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Planar chiral [2.2]paracyclophane-based phosphine-Brønsted acid catalysts bearing exceptionally high reactivity for aza-Morita–Baylis–Hillman reaction

Shinji Kitagaki *,†, Yuu Ohta, Ryohei Takahashi, Mika Komizu, Chisato Mukai

Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

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ABSTRACT

Several new planar chiral bifunctional phosphine compounds based on the [2.2]paracyclophane backbone with a *pseudo-ortho* substitution pattern have been synthesized and applied to the aza-Morita–Baylis–Hillman reaction. An enantiopure phosphine-phenol catalyst bearing an aryl group as a spacer connected to a phosphino group exhibited an exceptionally high reactivity (rt, 2–40 min) and good enantioselectivity (up to 85% ee).

The substituted [2.2]paracyclophanes have attracted considerable attention as a new type of planar chiral ligand[1,2] since [2.2]PHANEPHOS, the *pseudo-ortho*-bis(diphenylphosphino)[2.2]paracyclophane ligand, realized the highly enantioselective hydrogenation of olefins or ketones catalyzed by a rhodium or ruthenium complex.[3] However, there are a few examples using the cyclophane derivative as an organocatalyst,[4–12] among which only two catalysts with an additional chiral source, such as a sugar or oxazoline unit, have been proven to show a high enantioselectivity.[6,8] Thus, potential of the [2.2]paracyclophane as a planar chiral backbone of the organocatalyst has not yet been demonstrated.

We have been interested in the development of bifunctional[13] organocatalysts[14] based on the planar chiral *pseudo-ortho*-substituted aryl[2.2]paracyclophane that has no additional chiral source and that is expected to construct an efficient asymmetric environment different from the known functionalized cyclophanes. Our design concept is as follows: (1) Two functional groups (R^1 and R^2 in Fig. 1) are located, respectively, on the [2.2]paracyclophane backbone and the *meta* position of a spacer aryl group, connected to the *pseudo-ortho* position of the backbone. (2) The [2.2]paracyclophane backbone would provide the inherent conformational rigidity. (3) The spacer would offer not only a steric or electronic element based on the aryl group itself and/or its characteristic substituents, R^3, which interacts with the substrate and/or reactant,

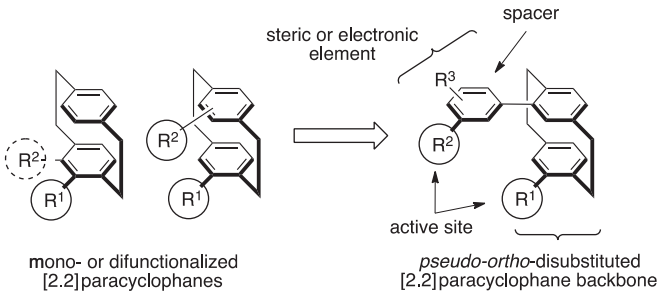

Figure 1. Design concept.

but also the conformational flexibility that makes the distance between the two functional groups suitable for performing the dual activation of the substrate and reactant. The synthesis of similar aryl[2.2]paracyclophanes, which have a functional group at the *ortho* position of the aryl group, and their application as chiral ligands or a reagent have already been reported by the Rozenberg group.[2,15,16]

We have recently developed a concise and efficient synthetic method for the chiral [2.2]paracyclophanes based on the above mentioned concept, which includes the stepwise successive palladium-catalyzed cross-coupling for the [2.2]paracyclophane bearing two different leaving groups in a *pseudo-ortho* relationship.[17] We now report the synthesis of several phosphine-Brønsted acid catalysts by the developed method and the evaluation of their catalytic reactivities based on the aza-Morita–Baylis–Hillman (aza-MBH) reaction.

* Corresponding author. Tel.: +81 52 839 2657; fax: +81 52 834 8090.
E-mail address: skitagak@meijo-u.ac.jp (S. Kitagaki).
† Current address: Faculty of Pharmacy, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya 468-8503, Japan.

