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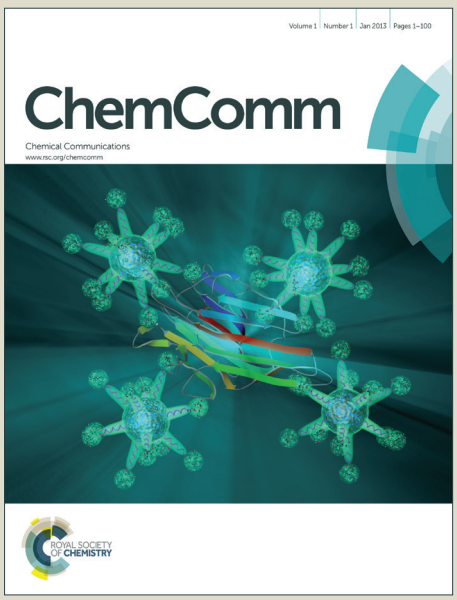

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Design of a Brønsted Acid with Two Different Acidic Sites: Synthesis and Application of Aryl Phosphinic Acid-Phosphoric Acid as a Brønsted Acid Catalyst

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A Brønsted acid with two different acidic sites, aryl phosphinic acid-phosphoric acid, has been synthesized. Its catalytic performance was assessed in the hetero-Diels–Alder reaction of aldehyde hydrates with Danishefsky's diene, achieving high reaction efficiency.

Brønsted acids are arguably one of the most conventional, yet reliable, catalysts in organic synthesis.[1] In the past decade, chiral Brønsted acids have been studied enthusiastically and become valuable tools in asymmetric synthesis.[2] Recently, we contributed to this field by developing a C_1-symmetric bis-phosphoric acid possessing both a sterically demanding 2,4,6-triisopropylphenyl group and an electron-withdrawing perfluorophenyl group (Fig. 1 (a)).[3] We demonstrated that two phosphoric acid groups with individually different acidities can play distinct roles in catalyst behaviour through hydrogen bonding interactions. Hence, we were interested to explore whether a combination of *different acidic functional groups,* in particular an aryl phosphinic acid-phosphoric acid, would function as an efficient Brønsted acid catalyst (Fig. 1 (b)). Although a variety of Brønsted acids have been designed and exploited as chiral molecular catalysts, none are designed aryl phosphinic acids, despite the inherent potential of their molecular recognition abilities.[4,5] We expected that the Brønsted acid-base nature of an aryl phosphinic acid, in combination with a phosphoric acid, would offer a new approach to the design of chiral Brønsted acid catalysts. However, research in this direction remains elusive, even for racemic syntheses. This prompted us to develop a synthetic methodology for this congested aryl phosphinic acid to verify the potential of a Brønsted acid catalyst system containing two different acidic sites.[6] Here, we describe the synthesis of an aryl phosphinic acid-phosphoric acid with a *meta*-quaterphenyl skeleton and its successful application as a hetero-combined Brønsted acid catalyst in the highly efficient hetero-Diels–Alder reaction of aldehyde hydrates with Danishefsky's diene.[7]

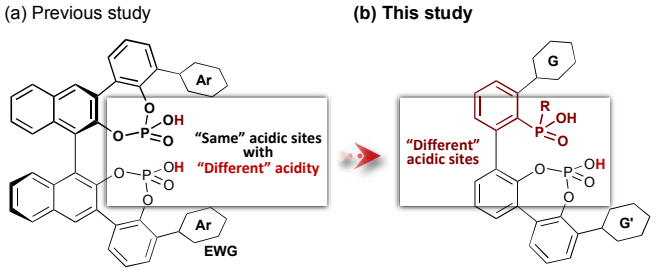
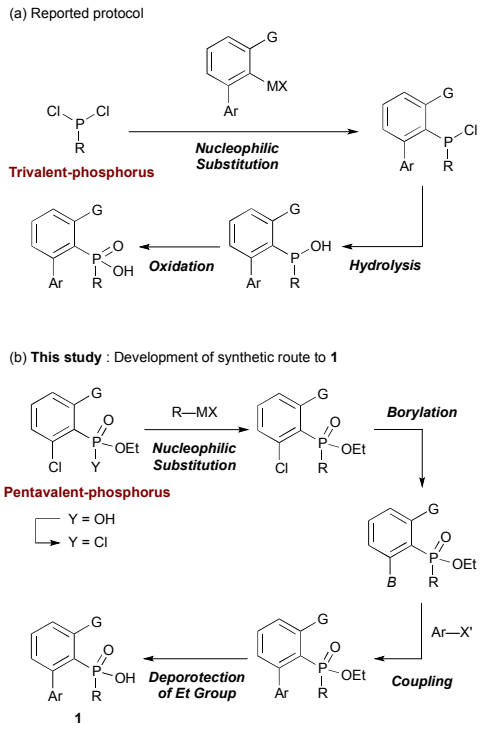


Fig. 1 Diagram of design components: (a) Chiral bis-phosphoric acid, (b) aryl phosphinic acid–phosphoric acid, a Brønsted acid containing two different acidic sites.

