Asymmetric Catalysis

DOI: 10.1002/anie.200702513

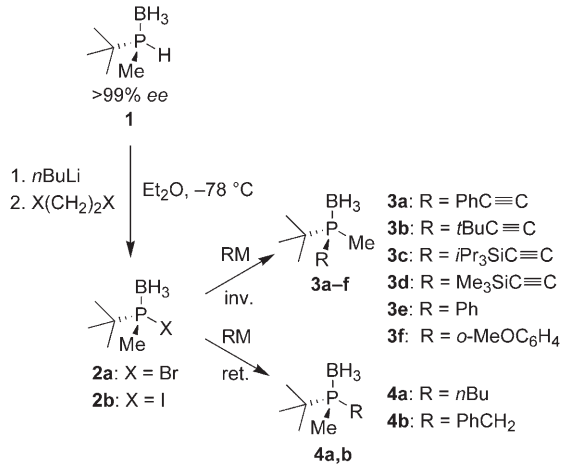
Synthesis and Enantioselectivity of P-Chiral Phosphine Ligands with Alkynyl Groups**

Tsuneo Imamoto, Youichi Saitoh, Aya Koide, Tomokazu Ogura, and Kazuhiro Yoshida*

In memory of Yoshihiko Ito

Stereospecific substitution reactions at stereogenic phosphorus atoms provide a variety of optically active organophosphorus compounds.[1] Such reactions are particularly useful for the preparation of key intermediates for the synthesis of P-chiral phosphine ligands.[2] We previously studied the stereochemistry of electrophilic substitution reactions of optically active secondary phosphinoboranes to demonstrate the utility of such transformations for the synthesis of P-chiral phosphine ligands.[3] Optically active phosphinoboranes with a halogen substituent on the phosphorus atom are also potentially useful as precursors to nonracemic organophosphorus compounds because they can undergo stereospecific nucleophilic substitution reactions. Jugé and co-workers have studied extensively the synthesis and reactivity of chlorophosphanylboranes for the preparation of various P-chiral phosphine ligands,[4] whereas Stankevic and Pietrusiewicz have described the reactivity of optically active phosphinous acid–boranes and related substrates.[5] However, these studies were limited to substrates with at least one aryl group on the phosphorus atom, and the stereospecificity of the substitution reactions was not always high. We envisaged that halophosphanylboranes with two different alkyl groups would react with various nucleophiles to give substitution products that are difficult to synthesize by existing methods.

To investigate the validity of this approach, we subjected enantiomerically pure (*S*)-(*tert*-butylmethylphosphanyl)borane (**1**)[3f,6] to deprotonation with *n*BuLi at −78 °C followed by halogenation with 1,2-dibromoethane or 1,2-diiodoethane to give the halophosphanylboranes **2a**,**b** as crystalline solids in high yields. These compounds, however, were configurationally unstable and racemized gradually at room temperature; hence, they were not isolated but treated directly with organometallic reagents to give a range of substitution products (Scheme 1).



Scheme 1. Generation and substitution reactions of the optically active halophosphanylboranes **2a** and **2b**.

All alkynyl lithium reagents tested reacted with **2a** to give the expected substitution product **3** in high yield and almost exclusively with inversion of configuration (Table 1, entries 1 and 3–5).[7] Although there have been many reports on substitution reactions at chiral phosphorus atoms,[1,2,4,5,8] to our knowledge, there has been no previous example of

Table 1: Substitution reactions of the halophosphanylboranes **2a**,**b**.[a]

