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Super hydride catalyzed ester and isocyanate hydroboration

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ABSTRACT

Commercially available, eco-friendly lithium triethylborohydride ($LiHBEt_3$, Super hydride) was shown to be an excellent catalyst for the solvent-free hydroboration of esters using pinacolborane at ambient reaction conditions. This was achieved with a low catalyst loading of 0.1 mol%. The protocol was further extended to the hydroboration of isocyanates with different stoichiometries, which displayed a clear chemoselective catalytic activity towards the cleavage of C=N and C=O bonds. Compared with the previously reported catalysts, $LiHBEt_3$ catalyzes in a short reaction time with solvent free conditions to provide nearly quantitative products.

1. Introduction

The development of environment-friendly reaction conditions generating quantitative chemical transformations from easily available catalysts is still a challenging area. The increasing demand for such sustainable chemical processes has made efficient, eco-friendly, and atomic economic catalysts at the core of modern industrial chemistry and academic research. This was primarily achieved by incorporating transition metals to develop catalytic systems. Since the late 90s, the chemistry of the main group elements has been advanced significantly. Because of such advancement in main group chemistry, chemists have come to the consensus that main group compounds can imitate the behavior transition metal complexes [1]. Since then a lot of effort has been put forward towards the development and invention of catalysts bearing a main group element.

In the regime of catalysis, hydroboration of unsaturated compounds have attracted considerable amount of attention as organoboranes are a significant synthetic intermediates in a variety of organic transformations [2, 3]. The reduction of esters is one of the most important chemical transformations in organic synthesis [4]. In 2016, J. Okuda and co-workers reported that $[LLi][HBPh_3]$ (L = Me_6TREN) which acts as a chemo-selective catalyst for the hydroboration of carbonyl group and CO_2, but is inactive to catalyze the hydroboration of esters [5]. However, $[Mg(thf)_6][HBPh_3]_2$ acts as an effective catalyst for the hydroboration of ethyl acetate [6]. Compared to aldehydes and ketones, the reduction of esters is more difficult (aldehydes > ketones > esters) because of their steric hindrance and electronic effects [7]. S. P. Thomas and co-workers reported that $LiAlH_4$ catalyzes the hydroboration of acetic ester at room temperature [8]. Although, there are several reports available for the hydroboration of esters [6-9], all those reactions were performed in highly toxic deuterated benzene, toluene or benzene. Therefore, there is a need to develop environmental friendly and efficient catalysts for the reduction esters. Recently, M. Ma and co-workers reported a low-valent magnesium(I) complex $[(^{Xyl}Nacnac)Mg]_2$ as a highly efficient pre-catalyst for the hydroboration of esters with HBpin under solvent-free and mild conditions [10].

Isocyanates represents a versatile class of organic molecules [11], with two unsaturated sites that can be reduced and utilized to synthesized a plethora of important intermediates, including alcohols [12], amines [13], and others. The partial reduction of isocyanates has proven to be synthetically challenging because of its tendency to get completely reduced by strong reducing agents to produce methylamines [14]. In a recent report, the treatment of isocyanates with Schwartz's reagent leads to a partial chemoselective reduction of the C=N bonds to generate formamides in high yield, leaving behind some other unsaturated groups [15]. Furthermore, M. S. Hill reported a β-diketiminato magnesium *n*-butyl for the catalytic transformation of the isocyanate functionality to a methyl amine [16]. Very recently, S. Nembenna and co-workers

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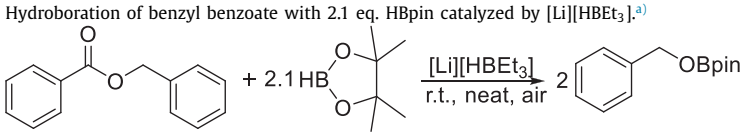
Table 1
Hydroboration of benzyl benzoate with 2.1 eq. HBpin catalyzed by [Li][HBEt$_3$].[a)]



Entry	LiHBEt$_3$[mol%]	T[h]	Yield[%] [b)]
1	10	6	99
2	1	6	99
3	1	1	99
4	0.5	1	99
5	**0.1**	**1**	**99**
6	0.05	4	99
7	0.01	6	65
8	0	6	0

