#### Tetrahedron Letters 57 (2016) 4754-4757

Contents lists available at ScienceDirect

**Tetrahedron Letters** 

journal homepage: www.elsevier.com/locate/tetlet

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



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#### ARTICLE INFO

Article history: Received 11 August 2016 Revised 3 September 2016 Accepted 8 September 2016 Available online 13 September 2016

Keywords: Introverted functionality Supramolecular catalysis Metallo-cavitands Phosphorus cavitands Resorcin[4]arene

### 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 phosphorous 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  $P[N(CH_2-CH_3)_2]_3$  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<sub>3</sub> 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,  $P(NMeBn)_3$  was generated in situ from 4 equiv of PCl<sub>3</sub> and 12 equiv of LiNMeBn in THF at -78 °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(OCH<sub>3</sub>)<sub>3</sub> 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 POC<u>H<sub>3</sub></u> of **5** located at 3.97 ppm with  ${}^{3}J_{PH}$  = 8.7 Hz, and two doublet peaks of POCH<sub>3</sub> of 7 positioned at 3.98 ppm with  ${}^{3}J_{PH}$  = 8.3 Hz and at 3.10 ppm with  ${}^{3}J_{PH}$  = 12.4 Hz. The upfield shifted peak of 7, that is 3.10 ppm, suggests that one of the OCH<sub>3</sub> 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 POCH<sub>3</sub> are fully consistent with those of previously reported mono-POCH<sub>3</sub> groups that are inwardly and outwardly tethered to triguinoxaline-spanned resorcin[4]arene.<sup>14</sup>

Reactions between AuCl-S(CH<sub>3</sub>)<sub>2</sub> and cavitands **2–5** gave the desired formation of corresponding bis-Au complexes, resulting in clear and predictable changes of <sup>1</sup>H and <sup>31</sup>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 <sup>1</sup>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 staring materials of ethynylbenzene and 1-octyne (part (a)), and the ethynylbenzene and 4-phenyl-1butyne (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 % 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-butynes 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).



Scheme 6. Complexation of AuCl-S(CH<sub>3</sub>)<sub>2</sub> with phosphorus cavitands 2-5.



**Scheme 7.** Cross-dimerization reaction between ethynylbenzene and (a) 1-octyne; (b) 4-phenyl-1-butyne.

For entries 1–3 in Table 1 and 1-2AuCl and 2-2AuCl afforded comparable ratios and yields although 3-2AuCl lowered the ratio to 3.0/1 and the yield to 56%. For entries 6–8, the chemical yields between all catalysts of 1-2AuCl and 2-2AuCl and 3-2AuCl were comparable; however, the ratios decreased from 2.9/1 to 2.2/1 and 1.5/1 in order of 1-2AuCl, 2-2AuCl and 3-2AuCl. Thus, one conclusion can be drawn from the above: larger alkyl moieties of PN (CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> of 2 and PNCH<sub>3</sub>(CH<sub>2</sub>Ph) of 3 than PN(CH<sub>3</sub>)<sub>2</sub> of 1 doesn't improve the efficacy of the catalytic cavitands. Presumably, such a bulky group would narrow the entrance to which guest molecules approach, and it might weaken the ability of molecular recognition between ethynylbenzene and its partner alkynes. For entries 1, 4, and 5, the ratios decreased from 4.1/1 to 3.7/1 and 3.0/1 along with



**Scheme 8.** (a) Complexation between 7 and AuCl-S( $CH_3$ )<sub>2</sub>; (b) evaluation of 7-2AuCl on the reaction conducted via Scheme 7 (a).

highest chemical yields of cross-adducts in **1**·2AuCl. On the other hand, for entries 6, 9, and 10, **4**·2AuCl and **5**·2AuCl gave slightly better ratios and yields than **1**·2AuCl. These results suggest that the dimerization event would be influenced by somewhat electronic factor of the phosphorus atom.

