



## Evaluation of tuned phosphorus cavitands on catalytic cross-dimerization of terminal alkynes



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### ABSTRACT

Synthesis of four new bis-phosphorus cavitands is described, including a description of their catalytic use on cross-dimerization of terminal alkynes. The commercially available  $P[N(CH_2CH_3)_2]_3$ ,  $PhP[N(CH_2CH_3)_2]_2$ ,  $P(OCH_3)_3$ , and in situ generated  $P(NMeBn)_3$  were reacted with a tetra-ol cavitand platform to provide new phosphorus ligands. These ligands readily formed bis-Au complexes that were examined to generate a reactivity profile for the catalytic cross-dimerization of terminal alkynes. We found that the ligand derived from  $P[N(CH_3)_2]_3$  gave best product selectivity.

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Mother nature is a master of chemical transformations. She serves as an incredibly well-organized chemical transformation machine, performing countless cascades of catalysis giving products with breathtaking molecular diversity. Recently, enzymes with multiple metals that activate otherwise inert substrates inside an enforced cavity have caught our attention.<sup>1</sup> Development of artificial catalysts of comparable ability to such enzymes is a vital matter, especially from the viewpoint of green chemistry.<sup>2</sup> Using principles from the fields of both supramolecular and organometallic chemistry, we have sought to develop active metal centers embedded inside cavities.<sup>3</sup> However, such “introverted” functionalized cavitands have not yet attained the status associated with what we consider a powerful synthetic scaffold.<sup>4</sup> The shortcomings we have encountered continued to challenge us. The synthetic difficulty not only to install a metal center, but also to fine-tune its substructure has hindered these efforts.<sup>5</sup> Within a confined space there has been little room for a metal, a ligand set, let alone a substrate. Overcoming these drawbacks will allow cavitands to be utilized as efficient chemical catalysts.<sup>6</sup>

We recently reported the synthesis of an introverted bis-Au species tethered to a cavitand of diquinoxaline-spanned resorcin[4]arene (Scheme 1).<sup>7</sup> The arrangement of two Au atoms, pointing inward and flanked by 2 aromatic walls, provided a new architecture for catalytic cross-dimerization of terminal alkynes: the

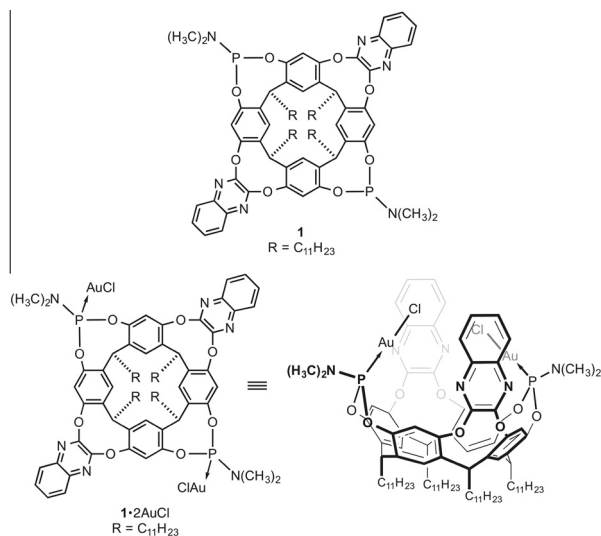
enforced cavity was not only large enough to accommodate multiple metals, more importantly this new entity entices two different reaction partners inside AND carries out a coupling between them. While yields still remained modest we were greatly encouraged. We think the tuning of the metal centers through remote electronic effects might further influence the reaction efficiency.<sup>8,9</sup> Thus, we have systematically manipulated the phosphorus ligands of **1** while simultaneously maintaining the enforced cavity. Herein we present a preparation of new bis-phosphorus cavitands **2–5** that are synthetic variants of **1**. For **2–5** different substituents were induced onto the two phosphorus atoms (Scheme 2). We anticipated that these fine-tuned ligands would regulate both the fitting of two guests into the space, as well as have some electronic effect, thus influencing both the yields and selectivity in the cross-dimerization of terminal alkynes.

