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# Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/uopp20

## Pd-Nanoparticle (PdNP)-catalyzed Negishi Coupling of Acid Chlorides using Zinc Reagents

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To cite this article: Lei Yu , Lingfeng Ren , Tian Chen , Rong Yi , Yulan Wu & Rong Guo (2012) Pd-Nanoparticle (PdNP)-catalyzed Negishi Coupling of Acid Chlorides using Zinc Reagents, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 44:2, 169-174, DOI: <u>10.1080/00304948.2012.657565</u>

To link to this article: <u>http://dx.doi.org/10.1080/00304948.2012.657565</u>

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### Pd-Nanoparticle (PdNP)-catalyzed Negishi Coupling of Acid Chlorides using Zinc Reagents

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Ketones are important building blocks and useful intermediates in organic synthesis. In our investigations on the novel reactions of methylenecyclopropanes (MCPs) and methylenecyclobutanes (MCBs),<sup>1,2</sup> we needed a series of different substituted ketones to prepare the substrates.<sup>3</sup> One of the usual methods for the preparation of ketones is the reaction of Grignard reagent with aldehydes followed by the Jones oxidation.<sup>4</sup> The use of toxic chromium reagent makes this method harmful to environment and restricts its application in large-scale preparation.

Transition metal-catalyzed cross-coupling reactions are potent tools in organic synthesis. Over the past 30 years, chemists have paid much attentions in this area and a series of novel reactions have been discovered, including Kumada,<sup>5-9</sup> Negishi,<sup>10–13</sup> Suzuki<sup>14,15</sup> and Stille cross-coupling.<sup>16,17</sup> Hence, the synthesis of ketones through the cross-coupling of metal reagents with acid chlorides is attractive.<sup>18–23</sup>

Recently, the catalytic ability of metal nanoparticles has attracted chemists' attention and examples of nanocatalysts have been reported, including CuO nanoparticle,<sup>24</sup> In<sub>2</sub>O<sub>3</sub> nanoparticle,<sup>25</sup> Co/Rh heterobimetallic nanoparticle<sup>26–28</sup> as well as Au nanoparticles (AuNP).<sup>29</sup> *In situ* reduction of Pd(OAc)<sub>2</sub> to Pd (0) in the presence of tetrabutylamonium salts (TBAX) could generate Pd nanoparticles (PdNP), which recently have been used to catalyze the cross-coupling reactions of allyl acetates.<sup>30–32</sup> In 2008, the first example of PdNP-catalyzed Negishi cross-coupling reaction of aryl iodides was reported, providing a convenient access to biphenyls.<sup>33</sup> Nano catalysts could catalyze the reactions efficiently with low loadings. Avoidance of phosphorus ligands made these reactions more environmentally friendly. Thus, stimulated by the report in the literature, we became interested in the transition metal nanoparticle-catalyzed reactions and developed PdNP-catalyzed

Submitted November 5, 2011.

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	R <sup>1</sup> ZnCl +	$\mathbf{R}^{2}  \mathbf{CI}  \frac{\mathrm{Pd}(\mathrm{OA})}{\mathrm{Bu}_{4}}$	Ac) <sub>2</sub> (0.5 mol%) NBr, THF, rt		
Entry	$R^1$	R <sup>2</sup>	Yield of <b>3</b> (%) <sup>b</sup>	mp. (°C)	<i>lit</i> . mp. (°C)
1	Ph	Ph	82 ( <b>3a</b> )	48–49	49–51 <sup>34</sup>
2	1-Naph	Ph	84 ( <b>3b</b> )	_	
3	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Ph	79 ( <b>3c</b> )	56–57	57-58 <sup>35</sup>
4	o-MeC <sub>6</sub> H <sub>4</sub>	Ph	73 ( <b>3d</b> )	_	_
5	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Ph	80 ( <b>3e</b> )	61–62	62–64 <sup>36</sup>
6	Ph	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	81 ( <b>3c</b> )	56–57	57-58 <sup>35</sup>
7	Ph	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	75 ( <b>3e</b> )	61–62	62–64 <sup>36</sup>
8	Ph	p-ClC <sub>6</sub> H <sub>4</sub>	70 ( <b>3f</b> )	73–75	73–74 <sup>37</sup>
9	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	78 ( <b>3g</b> )	140-141	140-14238
10	$\alpha$ -Naph	CH <sub>3</sub>	74 ( <b>3h</b> )	_	
11	Ph	CH <sub>3</sub>	67 ( <b>3i</b> )	_	
12	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	72 ( <b>3j</b> )		

Table 1
PdNP-catalyzed Reactions of Zinc Reagents with Acid Chlorides <sup>a</sup>

a) Five mmol of zinc reagent, 2.5 mmol of acid chloride, 2.5 mmol of TBAB, 10 ml of THF and 0.0125 mmol of Pd  $(OAc)_2$  were employed. b) Yields based on acid chloride.