[a)] Benzyl benzoate (1.0 mmol), and HBpin (2.1 mmol) were charged in a 10 mL Schlenk flask without solvent in the air.
[b)] Yields were determined by ^{1}H NMR from the crude reaction mixture.

reported that zinc catalyzes exceptional chemo-selective reduction of isocyanates via hydroboration. [17]

Lithium triethylborohydride (LiHBEt$_3$, 1 M in THF) being a powerful reducing agent can efficiently reduce a wide array of functional groups, but with low selectivity [18]. It was previously used to catalyse the hydroboration of aldehydes and ketones under mild reaction conditions and exhibits an exceptionally high activity in air [19]. M. Findlater and co-workers reported NaHBEt$_3$ as an efficient catalyst for the double hydroboration of nitriles at room temperature [20]. Considering the fact that LiHBEt$_3$ is inexpensive and eco-friendly, herein, we present an efficient method for the hydroboration of esters and isocyanates, mediated by lower catalyst loading of LiHBEt$_3$. The high yielding remarkable reactions were carried out in mild conditions under solvent-free environment and at ambient temperature in air atmosphere.

2. Results and discussion

The hydroboration of benzyl benzoate was selected as a model reaction to establish a protocol which can be used widely (Table 1). Initially, the hydroboration was carried out by using 1.0 mmol of benzyl benzoate with 2.1 mmol of pinacolborane (HBpin) at room temperature in the presence of catalyst LiHBEt$_3$ (10 mol%) under neat conditions and air atmosphere. After stirring for 6 h, quantitative conversion of benzyl benzoate was observed without any side-product formation (Table **1** entry 1). After getting such an excellent catalytic activity, we considered to reduce the catalyst loading and shorten the reaction time to further investigate the activity of LiHBEt$_3$. When the catalyst loading was 1%, the catalytic effect was unprecedented (Table **1** entry 2). Similarly, the reaction was finished within 1 h in quantitative yield (Table **1** entry 3). These encouraging results prompted us to study the effect of lowering the catalyst loadings to 0.5%, 0.1%, 0.05%, and 0.01%, respectively. These results showed that the reaction proceeds to quantitative yields within 1 h with the catalyst loadings of 0.5% and 0.1% (Table **1** entries 4 and 5). However, reducing the catalyst loading to 0.05%, the conversion took 4 h (Table **1** entry 6). In contrast, after reducing the catalyst loading to 0.01%, the yield descended to 65% despite extending the reaction time to 6 h (Table **1** entry 7). In the absence of LiHBEt$_3$, mixtures of benzyl benzoate and HBpin did not provide any conversion at 298 K for 6 h (Table **1** entry 8). In order to find the true nature of the catalyst, we also carried out the reaction with other catalysts. The result shows that BEt$_3$ or NaH has almost no catalytic activity. NaHBEt$_3$ shows a perfect catalytic activity with the yield of 92% within 2 h. However, *n*BuLi catalyzes the reaction to give the product in 50% yield within 16 h. Apparently, the catalytic activity is arising from [HBEt$_3$], Li plays a secondary role. Sen and Vanka have reported a series of HB with

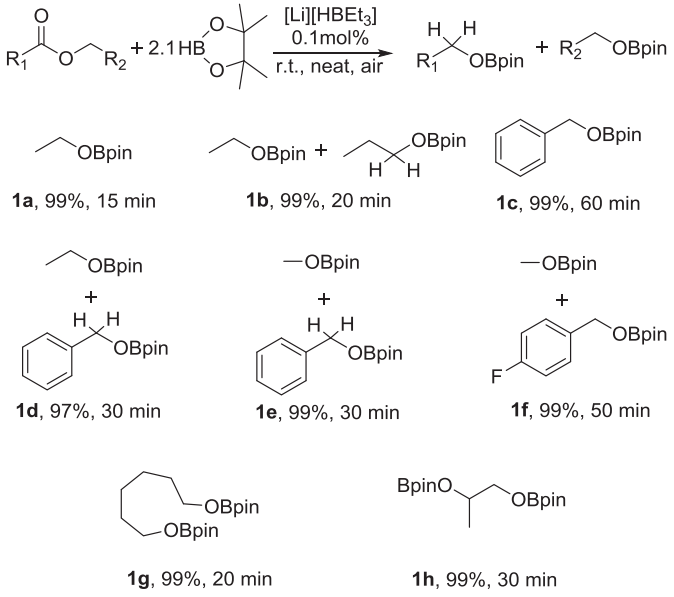


Figure 1. Hydroboration of various esters catalyzed by LiHBEt$_3$.

various organic substrates using Li compounds, where they have shown using theoretical calculations that the Li acts as a single site catalyst [21].

