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Use of boron enolates in water. The first boron enolate-mediated diastereoselective aldol reactions using catalytic boron sources

Yuichiro Mori, Juta Kobayashi, Kei Manabe and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Abstract—Highly diastereoselective aldol reactions in water using a catalytic amount of diarylborinic acid have been developed. The reactions proceeded smoothly in the presence of a small amount of an anionic surfactant and a Brønsted acid. Water was the most suitable solvent, and organic solvents such as ether and dichloromethane were ineffective in this system. Use of bis(4-trifluoromethylphenyl)borinic acid gave high catalytic activity. It is most plausible to conclude that the active species of the reactions are boron enolates, and this is the first example of catalytic use of a boron source in boron enolate-mediated diastereoselective aldol reactions. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Boron enolate-mediated aldol reactions provide powerful tools for diastereoselective aldol methodologies.[1] Since they were first developed in 1973 by Mukaiyama,[2] many groups (Köster's group,[3] Masamune's group,[4] Evans' group,[5] etc.) have improved the reaction systems. Boron enolate-mediated aldol reactions proceed via six-membered transition states, and the small size of boron atom results in high diastereoselectivity because the steric effect plays a significant role. Boron enolates are usually generated from a boron source (e.g. dialkylboron triflates), a tertiary amine (e.g. triethylamine), and a substrate (carbonyl compound). To the best of our knowledge, stoichiometric amounts of boron sources are necessary in all examples previously reported. Therefore, development of boron enolate-mediated reactions using a catalytic amount of a boron source is a challenging subject in synthetic organic chemistry.

Recently, organic reactions in water have received much attention because water is a cheap, safe, and environmentally benign solvent. In our group, several types of catalyst systems that work efficiently in water have already been developed so far. The first one is a system composed of scandium trifluoromethanesulfonate ($Sc(OTf)_3$) and a surfactant.[6–8] By applying this system, various C–C bond forming reactions such as Mukaiyama aldol reactions and allylation reactions proceed in water without using any organic solvents. The second one is a system using a Lewis acid–surfactant-combined catalyst (LASC),[9–19] and the representative LASC is scandium tris(dodecyl sulfate) ($Sc(DS)_3$). In the presence of a catalytic amount of a LASC, useful synthetic reactions such as aldol, allylation, Mannich, and Michael reactions proceed smoothly in water. The third one is a system using a Brønsted acid–surfactant-combined catalyst (BASC).[20–25] In the presence of a catalytic amount of a BASC, Mannich-type reactions, esterification, etherification, and thioetherification reactions are successfully conducted in water. In these surfactant-aided systems, organic substrates form emulsion droplets that function as reaction media in water.

In the course of our investigation on new reaction systems in water, we have developed the first example of a catalytic use of a boron source in boron enolate-mediated diastereoselective aldol reactions.[26] In our system, boron enolates are generated in situ from silyl enol ethers and diarylborinic acid. A remarkable feature of the reaction system compared with conventional boron enolate chemistry is that the reactions proceed smoothly in water, not in organic solvents. It seems curious because boron enolates are known to be easily decomposed by water. Here, we describe detailed studies in the boron-catalyzed reactions in water.

2. Results and discussion

In our search for new reaction systems in water, we tested various compounds that might act as better catalysts in water. We chose Mukaiyama aldol reaction as a model reaction. After screening various compounds, we found that diphenylborinic acid (Ph_2BOH, **1**),[27] which was prepared from its ethanolamine ester,[28] was an effective catalyst in the presence of sodium dodecyl sulfate (SDS), an anionic

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Keywords: boron enolate; water; aldol reaction; surfactant; aldehyde; electron-withdrawing group.