Negishi-coupling of acid chlorides with zinc reagents to aromatic ketones. Herein, we report our results.

On the basis of results of Liu *et al.*<sup>33</sup> we chose tetrabutylammonium bromide (TBAB) as the stabilizer and Pd(OAc)<sub>2</sub> as the Pd precursor. Under the protection of a nitrogen atmosphere, TBAB and Pd(OAc)<sub>2</sub> were added to phenylzinc (in THF) successively. Then, benzoyl chloride was injected *via* a syringe, and the mixture was stirred at room temperature. TLC analysis indicated that the reaction proceeded rapidly and was complete within 1 hour. Further purifications by preparative TLC gave the desired product benzophenone (**3a**) in 82% yield. The scope of this reaction was then examined by employing a series of different arylzinc reagents and acid chlorides. The corresponding ketones were obtained smoothly with both aroyl chlorides (*Table 1, Entries 1–9*) as well as aliphatic acid chlorides (*Table 1, Entries 10–12*). The zinc reagents were prepared by the metal exchange of Grignard reagents with anhydrous ZnCl<sub>2</sub>. Since both the Grignard and the zinc reagents aresensitive to moisture and might partially decompose during the operations, we employed an excess of the zinc reagents (two equivalents); the yields are calculated on the acid chlorides.

With these results in hand, we then synthesized aryl ketones on a larger scale for practical application; for example, ketone 3c was prepared from 40 mmol of the zinc reagent and 20 mmol of the acid chloride in 83% yield.

The reaction of alkyl zinc reagents with acid chlorides was also examined. However, the results were not satisfactory. Reaction of benzylzinc with benzoyl chloride led to the desired ketone **3k** in only 36% yield; an unexpected by-product benzyl benzoate (**4a**) was also obtained in 45% yield (*Scheme 1*). When cyclohexylzinc was employed, only cyclohexyl benzoate (**4b**) was obtained (*Scheme 1*).





In conclusion, we have developed a direct synthesis of ketones from aryl zinc reagent and acid chlorides. To the best of our knowledge, this is the first example for the synthesis of ketones through Negishi cross-coupling catalyzed by a nano catalyst. Although the scope of this reaction is limited to only aryl ketones, it still has some obvious advantages. The reaction occurred rapidly at room temperature. The dosage of catalyst was very low (0.5%) and no phosphorus ligand was required. Considering these advantages, we believe that this reaction is environmentally friendly and may have more application value in large-scale preparation.

#### **Experimental Section**

<sup>1</sup>H NMR and <sup>13</sup>C NMR were recorded for a solution in CDCl<sub>3</sub> with TMS as the internal standard. *J*-values are in Hz. Melting points are uncorrected. Organic solvents were dried by standard methods. All reactions were performed under a nitrogen atmosphere and monitored by TLC with silica gel coated plates. Zinc reagents were prepared by the reaction of Grignard reagents with anhydrous ZnCl<sub>2</sub> in THF. Aryl Grignard reagents were prepared in ether and the ether was evaporated and replaced by THF; alkyl Grignard reagents were generated in THF directly.

#### **General Procedure**

To a solution of arylzinc (5 mmol) in THF (10 mL) under a nitrogen atmosphere was added TBAB (2.5 mmol) and Pd(OAc)<sub>2</sub> (0.0125 mmol) successively. The mixture was then stirred at rt for 5 min. Then, the acid chloride (2.5 mmol) was injected using a syringe; the reaction was monitored by TLC (eluent:petroleum ether). When the reaction was complete, water (20 mL) was added. The mixture was extracted with ether (20 mL × 3). The combined organic layers were dried (anhydrous MgSO<sub>4</sub>). And evaporated under

vacuum to afford the crude product, which was purified by column chromatography (silica gel, eluent:petroleum/EtOAc 10:1).

