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# Borinic acid catalyzed $\alpha$ -addition to isocyanide with aldehyde and water

Takahiro Soeta\*, Yuuki Kojima, Yutaka Ukaji, Katsuhiko Inomata\*

Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan

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Isocyanides, which have formal divalent carbon functionalities, are ideal candidates for the development of multicomponent reactions. An addition of isocyanide to aldehyde or imine, which is the key step of the Passerini or Ugi reactions,<sup>1,2</sup> has shown the power of constructing polyfunctional molecules such as  $\alpha$ -acyloxyamide or  $\alpha$ -acylaminoamides in practical, one-pot operations, as well as the generation of molecular diversity for drug discovery and natural product synthesis.<sup>3</sup> Passerini reaction requires a carboxylic acid, which activates an aldehyde and traps a nitrilium ion to form an acyloxylated intermediate. The subsequent acyl transfer leads to the corresponding  $\alpha$ -acyloxyamide. Since then, the modification of Passerini reaction attracts chemists to look for wider applications, especially in the development of carboxylic acid-free conditions. The reaction of isocyanide with aldehyde mediated by Brønsted or Lewis acid has been developed to afford the corresponding  $\alpha$ -hydroxyamide, however, the nitrilium intermediate is subject to further addition of isocyanide and often leads to undesired products.<sup>4</sup> Moreover, the cleavage of the Lewis acid from the product is required.<sup>5</sup> In 2002, dramatic improvement has been reported by Denmark, which is the first example of the enantioselective  $\alpha$ -addition to isocyanide with aldehyde mediated by SiCl<sub>4</sub> by applying the concept of Lewis base activation of Lewis acid, affording the chiral  $\alpha$ -hydroxyamide.<sup>6</sup> Mereddy very recently reported the  $\alpha$ -addition to isocyanide with aldehyde and water mediated by boric acid, giving the products in good yields.<sup>7</sup> However, both of these reactions need a stoichiometric amount of Lewis or Brønsted acid. As far as we know, there are no examples of catalytic

## ABSTRACT

A first example of diphenylborinic acid catalyzed  $\alpha$ -addition to isocyanide with aldehyde and water is described. The reaction proceeded smoothly in the presence of water and 5 mol % of borinic acid to give the corresponding  $\alpha$ -hydroxyamides in good to high yields. A wide range of aldehydes and isocyanides are applicable to this reaction.

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 $\alpha$ -addition to isocyanide with aldehyde and water in the absence of carboxylic acid to give the corresponding  $\alpha$ -hydroxyamide.<sup>8</sup> Herein, we wish to describe the first example for borinic acid catalyzed  $\alpha$ -addition to isocyanide with aldehyde and water.

In the Passerini reaction, the acyl group in the carboxylic acid consequently acts as an electrophile and the OH group works as a nucleophile to the nitrilium intermediate. Thus, if a molecule (Z–OH) consists of an electrophile (Z) and a nucleophilic group (OH), it could act like a carboxylic acid in the Passerini reaction. Based on this hypothesis, we have already developed an *O*-silylative Passerini reaction by using silanol instead of carboxylic acid.<sup>9</sup> We expected that Z–OH would act as a catalyst in the presence of water, which would trap the nitrilium intermediate **A** and tautomerizes to afford **C**, which could be hydrolyzed to regenerate Z–OH (Scheme 1). At first, we examined whether the borinic acid



Scheme 1. Working hypothesis.





<sup>\*</sup> Corresponding authors. Tel.: +81 76 264 5732; fax: +81 76 264 5742 (T.S.); tel.: +81 76 264 5700; fax: +81 76 264 5742 (K.I.).

*E-mail addresses:* soeta@se.kanazawa-u.ac.jp(T.Soeta), inomata@se.kanazawa-u. ac.jp (K. Inomata).

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can catalyze the  $\alpha$ -addition to isocyanide with aldehyde and water to afford the corresponding  $\alpha$ -hydroxyamides.

Our initial study began using aldehyde, isocyanide, water and borinic acid in dichloroethane (entry 1 in Table 1). To our delight, *t*-octyl isocyanide (**2a**) cleanly reacted with 3-phenylpropanal (**1a**) and water in dichloroethane (DCE) at room temperature in the presence of diphenylborinic acid (**3a**) (5 mol %) to afford the expected  $\alpha$ -hydroxyamides **4aa** in 90% yield after 23 h.