Entry	2	Reagent	Product	Yield [%][b]	*ee* [%][c]
1	**2a**	PhCCLi	**3a**	83	97 (*S*) inversion
2	**2b**	PhCCLi	**3a**	12	32 (*S*) inversion
3	**2a**	*t*BuCCLi	**3b**	82	98 (*S*) inversion
4	**2a**	$iPr_3SiCCLi$	**3c**	86	98 (*S*) inversion
5	**2a**	$Me_3SiCCLi$	**3d**	81	99 (*S*) inversion
6	**2a**	PhMgBr	**3e**	28	83 (*S*) inversion
7	**2b**	PhMgBr	**3e**	0[d]	–
8	**2a**	$o\text{-}MeOC_6H_4MgBr$	**3f**	68	93 (*S*) inversion
9	**2a**	*n*BuLi	**4a**	63	91 (*S*) retention
10	**2b**	*n*BuLi	**4a**	79	89 (*S*) retention
11	**2a**	$PhCH_2MgCl$	**4b**	94	96 (*S*) retention
12	**2b**	$PhCH_2MgCl$	**4b**	92	93 (*S*) retention
13	**2a**	1. 2 *t*BuLi, 2. $PhCH_2Br$	**4b**	80	99 (*S*) retention

[a] All reactions were carried out in diethyl ether. The reagents were combined at −78 °C, and the reaction mixture was allowed to warm to room temperature (see details in the Supporting Information). [b] Yield of the isolated product. [c] The configuration of the major enantiomer is given in parentheses. [d] (*S*)-*tert*-Butylmethylphosphanylborane was isolated in high yield.

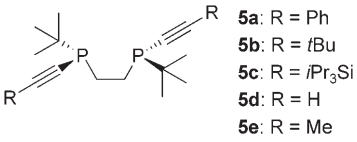
[*] Prof. Dr. T. Imamoto, Y. Saitoh, A. Koide, T. Ogura, Prof. Dr. K. Yoshida
Department of Chemistry
Graduate School of Science, Chiba University
Yayoi-cho, Inage-ku, Chiba 263-8522 (Japan)
Fax: (+81) 43-290-2791
E-mail: imamoto@faculty.chiba-u.jp

[**] This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (Advanced Molecular Transformations of Carbon Resources) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

stereospecific substitution by alkynyl nucleophiles. The treatment of **2a** with phenyl and *o*-methoxyphenyl Grignard reagents under similar conditions also provided inversion products (Table 1, entries 6 and 8). In sharp contrast, the treatment of **2a**,**b** with *n*-butyllithium and benzylmagnesium chloride gave substitution products with retention of configuration (Table 1, entries 9–12).[9] This stereochemical outcome may result from metal–halogen exchange followed by the reaction of the phosphoranyl anion and halobutane or benzyl halide thus generated to give **4a** or **4b**. In fact, the successive treatment of **2a** with *tert*-butyllithium (2 equiv) and benzyl bromide resulted in the formation of (*S*)-**4b** with 99% *ee* (Table 1, entry 13).

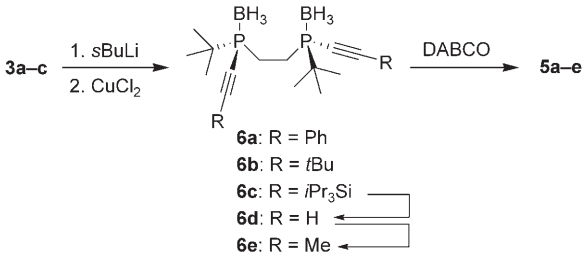
Among the substitution products, we were especially interested in alkynylated phosphinoboranes. The alkynyl groups considered in their entirety are much larger than a methyl group; however, the carbon–carbon triple bond moiety is slim owing to the linearity of the arrangement of atoms around sp-hybridized carbon atoms,[10] and these groups seem to behave like small alkyl groups, such as the methyl group. This idea led us to synthesize new ligands in the form of the (*S*,*S*)-1,2-bis(alkynyl(*tert*-butyl)phosphanyl)-ethanes **5a**–**e**. Although these ligands are structurally similar



