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Chemoselective Hydroboration of Isocyanates Catalyzed by Commercially Available NaH

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A simple, efficient, and economical method for the chemoselective hydroboration of isocyanates is reported. Commercially available NaH, at very low loadings, efficiently catalyzes the selective conversion of isocyanates to *N*-boryl formamides, bis(boryl)hemiaminals, and *N*-boryl methyl amines. NaH catalyzes isocyanates to controllably open the N=C bond to build an amide bond, and can also remove the C=O bond to obtain *N*-boryl methyl amines. Both aliphatic and aromatic isocyanates can be quantitatively converted to the corresponding hydroboration products. Furthermore, there is excellent functional group selectivity over imines, nitriles, and olefins. Additionally, through in situ monitoring, a possible reaction mechanism is proposed. And the chemical intermediates generated by NaH and HBpin are responsible for all the reduction steps.

Introduction

As important chemical intermediates, isocyanates are used in various organic reactions.[1] Isocyanates are important precursors of amides.[2] In particular, they are unavoidable starting materials of urea and urethane linkages found in pharmaceuticals, polyurethanes, and pesticides.[3] At the earliest, amides were obtained by formylation reagents, but a large amount of waste was generated in this process.[4] Generally, amide compounds are obtained by reacting carboxylic acid derivatives with amine compounds.[5] In addition, amides can also be obtained from amine compounds and alcohol compounds with the participation of heterogeneous catalysts.[6] Recently, studies on the preparation of amides have mainly focused on the coupling reaction of isocyanates.[7] In 2016, Pace et. al reported the chemoselective reduction of isocyanates to formamides catalyzed by in situ generated organozinc complexes.[8] Additionally, before these works, there were reports on the reaction of Grignard or other metals reagents with isocyanates to synthesize amides.[9] Hydroboration reactions have received more and more attention and are widely used in organic synthesis.[10] However, there are few reports on the hydroboration of isocyanates to *N*-boryl formamides. Nonetheless, there have been a few pieces of research on the selective monohydrosilylation of isocyanates to *N*-silylformamides and hydrogenation of isocyanates to formamides.[11] As an important class of chemical intermediates, *N*-methylamine is mainly used in the production of higher fine chemicals, natural product derivatives, and dyes.[12] Currently, the main methods are direct amine alkylation with alcohols and metal-catalyzed reduction of carbon dioxide surrogates.[13] However, these methods are limited because of harsh reaction conditions and the use of hazardous chemicals.

Generally, the reduction of isocyanates using stoichiometric amounts of metal reagents was mainly studied.[14] Rueping et al.[15] reported the $MgBu_2$-catalyzed hydroboration of formamide to *N*-methyl amine. In addition, Zhang et al.[16] and Beller et al.[17] reported a similar reaction. In this context, researchers hoped to achieve chemoselective reduction (step reduction) for isocyanates. However, for the hydrodeoxygenation of isocyanates, there are only three research reports. Hill et al.[18] were the first to publish the hydroboration of isocyanates. In the presence of organomagnesium catalysts, isocyanates were converted to amines with three equivalents of HBpin (pinacolborane). Recently, Nembenna et al.[19] first proposed the organozinc-catalyzed chemoselective hydroboration of isocyanates (Figure 1). However, these catalysts are difficult to prepare and difficult to store. Herein, we provided a simpler and more efficient alternative strategy.

Results and Discussion

At the beginning of this investigation, we screened suitable catalysts and reaction conditions for monohydroboration of isocyanates. The catalytic hydroboration of 1 equiv. amount of *p*-tolyl isocyanate with 1 equiv. of HBpin at room temperature in the presence of NaH (0.1 mmol%) under neat conditions was carried out (SI). Next, we expanded the substrate range for NaH-catalyzed hydroboration of isocyanates under the selected reaction conditions. Various aryl mono- and diisocyanates have been investigated, as well as cyclic and chain alkyl isocyanates. All reactions were completed within 3 h to afford the selective monoboration product *N*-boryl formamide in quantitative yield