This reaction proceeded smoothly both in haloalkane and aromatic solvents to afford **4aa** in good to high yields (entries 1–5). Especially, the reaction was completed within 5 h in dichloromethane to afford the product in 93% yield (entry 2). Tetrahydrofuran is also effective for this reaction (entry 6), however, diethylether and polar solvents were less effective (entries 7–9). In the case of methanol, which has been used in Ugi reaction as a protic solvent, the reaction was complicated and only 42% of the product was obtained (entry 9), probably due to coordination of methanol to borinic acid to retard the expected reaction. Even at lower catalyst loadings (3 and 1 mol %), the reaction proceeded cleanly to afford the product in good to high yields, especially in refluxing dichloromethane (entries 10–12).

As an efficient method for a catalytic  $\alpha$ -addition to isocyanide with aldehyde and water, we set out to evaluate boron derivatives. When phenylboronic acid (**3b**) was used, low reaction efficiency was observed (entry 13). Next, borinic acids bearing electron donating or withdrawing group on the aromatic ring were examined (entries 14 and 15). In the case of 5 mol % of bis(4-methoxy-phenyl)borinic acid (**3c**), the reactivity was decreased and the product was obtained in 73% yield after 23 h (entry 14). However, bis(4-fluorophenyl)borinic acid (**3d**) showed the same reactivity as **3a**, affording the product in 92% yield after 4 h (entry 15). These results indicated that the Lewis acidity of the boron atom is crucial for the reaction to proceed efficiently.<sup>10</sup>

It was attempted to expand the scope of isocyanides and aldehydes utilizing a catalytic amount of diphenylborinic acid (**3a**) as shown in Table 2. In these reactions, the optimal amounts of aldehydes **1a–k** (1.0 equiv), isocyanides **2a–h** (1.1 equiv) and water (1.0 equiv) were used in the presence of 5 mol % of borinic acid

#### Table 1

 $\alpha$ -Addition to isocyanide catalyzed by Ar<sub>n</sub>B(OH)<sub>3-n</sub>

Ph	+ CN-t-Oct $\frac{Ar_r}{H_2 r}$	B(OH) <sub>3-n</sub> ( <b>3</b> ) O (1.0 equiv) vent, rt, time Ph	OH N_t-Oct
1a	2a		4aa
<i>t</i> -Oct = 1,1,3,3-tetramethylbutyl			

Entry <sup>a</sup>	$Ar_nB(OH)_{3-n}$ 3 (mol %)	Solv	Time (h)	Yield (%)
1	Ph <sub>2</sub> BOH <b>3a</b> (5)	DCE	23	90
2	Ph <sub>2</sub> BOH <b>3a</b> (5)	$CH_2Cl_2$	5	93
3	Ph <sub>2</sub> BOH <b>3a</b> (5)	CHCl <sub>3</sub>	23	90
4	$Ph_2BOH$ <b>3a</b> (5)	PhMe	23	78
5	$Ph_2BOH$ <b>3a</b> (5)	PhH	23	80
6	Ph <sub>2</sub> BOH <b>3a</b> (5)	THF	23	83
7	Ph <sub>2</sub> BOH <b>3a</b> (5)	Et <sub>2</sub> O	23	67
8	Ph <sub>2</sub> BOH <b>3a</b> (5)	MeCN	23	65
9	Ph <sub>2</sub> BOH <b>3a</b> (5)	MeOH	23	42
10	Ph <sub>2</sub> BOH <b>3a</b> (3)	$CH_2Cl_2$	23	83
11	Ph <sub>2</sub> BOH <b>3a</b> (1)	$CH_2Cl_2$	23	71
12 <sup>b</sup>	Ph <sub>2</sub> BOH <b>3a</b> (1)	$CH_2Cl_2$	23	79
13	PhB(OH) <sub>2</sub> 3b (5)	$CH_2Cl_2$	23	56
14	$(4-MeOC_6H_4)_2BOH \ 3c \ (5)$	$CH_2Cl_2$	23	73
15	(4-FC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> BOH <b>3d</b> (5)	$CH_2Cl_2$	4	92

<sup>a</sup> Reaction conditions: 3-phenylpropanal (**1a**) (1.0 mmol), *t*-octylisocyanide (**2a**) (1.1 mmol), water (1.0 mmol) and  $Ar_nB(OH)_{3-n}$  **3** were used in solvent (1.5 mL).