* Corresponding author. Tel.: +81-3-5841-4790; fax: +81-3-5684-0634; e-mail: skobayas@mol.f.u-tokyo.ac.jp

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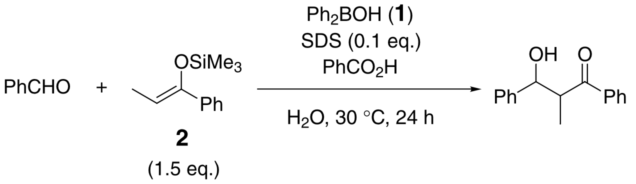
Table 1. Mukaiyama aldol reaction using **1** in water



Run	**1** (equiv.)	$PhCO_2H$ (equiv.)	Yield (%)	*syn*/*anti*
1	0.1	–	Trace	–
2	0.1	0.01	90	92/8
3	–	–	2	53/47
4	–	0.01	27	58/42
5[a]	0.1	0.01	4	91/9
6[b]	0.1	0.01	93	94/6

[a] Without SDS.

[b] 0°C.

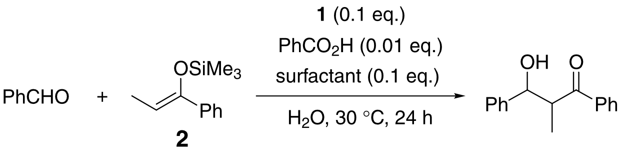
surfactant. We chose the reaction of benzaldehyde with the silyl enol ether derived from propiophenone (**2**), and several reaction conditions were examined (Table 1).

While the reaction proceeded very slowly in the presence of **1** and SDS, a dramatic improvement of the yield was observed when a small amount of benzoic acid was added to this system (runs 1, 2). To our surprise, the diastereoselectivity (*syn*/*anti*) of the aldol product was much better than that of the previously reported LASC system.[17] In the absence of **1**, not only the diastereoselectivity but also the yield were significantly lower (runs 3, 4). The reaction proceeded very slowly with high diastereoselectivity in the absence of SDS (run 5). The best yield and selectivity were obtained when **1** (0.1 equiv.), SDS (0.1 equiv.), and benzoic acid (0.01 equiv.) were used at 0°C (run 6).

The effect of other surfactants was investigated (Table 2). Sodium dodecylbenzenesulfonate, which is also an anionic surfactant, accelerated the reaction and gave high *syn* selectivity (run 2). Triton X-100 (nonionic surfactant) and cetyltrimethylammonium bromide (cationic surfactant) were much less effective (runs 3, 4).

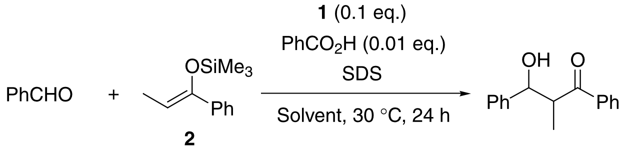
In order to know whether the reaction proceeded in water specifically, the solvent effect was studied (Table 3). Ether and dichloromethane, which had been used as representative solvents for boron enolates-mediated aldol reactions, were not suitable for this reaction system (runs 2, 3). Under neat conditions, the reaction was very slow, though high diastereoselectivity was maintained (run 4). Under water/THF and water/ethanol conditions, which were often used for aqueous reactions, the reaction was significantly suppressed (runs 5, 6).

Table 2. Effect of surfactants



Run	Surfactant	Yield (%)	*syn*/*anti*
1	SDS	90	92/8
2	$NaO_3SC_6H_4C_{12}H_{25}$	81	93/7
3	TritonX-100	Trace	–
4	$C_{16}H_{33}N^+(CH_3)_3Br^-$	8	87/13

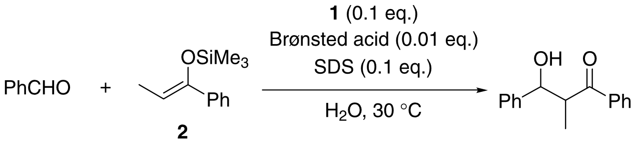
Table 3. Effect of solvents



Run	Solvent	SDS (equiv.)	Yield (%)	*syn*/*anti*
1	H_2O	0.1	90	92/8
2	Et_2O	0.1	Trace	–
3	CH_2Cl_2	0.1	Trace	–
4	–	0.1	24	90/10
5	H_2O/THF (1/9)	–	Trace	–
6	H_2O/EtOH (1/9)	–	13	73/27