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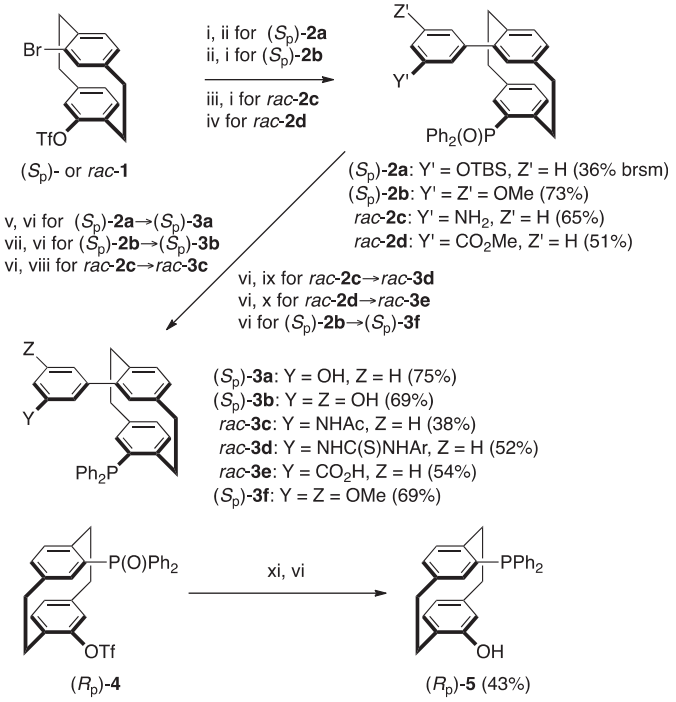
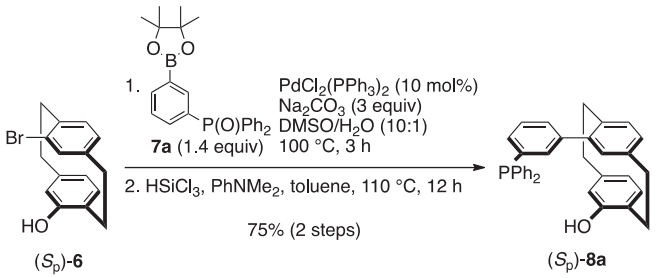
We designed the planar chiral [2.2]paracyclophanylphosphines **3a–e** containing the *m*-hydroxy-, amido-, thioureido-, or carboxyphenyl group at the *pseudo-ortho* position and the cyclophane **8** bearing a phosphino group and an acid functionality in the opposite way to the above mentioned one. 3,5-Dimethoxyphenyl- and 3-aminophenyl-[2.2]paracyclophanylphosphine oxide **2b** and **2c** were prepared from bromo[2.2]paracyclophanyl triflate **1** by the Suzuki–Miyaura coupling/phosphinylation sequence since 3-siloxyphenyl one **2a** was obtained in lower yield by the reverse order method (Scheme 1).[17] The one-pot installation of the aryl group and phosphinyl group was accomplished with 51% yield for the cyclophane **2d** bearing a methoxycarbonyl group on the spacer aryl group. The cyclophanylphosphine **3a** or **3b**[17] with one or two hydroxy groups on the spacer was obtained by the deprotection of **2a** or **2b** and subsequent reduction of the phosphinyl group using trichlorosilane. The treatment of **2c** with trichlorosilane produced the amide **3c** or thiourea **3d** after acetylation or the thiourea-forming reaction. The phosphine-carboxylic acid **3e** was prepared from **2d** by the reduction/hydrolysis sequence. The phosphine **3f** having no acid functionality was also prepared. The phosphine-alcohol **5**, which contained no spacer in its structure, was synthesized by the alkaline hydrolysis of phosphinylcyclophanyl triflate **4**[17] and subsequent trichlorosilane reduction.

The cyclophane **8a** bearing a phosphino group and a hydroxy functionality in the opposite way to **3a** was synthesized from the bromocyclophanol **6**[18] via the Suzuki–Miyaura coupling using the phosphinylboronic ester **7a**[19] (Scheme 2).

With several bifunctional cyclophanylphosphines in hand, we turned our attention to their application in organocatalytic asymmetric reactions. The aza-MBH reaction[20] using the *N*-tosylaldimine **9a** and methyl vinyl ketone (MVK) **10** was selected and the results of the reaction in THF at room temperature are summarized in Table 1.