We began our investigation from synthesis of **2** and **4** in accordance with the experimental procedure of **1** (Scheme 3).<sup>10</sup> The tetra-ol cavitand **6** reacted with commercially available  $P[N(CH_2CH_3)_2]_3$  and  $PhP[N(CH_2CH_3)_2]_2$  in 64% and 38% yields, respectively. The phosphonite **4** was prepared three times and every sample decomposed 1 month later despite storage in the dark under an argon atmosphere; thus, **4** proved to be unexpectedly fragile.<sup>11</sup>

For the synthesis of **3** in Scheme 4, the corresponding  $P(NMeBn)_3$  was not commercially available, and we explored an access to in situ generation of  $P(NMeBn)_3$  and the following reaction with the tetra-ol cavitand **6**. Among several attempts, the use of 9.6 equiv of  $PCl_3$  and 35 equiv of  $HNMeBn$  was best for

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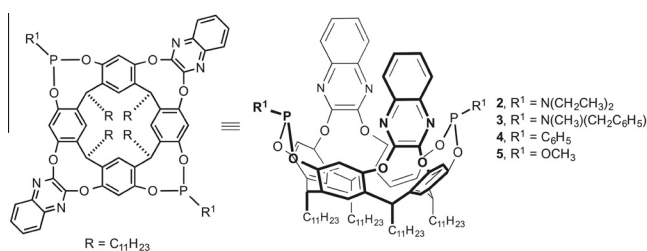


**Scheme 1.** Dimethyl-phosphoramidite **1** and introverted bis-Au catalyst **1.2AuCl** for cross-dimerization of terminal alkynes.

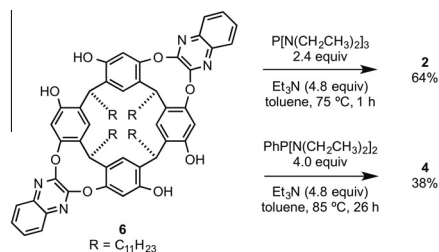
yielding **3** in 25%. As an alternative,  $P(\text{NMeBn})_3$  was generated in situ from 4 equiv of  $\text{PCl}_3$  and 12 equiv of  $\text{LiNMeBn}$  in THF at  $-78^\circ\text{C}$  and the following reaction with **6** was performed in refluxing toluene giving comparable yields (23%).

Products of **2–4** were not accompanied by any isomers and were readily isolated, like previously reported **1**. On the other hand, the reaction between commercially available  $P(\text{OCH}_3)_3$  and the tetra-ol **6** afforded two of three possible isomers (“out-out”, “in-out”, and “in-in”) as illustrated in [Scheme 5](#).<sup>13</sup> These two were readily separated with silica-gel column chromatography in 36% yield of “out-out” **5** and 22% yield of “in-out” **7**.<sup>12</sup> The one doublet peak of  $\text{POCH}_3$  of **5** located at 3.97 ppm with  $^3J_{\text{PH}} = 8.7$  Hz, and two doublet peaks of  $\text{POCH}_3$  of **7** positioned at 3.98 ppm with  $^3J_{\text{PH}} = 8.3$  Hz and at 3.10 ppm with  $^3J_{\text{PH}} = 12.4$  Hz. The upfield shifted peak of **7**, that is 3.10 ppm, suggests that one of the  $\text{OCH}_3$  groups experiences anisotropic effects of the aromatic  $\pi$ -clouds and is oriented inwardly; thus, the P–O bond of **5** directs outwardly. In addition, these chemical shifts of  $\text{POCH}_3$  are fully consistent with those of previously reported *mono*- $\text{POCH}_3$  groups that are inwardly and outwardly tethered to triquinoxaline-spanned resorcin[4]arene.<sup>14</sup>

