1,2,3-Triazole-boranes: stable and efficient reagents for ketone and aldehyde reductive amination in organic solvents or in water†

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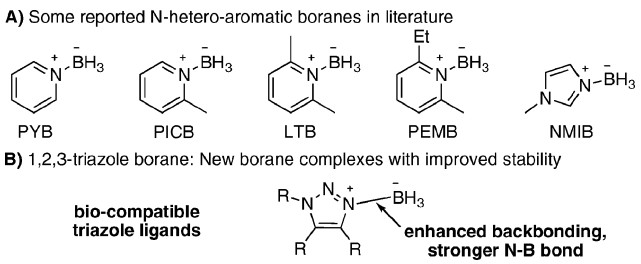
Air, moisture and thermally stable 1,2,3-triazole-borane complexes were developed as new practical reagents for ketone/aldehyde amination with high efficiency and excellent substrate diversity.

Borane compounds are important reagents in organic synthesis with a long history.[1] The key function of these compounds is donating hydride in reductive processes.[2] In the past, different borane compounds have been developed in order to promote attractive transformations.[3] Among those borane compounds, nitrogen coordinated borane complexes are particularly attractive to chemists due to their unique reactivity.[4] However, one big concern regarding these complexes is their stability, especially at high temperature and in reactions in protic solvents (H_2 formation).

Amine-coordinated borane complexes suffer from poor stability, thus limiting their application in synthesis.[5] On the other hand, N-heteroaromatic compound-coordinated boranes, such as $PyBH_3$, provide improved stability and have been applied to several interesting transformations recently.[6] Some reported N-heteroaromatic boranes include pyridine boranes and pyridine derivative boranes, imidazole boranes and 1,2,4-triazole-boranes as shown in Scheme 1A.[7] However, to the best of our knowledge, 1,2,3-triazole-boranes have never been explored. Herein, we report the first 1,2,3-triazole-borane complexes (TAB) and their application as highly efficient reagents in ketone and aldehyde reductive amination, both in organic solvents and in water.



Scheme 1

Our interest in developing 1,2,3-triazole-coordinated complexes was initiated by our recent success with a metal-free 1,2,3-NH-triazole synthesis[8] and post-triazole regio-selective derivatization.[9] Compared to other N-heterocyclic aromatic compounds, the 1,2,3-triazoles possess unique functions: high polarity and high electron density on the nitrogen (more nucleophilic and less basic) allow them to coordinate well with Lewis acids and a lower LUMO in the aromatic ring enhances back bonding, giving stable triazole–metal binding. To evaluate 1,2,3-triazoles as potential binding ligands, our group recently reported triazole-Rh(I) complexes and triazole-Au complexes.[10] To our delight, the triazole–metal complexes indeed provided much better stability toward air, moisture and heat. Therefore, we wondered whether 1,2,3-triazoles could be applied as effective ligands for borane. One clear advantage of triazole-boranes, besides the improved stability of the N–B bond, is that triazoles are biocompatible, non-toxic ligands (unlike pyridine), which is crucial for bio-related transformations.

With the presence of an acidic proton, the NH-triazoles would likely bind to other Lewis acids as anionic ligands. The N-substituted triazoles, on the other hand, could serve as neutral ligands. But the different substitution patterns, N-1 or N-2 positions, might also influence the overall coordination properties. With this concern in mind, to prepare the triazole-borane complexes, different NH-triazoles and N-substituted triazoles were applied to react with BH_3·THF. The results are summarized in Table 1.

The reactions between NH-triazoles (**1a** and **1f**) and BH_3·THF gave complex mixtures, whose structure could not be identified. This was probably due to the multiple nitrogen binding sites on the triazoles and possible formation of a B–H–B 3c2e bond. The N-2 substituted benzyl triazoles (**1c**, **1e** and **1h**) indicated no complex formation even when treated at a higher temperature (50 °C). This lack of coordination was likely caused by the steric hindrance of the N-2 substituted groups. The 1,4-disubstituted triazole **1g** is the major triazole derivative product prepared from "click-chemistry".[11] Unfortunately, the reaction between **1g** and BH_3·THF gave multiple complexes with low reaction rate (more than 12 h at room temperature) and the complexes decomposed during attempts at isolation.

