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Palladium catalyzed activation of borane–amine adducts: rate enhancement of amine–borane methanolysis in the reduction of nitrobenzenes to anilines

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Abstract—Hydrolytically stable borane–amines can be activated in situ through palladium catalysis and perform reductions not possible otherwise. Hence, borane–trimethylamine is an efficient hydrogen-transfer reagent for the open vessel reduction of nitroaryls to anilines. Likewise, the palladium catalyzed methanolysis/decomplexation of stable borane–amine adducts is accelerated by the action of nitrobenzene. © 2001 Elsevier Science Ltd. All rights reserved.

Borane adducts with amines are an important class of reducing agents with several applications in organic synthesis[1] and industrial processes.[2] In fact, over a dozen borane–amine complexes are commercially available[3] and some are even prepared on a tonnage scale.[4] Unlike common hydride reducing agents, borane–amine adducts are generally hydrolytically and thermally stable, soluble in both protic and aprotic solvents and most often crystalline compounds that offer safe handling convenience over the former.[5] As expected, their reactivity is somewhat diminished, and some can even be utilized in aqueous acidic solutions.[6] In consequence, their scope in organic synthesis has been limited relative to loosely bound borane–Lewis base complexes such as borane–tetrahydrofuran (BH_3–THF) and borane–dimethyl sulfide (BMS).[7] However, the activity of borane–amine adducts has been shown to increase in the presence of Bronsted[8] and Lewis acids.[9] Pyridine–borane adsorbed on solid supports exhibits enhanced reducing properties as well.[10] In hopes of finding more reactive amine–borane reagents, Brown[11] and Soderquist[12] have designed borane carriers incorporating sterically demanding tertiary amines. The less basic aniline derivatives also form weaker and hence more reactive adducts with borane.[13] However, these structural modifications make the product isolation from the resulting higher boiling free-amine more cumbersome as compared to traditional borane–amines. To further broaden the reducing capabilities of borane carriers made from volatile amines, it would be a desirable advantage to activate these otherwise stable/inert hydride sources in neutral conditions through transition metal catalysis.

In this regard, we recently disclosed that palladium and Raney nickel activate the methanolic cleavage of stable borane–amine complexes.[14] In this process, palladium hydride is a likely transient species prior to molecular hydrogen liberation. Hence, we envisioned the use of commercially available borane–amines in methanol as a novel palladium catalyzed reducing system. It is noteworthy that borane–amine adducts have recently been employed as hydride sources in palladium catalyzed systems such as epoxide openings,[15] aryl triflate reductions[16] and *N*-alloc deprotections.[17] We report herein on the palladium catalyzed reduction of nitroaryls to anilines using commercially available borane–amine complexes.

To gain better understanding of the kinetics of the palladium-catalyzed methanolysis, the reaction rate was measured by profiling the pressure of hydrogen released over time. For this purpose, commercially available borane *t*-butylamine was decomplexed in methanol using 10% Pd/C, and the corresponding plot is illustrated in Fig. 1. The linearity of rate suggests an apparent zero-order kinetic profile under these reaction conditions. This implies that the concentration of borane *t*-butylamine is not rate determining, and the

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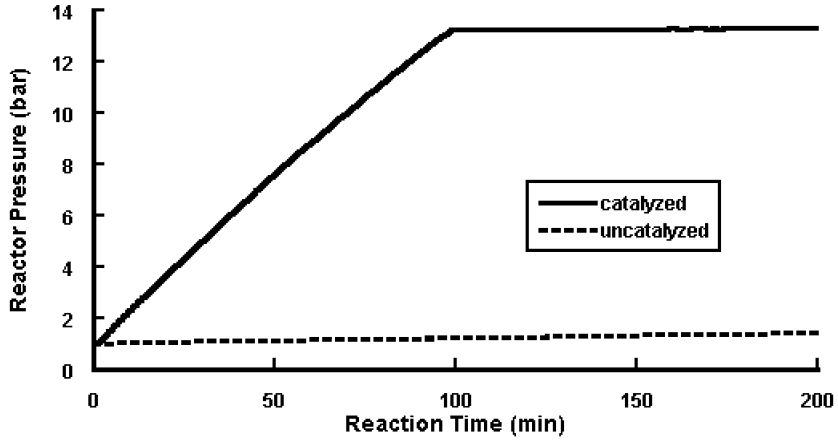


Figure 1. Pressure of hydrogen released by methanolysis of t-$BuNH_2$–BH_3 as a function of time.

