ORGANIC
LETTERS

2007
Vol. 9, No. 1
89−92

A Bowl-Shaped Phosphine as a Ligand in Palladium-Catalyzed Suzuki–Miyaura Coupling of Aryl Chlorides: Effect of the Depth of the Bowl

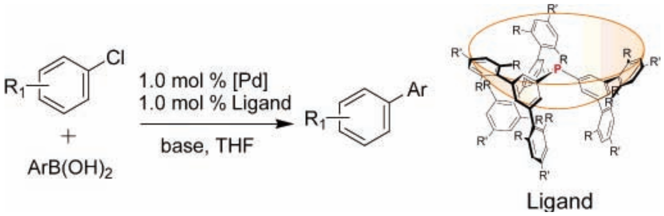
**Hidetoshi Ohta,[†,‡] Makoto Tokunaga,[‡] Yasushi Obora,[‡] Tomohiro Iwai,[‡]
Tetsuo Iwasawa,[‡] Tetsuaki Fujihara,[†] and Yasushi Tsuji*[,†]**

*Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering,
Kyoto University, CREST, Japan Science and Technology Agency (JST),
Kyoto 615-8510, Japan, and Catalysis Research Center and Division of Chemistry,
Graduate School of Science, Hokkaido University, Sapporo 001-0021, Japan*

ytsuji@scl.kyoto-u.ac.jp

Received October 24, 2006

ABSTRACT



Bowl-shaped phosphine ligands were found to be highly effective in Suzuki–Miyaura coupling of unactivated aryl chlorides, in which the depth of the bowl affected the catalytic activity considerably.

Phosphines are one of the most important ligands in a homogeneous transition-metal-catalyzed reaction. Therefore, a wide variety of phosphines have been designed to realize high catalytic activity and selectivity.[1] Recently, a bowl-shaped phosphine (BSP) has attracted much attention,[2] because BSP has a very unique shape.[3] Goto and Kawashima reported the first example of BSP, tris(2,2″,6,6″-tetramethyl-*m*-terphenyl-5′-yl)phosphine (**2**; Figure 1).[2a,b] Figure 2 shows optimized structures of **2** as a representative BSP and P(*t*-Bu)$_3$ by HF/6-31G(d) calculations,[4a] using initial structures optimized by CONFLEX[4b]/MM3[4c,d] (HF/6-31G(d)-CONFLEX/MM3). As shown in Figure 2, both **2** and P(*t*-Bu)$_3$ are obviously very bulky. However, the nature of the bulkiness is quite different between these two phosphines. The bulkiness of **2** occurs on the periphery of the phosphine (at the rim of the bowl) with substantial empty space around the phosphorus atom. In contrast, P(*t*-Bu)$_3$ has severe steric congestion within close proximity of the phosphorus atom. We recently reported the first application of BSP as a ligand in a transition-metal-catalyzed reaction, and found remarkable rate enhancement by BSP in the rhodium-catalyzed hydrosi-

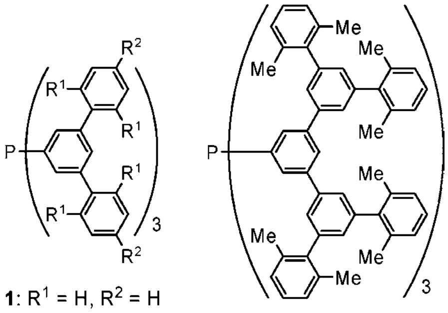
---

[†] Kyoto University.
[‡] Hokkaido University.

(1) (a) *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983. (b) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Applications of Transition Metal Catalysts in Organic Synthesis*; Springer: Berlin, Germany, 1999. (c) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 523−919.

(2) (a) Goto, K.; Ohzu, Y.; Sato, H.; Kawashima, T. *15th International Conference on Phosphorus Chemistry*, Sendai, Japan, 2001; Abstr. No. PB072. (b) Goto, K.; Ohzu, Y.; Sato, H.; Kawashima, T. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2002**, *177*, 2179. (c) Matsumoto, T.; Kasai, T.; Tatsumi, K. *Chem. Lett.* **2002**, 346−347. (d) Niyomura, O.; Tokunaga, M.; Obora, Y.; Iwasawa, T.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 1287−1289. (e) Ohzu, Y.; Goto, K.; Kawashima, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5714−5717. (f) Niyomura, O.; Iwasawa, T.; Sawada, N.; Tokunaga, M.; Obora, Y.; Tsuji, Y. *Organometallics* **2005**, *24*, 3468−3475. (g) Ohzu, Y.; Goto, K.; Sato, H.; Kawashima, T. *J. Organomet. Chem.* **2005**, *690*, 4175−4183.