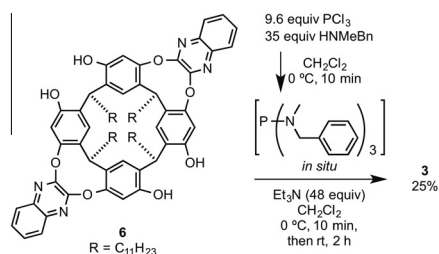
Reactions between  $\text{AuCl}\cdot\text{S}(\text{CH}_3)_2$  and cavitands **2–5** gave the desired formation of corresponding bis-Au complexes, resulting in clear and predictable changes of  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra ([Scheme 6](#)).<sup>15</sup> The purification was performed through a short-plugged silica-gel column chromatography, and high-yielding isolation was achieved for **2.2AuCl**, **3.2AuCl**, and **4.2AuCl**. For **5.2AuCl**, the yield was only 62%. These bis-Au cavitands remained stable for at least 3 weeks while stored in the dark under an argon atmosphere, except **4.2AuCl**. The **4.2AuCl** seemed to be more robust than parent **4** (stability problems noted above); however, three



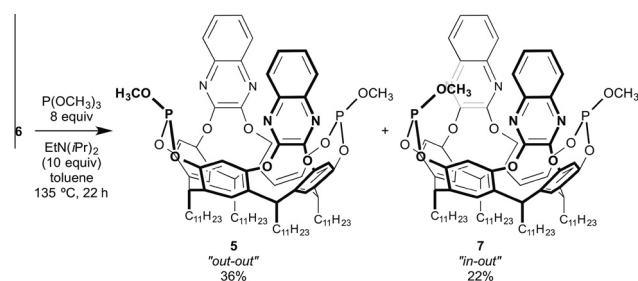
**Scheme 2.** New phosphorus cavitands **2–5** for catalytic use.



**Scheme 3.** Synthesis of **2** and **4**.



**Scheme 4.** Synthesis of **3**.



**Scheme 5.** Synthesis of ‘out-out’ **5** and ‘in-out’ **7**.

weeks later the color changed to reddish purple from an original white color and the  $^1\text{H}$  NMR spectrum became contaminated.

We evaluated the capabilities of **1–5** on by examining the two cross-dimerization reactions of terminal alkynes shown in [Scheme 7](#). In one case the starting materials of ethynylbenzene and 1-octyne (part (a)), and the ethynylbenzene and 4-phenyl-1-butyne (part (b)). Reactions were carried out in toluene at room temperature with 1 equiv of ethynylbenzene and 1.5 equiv of partner alkynes in the presence of 1 mol % of introverted bis-Au catalyst and 2 mol %  $\text{AgOTf}$  (to activate the Au species). The selective cross-dimerization of two different terminal alkynes, which doesn’t require any pre-activated alkynes, is one of the best ways to produce enynes from the view point of green chemistry. Among them, the formation of head-to-tail fashioned enyne is a rare pattern.<sup>16</sup> We previously reported the capability of standard **1.2AuCl** on these two reactions, which showed predominant formation of the head-to-tail fashioned adducts in 70% yield with 4.1/1 ratio for part (a), and in 53% yield with 2.9/1 ratio for part (b).<sup>7</sup> Under these conditions, the cross-adducts (namely, **cross** in [Scheme 7](#)) and homo-adducts (namely, **homo**) of two 1-octynes or two 4-phenyl-1-butyne were the only products obtained (no homo-adducts of two ethynylbenzene). The standard results were listed in entries **1** and **6** of [Table 1](#). Thus, comparison of **1.2AuCl** to **2.2AuCl** and **3.2AuCl** is a summary from the steric point of view (entries 1–3, and 4–6), and comparison of **1.2AuCl** to **4.2AuCl** and **5.2AuCl** is a summary from the electronic point of view (entries 1, 4, 5, 6 and 9–10).

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