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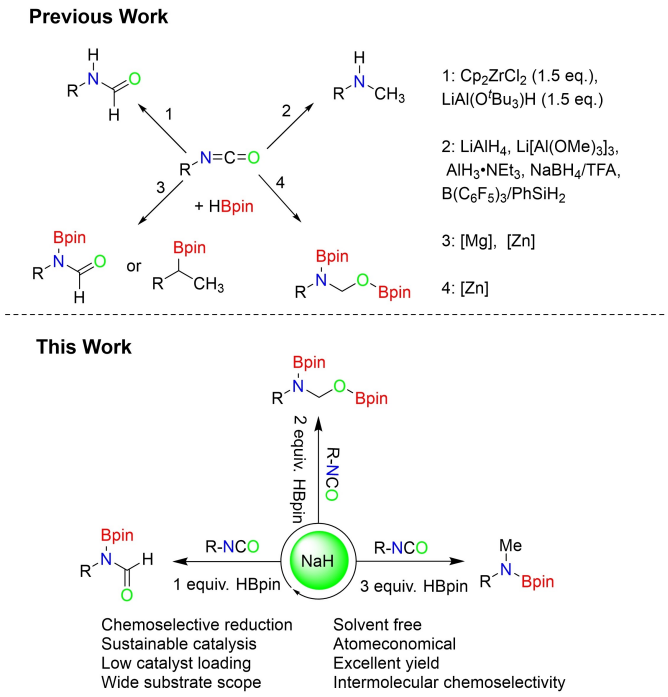


Figure 1. Reduction of isocyanates.

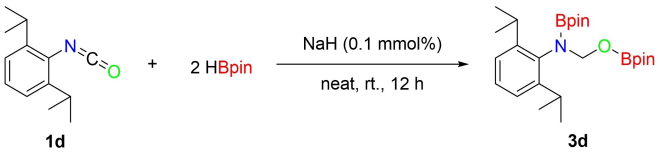
(> 99%) (Scheme 1). All aryl monoisocyanates, including those with electron-donating groups (**1a**–**1e**) and electron-attracting groups (**1h**), were converted in high yields to the corresponding *N*-boryl formamides (**2a**–**2e** and **2h**). Alkyl isocyanates were also converted to the corresponding *N*-boronylcarboxamides in excellent yields (**2h**–**2j**) (Scheme 1). To our delight, all other reactions showed no side products. Furthermore, those with electron withdrawing groups react much faster than isocyanates with electron donating groups. This may be because the isocyanates' carbon atoms of the former have higher electrophilicity.

Subsequently, we extended the dihydroboration under the optimum reaction conditions. Two equivalents of HBpin were added to isocyanates. In most cases, a mixture of products was observed. To our joy, when 2-isocyanato-1,3-diisopropylbenzene (**1d**) was added, the corresponding dihydroboration product bis(boryl)hemiminidine (**3d**) was delivered in high yield (Scheme 2). It implied that a larger steric hindrance is beneficial to the stability of dihydroboration products.

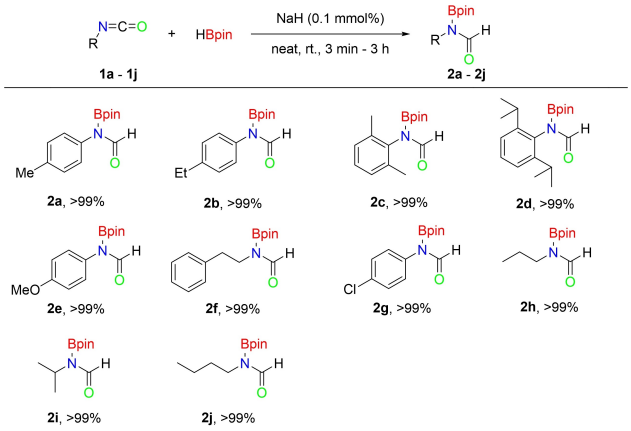
Next, we started to expand the substrate range. Fortunately, in all cases, the isocyanates (**1a**–**1j**) were quantitatively converted to their related *N*-borylated methyl-amines (**4a**–**4j**). All aryl and alkyl isocyanates, including electron-donating groups and electron-attracting groups, were converted in high yields to the corresponding *N*-borylated methyl-amines. Similar to monohydroboration reaction, we found that isocyanates with electron-withdrawing groups require less reaction time than electron-donating groups. Besides, diisocyanates were also converted to the corresponding *N*-borylated methyl amines in excellent yield. In addition, for every mole of *N*-boryl methylamine produced, one mole of $O(Bpin)_2$ was obtained (Scheme 3).