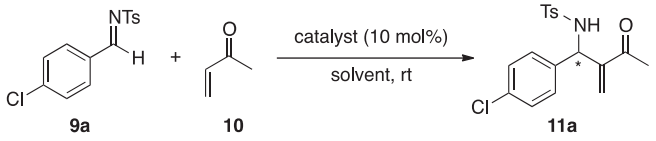


Scheme 1. Reagents and conditions: (i) $Ph_2P(O)H$, $Pd(OAc)_2$ (10 mol %), dppf (18 mol %), *i*-Pr_2NEt, DMSO, 100 °C; (ii) boronic acid, $PdCl_2$(dppf) (5 mol %), K_3PO_4, toluene, 80–100 °C; (iii) boronic acid, $Pd(PPh_3)_4$ (5 mol %), K_3PO_4, dioxane, 85 °C; (iv) boronic acid, $Ph_2P(O)H$, $PdCl_2(PPh_3)_2$ (5 mol %), Na_2CO_3, DMSO/H_2O (10:1), 85 °C; (v) TBAF, THF; (vi) $HSiCl_3$, *i*-Pr_2NEt, xylene, 140 °C; (vii) BBr_3, CH_2Cl_2, 0 °C → rt; (viii) AcCl, py; (ix) ArNCS, THF, 0 °C → rt; (x) KOH, MeOH, reflux; (xi) aq NaOH, dioxane/MeOH. Ar = 3,5–$(CF_3)_2C_6H_3$.



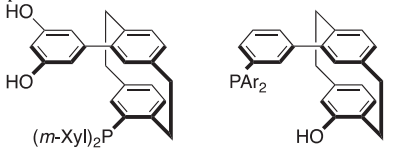
Scheme 2. Preparation of **8a** from **6**.

Table 1
Cyclophanylphosphine-catalyzed aza-MBH reaction



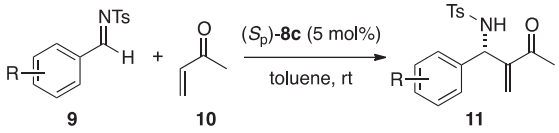
Entry	Catalyst (Y,Z)	Solvent	Time	Yield (%)	*ee* (%) (conf.)[a,b]
1	(S_p)-**3a** (OH,H)	THF	12 d	81	61 (*S*)
2	(S_p)-**3b** (OH,OH)	THF	5 d	96	70 (*S*)
3	(R_p)-**3b** (OH,OH)	THF	5 d	91	69 (*R*)
4	(S_p)-**3f** (OMe,OMe)	THF	15 d	34[c]	0
5	*rac*-**3c** (NHAc,H)	THF	7 d	23[c]	—
6	*rac*-**3d** (NHCSNHAr,H)	THF	12 d	24[c]	—
7	*rac*-**3e** (COOH,H)	THF	7 d	22[c]	—
8	(R_p)-**5**	THF	2 d	99	18 (*R*)
9[d]	(S_p)-**8a**	THF	2 h	99	34 (*S*)
10[d]	(S_p)-**8a**	Toluene	10 min	99	48 (*S*)
11[d]	(S_p)-**8b**	Toluene	15 min	89	66 (*S*)
12[d]	(S_p)-**8c**	Toluene	10 min	99	75 (*S*)
13[d,e]	(S_p)-**8c**	Toluene	15 min	88	67 (*S*)
14	(S_p)-**3g** (OH,OH)	THF	3.4 d	89	40 (*S*)

[a] Determined by HPLC analysis using Daicel Chiralpak AS-H.
[b] Determined by the sign of the specific rotation.
[c] Reaction was not completed.
[d] Used 5 mol % of the catalyst.
[e] Reaction was performed at 0 °C.



Among the cyclophanylphosphines **3a–e** bearing a different Brønsted acid functionality on the spacer aryl group, only the phosphine-phenol catalysts **3a** and **3b** gave the desired MBH adduct **11a** in good to excellent yields, although the reaction time was long (5–12 days) at the catalyst loading of 10 mol %. In addition, the chiral, non-racemic **3a** and **3b** exhibited good asymmetric induction abilities, and (S_p)-**3b** produced (*S*)-**11a** in 70% ee (entries 1 and 2). The use of (R_p)-**3b** also provided (*R*)-**11a** with 69% ee (entry 3). Thus, both enantiomers of **11a** are equally available using both enantiomers of **3b** obtained via the optical resolution process of **6**.[17,18] The unsatisfactory results using the phenol-protected phosphine (S_p)-**3f** suggested that the hydroxy functionality would play a crucial role in both the rate acceleration and the asymmetric induction (entry 4). On the other hand, phosphine-amide **3c**, -thiourea **3d**, or -carboxylic acid **3e** was found not to have a sufficient