Is there a difference in catalyst capability between 'out-out' **5** and '*in-out*' **7**? As depicted in part a of Scheme 8, complexation of **7** with AuCl-S(CH<sub>3</sub>)<sub>3</sub> smoothly proceeded to give **7**·2AuCl in 93% yield. The complex undertook the catalytic cross-dimerization between ethynylbenzene and 1-octyne (part b of Scheme 8); almost all the alkynes remained intact and hydration of 1-octyne happened to give small amounts of 2-octanone. No formation of the corresponding cross- or homo-adducts was found. This result indicates that the arrangement of two Au atoms facing each other is quintessential for its catalysis.

In summary, the synthetic tuning of bis-phosphorus moieties tethered to the diquinoxaline-spanned resorcin[4]arene was achieved to prepare four new cavitand ligands. Although yields still remain modest, the precursors of P(NRR')<sub>3</sub>, PhP[N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>]<sub>2</sub> and P(OCH<sub>3</sub>)<sub>3</sub> allow us to install phosphorus atoms into the rim of resorcin[4]arene, and the functionalization also allows the ligands to tightly embrace two Au atoms in the confined space. The resultant bis-Au complexes catalyzed cross-dimerization of terminal alkynes, which influenced chemical yields and product selectivity. These show that we could conduct the reactivity and selectivity with a tuned moiety of cavitand substructures. As the ligand scaffold described here would ensure varied phosphorus moieties and metal centers, there are many more variations of reactions to try. In these endeavor we look forward to reporting supramolecular advantages of this easily accessed phosphorus platform, and to getting closer step by step to the lofty standards of Mother Nature.

Table 1	L
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Evaluation of performance of 1-5 on the cross-dimerization conducted via Scheme 7

Entry	Scheme 7 (a) or (b)	Catalyst	Ratios of <b>cross/homo</b> <sup>a</sup>	Isolated yields of <i>cross</i> [%]
1	(a)	1.2AuCl	4.1/1	70
2		2.2AuCl	4.3/1	73
3		3.2AuCl	3.0/1	56
4		4-2AuCl	3.7/1	53
5		5-2AuCl	3.0/1	58
6	(b)	1.2AuCl	2.9/1	53
7		<b>2</b> ·2AuCl	2.2/1	64
8		3.2AuCl	1.5/1	53
9		4-2AuCl	3.0/1	57
10		5·2AuCl	3.1/1	57

<sup>a</sup> Molar ratios determined by <sup>1</sup>H NMR spectroscopy of the crude state.

#### Acknowledgments

We thank Japan Society of the Promotion of Science Invitation Fellowships for Research in Japan (Long-term, L-15528, M.P.S). The authors thank Dr. Toshiyuki Iwai and Dr. Takatoshi Ito at OMTRI for assistance with measurement of HRMS. Prof. Dr. Hajime Iwamoto at Niigata University is gratefully thanked for measurement of HRMS (ESI).

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.09. 039.

