0 mL) and then into AcOEt (7.0 mL). The organic layers were combined and concentrated in vacuo. The obtained crude residue was purified by

flash chromatography (hexane), giving 214 mg of 1-ethenyl-naphthalene as a white solid (92%). *R<sub>f</sub>* 0.36 (hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.10 (d, 1H, *J* = 8.0 Hz), 7.83 (d, 1H, *J* = 7.7 Hz), 7.77 (d, 1H, *J* = 8.1 Hz), 7.61 (d, 1H, *J* = 7.0 Hz), 7.42–7.51 (m, 4H), 5.78 (d, 1H, *J* = 17.3 Hz), 5.46 (d, 1H, *J* = 10.9 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 135.7, 134.5, 133.7, 131.2, 128.6, 128.2, 126.2, 125.8, 125.7, 123.9, 123.7, 117.2; *m/z* (MS) 154 [M]<sup>+</sup>.

**General Procedure for Ni-Catalyzed Vinylation of Aryl Halides (slow addition, entries 6–9 in Table 2 and all entries in Table 3).** In a 10 mL test tube sealed with a rubber septum, Ni(acac)<sub>2</sub> (0.075 mmol) and Xantphos (0.075 mmol) were dissolved in dry THF (1.5 mL) with a magnetic stirring bar under an Ar atmosphere. An aryl halide (1.5 mmol) and 0.3 mL of a 1.0 mol/L THF solution of mesitylmagnesium bromide (0.3 mmol) were added to the solution at room temperature and the resulting mixture was stirred at 70 °C. The prepared THF solution of vinylzinc bromide ([vinylzinc bromide] = 1.0 mol/L, 1.8 mL) was added dropwise to the solution for 1–6 h. Then the reaction mixture was stirred at 70 °C for 1 h. After the reaction mixture was cooled to room temperature, a saturated aqueous solution of NH<sub>4</sub>Cl (3.0 mL) was added. An aliquot of the organic layer of the reaction mixture was diluted with hexane (7.0 mL) and the solution was subjected to quantitative analysis by GC. The desired product was extracted into hexane (2 × 7.0 mL) and then AcOEt (7.0 mL). The organic layer was combined and concentrated in vacuo. The obtained crude residue was purified by passing it through a silica gel column with a hexane/ethyl acetate (100:0 to 100:5) eluent.

**1-Ethenyl-4-methoxybenzene<sup>14</sup> (2d).** To a solution of Ni(acac)<sub>2</sub> (19.3 mg, 0.075 mmol), Xantphos (43.4 mg, 0.075 mmol), and 4-chloroanisole (214 mg, 1.5 mmol) in dry THF (1.5 mL) was added a THF solution of MesMgBr ([MesMgBr] = 1.0 mol/L, 0.3 mL) under Ar atmosphere at room temperature. 1.8 mL of a 1.0 mol/L THF solution of vinylzinc bromide (1.8 mmol) was added dropwise to the solution for 5 h at 70 °C. The reaction mixture was stirred at 70 °C for 1 h. After it was cooled to room temperature, a saturated aqueous solution of NH<sub>4</sub>Cl (3.0 mL) was added to it. An aliquot of the organic layer of the reaction mixture was diluted with hexane (7.0 mL) and the solution was subjected to quantitative analysis by GC, then NH<sub>4</sub>Cl (3.0 mL) was added to it. An aliquot of the organic layer of the reaction mixture was diluted with hexane (7.0 mL) and the solution was subjected to quantitative analysis by GC. The desired product was extracted into hexane (2 × 7.0 mL) and then AcOEt (7.0 mL). The organic layer was combined and concentrated in vacuo. The obtained crude residue was purified by flash chromatography (hexane), giving 163 mg of 1-ethenyl-4-methoxybenzene as a colorless liquid (81%). *R<sub>f</sub>* 0.16 (hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.30 (d, 2H, *J* = 8.4 Hz), 6.81 (d, 2H, *J* = 8.4 Hz), 6.63 (dd, 1H, *J* = 17.2 Hz, 10.9 Hz), 5.58 (d, 1H, *J* = 17.6 Hz), 5.09 (d, 1H, *J* = 10.8 Hz), 3.72 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 159.5, 136.4, 130.6, 127.6, 114.1, 111.6, 55.3; *m/z* (MS) 134 [M]<sup>+</sup>.

**Supporting Information Available:** Experimental details and characterization of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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