As mentioned earlier, there are only three examples of metal-catalyzed reduction of isocyanates to *N*-borylmethylamines. Therefore, we decided to study the NaH-catalyzed deoxyboration of isocyanates. The catalytic hydroboration of 1 equiv. amount of *p*-tolyl isocyanate with 3 equiv. of HBpin at 60 °C in the presence of NaH (0.1 mmol%) in neat conditions was carried out. Under similar reaction conditions without catalyst, we observed that the product was a mixture of three hydroboration products.

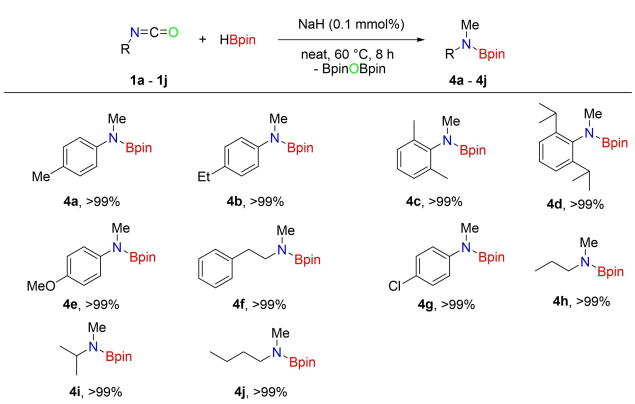
Encouraged by the excellent catalytic effects of monohydroboration and hydrodeoxygenation, we decided to inves-



Scheme 2. Dihydroboration of isocyanates catalyzed by NaH. The yield was calculated by ^{1}H NMR spectroscopy based on isocyanate consumption.

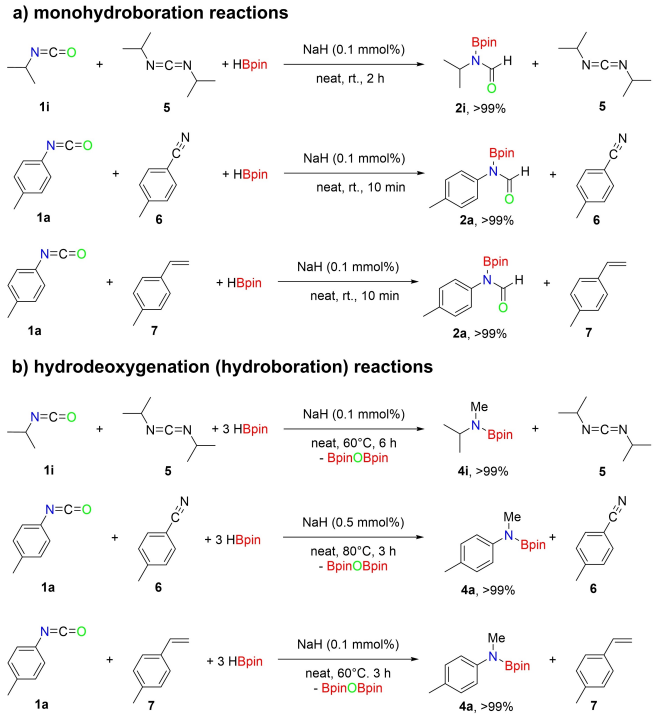


Scheme 1. Monohydroboration of isocyanates catalyzed by NaH. The yield was calculated by ^{1}H NMR spectroscopy based on isocyanates consumption.



Scheme 3. Hdrodeoxygenation (hydroboration) of isocyanates catalyzed by NaH. The yield was calculated by ^{1}H NMR spectroscopy based on isocyanate consumption.

tigate the chemoselectivity of these two types of reactions. One equivalent isopropyl isocyanate (**1 i**), one equivalent *N,N'*-diisopropylcarbodiimide (**5**) and HBpin were mixed with NaH (0.1 mmol%) at room temperature for 2 h, which afforded the *N*-borylated formamide (**2 i**) in 99 % yield over *N,N'*-diisopropylcarbodiimide (**5**). Likewise, under the same conditions, *p*-tolyl isocyanate (**1 a**) afforded the product the *N*-borylated formamide (**2 a**), in a quantitative yield in preference to the *p*-tolunitrile (**6**). Furthermore, in the system where *p*-tolyl isocyanate (**1 a**) and 4-methylstyrene (**7**) coexist, HBpin reacted with **1 a** preferentially to form the *N*-borylated formamide (**2 a**) (Scheme 4a).