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- 11. The white solid materials of freshly prepared **4** turned to bright yellow ones in 1 month.
- 12. The small peaks of plausible 'in-in' compound was found in <sup>1</sup>H NMR spectrum of the crude state, and the 'in-in' product was readily removed from **5** and **7**.
- 13. Representative procedure for synthesis of 5 and 7 (Scheme 5): To the Schlenk tube charged with a solution of the tetra-hydroxy cavitand platform (136 mg, 0.1 mmol) in dry toluene (1 mL) under  $N_2$  atmosphere at 135 °C (oil-bath temp.), EtN(iPr)<sub>2</sub> (0.17 mL, 1 mmol) and P(OCH<sub>3</sub>)<sub>3</sub> (0.09 mL, 0.8 mmol) were added. After stirred for 22 h, the mixture was allowed to cool to room temperature, and followed by concentration to give 156 mg of crude products as yellow viscous materials. Purification by silica-gel column chromatography (eluent: hexane/EtOAc, 9/1) afforded 54 mg of 5 (out-out) as colorless solid materials in 36% yield and 32 mg of 7 (in-out) as colorless solid materials in 22% yield. Data for 5: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.84 (dd, J = 6.4, 3.4 Hz, 4H), 7.54 (dd, J = 6.4, 3.4 Hz, 4H), 7.41 (s, 4H), 7.25 (s, 4H), 5.74 (t, J = 8.2 Hz, 2H), 4.58 (t, j = 7.6 Hz,2H), 3.97 (d,  ${}^{3}J_{8.7}$  = 8.7 Hz, 6H), 2.31–2.24 (m, 8H), 1.46–1.30 (m, 72H), 0.93–0.88 (m, 12H) ppm.  ${}^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>) 152.8, 152.4, 147.1 (d, J<sub>CP</sub> = 7.6 Hz), 139.8, 137.0 (d, J<sub>CP</sub> = 2.1 Hz), 135.2, 129.4, 128.0, 122.8, 117.4 (d, J<sub>CP</sub> = 2.6 Hz), 50.1 (d, J<sub>CP</sub> = 3.6 Hz), 35.9, 34.0, 32.0 (many peaks are overlapped), 31.8, 29.8 (many peaks are overlapped), 29.5, 28.1, 28.0, 22.7 (many peaks are overlapped), 14.2 (many peaks are overlapped) ppm. <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) 127.5 ppm. MS (MALDI-TOF) *m/z*: 1478 [MH]<sup>+</sup>. IR (neat): 2925, 2852, 1572, 1487, 1395, 1335, 1159, 1032, 898 cm<sup>-1</sup>. HRMS (ESI) calcd for C<sub>90</sub>H<sub>119</sub>N<sub>4</sub>O<sub>10</sub>P<sub>2</sub>: 1477.8396 [MH]<sup>+</sup>, found: 1477.8370. Data for **7**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.85-7.83 (m, 2H), 7.75-7.73 (m, 2H), 7.54-7.52 (m, 4H), 7.35 (s, 2H), 7.28 (s, 2H), 7.25 (s, 2H), 7.16 (s, 2H), 5.70 (t, J = 8.0 Hz, 2H), 4.57 (t, J = 7.8 Hz, 1H), 4.51 (t, J = 8.0 Hz, 1H), 3.98 (d,  ${}^{3}J_{PH} = 8.3$  Hz, 3H), 3.10 (d, <sup>3</sup>J<sub>PH</sub> = 12.4 Hz, 3H), 2.29–2.24 (m, 8H), 1.44–1.28 (m, 72H), 0.91–0.87 (m, 12H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 153.7, 153.6, 153.1, 152.5, 149.3 (d, J<sub>CP</sub> = 15.0 Hz), 147.5 (d, J<sub>CP</sub> = 5.5 Hz), 140.5, 140.4, 137.8 (d, J<sub>CP</sub> = 2.4 Hz), 136.0, 135.8, 135.2, 130.1, 129.9, 128.8, 128.2, 123.9, 122.8, 118.0, 117.8, 52.1 (d, J<sub>CP</sub> = 22.1 Hz), 50.9 (d, J<sub>CP</sub> = 3.8 Hz), 37.1, 36.5, 34.6, 32.6 (many peaks are overlapped), 32.5, 32.4, 32.0, 30.4 (many peaks are overlapped), 30.1 (many peaks are overlapped), 28.7, 23.4 (many peaks are overlapped), 14.8 (many peaks are overlapped), ppm. <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) 127.3, 111.6 ppm. MS (MALDI-TOF) *m/z*: 1479 [MH<sub>2</sub>]<sup>+</sup>. IR (neat): 2925, 2852, 1482, 1402, 1323, 1153, 1032, 898 cm<sup>-1</sup>. Anal. Calcd for C<sub>90</sub>H<sub>118</sub>N<sub>4</sub>O<sub>10</sub>P<sub>2</sub>: C, 73.14; H, 8.05; N, 3.79. Found: C, 73.14; H, 8.10; N, 3.88.
- 14. The chemical shifts (CDCl<sub>3</sub>) of outwardly and inwardly directed POCH<sub>3</sub> tethered to triquinoxaline-spanned resorecin[4]arene are 3.92 ppm (d, <sup>3</sup>*J*<sub>PH</sub> = 8.3 Hz, 3H) and 2.99 (d, <sup>3</sup>*J*<sub>PH</sub> = 12.4 Hz, 3H), respectively. See: Schramm, M. P.; Kanaura, M.; Endo, N.; Iwasawa, T. *Eur. J. Org. Chem* 2016, 813–820.
- 15. These data of <sup>1</sup>H and <sup>31</sup>P NMR were summarized in Supporting Information.
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