10.1021/ol0626138 CCC: $37.00



1: $R^1 = H$, $R^2 = H$
2: $R^1 = Me$, $R^2 = H$
3: $R^1 = Me$, $R^2 = Me$
4: $R^1 = Me$, $R^2 = t$-Bu

5

Figure 1. Bowl-shaped phosphines.

lylation of ketone.[2d,f] During our continuous effort to explore the efficacy of BSP as a ligand in transition-metal-catalyzed reactions, we found a new efficiency of BSP and wish to report that BSP is a highly effective ligand in the palladium-catalyzed Suzuki−Miyaura coupling of unactivated aryl chlorides.

The palladium-catalyzed Suzuki−Miyaura coupling is one of the most important and versatile methods for construction of carbon−carbon bonds.[5] It is well-known that Suzuki−Miyaura coupling is considerably affected by the nature of the catalyst precursor, the added base, and solvent.[5] Therefore, the proper choice of reaction conditions is very important to evaluate the effect of a ligand in Suzuki−Miyaura coupling. In the present study, five BSP ligands (**1**−**5** in Figure 1) were employed. They are phosphines having *m*-terphenyl (**1**−**4**) or the higher dendritic moieties (**5**[6]).

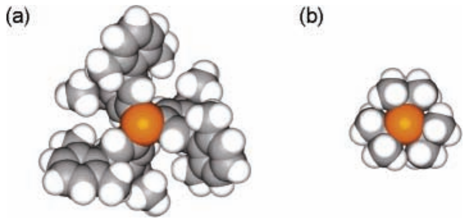
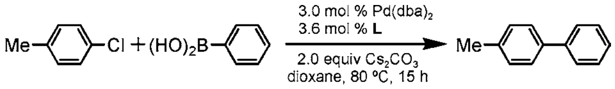


Figure 2. Optimized structures of (a) **2** and (b) P(t-Bu)$_3$ by HF/6-31G(d)-CONFLEX/MM3.

Recently, Fu and Buchwald have shown that catalyst systems with very basic and bulky phosphines are effective in Suzuki−Miyaura coupling of unactivated aryl chlorides.[7] Such bulky phosphines are also effective ligands in the Mizoroki−Heck reaction of unactivated aryl chlorides.[8] Actually, P(t-Bu)$_3$ and tricyclohexylphosphine (PCy$_3$) effectively worked as ligands in the coupling of 4-chlorotoluene with phenylboronic acid in the presence of Pd(dba)$_2$ with Cs$_2$CO$_3$ as a base in dioxane at 80 °C[7a] as shown in Scheme 1. To evaluate the effectiveness of the BSP ligand in Suzuki−Miyaura coupling, we carried out the reaction with BSP ligands under the same reaction conditions. The BSP ligand **1** having a *m*-terphenyl moiety without any substituents afforded the product only in 2% yield. On the other hand, the BSP ligands **2** and **4** bearing methyl substituents at the 2,2″,6,6″ positions of the *m*-terphenyl moiety and the BSP ligand **5** bearing the higher dendritic moiety afforded the product in much higher yields (75−91%). Thus, the BSPs with the methyl substituents were found to be effective ligands that are comparable to the very basic and bulky phosphine (Scheme 1).

Scheme 1



Yields of the product with various **L**: 86% with P(t-Bu)$_3$, 83% with PCy$_3$, 2% with **1**, 91% with **2**, 84% with **4**, 75% with **5**.