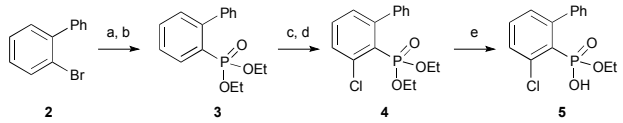
Our prime concern was synthesis of the sterically congested aryl phosphinic acid essential to the design concept for the Brønsted acid containing different acidic sites. Construction of the aryl phosphinic acid moiety is generally conducted by nucleophilic substitution of dichloroarylphosphine with aryllithium precursors, followed by oxidation from trivalent to a pentavalent phosphorus compound (Scheme 1 (a)).[8] Unfortunately, during this study, we faced difficulties applying this general oxidation procedure to other strucures, presumably due to steric constrains.[9] In addition, it was hard to modify the substituent on phosphorous, preventing further elaboration of the catalyst system. To circumvent this issue, we sought to develop a reliable and a flexible synthetic route to aryl phosphinic acid-phosphoric acid **1**.

Our strategy to overcome this issue was through initial attachment of a pentavalent phosphorus group (Scheme 1 (b)). We planned the nucleophilic substitution of Grignard reagents to aryl phosphonic chloride ethyl ester,[10] followed by Miyaura borylation[11] and Suzuki-Miyaura coupling.[12] Since a variety of Grignard reagents are readily available, this synthetic route was expected to be far more feasible than previous route *via* a trivalent phosphorus compound.



Scheme 1 Key steps in the synthesis of aryl phosphinic acid-phosphoric acid.

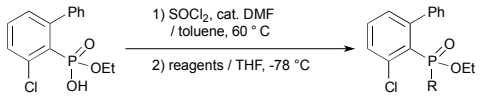
As shown in Scheme 2, we initially prepared diethyl [1,1'-biphenyl]-2-ylphosphonate (**3**) from commercially available 2-bromobiphenyl (**2**) *via* standard procedure.[13] Selective *ortho*-lithiation[14] of **3** and subsequent chlorination were then performed, affording phosphate **4** in 85% yield. Subsequent saponification of **4** resulted in the formation of phosphonic acid monoethyl ester **5** (98%).[15]



Scheme 2 Synthesis of phosphonic acid monoester 5. (a) *n*-BuLi, THF, –90 °C; (b) ClP(=O)(OEt)$_2$, THF, –90 °C, 90%; (c) *s*-BuLi, TMEDA, Et$_2$O, –78 °C; (d) C_2Cl_6, –78 °C to rt; 85%; (e) 25% KOH aq., 1,4-dioxane, 100 °C, 98%.

With phosphonic acid monoethyl ester **5** in hand, we examined the nucleophilic substitution of **5**, which was key to delivering structurally diverse aryl phosphinic acid units (Table 1). Treatment of **5** with thionyl chloride (10 equiv.) in the presence of a catalytic amount of DMF in toluene at 60 °C for 9 h, then reaction with aryl Grignard reagents at –78 °C furnished ethyl diarylphosphinates **6a** and **6b** in yields of 96% and 73%, respectively (Entries 1 and 2).[10] With the same procedure, a considerable decline in the yield was observed when the reaction was conducted using benzyl Grignard reagent (Entry 3). Fortunately, adding cerium chloride significantly improved the yield of **6c** from 41% to 80% (Entry 4).[16] Furthermore, this allowed other alkyl Grignard reagents, such as *iso*-propyl Grignard, to become applicable, affording the substitution product **6d** in a moderate yield (Entry 5).