Scheme 4. Intermolecular chemoselective hydroboration catalyzed by NaH.

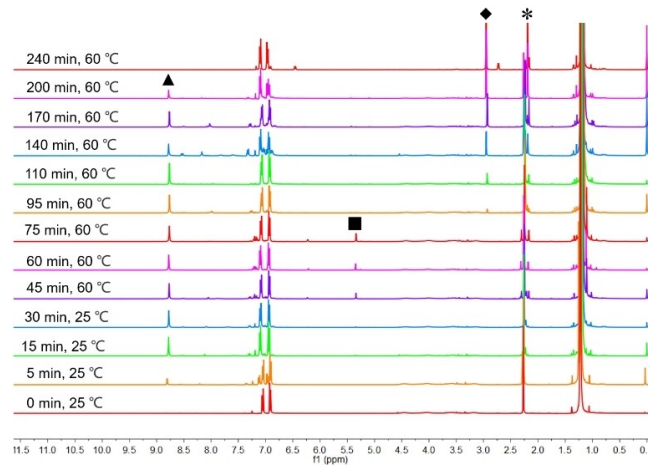


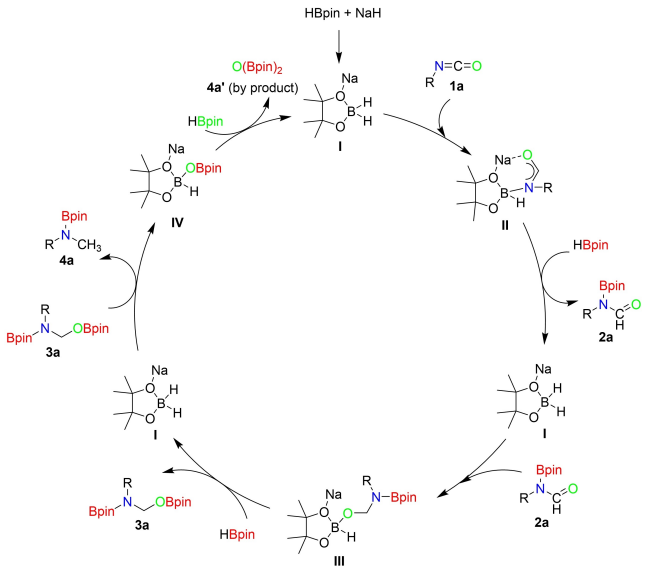
Figure 2. Stacked ^{1}H NMR spectra (400 MHz) for the reaction of *p*-methylphenyl isocyanate (1 mmol) and HBpin (3 mmol), and NaH (0.1 mmol%). Spectra were recorded at different temperature and time intervals between T = 25 °C to 60 °C and t = 0 min - 240 min, respectively. ▲ = 4-MePhN(Bpin)CHO, ■ = *N*-,*O*-(bis)-boryl hemiaminal, ◆ = 4-MePhN(Bpin)Me, * = CH_3 peak of *p*-methylphenyl isocyanate.

Next, the chemoselectivity of the hydrodeoxygenation (hydroboration) with isocyanates was tested. Equimolar amounts of isopropyl isocyanate (**1 i**) and *N,N'*-diisopropylcarbodiimide (**5**) and 3 equiv. HBpin was mixed with NaH (0.1 mol%) under neat conditions for 6 h at 60 °C, which produced the *N*-borylmethylamine (**2 i**) over the *N,N'*-diisopropylcarbodiimide (**5**). Similarly, *p*-tolyl isocyanate (**1 a**) afforded hydrodeoxygenation product, *N*-borylmethylamine (**2 a**) in 99 % yield over either *p*-tolunitrile (**6**) or 4-methylstyrene (**7**) (Scheme 4b).

To better understand the NaH catalyzed selective hydroboration of isocyanates to *N*-borylformamides, bis-(boryl)hemiaminals, and *N*-borylmethylamines, the catalytic mechanism was verified by in situ monitoring (^{1}H NMR spectroscopy) of the reaction of HBpin and *p*-chlorophenyl isocyanate catalyzed by 0.1 mmol% NaH at room temperature to 60 °C. Figure 2 showed the progress of the reaction over 240 minutes and reveals the sequential formation of *N*-boronylcarboxamides, *N*-,*O*-(bis)-(boryl)hemiaminals, and *N*-boronylmethanamine products.