The BSPs are still effective even at a lower reaction temperature (50 °C) with KF as a base in THF[7b] (eq 1, Table 1). Although the BSP ligand **1** afforded the product only in 1% yield (entry 1), the BSP ligands **2**, **3**, **4**, and **5** afforded

---

(3) For utilization of bowl-shaped molecules and moieties, see: (a) Maverick, E.; Cram, D. J. *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Elsevier: Oxford, UK, 1996; Vol. 2, pp 367−418. (b) Goto, K.; Okumura, T.; Kawashima, T. *Chem. Lett.* **2001**, 1258−1259. (c) Goto, K.; Nagahama, M.; Mizushima, T.; Shimada, K.; Kawashima, T.; Okazaki, R. *Org. Lett.* **2001**, *3*, 3569−3572. (d) Naiki, M.; Shirakawa, S.; Kon-i, K.; Kondo, Y.; Maruoka, K. *Tetrahedron Lett.* **2001**, *42*, 5467−5471.

(4) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford CT, 2004. (b) Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950−8951. Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187−198. (c) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 720−729. (d) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490−519.

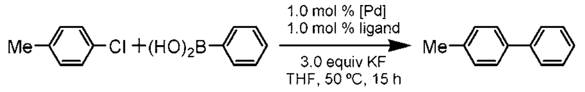
(5) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Miyaura, N. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Willy-VCH: Weinheim, Germany, 2004; Vol. 1, pp 41−123.

(6) The phosphine **5** and palladium(II) complexes bearing **5** were first reported by Goto and Kawashima: Ohzu, Y.; Goto, K.; Sato, H.; Kawashima, T. presented in part at *The 49th Symposium on Organometallic Chemistry*, Japan, 2002; Abstr. No. PA110.

(7) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211 and references cited therein. (e) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101−4111.

(8) (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000. (b) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11.

Table 1. Effect of Phosphine Ligands on the Suzuki−Miyaura Coupling of 4-Chlorotoluene with Phenylboronic Acid[a]



(1)

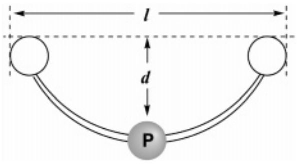
entry	ligand	basicity		cone angle (deg)[b]	yield (%)[d]
		$V_{\min}$[b]	$^1J_{P-Se}$		
1	**1**	−41.6	766	193	1
2	**2**	−41.0	770	205	50
3	**3**	−42.8	741	210	74
4	**4**	−42.5	743	221	86
5	**5**	−39.8	770	268	89 (88[e])
6	PPh$_3$	−42.2	735	168	0
7	P(*o*-tol)$_3$	−44.4	732	218	1
8	P(Mes)$_3$	−44.6	–[c]	243	0
9	P(*t*-Bu)$_3$	−54.4	686	181	0 (5[f])
10	PCy$_3$	−54.4	674	188	13 (46[f])

[a] Reaction conditions: 4-chlorotoluene (1.0 mmol), phenylboronic acid (1.5 mmol), KF (3.0 mmol), THF (1 mL), Pd$_2$(dba)$_3$·CHCl$_3$ (0.005 mmol), ligand (0.010 mmol), P/Pd = 1, 50 °C, 15 h. [b] HF/6-31G(d). [c] Corresponding phosphine selenide is not available. [d] GC yield. [e] Isolated yield. [f] Reaction under reflux.

the product in 50%, 74%, 86%, and 89% yields, respectively (entries 2−5). In contrast, representative triarylphosphines such as PPh$_3$, P(*o*-tol)$_3$, and P(Mes)$_3$ gave almost no coupling adduct (entries 6−8). P(*t*-Bu)$_3$ and PCy$_3$ were not so effective as shown in entries 9 and 10.