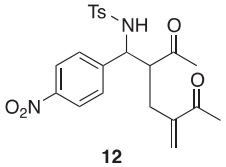
Table 2
Aza-MBH reaction of aldimine **9** catalyzed by (S_p)-**8c** in toluene



9 **10** **11**

Entry	Substrate **9** (R)	Time (min)	Product **11**	Yield (%)	*ee*[a,b] (%)
1	**9a** (*p*-Cl)	10	**11a**	99	75
2	**9b** (*p*-NO_2)	10	**11b**	57[c]	69
3	**9c** (*p*-Me)	10	**11c**	71	79
4	**9d** (*p*-OMe)	25	**11d**	96	85
5	**9e** (*m*-OMe)	10	**11e**	97	76[d]
6	**9f** (*o*-Me)	40	**11f**	85	40[e]

[a] Determined by HPLC analysis using chiral stationary phase column.
[b] Preferred configuration was determined by the sign of the specific rotation.
[c] Cascade adduct of aza-MBH/MBH reaction **12** was obtained in 27% yield.
[d] Preferred configuration was determined by comparison of elution order of HPLC using the reported value.
[e] Preferred configuration was not determined.



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reactivity to complete the aza-MBH reaction; therefore, the asymmetric induction using the optically active **3c–e** was not tested (entries 5–7). The phosphine-phenol (S_p)-**8a** bearing an aryl group as a spacer not connected to a hydroxyl group but to a phosphino group showed a higher reactivity and lower enantioselectivity compared to (S_p)-**3a** (entry 1 vs entry 9). Although the phosphine-phenol (R_p)-**5**, both of whose functionalities were directly connected to the cyclophane backbone, generated the aza-MBH adduct **11a** in quantitative yield after stirring for 2 days, the ee was poor, demonstrating that our design concept, in which an aryl group as a spacer is a characteristic of the catalyst, was reasonable for both the rate acceleration and the asymmetric induction (entry 8).

The relatively higher reactivity of (S_p)-**8a** prompted us to try the use of solvents other than THF. Surprisingly, the reaction in toluene was completed within 10 min and the desired product was obtained in quantitative yield with 48% ee (entry 10). The change in the two phenyl groups on the phosphorous atom of (S_p)-**8a** significantly influenced the enantioselectivity of the product. In fact, (S_p)-**8b**[‡] bearing two *p*-tolyl groups instead of phenyl groups and (S_p)-**8c**[‡] equipped with *m*-xylyl groups improved the product ee for the reaction in toluene to 66% and 75%, respectively, without any loss of reactivity (entries 11 and 12).[21,22] Lowering the reaction temperature to 0 °C did not improve the product ee (entry 13). The use of (S_p)-**3g**,[§] bearing two *m*-xylyl groups instead of phenyl groups on the phosphorous atom of **3b**, in THF did not improve the product ee (entry 14).

A preliminary assessment of the scope of the imine substrates was made using 5 mol % of (S_p)-**8c** in toluene at room temperature. The electron-rich arylaldimines were found to be susceptible to undergo the aza-MBH reaction with a higher enantioselectivity (Table 2). The highest ee was obtained with *p*-methoxybenzaldimine **9d**, in which the reaction afforded the product in 96% yield with 85% ee (entry 4). The substituent at the *ortho* position led to a significant decrease in the reactivity and enantioselectivity (entry 6).

In conclusion, we synthesized phosphine-Brønsted acid catalysts based on the *pseudo-ortho*-substituted [2.2]paracyclophane backbone and evaluated their reactivity and chiral discrimination ability based on the aza-MBH reaction using the tosylaldimine **9** and MVK **10**. Our efforts led to the development of the phosphine-phenol **8c**, which showed an exceptionally high reactivity and good enantioselectivity in the aza-MBH reaction by virtue of a spacer aryl group. To the best of our knowledge, this is the first successful example of a planar chiral acid-base bifunctional organocatalyst based on the [2.2]paracyclophane, which might provide a new direction to the design of the chiral catalyst backbone. Efforts toward the improvement of the enantioselectivity including further modification of the catalyst structure and further studies of the application of **8c** in the asymmetric reaction are currently in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.021.