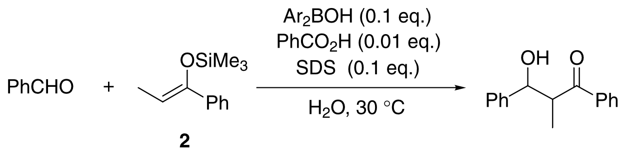
The effect of Brønsted acids was also investigated (Table 4). The use of acetic acid gave almost the same result as that of benzoic acid (run 2). When stronger acids such as hydrochloric acid and *p*-toluenesulfonic acid were used, the yields became lower because the hydrolysis of the silyl enol ether was also accelerated (runs 3, 4). In these cases, diastereoselectivities were also lowered probably because these strong acids themselves function as catalysts of the

Table 4. Effect of Brønsted acids



Run	Brønsted acid	Time (h)	Yield (%)	*syn*/*anti*
1	$PhCO_2H$	24	90	92/8
2	CH_3CO_2H	18	93	92/8
3	HCl	2	76	89/11
4	TsOH	2	69	89/11

Table 5. Effect of catalysts



Run	Ar	Yield (%)	*syn*/*anti*
1	Ph (**1**)	90	92/8
2	4-Trifluoromethylphenyl (**3**)[29]	87	89/11
3	3-Trifluoromethylphenyl	91	85/15
4	3,5-Bis(trifluoromethyl)phenyl[30]	57	64/36
5	4-Fluorophenyl[31]	77	90/10
6	4-Bromophenyl[32]	78	87/13
7	4-Tolyl[33]	32	72/28
8	4-Methoxyphenyl[34]	33	74/26
9	Mesityl	9	55/45
10	1-Naphthyl[35]	38	70/30
11	2-Naphthyl	70	88/12

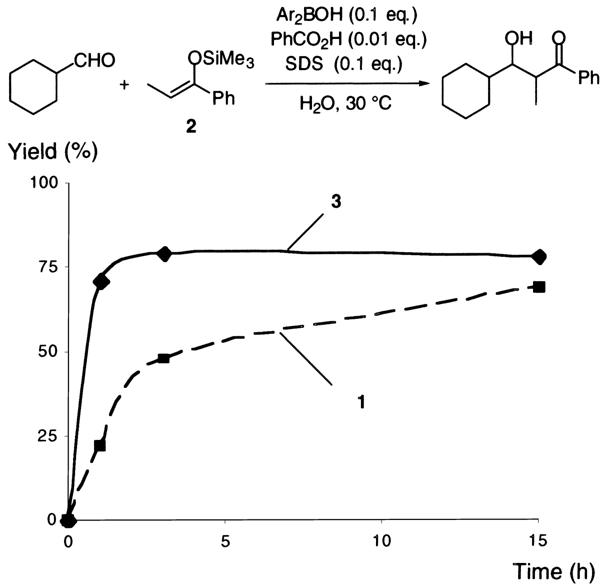


Figure 1. Catalytic activity of **1** and **3**.

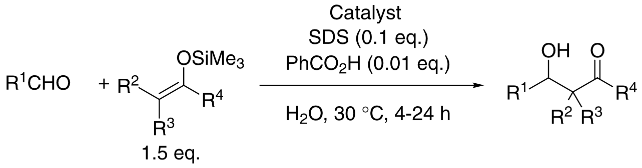
aldol reaction between the aldehyde and the silyl enol ether, which gave the same product with low selectivity.

Catalytic activity of other diarylborinic acids[30] was examined (Table 5). These diarylborinic acids were prepared from the corresponding aryl bromides and trialkylborates (trimethylborate or tributylborate). When an electron-donating group such as methyl or methoxy group was at *para* position, the yield and diastereoselectivity were lowered. On the other hand, an electron-withdrawing group such as bromo group, fluoro group, or trifluoromethyl group was at *para* position, high diastereoselectivity was maintained. When trifluoromethyl group was at *para* position, the reaction proceeded significantly faster than that using **1**. Comparison of the reaction rate is shown in Fig. 1. Under standard conditions (Ar_2BOH 0.1 equiv.; $PhCO_2H$ 0.01 equiv.; SDS 0.1 equiv.), bis(4-trifluoromethylphenyl)borinic acid (**3**) accelerated the aldol reaction of cyclohexanecarboxaldehyde with **2** more significantly than **1** did (Fig. 1).