It is known that the N-1 and N-3 nitrogens of 1,2,3-triazoles are more nucleophilic than the N-2 nitrogen. Therefore, to form stable triazole-borane complexes, the N-1 substituted triazole, with less steric hindrance on the N-3 position, could be a good choice. Based on this hypothesis, we examined the N-1 substituted benzotriazoles **1b** and **1d**. To our great

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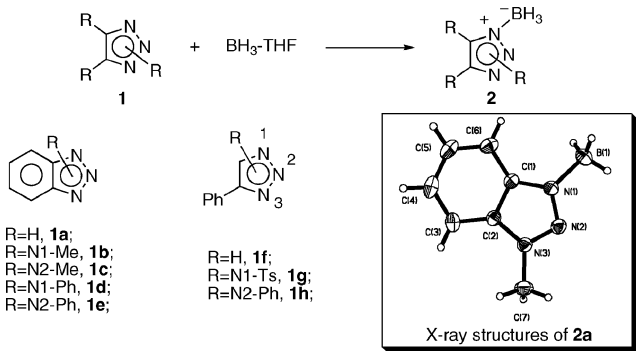
Table 1 Formation of triazole-boranes[a]



Triazole	Reaction results	Yield (%)[b]	Triazole	Reaction results	Yield (%)[b]
1a	Complex mixtures	n.d.	**1e**	No reaction	—
1b	Stable white solid	**2a**: >99%[c]	**1f**	Complex mixtures	n.d.
1c	No reaction	—	**1g**	Complex mixtures	n.d.
1d	Stable white solid	**2b**: >99%	**1h**	No reaction	—

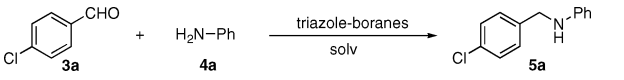
[a] Reactions were carried out by mixing triazole **1** (1.1 equiv.) and BH_3·THF (1.0 M, 1.0 equiv.) at rt. [b] Isolated yields. [c] Structures determined by X-ray.

pleasure, the triazole-borane complexes **2a** and **2b** were formed as white solids in nearly quantitative yields. The structure of **2a** was confirmed by X-ray crystallography, with BH_3 bound on the N-3 position as expected. Notably, the triazole-boranes were very stable toward air and moisture and can even be purified by column chromatography. In addition, the complexes were also thermally stable at 80 °C (no decomposition).

With these new triazole-boranes **2a** and **2b** in hand, we then explored their reactivity as reductants. The transformation that particularly interested us was aldehyde and ketone reductive amination, a very important reaction in organic synthesis, especially for biological related systems.[12] According to the literature, various reducing reagents, such as $NaBH_3CN$, pyr–BH_3, Bu_3SnH/SiO_2, $PhSiH_3/Bu_2SnCl_2$ *etc.*, have been developed for this conversion.[13] As a very attractive approach for bio-elongation, the key concerns regarding "good" reductive amination reagents are: (a) good chemoselectivity (selectively reducing imine rather than aldehydes and ketones); (b) bio-compatibility ("green" reaction conditions), and (c) stability in protic solvents. Among these factors, the hydride stability under acidic conditions is particularly challenging, due to H_2 formation. As a result, reductive amination of ketones is an extremely difficult task, since acid activation of ketone is often required for effective imine formation.