After optimizing the reaction parameters, the scope of the catalytic system was conveniently explored under the condition of entry 5 in Table **1**. Eight typical esters were selected for substrate expansion, and the yields were almost quantitative (Figures **S1** - **S8** in SI). The results are shown in Figure **1**. It can be concluded from Figure **1** that the reaction time about the symmetrical ethyl acetate was less (Figure **1**, **1a**), whereas it was more (Figure **1**, **1c**) about the benzyl benzoate moiety. The reaction time of the asymmetric ethyl propionate (Figure **1**, **1b**) was also less than that of the ethyl benzoate and methyl benzoate (Figure **1**, **1d** and **1e**). Similarly, symmetric ethyl acetate took a lesser reaction time than the asymmetric ethyl propionate. The asymmetric ethyl benzoate and methyl benzoate took a lesser reaction time than the symmetric benzyl benzoate. Then we tested the methyl 4-fluorobenzoate (Figure **1**, **1f**), which finished the reaction in 50 min. The ε-caprolactone was quantitatively reduced to ring-opened bis-borane (Figure **1**, **1g**) within 20 min, with no evidence of any polymerized product. While the lactide was reduced to produce the corresponding dialkoxyl boronates (Figure **1**, **1h**) in quantita-

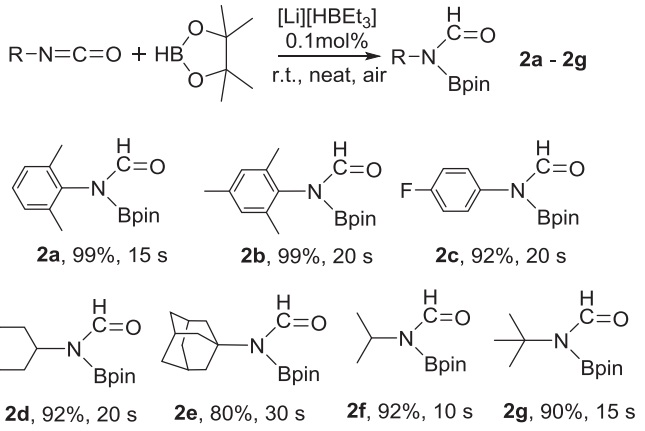


Figure 2. Hydroboration of isocyanates with equivalent of HBpin catalyzed by $LiHBEt_3$.

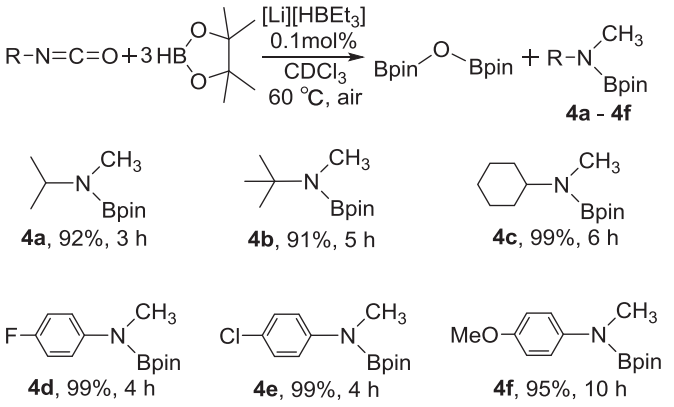


Figure 3. Hydroboration of isocyanates with 3 equivalents of HBpin catalyzed by $LiHBEt_3$.

tive yield within 30 min. These results displays that the steric hindrance of the reactants possesses a great influence on the reaction time in the process of the reduction.

The highly unsaturated structure of isocyanate group (-NCO) determines its high reactivity. With the perfect hydroboration of ester in hand, we intended to extend the same protocol for the hydroboration of isocyanate. Highly unsaturated isocyanates have two unsaturated bonds C=N and C=O, and $LiHBEt_3$ might exhibit excellent chemo-selective catalytic properties.