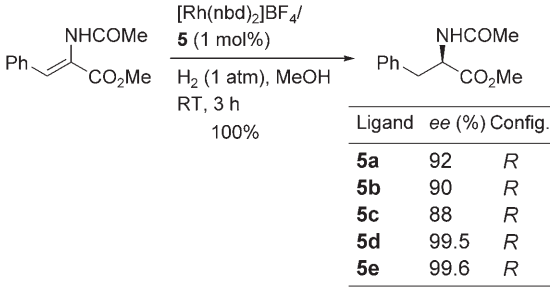
to 1,2-bis(*tert*-butylmethylphosphanyl)ethane (*t*Bu-BisP*),[11] we believed that the large difference in the steric bulk of the *tert*-butyl and alkynyl groups on the stereogenic phosphorus atom might induce outstanding enantioselectivities in transition-metal-catalyzed asymmetric reactions. Furthermore, the electron-withdrawing nature of the alkynyl group decreases the electron density on the phosphorus atom and should lead to a difference in the catalytic activities of ligands **5** with respect to those observed for BisP*.

The alkynylated phosphinoboranes in hand were converted into the target ligands. The deprotonation of compounds **3a**–**c** with *s*BuLi or *t*BuLi and subsequent oxidative coupling produced compounds **6a**–**c**, which were deprotected to furnish the desired diphosphine ligands **5a**–**c**. Compound **6d** was formed from **6c** by desilylation, and subsequent methylation gave **6e**. Finally, the deprotection of **6d** and **6e** led to **5d** and **5e**, respectively (Scheme 2).

The enantioinduction ability of ligands **5a**–**e** was tested in a typical Rh-catalyzed hydrogenation reaction with methyl (*Z*)-α-acetamidocinnamate (Scheme 3).[12] Ligands **5a**–**c** with phenyl, *tert*-butyl, or triisopropylsilyl groups at the alkyne termini were found to induce relatively high enantioselectivities (88–92% *ee*) in the range expected for this general type of ligand: Apparently the asymmetric reaction center is not affected significantly by the spatial effects of the alkyne substituents. However, almost perfect enantioselectivity was observed when **5d** and **5e** were used. In the case of **5d** and **5e**,



Scheme 2. Synthesis of the alkynyl phosphine ligands **5a**–**e**. DABCO = 1,4-diazabicyclo[2.2.2]octane.



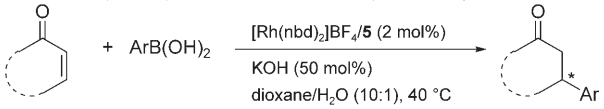
Ligand	*ee* (%)	Config.
5a	92	*R*
5b	90	*R*
5c	88	*R*
5d	99.5	*R*
5e	99.6	*R*

Scheme 3. Rhodium-catalyzed hydrogenation of methyl (*Z*)-α-acetamidocinnamate in the presence of ligands **5a**–**e**. nbd = norbornadiene.

the alkynyl groups (ethynyl and 1-propynyl) appear to behave as very small substituents.

The new ligands were also tested in the Rh-catalyzed asymmetric 1,4-addition of aryl boronic acids to α,β-unsaturated carbonyl compounds (Table 2). The use of **5a** and **5e** in

Table 2: Asymmetric 1,4-addition of aryl boronic acids to α,β-unsaturated carbonyl compounds under the catalysis of Rh^{I}/**5**.



enone: 2-cyclohexenone (**7**), 2-cyclopentenone (**8**), (*E*)-5-methyl-3-hexen-2-one (**9**)

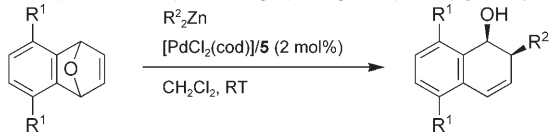
Entry	5	Enone	Ar	*t* [h]	Yield [%][a]	*ee* [%][b]
1[c]	**5a**	**7**	Ph	2	93	99.4 (*R*)
2[c,d]	**5b**	**7**	Ph	2	94	46 (*R*)
3[c,e]	**5c**	**7**	Ph	12	64[f]	68 (*R*)
4[c,g]	**5d**	**7**	Ph	12	trace	–
5	**5e**	**7**	Ph	3	91	99.1 (*R*)
6[c]	**5a**	**8**	Ph	2	90	91 (*R*)
7[c]	**5a**	**9**	Ph	2	91	97.2 (*R*)
8[c]	**5a**	**7**	4-$CF_3C_6H_4$	2	96	96.0 (*R*)
9[c]	**5a**	**7**	4-$MeOC_6H_4$	2	99	98.4 (*R*)
10	**5e**	**8**	Ph	3	92	93 (*R*)
11	**5e**	**9**	Ph	3	88	98.7 (*R*)
12	**5e**	**7**	4-$CF_3C_6H_4$	3	97	97.6 (*R*)
13	**5e**	**7**	4-$MeOC_6H_4$	3	97	99.5 (*R*)