To evaluate the reactivity of triazole-boranes, aldehyde **3a** and aniline **4a** were first applied as shown in Table 2. These triazole-boranes showed excellent reactivity toward aldehyde reductive amination in various solvents (Table 1), giving near quantitative yields in most of the cases. Although both **2a** (TAB-M) and **2b** (TAB-P) produced stable triazole-borane complexes, the *N*-1-phenyl-benzotriazole-borane **2b** showed improved solubility in the organic solvents. As a result, a

Table 2 Screening of reaction conditions[a]



Entry	TAB (equiv.)	Solvent	*T*/°C	*t*/h	Yield (%)[b]
1	**2a** (0.7)	CH_2Cl_2	rt	5	>99
2	**2b** (0.7)	CH_2Cl_2	rt	3.5	>99
3	**2b** (0.7)	DMSO	rt	0.5	95
4	**2b** (0.7)	DMF	rt	5	91
5	**2b** (0.7)	THF	rt	15 min	72
6	**2b** (0.7)	Toluene	rt	1.5	>99
7	**2b** (0.7)	CH_3CN	rt	4	>99
8	**2b** (0.7)	MeOH	rt	2	>99
9	**2b** (0.7)	Neat	rt	5 min	94
10	**2b** (0.4)	DCE	rt	3	>99
11	**2b** (0.4)	DCE	60	0.5	>99
12	**2b** (0.4)	MeOH	rt	1	48

[a] Reactions were carried out by mixing **3a** (1.05 equiv.), **4a** (1.0 equiv.) and **2** (0.4–0.7 equiv.) and monitored by TLC. [b] NMR yields. DCE: 1,2-dichloroethane.

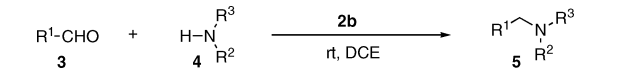
slightly faster reaction rate was observed (entries 1 and 2). The reaction in THF gave lower yield, which was likely due to solvent coordination with borane, leading to side reactions. Notably, these new borane complexes indicated great stability in protic solvent MeOH or at a higher temperature (entries 8 and 11). Impressively, the reaction gave quantitative yield in DCE even with only 0.4 equiv. of reductant (a slight increase of reductant was needed for protic solvent, entries 8 and 12). Considering that 1 equiv. of water was produced in this process, the fact that only the theoretical limit amount of borane was needed indicated the extremely high hydride transfer efficiency and superior stability of the triazole-borane reductants. Representative aldehydes and amines were applied as shown in Table 3.

The results demonstrated that this transformation is suitable for a large variety of aldehydes (aromatic, aliphatic and heteroaromatic) and amines (aromatic, aliphatic and secondary amines). Excellent yields were obtained for almost all cases. Meanwhile, the benzotriazole by-product could be recovered in nearly quantitative yield.

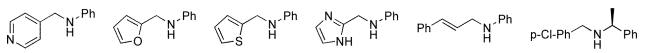
Encouraged by this success, we extended the investigation to ketones. Since acids were often required for the imine formation, 30% of AcOH was added as the catalyst (no reaction was observed without acid catalyst at room temperature). Again, effective reductive amination of ketone was achieved using triazole-boranes with a slightly higher loading of TAB (0.8–1.2 equiv.). Moreover, this ketone reductive amination could also be achieved by increasing the reaction temperature without further addition of acid catalyst (condition B). Selected reaction substrates are shown in Table 4.

As shown in Table 4, this reaction was suitable for primary amines, secondary amine and aniline. Meanwhile, the two different reaction conditions provided orthogonal approaches for sensitive substrates. For example, in the synthesis of **7f**, the furanyl ketone decomposed under acidic conditions. Therefore, using condition A gave **7f** in less than 50% yield along with ketone decomposition by-products. Application of condition B could help to avoid the decomposition of ketone, giving **7f** in excellent yield. The enone substrate has also been

Table 3 Aldehyde–amine reductive coupling by TAB[a]