#### Spectral Data

**Compound 3b,** oil, IR (film): 3059, 1660, 1594 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  7.43–7.58 (m, 7H), 7.86–8.10 (m, 5H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  124.4, 125.7, 126.5, 127.3, 127.8, 128.4, 128.5, 130.4, 131.0, 131.3, 133.3, 133.8, 136.4, 138.3, 198.0; MS (EI, 70 eV): *m/z* (%) 233 (20) [M<sup>+</sup> + 1], 232 (100) [M<sup>+</sup>].

Anal. Calcd for C<sub>17</sub>H<sub>12</sub>O: C, 87.90; H, 5.21. Found: C, 87.63; H, 5.47

**Compound 3d,** oil, IR (fim) 3063, 1667, 1599 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, TMS): δ 2.33 (s, 3H), 7.24–7.80 (m, 9H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 20.0, 125.2, 128.5(d), 130.2, 130.3, 131.0, 133.2, 136.8, 137.8, 138.7, 198.7.

Anal. Calcd for C<sub>14</sub>H<sub>12</sub>O: C, 85.68; H, 6.16. Found: C, 85.72; H, 6.34.<sup>39</sup>

**Compound 3h,** oil, IR (film): 3054, 1678, 1596 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, TMS): δ 2.68 (s, 3H), 7.41–8.76 (m, 7H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 30.0, 124.4, 126.1, 126.5, 128.1, 128.5, 128.8, 130.2, 133.1, 134.0, 135.4, 201.9;

Anal. Calcd for C<sub>12</sub>H<sub>10</sub>O: C, 84.68; H, 5.92. Found: C, 84.56; H, 6.00.40

**Compound 3i,** oil, IR (film): 2960, 1691, 1600 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, TMS): δ 2.57 (s, 3H), 7.30–7.89 (m, 5H).

Anal. Calcd for C<sub>8</sub>H<sub>8</sub>O: C, 79.97; H, 6.71. Found: C, 80.12; H, 6.73.<sup>41</sup>

**Compound 3j,** oil, IR (film): 1679, 1600 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  2.36 (s, 3H), 2.51 (s, 3H), 7.18–7.76 (m, 4H).

Anal. Calcd for C<sub>9</sub>H<sub>10</sub>O: C, 80.56; H, 7.51. Found: C, 80.42; H, 7.79.<sup>42</sup>

**Compound 3k,** oil, IR (film): 3087, 3060, 3029, 1686 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, TMS): δ 4.28 (s, 2H), 7.25–8.02 (m, 10H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 45.5, 126.9, 128.6, 128.7(d), 129.5, 133.2, 134.6, 136.6, 197.7.

Anal. Calcd for C<sub>14</sub>H<sub>12</sub>O: C, 85.68; H, 6.16. Found: C, 85.53; H, 6.08.<sup>43</sup>

**Compound 4a,** oil, IR (film): 3034, 1720 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  5.36 (s, 2H), 7.33–8.08 (m, 10H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ 66.7, 128.2, 128.3, 128.4, 128.6, 129.8, 130.2, 133.1, 136.1, 166.5.

Anal. Calcd for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>: C, 79.22; H, 5.70. Found: C, 79.48; H, 5.88.<sup>44</sup>

**Compound 4b,** oil, IR (film): 2937, 1716 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  1.34–1.37 (m, 1H), 1.42–1.47 (m, 2H), 1.56–1.62 (m, 3H), 1.78–1.79 (m, 2H), 1.91–1.93 (m, 2H), 5.03 (t, J = 3.6 Hz, 1H), 7.41–8.06 (m, 5H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  23.7, 25.5, 31.7, 73.0, 128.3, 129.5, 131.0, 132.7, 166.0.

Anal. Calcd for C<sub>13</sub>H<sub>16</sub>O<sub>2</sub>: C, 76.44; H, 7.90. Found: C, 76.23; H, 8.04.<sup>45</sup>

#### Acknowledgment

This work was supported by the Priority Academic Program of Jiangsu Higher Education Institutions, Natural Scientific Foundation of Jiangsu Province (NO. BK2010321), University Natural Scientific Foundation of Jiangsu Province (NO. 09KJB150014), the Opening Laboratory Foundation of Jiangsu Province (K100027); the Opening Laboratory Foundation of Zhejiang Province (100061200138) and the National Natural Scientific Foundation of China (20773106).

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