Various aldehydes and silyl enol ethers were applied to this reaction system (Table 6). Not only aromatic aldehydes but also α,β-unsaturated, and aliphatic aldehydes could be used. Silyl enol ethers derived from aliphatic ketones and thioesters could also be applied. The highest diastereoselectivity (*syn*/*anti*=97/3) was obtained when 2-naphthaldehyde and the silyl enol ether derived from 3-pentanone were employed (run 16). A remarkable point was that low selectivity or reverse selectivity was obtained when *trans*-enolates were used (runs 4, 5, 7, 10, 11, and 15). The diastereoselectivity was dependent on the geometry of the enolates when both regioisomers of the silyl enol ethers from *tert*-butyl thiopropionate were used (runs 8–11).

The high diastereoselectivity observed in these reactions

Table 6. Mukaiyama aldol reactions using **1** and **3** in water



Run	Catalyst	R^1	R^2	R^3	R^4	*Z*/*E*	Yield (%)	*syn*/*anti*
1	**1**	Ph	Me	H	Ph	>99/<1	90	92/8
2	**3**	Ph	Me	H	Ph	>99/<1	87	89/11
3[a]	**1**	Ph	Me	H	Et	>99/<1	60	96/4
4[a]	**1**	Ph	H	Me	Et	19/81	72	53/47
5[a]	**3**	Ph	H	Me	Et	19/81	60	29/71
6[a]	**1**	Ph	Me	H	^{i}Pr	96/4	72	95/5
7	**1**	Ph	H	$(CH_2)_4$		0/100	58	56/44
8[a,b]	**1**	Ph	Me	H	S^{t}Bu	2/98	62	96/4
9[a–c]	**3**	Ph	Me	H	S^{t}Bu	2/98	76	95/5
10[a,b,d]	**1**	Ph	H	Me	S^{t}Bu	97/3	84	39/61
11[a–c]	**3**	Ph	H	Me	S^{t}Bu	97/3	43	18/82
12	**1**	4-ClC_6H_4	Me	H	Ph	>99/<1	92	90/10
13[a]	**1**	4-ClC_6H_4	Me	H	Et	>99/<1	51	95/5
14	**1**	1-Naphthyl	Me	H	Ph	>99/<1	80	92/8
15	**1**	1-Naphthyl	H	$(CH_2)_4$		0/100	79	47/53
16[a]	**1**	2-Naphthyl	Me	H	Et	>99/<1	74	97/3
17[e]	**1**	PhCH=CH	Me	H	Ph	>99/<1	76	91/9
18[b]	**3**	PhCH=CH	Me	H	Ph	>99/<1	80	90/10
19	**1**	$PhCH_2CH_2$	Me	H	Ph	>99/<1	61	92/8
20	**3**	$PhCH_2CH_2$	Me	H	Ph	>99/<1	65	93/7
21	**3**	Cyclohexyl	Me	H	Ph	>99/<1	78	96/4

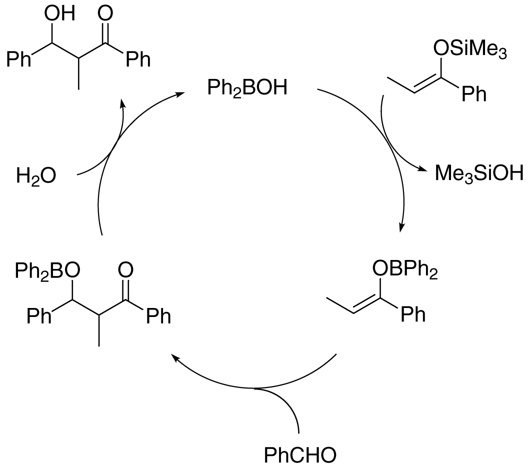
[a] Silyl enol ether (3.0 equiv.)

[b] At 0°C.

[c] 2 days.