[a] Yield of the isolated product. [b] The configuration of the major enantiomer is given in parentheses. [c] A quantity of 1 mol% of the catalyst was used. [d] The reaction was carried out at 50°C. [e] The reaction was carried out at 70°C. [f] 2-Cyclohexen-1-one was recovered in 31% yield. [g] The reaction was carried out at 90°C.

a variety of substrate–reagent combinations revealed their exceedingly high enantioinduction ability. The addition products were formed with 99.1% *ee* or higher in the best cases (Table 2, entries 1, 5, and 13). The use of ligands **5b** and **5c** resulted in significantly lower selectivities (46 and 68% *ee*, respectively; Table 2, entries 2 and 3), and the addition reaction proceeded sluggishly when **5d** was used (Table 2, entry 4), probably because the terminal alkyne inhibits the Rh-catalyzed reaction under these basic conditions. The results obtained with **5e** are comparable or superior to those obtained with binap,[13] QuinoxP*,[3f] or *t*Bu-BisP*.[14]

The high utility of ligands **5d** and **5e** was also demonstrated in a Pd-catalyzed asymmetric ring-opening reaction,[15] which proceeded rapidly at room temperature in the presence of catalysts prepared from [$PdCl_2$(cod)] and the ligands to give the desired products in high yields and with outstanding enantioselectivities of up to 99.9% *ee* (Table 3, entries 4–6 and 9). These enantioselectivities are higher than those observed upon the use of previously reported P-chiral phosphine ligands (*t*Bu-QuinoxP*: up to 97.6% *ee*;[3f] Ad-QuinoxP*: 98.5% *ee*;[16] *t*Bu-BisP*: 94% *ee*[17]) and are the highest reported to date for this class of reactions.[15]

Table 3: Asymmetric alkylative ring opening catalyzed by [$PdCl_2$(cod)]/**5**.



Entry	5	R^1	R^2	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**5a**	H	Me	1.5	92	95.8
2	**5b**	H	Me	1.5	90	96.3
3	**5c**	H	Me	1.5	92	95.8
4	**5d**	H	Me	2	93	99.9
5	**5e**	H	Me	2	94	99.8
6	**5d**	H	Et	6	90	99.9
7	**5d**	$MeOCH_2O$	Me	4	92	94
8	**5d**	$MeOCH_2O$	Et	8	89	98.4
9	**5e**	H	Et	6	89	99.2
10	**5e**	$MeOCH_2O$	Me	4	93	94
11	**5e**	$MeOCH_2O$	Et	8	92	97.8

[a] Yield of the isolated product. [b] Configuration of the major enantiomer: 1*S*,2*S*. cod = cyclooctadiene.

In conclusion, we found that (bromo(*tert*-butyl)methylphosphanyl)borane undergoes stereospecific nucleophilic substitution reactions with alkynyl lithium reagents to give alkynylated products in high yields with excellent enantioselectivities. The products were converted into the P-chiral phosphine ligands **5a–e**, which induced high to almost perfect enantioselectivity in representative transition-metal-catalyzed asymmetric reactions. These ligands, particularly **5d** and **5e**, have potential for use in other asymmetric catalytic reactions.

