

Cite this: DOI: 10.1039/c1cc12052b

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## COMMUNICATION

## A regio- and stereoselective synthesis of trisubstituted alkenes via gold(I)-catalyzed hydrophosphoryloxylation of haloalkynes†

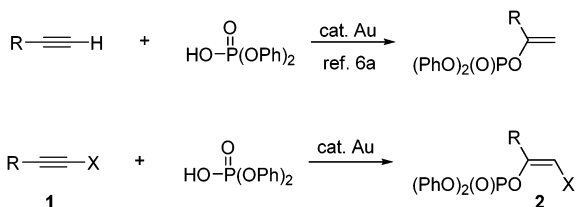
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Received 11th April 2011, Accepted 24th May 2011

DOI: 10.1039/c1cc12052b

A new stereoselective synthesis of trisubstituted alkenes is developed. Hydrophosphoryloxylation of haloalkynes provides *Z*-alkenyl halophosphates, which undergo Pd-catalyzed consecutive cross-coupling reactions to afford regio- and stereodefined trisubstituted alkenes.

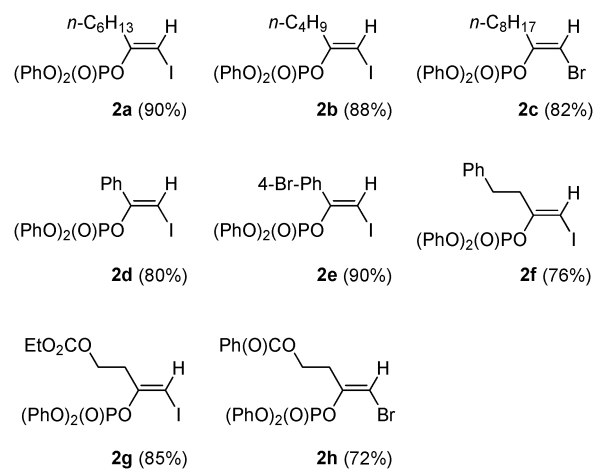
Synthesis of stereodefined trisubstituted alkenes is very important in organic synthesis and many ingenious approaches have been devised.<sup>1</sup> Among various approaches, one of the most attractive approaches is to utilize the transition-metal-catalyzed cross-coupling reactions of stereodefined alkenyl derivatives and depends very much on the regio- and stereospecific synthesis of alkenyl derivatives from alkynes.<sup>2</sup> In this regard, highly regio- and stereoselective synthesis of trisubstituted alkenes using boration,<sup>3</sup> bromoboration,<sup>4</sup> and iodination<sup>5</sup> of alkynes or haloalkynes has been reported. During our investigation of gold (I)-catalyzed hydrophosphoryloxylation and hydroacyloxylation of alkynes,<sup>6</sup> we have been interested in the possibility of hydrophosphoryloxylation of haloalkynes<sup>7</sup> because the regio- and stereoselective hydrophosphoryloxylation would provide alkenyl halophosphates. Since this approach would provide an easy access to stereodefined trisubstituted alkenes via transition-metal-catalyzed consecutive cross-coupling reactions, we have studied the hydrophosphoryloxylation of haloalkynes (Scheme 1).



Scheme 1 Addition of diphenylphosphate to haloalkynes.

When iodoalkyne **1a** was treated with diphenyl phosphate in the presence of 5 mol% Ph<sub>3</sub>PAuCl and 5 mol% AgOTf in toluene at room temperature, the reaction proceeded cleanly and was complete within 4 h, yielding *Z*-alkenyl iodophosphate **2a** in 90% yield. The hydrophosphoryloxylation to 1-iodoalkyne was regio- and stereoselective. The geometric structure of **2a** was determined from NOESY measurement. Apparently, the regioselectivity was controlled by the electron-withdrawing effect of the iodo group rather than the resonance effect,<sup>8</sup> although the regioselectivity of vinyl halides in the addition reaction is governed by the resonance effect.<sup>9</sup> In addition, *Z*-stereoselectivity may be due to *trans*-addition of a nucleophile to a gold-complex alkyne intermediate.<sup>10</sup> As shown in Table 1, when the hydrophosphoryloxylation of several iodo- and bromoalkynes were carried out under the same conditions, the corresponding *Z*-alkenyl halophosphates were isolated in high yields.