[d] 3 days.

[e] $PhCO_2H$ (0.1 equiv.).



Scheme 1. Assumed catalytic cycle.

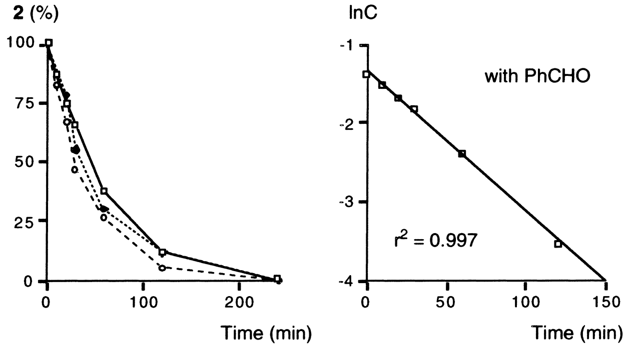


Figure 2. Changes of the amount of **2** during the reactions using **1** as a catalyst in water (□: benzaldehyde, ◆: cyclohexanecarboxaldehyde, ○: no aldehyde, C: concentration of **2** in water (mol/L)). *Conditions*: **2** (1.5 equiv.), **1** (0.1 equiv.), PhCO$_2$H (0.1 equiv.), SDS (0.1 equiv.), H$_2$O (aldehyde: 167 mM), 30°C. The amount of **2** was determined by HPLC (acetophenone was used as an internal standard).

was remarkable because lower diastereoselectivity had been obtained in the Lewis acid-catalyzed Mukaiyama aldol reactions in water so far. For the metal-catalyzed Mukaiyama aldol reactions of aldehydes with silyl enol ethers, only two reaction mechanisms are known. One is the Lewis acid mechanism, in which an aldehyde activated by a Lewis acid reacts with a silyl enol ether, and the other is the metal enolate mechanism in which a reactive metal enolate is formed from a silyl enol ether by silicon–metal exchange and reacts with an aldehyde.[36–39] In the present system, we proposed the latter reaction mechanism because it could explain the results shown above more clearly. In boron enolate chemistry, the aldol reaction proceeds via chair-like six-membered transition state and the diastereoselectivity is dependent on the geometry of the starting boron enolate. Furthermore, the trend that *syn* selectivity is higher than *anti* selectivity is observed.[40] In the present reaction system, the same trend was observed. As shown in Table 6, high *syn* selectivity was observed when a *cis* enolate was used. Additionally, lower selectivity was observed when *trans* enolate was used. Thus, we proposed the mechanism which involved a boron enolate as a reaction intermediate (the boron enolate mechanism, shown in Scheme 1). The mechanism is based on the hypothesis that **1** can react with a silyl enol ether to form the corresponding boron enolate under the conditions.[41,42] When a *cis* enolate was used, an aldehyde and the boron enolate would react via a chair-like six-membered transition state to give the *syn* aldol product. The initial aldol product is presumed to be easily cleaved by hydrolysis, and **1** can be regenerated. The role of benzoic acid may be acceleration of the Si–B exchange step, which is thought to be the rate-determining step. Since the leaving group in the step is hydroxyl group, which is a weak leaving group, of **1**, it seems necessary to protonate it to increase leaving ability by adding a proton source.

The substituents on boron atom would affect the Si–B exchange step. When an electron-withdrawing group such as trifluoromethyl group was introduced, electron density on boron atom was decreased and thus, the boron atom seems to be more easily attacked by oxygen atom of a silyl enol ether. An electron-donating group would have an opposite effect, and diastereoselectivity would be lower probably because nonselective Brønsted acid-mediated aldol pathway became significant.