Before the reaction started, there were only ^{1}H NMR resonances for *p*-methylphenyl isocyanate and HBpin. At the very beginning of the catalytic reaction, the formation of 4-MePhN(Bpin)CHO, was confirmed by a singlet at 8.78 ppm. And, as the reaction went on, the product continued to accumulate. When the reaction proceeded to 100 minutes, the corresponding characteristic peak of *N*-,*O*-(bis)-boryl hemiaminal at 5.34 ppm was observed. Next, when the temperature rises to 60 °C, the corresponding characteristic resonance of 4-MePhN(Bpin)Me at 2.26 ppm was noticed. At the same time, the characteristic peak of *N*-,*O*-(bis)-boryl hemiaminal started to disappear. This is related to the instability of *N*-,*O*-(bis)-boryl hemiaminal. It can easily continue to participate in subsequent reactions, eventually obtaining 4-MePhN(Bpin)Me. This is consistent with the fact that only one pure product can be obtained from the dihydroboration of isocyanates. At the end of the reaction, there was only 4-MePhN(Bpin)Me in the product, which also proved the high efficiency of NaH as a catalyst.

Based on the evidence for the in situ reaction, a catalytic mechanism of NaH-catalyzed hydroboration of isocyanates was proposed (Scheme 5). Before the catalytic cycle begins, NaH combines with isocyanate (**1 a**) and undergoes intramolecular rearrangement to generate intermediate **I**.[20] Then, in the first step at the beginning of the catalytic cycle, Intermediate **I** reacts with isocyanate (**1 a**) to form intermediate **II**. Next, the reaction between intermediate **II** and HBpin yields *N*-borylformamide (**2 a**). At the same time, intermediate **I** is regenerated. In addition, intermediate **III** is the product obtained by the reaction of intermediate **I** with *N*-borylformamide (**2 a**). Moreover, intermediate **III** reacts with another molecule of HBpin to generate *N*-,*O*-(bis)-(boryl)hemiaminal (**3 a**), and intermediate **I**. *N*-borylmethylamine (**4 a**) and the intermediate **IV** are obtained



Scheme 5. The proposed mechanism for chemoselective hydroboration of isocyanates is catalyzed by NaH.

by the reaction of *N*-,*O*-bis(boryl)amine (**3 a**) with intermediate **I**. The final step is the reaction of intermediate **IV** with HBpin to give $O(Bpin)_2$ (**4 a'**) and intermediate **I** that can be used in the next cycle.

Conclusion

In summary, commercially available NaH catalyzed the chemoselective hydroboration of isocyanates, under solvent-free and mild conditions, which is demonstrated for the first time. Both aliphatic and aromatic isocyanates can be efficiently converted to the corresponding hydroboration products. Furthermore, the reaction has excellent functional group tolerance and selectivity. Based on experimental evidence, the reaction mechanism has been demonstrated. Chemical intermediates from NaH and HBpin are responsible for all reduction steps. This broadens the range of applications for commercially available reagents. At the same time, it is also proved that the application of main group metals is completely comparable to transition metals in the field of catalysis.

Experimental Section

Materials: Sodium Hydride (60%, dispersion in mineral oil) is purchased from Sahn Chemical Technology co., Ltd. Isocyanates and HBpin (pinacolborane) were purchased from Shanghai Haohong Scientific Co., Ltd. All commercially available reagents were used directly without purification. Reagents addition is done in the Etelux MB 200G glovebox. ^{11}H and ^{13}C NMR spectra were recorded with a Bruker AM 400 spectrometer.

Catalytic Procedure: In a sealed reaction tube, 0.1 mmol% NaH, and 1 mmol isocyanates were added. Then, add 1, 2, or 3 equivalents of HBpin depending on the reaction needs. Finally, the yield of the corresponding products was obtained according to the ^{1}H NMR spectrum. The structure of the product was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy.

Supporting Information Summary

SI contains detailed experimental procedures, characterization data and NMR spectra's of all synthesized compounds

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Catalysis · Chemoselectivity · Commercial catalyst · Hydroboration · Green chemistry

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