Received: June 9, 2007
Revised: July 31, 2007
Published online: October 5, 2007

Keywords: asymmetric catalysis · boranes · hydrogenation · nucleophilic substitution · phosphane ligands

[1] For representative reviews, see: a) A. Grabulosa, J. Granell, G. Muller, *Coord. Chem. Rev.* **2007**, *251*, 25–90; b) B. Carboni, L. Monnier, *Tetrahedron* **1999**, *55*, 1197–1248; c) M. Ohff, J. Holz, M. Quirmbach, A. Börner, *Synthesis* **1998**, 1391–1415; d) J. M. Brunel, B. Faure, M. Maffei, *Coord. Chem. Rev.* **1998**, *178–180*, 665–698; e) O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry* **1998**, *9*, 1279–1332; f) H. B. Kagan, M. Sasaki in *The Chemistry of Organophosphorus Compounds*, *Vol. 1* (Ed.: F. R. Hartley), Wiley, New York, **1990**, chap. 3; g) D. Valentine, Jr. in *Asymmetric Synthesis*, *Vol. 4* (Eds.: J. D. Morrison, J. W. Scott), Academic Press, New York, **1984**, chap. 3, p. 263; h) T. Imamoto in *Handbook of Organophosphorus Chemistry* (Ed.: R. Engel), Marcel Dekker, New York, **1992**, chap. 1, pp. 1–52.

[2] For representative reviews, see: a) P.-H. Leung, *Acc. Chem. Res.* **2004**, *37*, 169–177; b) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3069; c) K. V. L. Crépy, T. Imamoto, *Adv. Synth. Catal.* **2003**, *345*, 79–101; d) K. V. L. Crépy, T. Imamoto, *Top. Curr. Chem.* **2003**, *229*, 1–40; e) K. M. Pietrusiewicz, M. Zablocka, *Chem. Rev.* **1994**, *94*, 1375–1411.

[3] a) T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, K. Sato, *J. Am. Chem. Soc.* **1990**, *112*, 5244–5252; b) T. Oshiki, T. Imamoto, *J. Am. Chem. Soc.* **1992**, *114*, 3975–3977; c) T. Imamoto, T. Oshiki, T. Onozawa, M. Matsuo, T. Hikosaka, M. Yanagawa, *Heteroat. Chem.* **1992**, *3*, 563–575; d) K. V. L. Crépy, T. Imamoto, *Tetrahedron Lett.* **2002**, *43*, 7735–7737; e) Y. Wada, T. Imamoto, H. Tsuruta, K. Yamaguchi, I. D. Gridnev, *Adv. Synth. Catal.* **2004**, *346*, 777–788; f) T. Imamoto, K. Sugita, K. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11934–11935 (*t*Bu-QuinoxP* = 2,3-bis(*tert*-butylmethylphosphanyl)quinoxaline).

[4] a) S. Jugé, M. Stephan, J. A. Laffitte, J.-P. Genêt, *Tetrahedron Lett.* **1990**, *31*, 6357–6360; b) E. B. Kaloun, R. Merdès, G.-P. Genêt, J. Uziel, S. Jugé, *J. Organomet. Chem.* **1997**, *529*, 455–463; c) D. Moulin, S. Bago, C. Bauduin, C. Darcel, S. Jugé, *Tetrahedron: Asymmetry* **2000**, *11*, 3939–3956; d) C. Bauduin, D. Moulin, E. B. Kaloun, C. Darcel, S. Jugé, *J. Org. Chem.* **2003**, *68*, 4293–4301; e) C. Darcel, D. Moulin, J.-C. Henry, M. Lagrelette, P. Richard, P. D. Harvey, S. Jugé, *Eur. J. Org. Chem.* **2007**, 2078–2090.

[5] M. Stankevic, K. M. Pietrusiewicz, *J. Org. Chem.* **2007**, *72*, 816–822, and references therein.

[6] K. Nagata, S. Matsukawa, T. Imamoto, *J. Org. Chem.* **2000**, *65*, 4185–4188.

[7] The stereochemical course of the reaction was confirmed on the basis of the absolute configuration of the substitution product **3a**. The absolute configuration of compound **6a**, which is derived from **3a**, was determined to be *S*,*S* by single-crystal X-ray analysis. Hence, **3a** has the *S* configuration, which indicates that the substitution reaction occurred with inversion of configuration (see the Supporting Information).