0.1 mol% of $LiHBEt_3$ was dropped to the mix-solution of 2,6-dimethylphenyl isocyanate with equivalent of HBpin at ambient temperature and air atmosphere, 15 seconds later the solution changed to a thick slurry. The reaction was so quick that the B–H bond of HBpin was cleaved, then selectively added to the C=N double bond to afford the formamide derivatives in 99 % yield. Spectroscopic data is consistent with the corresponding product formed after the addition to C=N double bond, the ^1H NMR spectrum exhibits a sharp peak around 8.55 ppm, while the ^{13}C NMR spectrum shows a signal around 163.6 ppm for the NCHO group. Likewise, the ^{11}B NMR spectrum shows single broad peak at 25.3 ppm, which also indicates that the Bpin group is bound to the nitrogen atom instead of oxygen [8, 17, 22].

The reaction was extended to other commercially available aliphatic and aromatic isocyanates with different substituents, and the results are shown in Figure **2**. In comparison with the aliphatic substrates the aromatic isocyanate reacted more absolutely with higher yields and cleaner products (Figures **S9** - **S15** in SI).

The excellent chemo-selective catalytic reactivity of $LiHBEt_3$ for the hydroboration of isocyanates with one equivalent HBpin prompted us to investigate the conversion with two equivalents of HBpin. To investigate this notion, controlled experiments were performed by reacting 2,6-dimethylphenyl isocyanate with 2 equivalents of HBpin for 12 h with catalyst $LiHBEt_3$ in $CDCl_3$. However, the product (**3a**) was obtained as a mixture containing $RN(Bpin)CH_2OBpin$, $RN(Bpin)CH(O)$, $RN(Bpin)CH_3$, and $O(Bpin)_2$. Similar results were obtained after performing the reactions for 30 min (Figure **S16.1** in SI). Next, we carried out the catalytic reaction at elevated temperature (60°C), the product (**3b**) was still a mixture of $RN(Bpin)CH_2OBpin$, $RN(Bpin)CH_3$, and $O(Bpin)_2$, and the yields of these products were similar (Figure **S16.2** in SI). This indicated that the C=O bond of isocyanates can be easily activated by $LiHBEt_3$ at ambient temperature. Elevated temperatures displays simultaneous addition to C=O bond as well as its cleavage.

In order to obtain a pure methyl amine, the reaction between ^iPrNCO and 3 equivalents of HBpin was performed at 60 °C in $CDCl_3$. The conversion was completed within 3 h which was confirmed by ^1H NMR spectroscopy. Notably, a predominant new organic product (**4a**) was formed, possessing a singlet resonance at 2.40 ppm in the ^1H NMR spectrum. By analyzing the corresponding ^{11}B NMR spectrum, it also revealed that there are two singlet resonances at 23.77 and 20.86 ppm, respectively. In comparison with the literature reports [16, 17, 23], it is confirmed that the resonance at 20.86 ppm is for $O(Bpin)_2$. This indicates that the reduction of ^iPrNCO by HBpin has cleaved the C=O bond in the substrate to form the N-borylated N-methyl isopropylamine $^iPrN(Bpin)CH_3$ (**4a**) and $O(Bpin)_2$. The reactivity extends to other commercially available alkyl isocyanates, as shown in Figure **3**. All the reactions were characterized by a new singlet methyl resonance from 2.4 ppm to 3.0 ppm in the^1H NMR spectra. Meanwhile, the ^{11}B NMR spectra showed a new single N-B resonance around 24 ppm for N-borylated N-methyl, as well as the signal at 21 ppm for $O(Bpin)_2$ (Figures **S17** – **S22** in SI).

Table 2
Energies for the proposed catalytic cycle based on DFT calculations (The values in parenthesis refers to the calculations where the fragments of the substrates involved in the reactions was considered).