As shown in Scheme 1 and Table 1, the BSP ligands **2**−**5** are effective in Suzuki−Miyaura coupling of 4-chlorotoluene. However, the structurally comparable **1** is not effective. To elucidate the unusual effectiveness of BSP in the coupling reaction, two critical parameters, basicity and cone angle, of the phosphines were examined. So far, these two electronic and steric parameters successfully rationalized the influence of phosphine ligands in many transition-metal-catalyzed reactions.[1] The basicity of phosphines was evaluated by two methods: theoretical calculation (HF/6-31G(d)) of the molecular electrostatic potential ($V_{\min}$;[9] more negative values indicate more basic phosphines) and $^1J_{P-Se}$ coupling constants[10] of the corresponding phosphine selenides $Se{=}PR_3$ (smaller values correspond to higher basicity). In addition, the cone angles of the phosphines were measured according to Tolman's definition[11] by using structures optimized by the HF/6-31G(d)-CONFLEX/MM3 calculations. These electronic and steric parameters are listed in Table 1. As shown in Table 1, the effective (**2**−**5**) and the ineffective (**1**) BSP have essentially similar basicity comparable to that of triarylphosphines such as PPh$_3$. Furthermore, a particular range of the cone angles for the effective ligands cannot be determined. Thus, neither the basicity nor the cone angle showed evident correlations with the efficacy of the phosphines. Hence, we turned our attention to the shape of BSP. The depths (*d*) and the diameters (*l*) of BSP (**1**−**5**) were measured on the optimized structures obtained by the HF/6-31G(d)-CONFLEX/MM3 calculations, and listed in Table 2. We previously reported that the depth of the bowl (*d*), not the diameter (*l*), is a critical parameter to determine the effectiveness of the BSP ligands in the rhodium-catalyzed hydrosilylation of ketones.[2d,f] In Table 1, the deeper bowls (**2**−**5**) are apparently effective, but the shallower bowl (**1**) is not, which is very reminiscent of the rhodium-catalyzed hydrosilylation of ketones with BSP.[2d,f]

Table 2. Depths and Diameters of BSPs[a]



phosphine	*d* [nm]	*l* [nm]
1	0.132	1.95
2	0.208	1.99
3	0.280	2.16
4	0.391	2.40
5	0.674	2.63

[a] By HF/6-31G(d), using initial structures optimized by CONFLEX/MM3.

The effect of the depth of the bowl on the catalytic activity was further examined with various aryl chlorides by using BSP/Pd$_2$(dba)$_3$·CHCl$_3$ catalyst in THF (Table 3). In the reaction of 2-chloro-1,3-dimethylbenzene with phenylboronic acid, the product was obtained in 91%, 91%, 40%, and 68% yields with BSPs **5**, **4**, **3**, and **2**, respectively (entries 1−4). In the more sterically demanding coupling reaction of 2-chloro-1,3-dimethylbenzene with 2-methylphenylboronic acid employing K$_3$PO$_4$ as a base, the deepest BSP **5** provided the product in much higher yield (89%) than with BSP **4**, **3**, and **2** (57%, 36%, and 36% yields, respectively) (entries 6−9). Among BSPs, the deepest BSP **5** is also the most effective ligand with the activated aryl chloride by the electron-withdrawing substituent (entries 11−15). Although the reactions of 4-chloroanisole were sluggish, the highest yield was obtained with **5** (entry 16). With 2-chloropyridine as a heteroaryl chloride, the deepest BSP **5** still was the most effective ligand (entry 21). In this case, however, some deeper BSPs (**4** and **3**: entries 22 and 23) were far less efficacious, and the shallower ligand (**1**) afforded the product in high yield (entry 25). Coordination of the pyridine functionality to a catalyst center[12] may affect the influence of the depth of BSP.

---

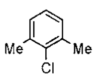
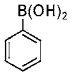
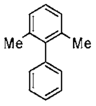
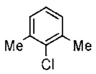
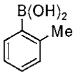
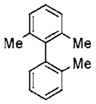
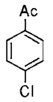
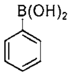
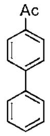
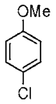
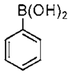
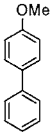
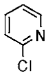
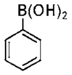
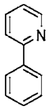
(9) Suresh, C. H.; Koga, N. *Inorg. Chem.* **2002**, *41*, 1573−1578.

(10) (a) Allen, D. W.; Taylor, B. F. *J. Chem. Soc., Dalton Trans.* **1982**, 51−54. (b) Socol, S. M.; Verkade, J. G. *Inorg. Chem.* **1984**, *23*, 3487−3493. (c) Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997−1030. (d) Alyea, E. C.; Malito, J. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1989**, *46*, 175−181.

(11) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313−348.

(12) (a) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030−3039. (b) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240−7241.