[8] R. M. Stoop, A. Mezzetti, F. Spindler, *Organometallics* **1998**, *17*, 668–675.

[9] The chlorinated compound (*R*)-(*tert*-butyl-(chloro)methylphosphanyl)borane was prepared by treating **1** with *n*BuLi and hexachloroethane. It exists as a stable crystalline solid and hardly reacted at all with benzylmagnesium chloride at room temperature.

[10] Gold(I) complexes of triethynylphosphine ligands with bulky substituents at the alkyne termini show unique catalytic activity: A. Ochida, H. Ito, M. Sawamura, *J. Am. Chem. Soc.* **2006**, *128*, 16486–16487; A. Ochida, M. Sawamura, *Chem. Asian J.* **2007**, *2*, 609–618.

[11] a) T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa, K. Yamaguchi, *J. Am. Chem. Soc.*

1998, *120*, 1635 – 1636; b) I. D. Gridnev, Y. Yamanoi, N. Higashi, H. Tsuruta, M. Yasutake, T. Imamoto, *Adv. Synth. Catal.* **2001**, *343*, 118 – 136.

[12] To examine the possibility that the alkynyl group of these ligands could be hydrogenated under the reaction conditions, a 1:1 mixture of **5a** and $[Rh(nbd)_2]BF_4$ in methanol was stirred under 1 atm of hydrogen pressure at room temperature for 3 h. The ^1H NMR spectra of the reaction mixture were very complicated, and we could not clarify whether the alkynyl group was hydrogenated or not. On the other hand, **6a** was recovered unchanged after being stirred as a solution in methanol in the presence of **5a**/$[Rh(nbd)_2]BF_4$ (5 mol%) under 3 atm of hydrogen pressure at room temperature for 5 h.

[13] a) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579 – 5580; b) T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052 – 5058; c) T. Hayashi, K. Ueyama, N. Tokunaga, K. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 11508 – 11509; d) T. Hayashi, *Pure Appl. Chem.* **2004**, *76*, 465 – 475; e) T. Hayashi, K. Yamazaki, *Chem. Rev.* **2003**, *103*, 2829 – 2844; f) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169 – 196, and references therein.

[14] The catalytic efficiency of the structurally analogous and electron-rich phosphine ligand *t*Bu-BisP* was tested in the reaction of 2-cyclohexenone with phenylboronic acid under the same conditions as those described in Table 2. The reaction at 40 °C for 2 h afforded the corresponding 1,4-addition product with 20% *ee* in 37% yield.

[15] a) M. Lautens, J.-L. Renaud, S. Hiebert, *J. Am. Chem. Soc.* **2000**, *122*, 1804 – 1805; b) M. Lautens, K. Fagnou, S. Hiebert, *Acc. Chem. Res.* **2003**, *36*, 48 – 58; c) M. Lautens, S. Hiebert, *J. Am. Chem. Soc.* **2004**, *126*, 1437 – 1447; d) S. Cabrera, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2004**, *116*, 4034 – 4037; *Angew. Chem. Int. Ed.* **2004**, *43*, 3944 – 3947; e) M. Li, X.-X. Yan, W. Hong, X.-Z. Zhu, B.-X. Cao, J. Sun, X.-L. Hou, *Org. Lett.* **2004**, *6*, 2833 – 2835.

[16] T. Imamoto, A. Kumada, K. Yoshida, *Chem. Lett.* **2007**, *36*, 500 – 501 (Ad-QuinoxP* = 2,3-bis(adamantylmethylphosphanyl)quinoxaline).

[17] Oxabenzonorbornadiene was treated with diethylzinc in the presence of $[PdCl_2(cod)]$/*t*Bu-BisP* (2 mol%) at room temperature for 6 h to give (1*S*,2*S*)-2-ethyl-1,2-dihydronaphthalen-1-ol in 93% yield with 94% *ee*.