<sup>b</sup> Reaction was carried out under refluxing conditions.

#### Table 2

Scope of isocyanides and aldehydes

O II ,	on 52	Ph <sub>2</sub> BOH ( <b>3a</b> ) (5 mol%) H <sub>2</sub> O (1.0 equiv)	
R <sup>1</sup> H	CN-R <sup>2</sup>	CH <sub>2</sub> Cl <sub>2</sub> , rt	
1	2		4

Entry	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Yield (%)
1	$PhCH_2CH_2$ ( <b>1a</b> )	<i>t</i> -Oct ( <b>2a</b> )	5	93 ( <b>4aa</b> )
2	$PhCH_2CH_2$ (1a)	t-Bu ( <b>2b</b> )	17	88 ( <b>4ab</b> )
3	$PhCH_2CH_2$ (1a)	c-Hex ( <b>2c</b> )	24	63 ( <b>4ac</b> )
4	$PhCH_2CH_2$ (1a)	Bn ( <b>2d</b> )	43	58 ( <b>4ad</b> )
		<b>(2e</b> )		
5	$PhCH_2CH_2$ (1a)	J. J. J. OTBS	36	61 ( <b>4ae</b> ) <sup>a</sup>
ah				
60	$PhCH_2CH_2$ ( <b>1a</b> )	$C_6H_5(2t)$	37	43 ( <b>4at</b> )
7	$PhCH_2CH_2$ ( <b>1a</b> )	$4-BrC_{6}H_{4}(2g)$	21	34 ( <b>4ag</b> )
8 <sup>b</sup>	$PhCH_2CH_2$ ( <b>1a</b> )	$4-MeOC_{6}H_{4}(2h)$	38	38 ( <b>4ah</b> )
9	<i>c</i> -Hex ( <b>1b</b> )	<i>t</i> -Oct ( <b>2a</b> )	9	92 ( <b>4ba</b> )
10	<i>t</i> -Bu ( <b>1c</b> )	<i>t</i> -Oct ( <b>2a</b> )	17	89 ( <b>4ca</b> )
	(1d)			
11		<i>t</i> -Oct ( <b>2a</b> )	28	82 ( <b>4da</b> ) <sup>a</sup>
	//			
12	$C_6H_5(1e)$	<i>t</i> -Oct ( <b>2a</b> )	40	70 ( <b>4ea</b> )
13 <sup>b</sup>	$C_6H_5$ (1e)	<i>t</i> -Oct ( <b>2a</b> )	40	80 ( <b>4ea</b> )
14	$4-O_2NC_6H_4$ ( <b>1f</b> )	<i>t</i> -Oct ( <b>2a</b> )	21	89 ( <b>4fa</b> )
15 <sup>b</sup>	$4-BrC_{6}H_{4}$ ( <b>1g</b> )	t-Oct ( <b>2a</b> )	48	88 ( <b>4ga</b> )
16 <sup>b</sup>	$4-MeOC_6H_4$ (1h)	t-Oct ( <b>2a</b> )	47	48 ( <b>4ha</b> )
17 <sup>b</sup>	1-Naphthyl ( <b>1i</b> )	t-Oct ( <b>2a</b> )	48	80 ( <b>4ia</b> )
18 <sup>b</sup>	2-Naphthyl (1i)	t-Oct ( <b>2a</b> )	48	74 ( <b>4ia</b> )
19 <sup>b</sup>	PhCH=CH $(1k)$	t-Oct ( <b>2a</b> )	35	56 ( <b>4ka</b> )

<sup>a</sup> A mixture of ca. 1:1 ratio of the diastereomers was obtained.

<sup>b</sup> Reaction was carried out under refluxing conditions. The yields at room temperature were shown in Supplementary data.

