

# Cycloisomerization of 1,6-Enynes: Asymmetric Multistep Preparation of a Hydrindane Framework in Water with Polymeric Catalysts

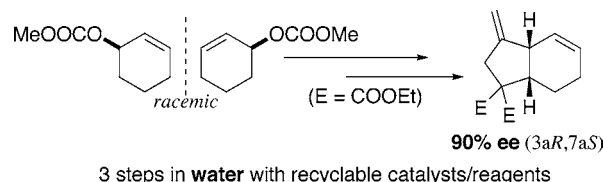
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Received November 9, 2004

## ABSTRACT



Cycloisomerization of 1,6-enynes proceeded smoothly in water under heterogeneous conditions in the presence of a palladium complex supported on polystyrene-poly(ethylene glycol) copolymer resin to give the corresponding cyclopentanes with a high level of chemical greenness. Multistep asymmetric synthesis of a hydrindane framework was achieved via palladium-catalyzed asymmetric  $\pi$ -allylic alkylation, propargylation, and cycloisomerization of 1,6-enynes, where all three steps were performed in water with recyclable polymeric catalysts.

The multistep process approach using polymeric reagents has become an important goal in synthetic organic chemistry.<sup>1</sup> Recently, we have developed various catalytic organic transformations in water with recyclable amphiphilic polymer-supported transition metal complexes combining the advantages of both aqueous- and heterogeneous-switching of a given reaction into a single system.<sup>2,3</sup> If a multistep asymmetric organic synthesis can be achieved in water under mild conditions with recyclable polymeric catalysts, the synthesis represents what may be considered an ideal chemical process.<sup>4</sup> Here we report the development of a fully

environmentally benign heterogeneous catalytic system under aqueous conditions for palladium-promoted cycloisomerization of 1,6-enynes to give cyclopentanes. The asymmetric synthesis of a hydrindane framework was achieved via a palladium-catalyzed asymmetric  $\pi$ -allylic alkylation,<sup>5,6</sup> propargylation of an active methine compound with a polymeric

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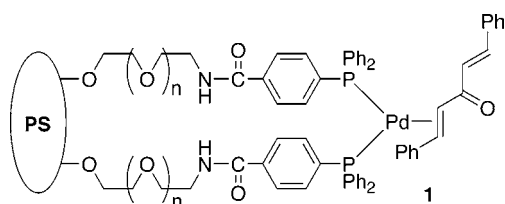
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PTC base, and palladium-catalyzed cycloisomerization of 1,6-enynes, where all three steps were performed in water with recyclable polymeric catalysts.

Transition metal-catalyzed carbocyclization of enynes offers a powerful means to construct a variety of synthetically useful carbo- and heterocycles with high levels of atom economy.<sup>7,8</sup> Cycloisomerization of 1,6-enynes **2** was found to proceed in water<sup>9</sup> in the presence of the amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium complex **1** (Figure 1) and HCOOH. Representative



**Figure 1.** PS-PEG-supported Pd(dba)(triarylphosphine)<sub>2</sub>.

results are summarized in Table 1. The acyclic enynes **2a** and **2b** gave the cyclopentanes **3a** and **3b** in 91 and 92% yields, respectively (entries 1 and 2). The cyclic enynes **2c–f** also underwent cyclization under similar conditions to afford the corresponding bicyclic products **3c–f** in high yields (entries 3–6).

A typical procedure for the reaction of the cyclohexenyl substrate **2d** is as follows. A mixture of the enyne **2d**, 1 mol % palladium of polymeric **1**, and 100 mol % HCOOH was shaken in water at 25 °C for 48 h. In the aqueous medium, the hydrophobic substrate **2** diffused into the hydrophobic PS matrix to undergo palladium-catalyzed cycloisomerization. The resin beads holding the resulting hydrophobic product **3** were then separated from the aqueous medium by filtration. They were extracted with supercritical carbon dioxide (scCO<sub>2</sub>) to give the polymeric catalyst and the desired product **3d** in 90% yield with high purity (>98% purity on <sup>1</sup>H NMR) without chromatographic purification. Both the recovered catalyst beads and the aqueous filtrate were reused several times without any additional charge of palladium and exhibited no loss of catalytic activity for this green protocol (Scheme 1).

With this efficient cycloisomerization protocol in hand, we turned our attention to demonstrating the synthetic

(5) For a recent review on asymmetric  $\pi$ -allylic substitution, see: (a) Acemoglu, L.; Williams, J. M. J. *Handbook of Organopalladium Chemistry*; Negishi, E., Ed.; Wiley: New York, 2002. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

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(7) For a recent review, see: Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