To develop a stereoselective synthesis of trisubstituted alkenes using alkenyl halophosphates, an initial study was carried out on the cross-coupling reactions of alkenyl iodophosphate **2a** using 2 mol% Pd catalyst and 10 mol% CuI in the presence of a base (3 equiv.).<sup>11</sup> As shown in Table 2, several noteworthy features are

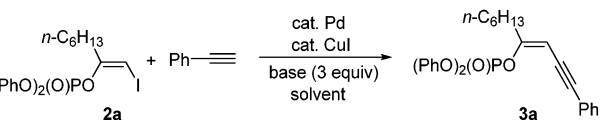
Table 1 Preparation of (*Z*)-alkenyl halophosphates<sup>a</sup>

<sup>a</sup> The reaction was carried out with haloalkyne (1.0 equiv.), diphenylphosphate (1.2 equiv.), and 5 mol% Ph<sub>3</sub>PAuCl/5 mol% AgOTf in toluene at room temperature for 3–4 h.

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† Electronic supplementary information (ESI) available: All the relevant synthetic details as well as <sup>1</sup>H and <sup>13</sup>C spectra for all compounds. See DOI: 10.1039/c1cc12052b

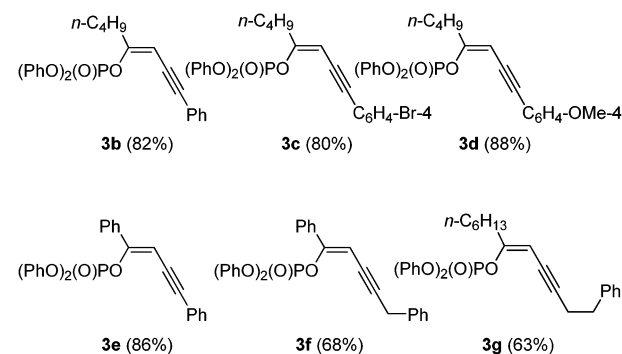
**Table 2** Optimization of the Sonogashira reaction of vinyl iodophosphate **2a**<sup>a</sup>


Entry	Catalyst	Solvent	Base	Temp/°C	Time/h	Yield (%)
1 <sup>b</sup>	Pd <sub>2</sub> dba <sub>3</sub> CHCl <sub>3</sub>	DMF	Et <sub>3</sub> N	80	3	51
2	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	DMF	Et <sub>3</sub> N	80	3	64
3	Pd(PPh <sub>3</sub> ) <sub>4</sub>	DMF	Et <sub>3</sub> N	80	2	76
4 <sup>b</sup>	Pd <sub>2</sub> (OAc) <sub>2</sub>	DMF	Et <sub>3</sub> N	80	3	51
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Dioxane	Et <sub>3</sub> N	25	2	81
6 <sup>c</sup>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Dioxane	Et <sub>3</sub> N	25	2	84
7	Pd(PPh <sub>3</sub> ) <sub>4</sub>	THF	Et <sub>3</sub> N	60	2	67
8	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Toluene	Et <sub>3</sub> N	40	2	65
9	Pd(PPh <sub>3</sub> ) <sub>4</sub>	DCE	Et <sub>3</sub> N	60	3	60
10 <sup>b</sup>	Pd <sub>2</sub> dba <sub>3</sub> CHCl <sub>3</sub>	Dioxane	Et <sub>3</sub> N	40	2	78
11	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Dioxane	Na <sub>2</sub> CO <sub>3</sub>	90	6	30
12	Pd(PPh <sub>3</sub> ) <sub>4</sub>	Dioxane	K <sub>2</sub> CO <sub>3</sub>	90	3	60

<sup>a</sup> 2 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 10 mol% CuI, and 3 equiv. of Et<sub>3</sub>N were used.  
<sup>b</sup> Ph<sub>3</sub>P as a ligand. <sup>c</sup> 4 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> was used.

apparent from experimental results. First, Pd(PPh<sub>3</sub>)<sub>4</sub> gave the best result among Pd catalysts tested here. Second, 1,4-dioxane was the choice of solvent and lowered the reaction temperature to room temperature together with better chemical yield. Third, triethylamine is the most effective additive among the bases. Finally, as we expected, the iodo group underwent the preferential and clean coupling reaction in the presence of the phosphate group. Some experimental results for the Sonogashira reaction are listed in Table 3. Several iodophosphates worked well with phenyl acetylene under the standard conditions and alkyl substituted alkynes gave somewhat lower yields.