To support the proposed mechanism, kinetic studies were undertaken. The rate of disappearance of silyl enol ether **2** was examined (Fig. 2 (left)). Benzaldehyde (more reactive) and cyclohexanecarboxaldehyde (less reactive, 34% yield under the conditions of Fig. 2) were chosen as substrates for investigation of the relation between the reactivity of these aldehydes and disappearance rate of **2**. It was found that the rate was independent of the reactivity of the aldehydes. The reactivity of the aldehydes has no significant effect on the disappearance rate of **2**. Furthermore, the amount of the silyl enol ether also decreased at the same rate in the case that no aldehyde was added to the reaction system. In addition, the rate was found to be dependent only on the amount of the remaining **2**, following first-order kinetics (k=3.0×10^{-4} s^{-1}, Fig. 2 (right)). These facts support the boron enolate mechanism rather than the Lewis acid mechanism, because the reactivity and the absence of the aldehyde are presumed to affect the rate of the disappearance of **2** in the Lewis acid mechanism. In our mechanism, the aldol addition step should be very fast because of the instability of the boron enolate in water. The results of the kinetic studies suggest the Si–B exchange step, not the aldol addition step, is the rate-determining step because the rate depends only on the amount of the remaining **2**. The formed boron enolate would react with an aldehyde rapidly or be hydrolyzed to form the corresponding ketone. The cleavage of the B–O bond of the initial aldol product should be fast because of the acidity of the reaction media (pH ca. 4). Thus, the boron enolate mechanism is much more likely than the Lewis acid mechanism. The same mechanism can be proposed for the case of using **3** because the same trend of diastereoselectivity was observed. When *trans*-enolates were used, higher diastereoselectivities were obtained by using **3** (Table 6, runs 4, 5, 10, and 11). When a more Lewis acidic catalyst was used,[30] diastereoselectivity was lowered probably because of side pathways such as Lewis acid-mediated aldol pathway and Brønsted acid-mediated aldol pathway (Table 5, run 4). As far as we know, this is the first example of the formation of a boron enolate using a catalytic amount of a boron source. In addition, it is noted that the reactions proceed smoothly in water as a solvent to attain high yields and selectivities.

3. Conclusion

We have developed a new reaction system in water. Highly diastereoselective Mukaiyama aldol reactions proceed smoothly in the presence of a catalytic amount of diarylborinic acid such as **1** or **3**, benzoic acid, and SDS. A remarkable point is that the reaction intermediate is a boron enolate which is formed in the reaction system. It should be noted that the reactions proceed smoothly in water at ambient temperature, while traditional boron enolate-mediated aldol reactions need lower temperatures and strictly anhydrous conditions. Water is used as the sole solvent, and this system is thought to lead to environmentally friendly systems. The new system described here will be a guideline for development of the methods of treating water-unstable compounds in water.

4. Experimental

4.1. A typical experimental procedure for diastereoselective aldol reactions in water

To a stirred white suspension of diarylborinic acid (0.025 mmol), benzoic acid (0.0025 mmol), and SDS (0.025 mmol) in water (1.5 mL), an aldehyde (0.25 mmol) and a silyl enol ether (0.375 mmol) were added successively at 30°C. After 24 h, saturated aq. $NaHCO_3$ and brine were added, and the mixture was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. The aldol product was purified by preparative TLC (SiO_2, ethyl acetate/hexane=1/3). All the aldol products are literature-known compounds.

4.1.1. Bis(4-trifluoromethylphenyl)borinic acid (3). To a stirred solution of 4-bromobenzotrifluoride (5.0 mmol) in ether (20 mL) were added *sec*-butyllithium (1.0 M cyclohexane and *n*-hexane solution, 5 mmol) and tributylborate (1.7 mmol) successively at −78°C. The reaction mixture was stirred overnight at room temperature and quenched with water. The ether layer was washed with 1N HCl, water, and brine, and dried over Na_2SO_4, and concentrated. The crude product was dissolved in 75% ethanol, and 2-ethanolamine (2.3 mmol) was added. The mixture was stirred for 1 h at 50°C and poured into ether. The ether layer was washed with water and brine, and dried over Na_2SO_4, and concentrated. The mixture was washed with chloroform on a glass filter and dried in vacuo. The product (ethanolamine ester) was hydrolyzed by 1N HCl aq./acetone/methanol at room temperature. The reaction mixture was extracted with ether and washed with water and brine, and dried over Na_2SO_4, and concentrated. The obtained crystal was dried in vacuo (56%). Mp 79–80°C; IR (KBr) 3399, 1323, 1127, 838, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (d, J=7.9 Hz, 4H), 7.88 (d, J=7.7 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 124.0 (q, J=272.1 Hz), 124.8, 133.1 (q, J=32.2 Hz), 134.8; MS (*m/z*) 318 [M^+], 173. Anal. calcd for $C_{14}H_9BF_6O$: C, 52.87; H, 2.85. Found: C, 53.17; H, 3.09.