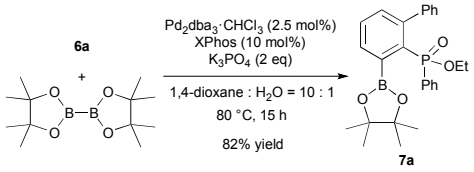
Table 1 Nucleophilic substitution of phosphinic acid monoester **5**[a]



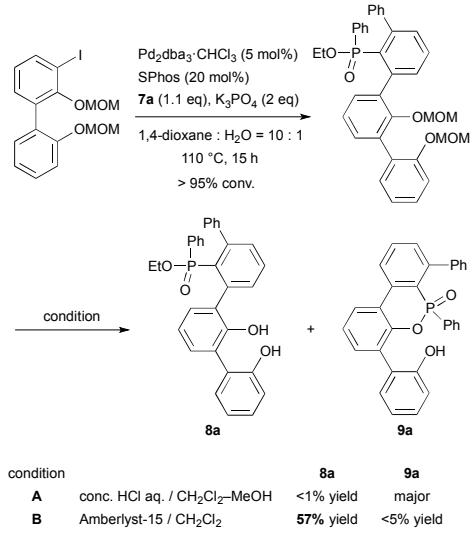
Entry	Reagents	Yield (%)[b]
1	PhMgBr	96
2	3,5-$(CF_3)_2C_6H_3$MgBr	73
3	BnMgCl	41
4	BnMgCl, $CeCl_3$	80
5	*i*-PrMgCl, $CeCl_3$	45

[a] See ESI for details. [b] Isolated yield. [c] Chlorination reactions were conducted without DMF, see ESI for details.

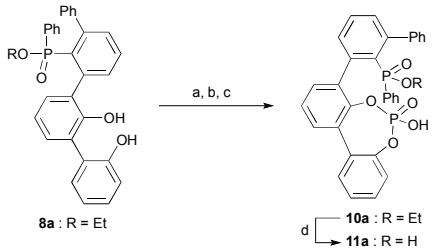
Among the synthesized arylphosphinates, **6a** was chosen as a representative strucure for further synthesis. Preparation of 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl arylphosphinate **7a** was achieved by a palladium-catalyzed borylation reaction[17] (Scheme 3). For instance, the reaction of **6a** with bis(pinacolato)diboron in the presence of $Pd_2dba_3{\cdot}CHCl_3$, XPhos, and K_3PO_4 in 1,4-dioxane/H_2O at 80 °C for 15 h gave rise to desired product **7a** in 82% yield. To consolidate the aryl phosphinate unit into a biphenol framework, the well-established Suzuki-Miyaura cross coupling[18] was conducted, and an aryl phosphinate **7a** was easily introduced. In the consecutive MOM ether deprotection, employment of Amberlyst-15 turned out to be essential to obtain desired product **8a**,[19] while treatment with aqueous conc. HCl solution was totally unsuccessful, affording only **9a** (Scheme 4). Construction of the cyclic phosphoric acid core was realized by deprotonation of **8a** with NaH and subsequent phosphorylation. Finally, removal of the ethyl group in **10a** by trimethylsilyl iodide afforded the requisite aryl phosphinic acid-phosphoric acid **11a** (Scheme 5).[20]



Scheme 3 Palladium-catalyzed borylation.



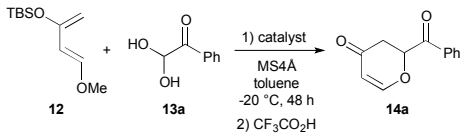
Scheme 4 Synthesis of biphenol-containg phosphinic acid monoester **8a**.

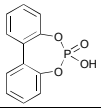


Scheme 5 Synthesis of phosphinic acid-phosphoric acid **11a**. (a) NaH, THF, 0 °C; (b) $POCl_3$, –78°C to rt; (c) H_2O, >95% conv.; (d) NaI, Me_3SiCl, CH_2Cl_2, rt, 44% (from **8a**).