Ester + 2HBpin → 2C	ΔE = -53.7 (-56.3) kcal·mol^{-1}	**I**
Ester + $LiHBEt_3$ → A	ΔE = -29.1 (-23.1) kcal·mol^{-1}	**II**
A + HBpin → C + B	ΔE = -28.4 (-27.6) kcal·mol^{-1}	**III**
B + HBpin → C + $LiHBEt_3$	ΔE = 3.8 (-5.6) kcal·mol^{-1}	**IV**

In order to verify the versatility and the air tolerance of the system, we scaled up the reduction of ethyl acetate with 2 equivalents of HBpin, ^iPrNCO with equivalent or 3 equivalents of HBpin. When the ratio of the substrate was amplified to 10 mmol; 99%, 87%, and 95% of the corresponding products (**1a, 2f, 4a**) were obtained. The yields of liquid **1a** and **4a** were obtained by ^1H NMR, and **2f** was calculated by drying and weighing the obtained solid product after washing it with cold $^npentane$ (^1H NMR Figures **S23** – **S25** in SI). However, product **4a** possessed an excess of $O(Bpin)_2$, which may have formed because of the long reaction time which compromises the air tolerance of the system.

We calculated the enthalpy of all the reactions involved in the proposed mechanism. To understand the reactions, we constructed a potential energy surface (PES) of the possible reaction channel. However, we only considered the fragment of the molecule which are involved in the reactions to construct the PES. The connections between TS and the reactant and product were established with intrinsic reaction coordinate (IRC) calculations.

The proposed reaction mechanism for the hydroboration of ethyl acetate (**I**) is presented in Figure 4. It involves three reaction steps (**II, III, IV**) in Table 2. All the reactants, products, and predicted transition states of molecules and reactive fragments are

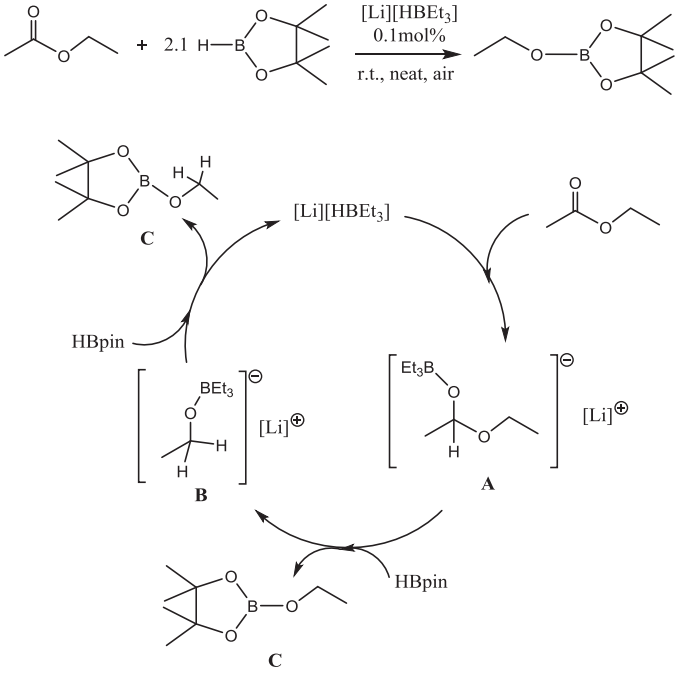


Figure 4. Proposed catalytic cycle based on DFT calculations for hydroboration of ethyl acetate.

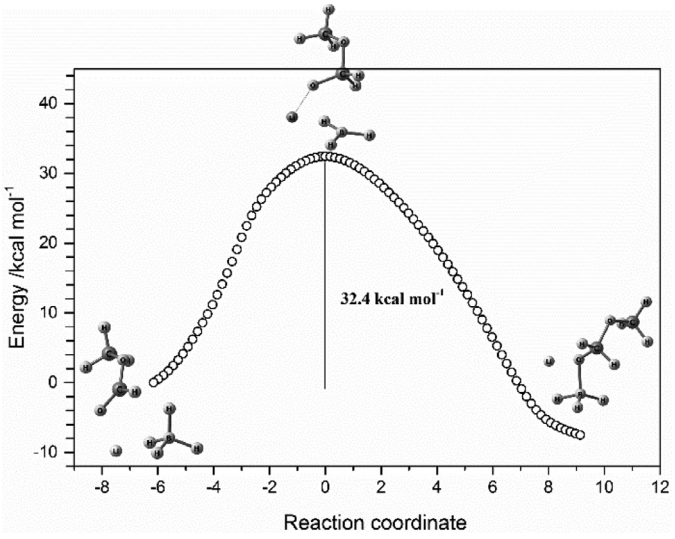


Figure 5. The potential energy surface of the reaction II for hydroboration of ethyl acetate using the QST2 method at the B3LYP/TZVP level of theory.