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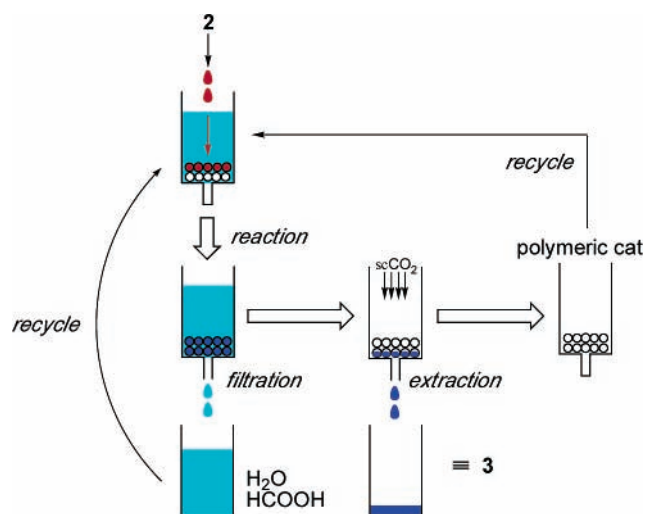
**Table 1.** Cycloisomerization of 1,6-Enynes in Water with a PS-PEG Resin-Supported Palladium Catalyst<sup>a</sup>

entry	1,6-enyne	product (yield %) <sup>b</sup>
1		 <b>3a</b> (91%) <sup>c</sup>
2		 <b>3b</b> (92%)
3		 <b>3c</b> (90%)
4		 <b>3d</b> (90%)
5		 <b>3e</b> (82%)
6		 <b>3f</b> (92%) <sup>c</sup>

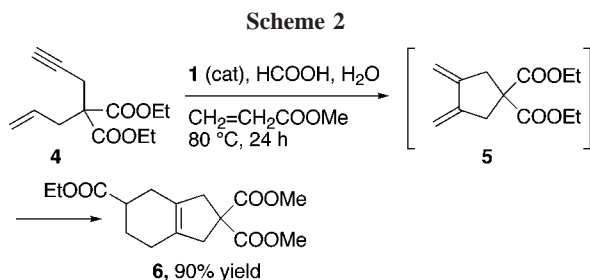
<sup>a</sup> All reactions were carried out in water at 25 °C for 48 h. **2** (mol)/**1** (mol)/HCOOH (mol)/H<sub>2</sub>O (L) = 1.0/0.01/1.0/3.3. <sup>b</sup> Isolated yield. <sup>c</sup> Small amount of olefin regioisomer was detected by <sup>1</sup>H NMR.

potential of the amphiphilic resin-based heterogeneous aqueous catalytic system in the synthesis of a bicyclic carbon

**Scheme 1**



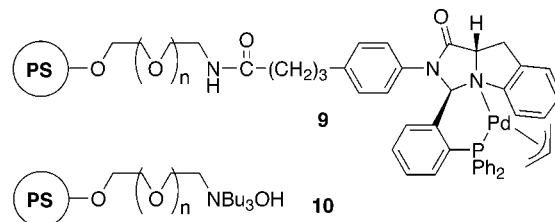
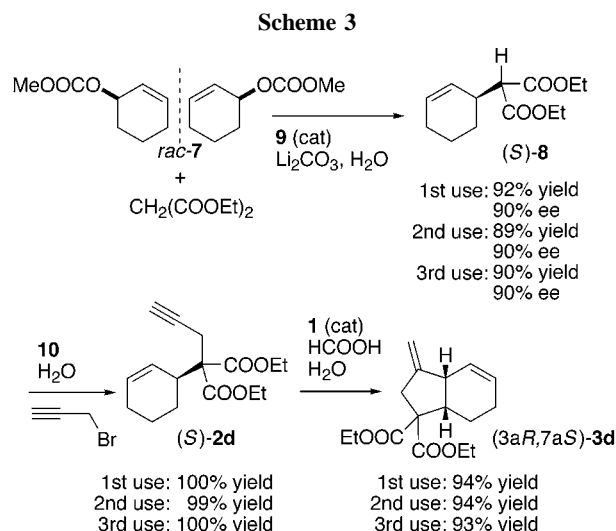
framework. When cycloisomerization of the 1,6-enyne **4** was carried out in the presence of methyl acrylate at 80 °C, a tandem cyclization took place to afford the hydrindane **6** in 90% yield via a one-pot cycloisomerization and subsequent Diels–Alder reaction (Scheme 2).<sup>10</sup>



Asymmetric synthesis of the hydrindane (3a*R*,7a*S*)-**3d** was also achieved in water with recyclable catalysts (Scheme 3). The racemic cyclohexenyl ester *rac*-**7** reacted with diethyl malonate in aqueous  $\text{Li}_2\text{CO}_3$  in the presence of PS–PEG resin-supported chiral imidazoindole phosphine–Pd complex **9** (10 mol %) to give 90% ee of **8** in 92% yield. The polymeric chiral palladium complex was reused three times without any loss of stereoselectivity. Propargylation of the cyclohexenylmalonate **8** with propargyl bromide was performed with PS-PEG ammonium hydroxide **10**, which has been developed as an immobilized PTC base with a view toward use in water to give a quantitative yield of the 1,6-enyne (*S*)-**2d**.<sup>11</sup> The polymeric ammonium reagent was recovered as its bromide salt, which was reactivated by washing with aqueous KOH and reused. The enyne (*S*)-**2d** underwent cycloisomerization with the amphiphilic polymeric palladium **1** to afford 90% ee of the hydrindane (3a*R*,7a*S*)-**3d** in 94% yield.

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In conclusion, we have developed a green and safe protocol for the preparation of a chiral indane framework to demonstrate the considerable potential of heterogeneous catalytic organic transformations in water.

**Acknowledgment.** This work was supported by the CREST program, sponsored by the JST.

**Supporting Information Available:** Characterization and experimental procedures for compounds **1–3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL047700J