4.1.2. Bis(3-trifluoromethylphenyl)borinic acid. Mp 37–38°C; IR (KBr) 3349, 1610, 1346, 1164, 934 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (dd, J=7.7, 7.7 Hz, 2H), 7.80 (d, J=7.9 Hz, 2H), 7.95 (d, J=7.3 Hz, 2H), 8.06 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 124.2 (q, J=272.0 Hz), 128.0 (q, J=3.7 Hz), 128.5, 130.5 (q, J=32.1 Hz), 130.9 (q, J=3.7 Hz), 138.0; MS (*m/z*) 318 [M^+], 173. Anal. calcd for $C_{14}H_9BF_6O$: C, 52.87; H, 2.85. Found: C, 53.04; H, 3.14.

4.1.3. Bis(4-fluorophenyl)borinic acid. Mp 31–32°C; IR (KBr) 3447, 1597, 1230, 1159, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 (dd, J=8.9, 8.9 Hz, 4H), 7.78 (dd, J=6.3, 8.5 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 115.1, 115.3, 136.9, 137.0; HRMS. Calcd for $C_{12}H_9BF_2O$: *m/z* 218.0715. Found: 218.0717.

4.1.4. Bis(4-bromophenyl)borinic acid. Mp 80–81°C; IR (KBr) 3569, 1584, 1389, 1072, 1009 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (d, J=8.3 Hz, 4H), 7.63 (d, J=8.3 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 126.4, 131.3, 136.1; HRMS. Calcd for $C_{12}H_9BBr_2O$: *m/z* 337.9113. Found: 337.9117.

4.1.5. Bis(4-tolyl)borinic acid. Mp 40–41°C; IR (KBr) 3399, 1605, 1328, 1184, 824 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (s, 6H), 7.26 (d, J=8.1 Hz, 4H), 7.71 (d, J=7.9 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.7, 128.7, 134.8, 141.2; HRMS. Calcd for $C_{14}H_{15}BO$: *m/z* 210.1216. Found: 210.1219.

4.1.6. Bis(4-methoxyphenyl)borinic acid. Mp 92–93°C; IR (KBr) 3602, 2962, 2041, 1918, 1279 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, 6H), 6.98 (d, J=8.8 Hz, 4H), 7.77 (d, J=8.6 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 55.1, 113.5, 136.6, 161.9; MS (*m/z*) 242 [M^+]. Anal. calcd for $C_{14}H_{15}BO_3$: C, 69.46; H, 6.25. Found: C, 69.22; H, 6.16.

4.1.7. Di-1-naphthylborinic acid. Mp 107–108°C; IR (KBr) 3399, 3046, 1571, 1287, 782 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.54 (m, 6H), 7.73 (dd, J=1.3, 6.8 Hz, 2H), 7.90–7.98 (m, 4H), 8.39 (d, J=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 125.1, 125.7, 126.4, 128.4, 128.7, 131.0, 133.4, 134.9, 136.0; MS (*m/z*) 282 [M^+]. Anal. calcd for $C_{20}H_{15}BO$: C, 85.14; H, 5.36. Found: C, 85.29; H, 5.50.

4.1.8. Di-2-naphthylborinic acid. Mp 129–130°C; IR (KBr) 3581, 3054, 1626, 1348, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.60 (m, 4H), 7.91–7.95 (m, 8H), 8.37 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 126.1, 127.2, 127.3, 127.8, 128.9, 130.2, 132.9, 134.8, 136.7; MS (*m/z*) 282 [M^+]. Anal. calcd for $C_{20}H_{15}BO$: C, 85.14; H, 5.36. Found: C, 84.85; H, 5.51.

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