presented in Figure **S26**. We found the transition state structures of the reactions **II** and **IV**. The transition states connecting both the reactant and products through their intrinsic reaction coordinate (IRC) of reactions **II** and **IV** are presented in Figure 5 and Figure 6, respectively.

The hydroboration of ethyl acetate is exothermic by -53.7 kcal·mol^{-1}, in our proposed mechanism it passes through three consecutive steps. It proceeds by the abstraction of acetic H atom of $LiHBEt_3$ by the ester and simultaneously formation of a bond between O atom ester and B atom of $LiHBEt_3$ resulting in the formation of A (reaction **II**). The process can be seen from the IRC path. The TS1 has a negative vibrational frequency mode of -323 cm^{-1} through which the reaction occurs. The energy barrier of this reaction is found to be 32.4 kcal·mol^{-1}. After formation of the molecule A, it reacts with HBpin and form molecules B and

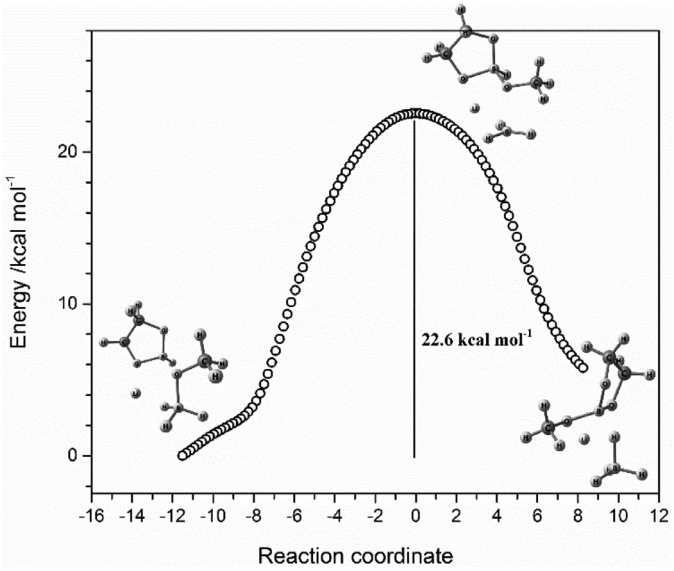


Figure 6. The potential energy surface of the reaction IV for hydroboration of ethyl acetate using the QST2 method at the B3LYP/TZVP level of theory.

C. This reaction is exothermic by -29.1 kcal·mol^{-1}. The molecule B then abstracts H atom from another molecule of HBpin from C gets back into $LiHBEt_3$ with the release of -28.4 kcal·mol^{-1} of energy. This reaction is proceeds through the TS2 transition state with energy barrier of 22.6 kcal·mol^{-1}. This calculated energy differences matches well with the already reported room temperature reaction using similar substrates.

3. Conclusions

In conclusion, we report an unusual hydroboration of esters and isocyanates under solvent-free and ambient temperature conditions by a simple and highly efficient catalyst $LiHBEt_3$. We have also performed scale-up reactions and DFT calculation on the catalytic reaction to derive a proposed catalytic cycle for the hydroboration. Compared with reported catalysts, $LiHBEt_3$ shows excellent catalytic performance. First, the reaction is rapid and clean, the yields are nearly quantitative. Second, the commercially available and eco-friendly catalyst $LiHBEt_3$ has a lower loading (0.1 mol%). Third, catalytic reactions can be carried out under solvent-free conditions and at room temperature. Last, the excellent chemoselectively for the hydroboration of isocyanates, enable us to use this catalytic reaction as a chemical tool to determine precisely the chemo-selectively of isocyanates. The present results make it clear that not only $LiHBEt_3$ is a powerful reducing agent but it can also act like a remarkable catalyst. We are continuing our active exploration in catalysis of $LiHBEt_3$.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2021.121982.

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