Table 3. Suzuki−Miyaura Coupling of Various Aryl Chlorides[a]

entry	ArCl	Ar′B(OH)₂	product	condition	ligand	yield (%)[c]
1				KF 50 °C 15 h	**5**	91
2					**4**	91 (88)
3					**3**	40
4					**2**	68
5					**1**	1
6				K_3PO_4 50 °C 15 h[b]	**5**	89 (85)
7					**4**	57
8					**3**	36
9					**2**	36
10					**1**	1
11				K_3PO_4 rt 30 h	**5**	87 (85)
12					**4**	70
13					**3**	56
14					**2**	72
15					**1**	8
16				KF 50 °C 15 h	**5**	56
17					**4**	15
18					**3**	6
19					**2**	16
20					**1**	1
21				KF 65 °C 15 h	**5**	82 (80)
22					**4**	6
23					**3**	9
24					**2**	72
25					**1**	73

[a] Reaction conditions: aryl chloride (1.0 mmol), arylboronic acid (1.5 mmol), base (3.0 mmol), THF (1 mL), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.005 mmol), ligand (0.010 mmol), P/Pd = 1. [b] Arylboronic acid (2.0 mmol). [c] GC yield, isolated yield in parentheses.

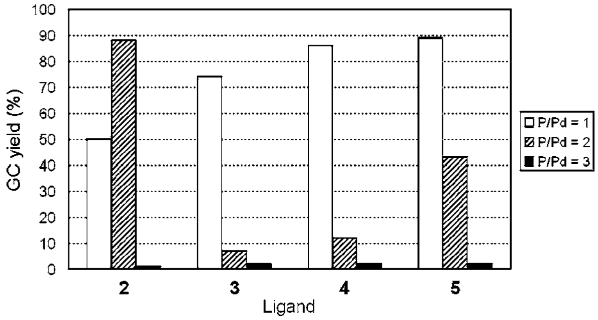


Figure 3. Effect of P/Pd on the Suzuki−Miyaura coupling of 4-chlorotoluene with phenylboronic acid (eq 1). Yields were 50%, 88%, and 1% with **2**; 74%, 7%, and 2% with **3**; 86%, 12%, and 2% with **4**; and 89%, 43%, and 2% with **5**, at P/Pd = 1, 2, and 3, respectively.

It is noteworthy that with effective BSPs **2**−**5** as the ligand the P/Pd ratio affects the catalytic activity significantly (Figure 3). At P/Pd = 1, BSPs **2**, **3**, **4**, and **5** afforded the product in 50%, 74%, 86%, and 89% yields in eq 1, respectively (entries 2−5 in Table 1 and Figure 3). However, at P/Pd = 2, the yield with **3**, **4**, and **5** decreased dramatically to 7%, 12%, and 43%, respectively (Figure 3). At P/Pd = 3, all the yields with **3**, **4**, and **5** further decreased to 2% (Figure 3). On the other hand, with **2** the yield of the product considerably increased to 77% at P/Pd = 1.2 (not shown in Figure 3), and to 88% at P/Pd = 2, but decreased drastically to 1% at P/Pd = 3 (Figure 3). In the presence of an excess of phosphines, bis- and trisphosphine Pd species, which have almost no catalytic activity under the present reaction conditions, might be predominant. It is well-known that bowl-shaped molecules stabilize highly reactive species within the bowl very effectively.[13] In the catalytic reaction, deeper BSP ligands could generate highly unsaturated monophosphine Pd species efficiently, since the deeper bowl ligand would exclude the other identical deeper ligand on coordination. The highly unsaturated monophosphine Pd species thus obtained have deeper bowl-shaped cavities (empty space) around a metal center and are expected to have very high catalytic activity.

In summary, BSP ligands were found to be highly effective in the palladium-catalyzed Suzuki−Miyaura coupling of unactivated aryl chlorides. The depth of the bowl affected the catalytic activity considerably: the deeper bowl ligand was more effective than the shallower bowls. Further catalytic application of BSP as a ligand is currently being investigated.

Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0626138

---

(13) (a) Goto, K.; Tokitoh, N.; Okazaki, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1124−1126. (b) Shimada, K.; Goto, K.; Kawashima, T.; Takagi, N.; Choe, Y.; Nagase, S. *J. Am. Chem. Soc.* **2004**, *126*, 13238−13239.