**3a.** From these results, we found that the present method was applicable to a wide variety of aldehydes and isocyanides and little side products were obtained. The reaction of tertiary isocyanides  $(R^2 = t$ -Oct, *t*-Bu) with **1a** in the presence of **3a** gave the products in high yields (entries 1 and 2). Aldehyde 1a was consumed in 17 h when t-butylisocyanide (2b) was used, giving the product 4ab in 88% yield (entry 2). In the case of secondary and primary isocyanides 2c, 2d, low reactivities were observed to afford the corresponding products 4ac and 4ad in 63% and 58% yields, respectively. (entries 3 and 4). Chiral isocyanide 2e, which was prepared from the corresponding amino acid, gave the product 4ae in moderate yield, however, no chiral induction was observed (entry 5). Aromatic isocyanides were also employed in this reaction (entries 6-8). When a phenylisocyanide (2f) was used, the corresponding  $\alpha$ -hydroxyamide **4af** was obtained in 43% yield (entry 6). Aromatic isocyanides bearing an electron withdrawing or donating group at the para position also showed low reactivities (entries 7 and 8) even when the reactions were carried out under refluxing conditions (entry 8). Reactivity of various aldehydes toward t-octyl isocyanide (2a) was next examined. Aliphatic aldehydes 1b and 1c gave the products in 92% and 89% yields, respectively (entries 9 and 10). Chiral aldehyde, (S)-(-)-citronellal (1d), gave the product in 82% yield after 28 h with ca. 1:1 ratio of diastereomers (entry 11). Aromatic aldehydes 1e-j also showed low reactivities at room temperature (except 1f), however, the corresponding  $\alpha$ -hydroxyamides were obtained in high yields when the reactions were carried out under refluxing conditions in dichloromethane (entries 12-16) except the case of 1h, which has an electron donating group at *para*-position to deactivate the carbonyl group. On the other hand, *p*-nitrobenzaldehyde (1f), which has electron withdrawing group showed high reactivity, affording the



Scheme 2. Proposed catalytic cycle.

product in 89% yield at room temperature (entry 14). Naphthylaldehydes **1i** and **1j** could be substrates for this reaction, affording **4ia** and **4ja** in good yields (entries 17 and 18). Cinnamaldehyde (**1k**) was less reactive and afforded the product **4ea** in 56% yield (entry 19).

To reveal the reaction mechanism, we conducted some control experiments. The addition reaction of isocyanide **2a** to aldehyde **1a** with 1.0 equiv of water in the absence of diphenylborinic acid (**3a**) did not proceed in dichloromethane at room temperature for 23 h (Eq. 1). When the reaction was carried out without water in the presence of 5 mol % of **3a**, the product was obtained less than 7% yield after 5 h (Eq. 2). These results indicate that the borinic acid considerably promotes the  $\alpha$ -addition to isocyanide and stoichiometric amount of water is also required to regenerate borinic acid **3a** in the catalytic cycle.



Based on these results, we propose the catalytic cycle for the present  $\alpha$ -addition to isocyanide with aldehyde and water in the presence of borinic acid as shown in Scheme 2. Aldehyde is initially activated by borinic acid through coordination of the carbonyl oxygen to the boron atom. Subsequently, nucleophilic

attack of isocyanide to carbonyl group provides a nitrilium intermediate **D**. There would be two possibilities for undergoing catalytic cycle: in *path a* in Scheme 2, the hydroxy group on the boron atom rearranges to the nitrilium carbon in **D** like shown in **E** (corresponds to **A** in Scheme 1), followed by tautomerization to afford **F** (corresponds to **C** in Scheme 1). Then the intermediate **F** is hydrolyzed by water to afford the corresponding  $\alpha$ -hydroxyamide and borinic acid is regenerated. On the other hand, in *path b*, nitrilium intermediate **D** is trapped by water and the following tautomerization affords **H**, from which the product is released and borinic acid regenerates. It is most likely that the reaction proceeds through *path a* rather than *path b*, because intramolecular rearrangement of hydroxy group on the boron atom in **E** seems much faster than intermolecular attack of water to nitrilium intermediate **D** (Scheme 2).

In summary, we developed the first catalytic  $\alpha$ -addition to isocyanides with aldehydes and water in the presence of catalytic amount of phenylborinic acid to afford the corresponding  $\alpha$ -hydroxyamides in moderate to high yields. A wide range of aldehydes and isocyanides are applicable to this reaction. Further studies on this reaction are in progress in our laboratory.

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## Supplementary data

Supplementary data (A Supplementary Data file containing experimental details and characterizational data [NMR spectra (<sup>1</sup>H, <sup>13</sup>C)] is available online.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.032.

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