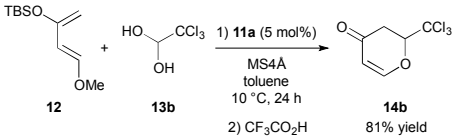
With an effective synthetic protocol in hand, we evaluated the activity of aryl phosphinic acid-phosphoric acid **11a** as a Brønsted acid catalyst to demonstrate the efficacy of the design. For this purpose, we initially chose the hetero-Diels–Alder reaction of phenylglyoxal hydrate (**13a**) with Danishefsky's diene **12**[21] (Table 2) due to these expected noteworthy advantages: (1) adequate acidity[22] from the phosphinic acid-phosphoric acid combination that directly generates a non-hydrate form of glyoxal, as a beneficial consequence, **13a** could exert a prominent electrophile without arduous distillation and manipulation[7]; (2) exquisite acidity from the phosphinic acid-phosphoric acid combination that could accommodate the use of acid-susceptible dienes such as Danishefsky's dienes without decomposition during the reaction. We found that the hetero-Diels–Alder reaction of **13a** with **12**, **11a** (5 mol%), and 4Å molecular sieves in toluene at –20 °C for 48 h gave rise to product **14a** in 82% yield (Entry 1). In contrast, reactions conducted in the presence of a commercially available phosphoric acid diphenyl ester, diphenyl phosphinic acid, or an easily synthesized biphenol-derived phosphoric acid, gave insufficient yields with even twice the catalyst loading (Entries 2, 3, and 4). Additionally, chloral hydrate (**13b**) was applicable,[23] with hetero-Diels–Alder adduct **14b** obtained in 81% yield (Scheme 6). These results suggested that aryl phosphinic acid-phosphoric acid **11a** would be a useful and valuable Brønsted acid catalyst for achieving high yields in the hetero-Diels–Alder reaction of hydrated aldehydes with acid-susceptible dienes, such as Danishefsky's diene.

Table 2 Evaluation of phosphinic acid–phosphoric acid catalyst in the hetero-Diels–Alder reaction of phenylglyoxal hydrate (**13a**) with Danishefsky's diene **12**[a]



Entry	Catalyst (mol%)	Yield (%)[b]
1	**11a** (5)	82
2	$Ph_2P(=O)OH$ (10)	21
3	$(PhO)_2P(=O)OH$ (10)	15
4	 (10)	10

[a] See ESI for details. [b] Isolated yield.



Scheme 6 Hetero-Diels–Alder reaction of chloral hydrate (**13b**) with Danishefsky's diene **12** catalyzed by Phosphinic acid–phosphoric acid **11a**.

In summary, we have developed a reliable synthetic route to sterically congested aryl phosphinic acids and have validated the utility of the design concept with a Brønsted acid with two different acidic sites, aryl phosphinic acid-phosphoric acid. The capability of this compound as a Brønsted acid catalyst has been demonstrated by successfully applying to a highly efficient hetero-Diels–Alder reaction of hydrated aldehydes, phenylglyoxal hydrate (**13a**) and chloral hydrate (**13b**), with Danishefsky's diene **12**. We believe that the concept of hetero-combined Brønsted acids provides a new paradigm for cultivating the potential functions of chiral Brønsted acid catalysts by taking full advantage of the sophisticated hydrogen-bonding network between catalyst and substrate. Further studies regarding chiral Brønsted acid catalysts with two different acidic sites are ongoing and will be reported in due course.

Notes and references

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† Electronic Supplementary Information (ESI) available: General experimental, reaction data, and spectra; copies of all the new compounds. See DOI: 10.1039/c000000x/. See DOI: 10.1039/c000000x/

1 For selected reviews of Brønsted acid catalysts, see: (a) T. Akiyama, *Chem. Rev.* 2007, **107**, 5744-5758. (b) C. H. Cheon, H. Yamamoto, *Chem. Commun.* 2011, **47**, 3043-3056. (c) H. Miyabe, Y. Takemoto, in *Comprehensive Organic Synthesis 2nd Ed.,* ed. P. Knochel and G. A. Molander, Elsevier, Oxford, 2014, 1, pp. 751-769.

2 For selected reviews of chiral Brønsted acid catalysts, see: (a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* 2006, **348**, 999-1010. (b) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* 2010, **291**, 395-456. (c) F. Z. Peng, Z. H. Shao, *Curr. Org. Chem.* 2011, **15**, 4144-4160. (d) Y. E. Trkmen, Y. Zhu, V. H. Rawal, in *Comprehensive Enantioselective Organocatalysis* ed. P. I. Dalko, Wiley, Weinheim, 2013, 2, pp. 241-288. (e) N. Mase, Y. Hayashi, in *Comprehensive Organic Synthesis 2nd Ed.,* ed. P. Knochel and G. A. Molander, Elsevier, Oxford, 2014, 1, pp. 751-769.

3 N. Momiyama, K. Funayama, H. Noda, M. Yamanaka, N. Akasaka, S. Ishida, T. Iwamoto, M. Terada, Manuscript is in preparation.

4 For reported examples of aryl phosphinic acid as Brønsted acid catalyst, see: (a) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* 2005, **127**, 15696-15697. (b) D. M. Rubush, T. Rovis, *Synlett*, 2014, **25**, 713-717.