References and notes

1. (a) Gibson, S. E.; Knight, J. D. *Org. Biomol. Chem.* **2003**, *1*, 1256; (b) Rosenberg, V.; Sergeeva, E.; Hopf, H. In *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 435; (c) Aly, A. A.; Brown, A. B. *Tetrahedron* **2009**, *65*, 8055; (d) Paradies, J. *Synthesis* **2011**, 3749.
2. Special Issue: Cyclophanes. *Isr. J. Chem.* **2012**, *52*, 1.
3. (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207; (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441.
4. Braddock, D. C.; MacGilp, I. D.; Perry, B. G. *Adv. Synth. Catal.* **2004**, *346*, 1117.
5. Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141.
6. Chai, Q.; Song, C.; Sun, Z.; Ma, Y.; Ma, C.; Dai, Y.; Andrus, M. B. *Tetrahedron Lett.* **2006**, *47*, 8611.
7. Zhang, T.-Z.; Dai, L.-X.; Hou, X.-L. *Tetrahedron: Asymmetry* **2007**, *18*, 1990.
8. Negru, M.; Schollmeyer, D.; Kunz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 9339.
9. Schneider, J. F.; Falk, F. C.; Fröhlich, R.; Paradies, J. *Eur. J. Org. Chem.* **2010**, 2265.
10. Fulton, J. R.; Glover, J. E.; Kamara, L.; Rowlands, G. J. *Chem. Commun.* **2011**, *47*, 433.
11. Enders, D.; Ludwig, M.; Raabe, G. *Chirality* **2012**, *24*, 215.
12. Beemelmanns, C.; Husmann, R.; Whelligan, D. K.; Özçubukçu, S.; Bolm, C. *Eur. J. Org. Chem.* **2012**, 3373.
13. Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117. and references cited therein.
14. For a recent review, see Lu, L.-Q.; An, X.-L.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2012**, 490.
15. (a) Rozenberg, V. I.; Antonov, D. Y.; Zhuravsky, R. P.; Vorontsov, E. V.; Starikova, Z. A. *Tetrahedron Lett.* **2003**, *44*, 3801; (b) Rosenberg, V.; Zhuravsky, R.; Sergeeva, E. *Chirality* **2006**, *18*, 95.
16. Schneider, J. F.; Fröhlich, R.; Paradies, J. *Synthesis* **2010**, 3486.
17. Kitagaki, S.; Ohta, Y.; Tomonaga, S.; Takahashi, R.; Mukai, C. *Tetrahedron: Asymmetry* **2011**, *22*, 986.
18. Zhuravsky, R.; Starikova, Z.; Vorontsov, E.; Rozenberg, V. *Tetrahedron: Asymmetry* **2008**, *19*, 216.
19. Lustenberger, P.; Diederich, F. *Helv. Chim. Acta* **2000**, *83*, 2865.
20. For selected examples of catalytic asymmetric aza-MBH reaction, see: (a) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1; (b) Ma, G.-N.; Jiang, J.-J.; Shi, M.; Wei, Y. *Chem. Commun.* **2009**, 5496; (c) Mansilla, J.; Saá, J. M. *Molecules* **2010**, *15*, 709; (d) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005.
21. The reaction in toluene with (S_p)-**8c** was completed even after 2 min (confirmed by TLC) and the desired product was obtained in 93% yield with 75% ee. For fast catalytic asymmetric aza-MBH reaction, see: Lei, Z.-Y.; Ma, G.-N.; Shi, M. *Eur. J. Org. Chem.* **2008**, 3817. See also Ref. 22.
22. Anstiss, C.; Garnier, J.-M.; Liu, F. *Org. Biomol. Chem.* **2010**, *8*, 4400.

[‡] According to the procedure shown in Scheme 2, (*Sp*)-**8b** and **8c** were prepared using the corresponding *m*-(diarylphosphinyl)phenylboronic acid ester.
[§] According to the procedure shown in Scheme 1, (S_p)-**3g** was prepared using the corresponding diarylphosphine oxide.