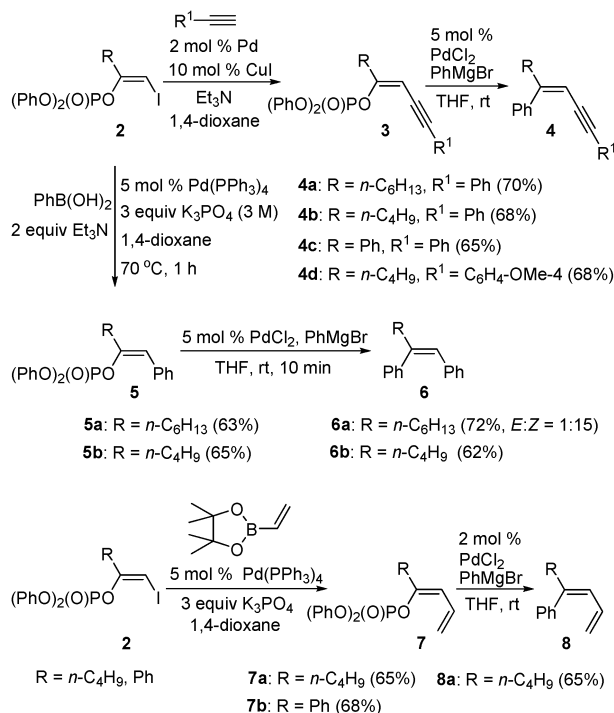
Alkenyl phosphates have attracted recent attention as a coupling partner due to their stability and easy preparation.<sup>12</sup> To complete the stereoselective synthesis of trisubstituted alkenes, recently reported Pd-catalyzed Kumada–Corriu coupling reactions of alkenyl phosphates were employed.<sup>13</sup> Treatment of **3a** with PhMgBr using a 5 mol% PdCl<sub>2</sub> catalyst in THF at room temperature for 15 min afforded trisubstituted alkene **4a** in 70% yield. Similarly, when **3e** and **3d** were subjected to the

**Table 3** Sonogashira coupled products<sup>a</sup>


**3b** (82%)      **3c** (80%)      **3d** (88%)

**3e** (86%)      **3f** (68%)      **3g** (63%)

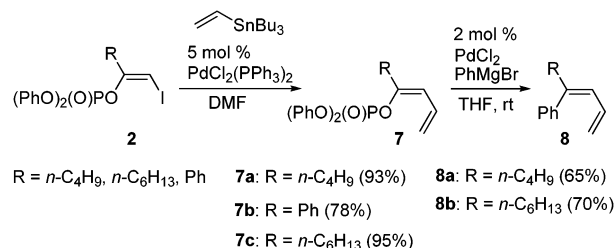
<sup>a</sup> The reaction was carried out using 4 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 3 equiv. of Et<sub>3</sub>N, and 10 mol% CuI in dioxane at room temperature for 2–3 h.

**Scheme 2** Preparation of trisubstituted alkenes.

same conditions, **4c** and **4d** were isolated in 65% and 68% yields, respectively (Scheme 2).

Our next attention was given to the Suzuki reaction.<sup>14</sup> When **2a** was treated with phenylboronic acid using 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, triethylamine (2 equiv.), and K<sub>3</sub>PO<sub>4</sub> (3 equiv.) in THF at 70 °C, the reaction was complete within 16 h, yielding the desired coupling product **5a** (51% yield). The reaction in DMF shortened the reaction time to 1.5 h but the yield was decreased to 40%. Similarly, toluene and dichloroethane did not give satisfactory results. The use of 1,4-dioxane gave the best result, giving **5a** in 63% yield at 70 °C after 1 h. A similar result was also obtained with **5b**. Furthermore, **7a** was obtained in 65% yield using vinylboronic acid pinacol ester. Similarly, treatment of **5a** with PhMgBr using 5 mol% PdCl<sub>2</sub> catalyst in THF at room temperature for 10 min afforded **6a** in 72% yield. When **5b** was subjected to the same conditions, **6b** was isolated in 62% yield.

Another approach involving the Stille reaction<sup>15</sup> and Kumada–Corriu reaction was briefly studied (Scheme 3). Treatment of **2** with vinyltributylstannane using 5 mol% PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> in DMF for 16 h provided **7a** in 93% yield, which was subjected to the Kumada–Corriu conditions to afford **8a** in 65% yield.

**Scheme 3** Preparation of trisubstituted alkenes *via* the Stille reaction.

In conclusion, we have developed a new stereoselective synthesis of trisubstituted alkenes, which is based on gold(I)-catalyzed regio- and stereoselective hydrophosphoryloxylation of haloalkynes and subsequent transition-metal-catalyzed cross-coupling reactions. The present approach provides an easy access to structurally diverse trisubstituted alkenes and will find many useful applications.

SK acknowledges financial support from Nanyang Technological University and PHL thanks the CRI Program (2011-0009011) funded by the National Research Foundation of Korea (NRF), an NRF grant funded by the Korean government (MEST 2009-0087013), and the 2nd phase BK21 program for financial support.

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