5 For selected examples of aryl phosphinic acids and their analogs as hydrogen bonding motif, see: (a) Y. Kobayashi, F. Morisawa, K. Saigo, *Org. Lett.* 2004, **6**, 4227-4230. (b) F. Ma, X. Shen, J. O. Yang, Z. Deng, C. Zhang, *Tetrahedron Asymmetry* 2008, **19**, 31-37. (c) N. Riberiro, Y. Kobayashi, J. Maeda, K. Saigo, *Chirality*, 2011, **23**, 438-448.

6 For reported examples of Brønsted acid catalyst with two different acidic sites, see: (a) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* 2005, **127**, 1080-1081. (b) A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara, Yamamoto, H. *Org. Lett.* 2006, **8**, 3175-3178.

7 (a) T. Tonoi, K. Mikami, *Tetrahedron Lett.* 2005, **46**, 6355-6358. (b) N. Momiyama, H. Tabuse, M. Terada, *J. Am. Chem. Soc.* 2009, **131**, 12882-12883. (c) B. Zhao, T. P. Loh, *Org. Lett.* 2013, **15**, 2914-2917.

8 (a) E. Rivard, A. D. Sutton, J. C. Fettinger, P. P. Power, *Inorg. Chim. Acta.* 2007, **360**, 1278-1286. (b) B. Hoge, B. Kurscheid, S. Peuker, W. Tyrra, H. T. M. Fischer, *Z. Anorg. Allg. Chem.* 2007, **633**, 1679-1685. (c) J. P. Abell, H. Yamamoto, *J. Am. Chem. Soc.* 2009, **131**, 15118-15119.

9 Initial study based on reported protocol was shown in Electronic supplementary information (ESI).

10 M. Hatano, R. Gouzu, T. Mizuno, H. Abe, T. Yamada, K. Ishihara, *Catal. Sci. Technol.* 2011, **1**, 1149-1158.

11 For representative review, see: T. Ishiyama, N. Miyaura, *Chem. Rec.* 2004, **3**, 271-280.

12 For representative reviews, see: (a) A. Suzuki, *J. Organomet. Chem.* 1999, **576**, 147-168. (b) A. J. J. Lennox, G. C. L. Jones, *Angew. Chem., Int. Ed.* 2013, **52**, 7362-7370. (c) A. J. J. Lennox, G. C. L. Jones, *Chem. Soc. Rev.* 2014, **43**, 412-443.

13 L. Deng, J. Diao, P. Chen, V. Pujari, Y. Yao, G. Cheng, D. C. Crick, B. V. V. Prasad, Y. Song, *J. Med. Chem.* 2011, **54**, 4721-4734.

14 E. Vedejs, O. Daugulis, S. T. Diver, D. R. Powell, *J. Org. Chem.* 1998, **63**, 2338-2341.

15 S. Saito, J. Kawabata, *Helv. Chimi. Acta.* 2006, **89**, 1395-1407.

16 T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, Y. Kamiya, *J. Am. Chem. Soc.* 1989, **111**, 4392-4398.

17 K. L. Billingsley, T. E. Barder, S. L. Buckwald, *Angew. Chem., Int. Ed.* 2007, **46**, 5359-5363.

18 T. E. Barder, S. D. Walkler, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* 2005, **127**, 4685-4696.

19 (a) H. Dulphy, J. L. Gras, T. Lejon, *Tetrahedron*, 1996, **52**, 8517-8524. (b) K. Tangdenpaisal, S. Sualek, S. Ruchirawat, P. Ploypradith, *Tetrahedron*, 2009, **65**, 4316-4325.

20 G. M. Blackburn, D. Ingleson, *J. Chem. Soc., Perkin, Trans. 1* 1980, 1150-1153.

21 Representative reports of Danishefsky's dienes, see: (a) D. Danishefsky, T. Kitahara, *J. Am. Chem. Soc.* 1974, **96**, 7807-7808. (b) S. Danishefsky, *Acc. Chem. Res.* 1981, **14**, 400-406. (c) S. J. Danishefsky, M. P. DeNinno, *Angew. Chem., Int. Ed.* 1987, **26**, 15-23.

22 A. N. Matveeva, I. Y. Kudryavtsev, A. A. Grigoreva, E. I. Matrosov, E. K. Kuznetsova, L. S. Zakharov, M. I. Kabachnik, *B. Acad. Sci. USSR Ch+*, 1982, **31**, 1329-1335.

23 (a) W. J. Dale, A. J. Sisti, *J. Am. Chem. Soc.* 1954, **76**, 81-82. (b) A. Sera, Y. Iwasaki, M. Umeda, K. Itoh, *Heterocycles*, 1991, **32**, 273-278.