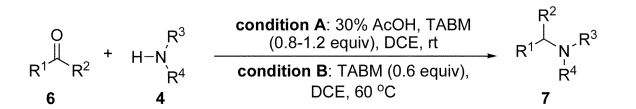


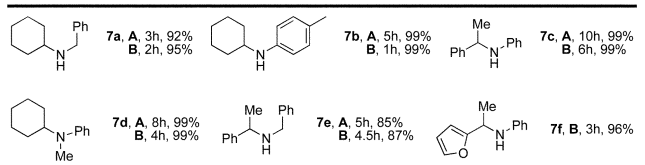
R^1	**4**	*t*/h	Yield (%)[b]
p-ClC_6H_4	$C_6H_5NH_2$	3	**5a**: 99
p-$MeOC_6H_4$	$C_6H_5NH_2$	3	**5b**: 99
C_6H_5	$C_6H_5NH_2$	3	**5c**: 99
p-ClC_6H_4	*p*-$MeOC_6H_4NH_2$	3	**5d**: 99
p-ClC_6H_4	*p*-$FC_6H_4NH_2$	6	**5e**: 99
p-ClC_6H_4	$C_6H_5CH_2NH_2$	4	**5f**: 95
p-ClC_6H_4	*p*-$MeOC_6H_4CH_2NH_2$	4	**5g**: 96
p-$NO_2C_6H_4$	*p*-$MeOC_6H_4CH_2NH_2$	3	**5h**: 82
p-ClC_6H_4	$C_4H_9NH_2$	4	**5i**: 91
p-ClC_6H_4	Pyrrolidine	4	**5j**: 95
p-ClC_6H_4	$C_6H_5NHCH_3$	3	**5k**: 99
$C_6H_5CH_2CH_2$	$C_6H_5NH_2$	3	**5l**: 99



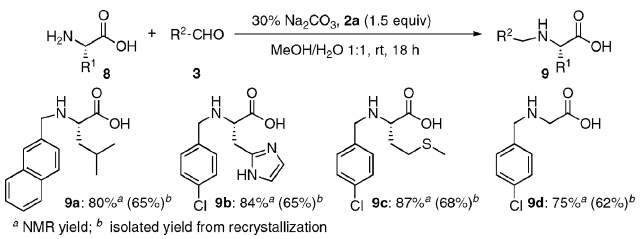
[a] Reactions were carried out by mixing **3** (1.05 equiv.), **4** (1.0 equiv.) and **2b** (0.4 equiv.) and monitored by TLC. [b] Isolated yields.

Table 4 Ketone reductive amination[a,b]





[a] Reactions were carried out by mixing **6** (1.3 equiv.), **4** (1.0 equiv.) and **2** (0.6-1.2 equiv.) and monitored by TLC. [b] Isolated yields.



[a] NMR yield; [b] isolated yield from recrystallization

Scheme 2

investigated (cyclohexenone). A mixture of different reduction products (including the desired allylic amine) was observed. The lack of chemoselectivity was likely caused by the harsher conditions. Overall, to the best of our knowledge, the triazole-boranes are one of the most efficient metal-free reagents for the challenging ketone reductive amination. With clear evidence for improved proton and thermal stability of TAB, we then applied this reagent in the reductive amination of unprotected amino acids in water.

To increase the solubility of amino acid in water, 30% Na_2CO_3 was added (Scheme 2). This modification helped the further evaluation of the triazole-borane reductant under basic conditions. As anticipated, good yields were obtained. Notably, this reaction tolerated functional groups that may potentially coordinate with borane, such as imidazole and sulfur (**9b** and **9c**), which further enhanced the synthetic utility of the reported TAB.

In conclusion, triazole-boranes were successfully prepared and applied as reductants in ketone/aldehyde reductive amination. Compared to literature reported systems, the triazole-boranes showed clear advantages regarding efficiency, and proton and thermal stability, which made them new practical reagents for related chemical and biological research. Detailed studies regarding reaction mechanism (borane dissociation process) and application of this new reagent for other important transformations are currently under investigation in our group.

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Notes and references

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