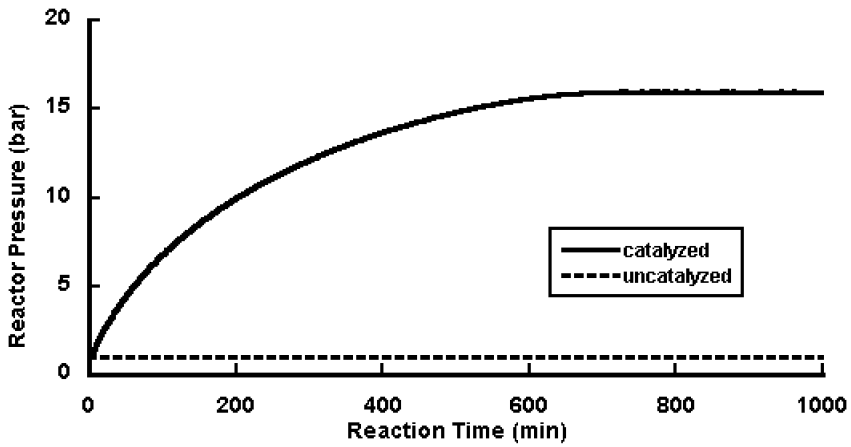


Figure 2. Pressure of hydrogen released by methanolysis of Me_3N–BH_3 as a function of time.

limiting factor would be either protonolysis and/or extrusion of hydrogen from the catalytic surface.

Based on this observation, it is conceivable that borane–amines would act as hydrogen-transfer reagents, provided that the reduction is faster than hydrogen liberation. If this requirement is met, then a reduction could be carried out in an open vessel without loss of molecular hydrogen. To further expand on the synthetic utility of borane–amines, we sought substrates that would be reduced exclusively by the catalytic action of palladium. Nitroaryls were chosen as substrates for reduction to anilines since they are known to be inert towards borane–amines alone.[8c,11b,13a,18] *Although t-butylamine-borane itself is unreactive with nitrobenzene*,[19] *the addition of less than 1 mol% of Pd/C led to an uncontrollable exothermic reaction!* In light of this high reactivity, a system with reduced reactivity would be preferable in the hope of controlling the reaction rate. Based on our previous experience,[14] borane–trimethylamine is the least reactive in palladium catalyzed methanolysis, and, as illustrated in Fig. 2, does not exhibit a first-order behavior. Indeed, under these favorable conditions, the reduction of nitrobenzene was milder and under control with a reaction time of 15 minutes. It is noteworthy that the palladium-catalyzed methanolysis takes 20 hours to complete in the absence of nitrobenzene (Table 1).[14] Hence, the palladium catalyzed decomplexation of borane–amines is further accelerated by the action of nitrobenzene, and substantiates the fact that extrusion

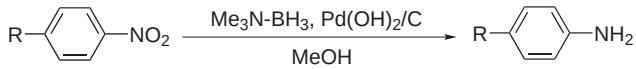
Table 1. Comparative rates of borane–trimethylamine methanolysis at room temperature with Pd/C and nitrobenzene[a]

$$Me_3N{\cdot}BH_3 \xrightarrow[MeOH]{\text{additive}} \text{amine} + B(OMe)_3$$

Entry	Additive	Time (h)
1	None	6800
2	10% Pd/C	20
3	10% Pd/C + $PhNO_2$	0.25

[a] Reaction of a 1 M solution of borane–trimethylamine in methanol using 1 mol% of Pd/C and 1.2 equiv. of nitrobenzene at rt.

Table 2. Palladium catalyzed reduction of nitroaromatics using trimethylamine–borane in methanol



1 **2**

Entry	**1**,**2** a–x	R =	Temperature	Time (h)	Yield (%)[a]
1	a	H	Rt	6.0	90
2	b	CH_3	Rt	22.0	95
3	b	CH_3	Reflux	0.5	95
4	c	CO_2Me	Rt	0.7	>99
5	d	CN	Reflux	1.5	>99
6	e	CH_2CN	Reflux	0.7	>99
7	f	CH_2OH	Reflux	2.0	94
8	g	OH	Reflux	0.2	98
9	h	OCH_3	Reflux	0.7	98
10	i	NHAc	Reflux	3.5	99
11	j	F	Rt	12	99

[a] Isolated yields.

of hydrogen from the surface of the catalyst is slower than the actual nitro reduction. Chemoselective reduction of nitroaryls to the corresponding anilines is of importance in synthetic organic chemistry. Methods are numerous[20] and commonly utilized procedures, which do not require molecular hydrogen, include tin chloride,[21] formic acid[22] or triethylammonium formate–palladium[23] and cyclohexene–palladium.[24] Several recent methods have also been reported using formic acid–Raney nickel under sonication,[25] samarium–ammonium chloride,[26] decaborane–acetic acid–palladium in methanol,[27] zirconium chloride–sodium borohydride,[28] electrochemically generated nickel in DMF,[29] samarium–iodine,[30] diethyl chlorophosphite,[31] and indium–ammonium chloride in ethanol.[32] Each procedure has its own advantages and disadvantages. In general, their main drawbacks are lack of chemoselectivity, extended reaction times, functional group incompatibility and complicated work-up procedures. After our successful reduction of nitrobenzene to aniline, we wanted to explore the scope and limitations of the present procedure.

In this exercise, we challenged the generality of this concept by reducing a wide variety of functionalized nitrobenzenes. As illustrated in Table 2, the atmospheric pressure reductions were performed using 1.2 hydride equivalents and 1 mol% of Pearlman's catalyst.[33] In some cases, the substrates were insoluble in methanol, which slowed the reduction time. However, we found that the reaction rate is increased when the reductions are performed at reflux, without concomitant loss of hydrogen. Upon reaction completion, the excess borane–amine reagent is simply consumed by methanolysis. The present procedure has been found to be tolerant of benzylic functionalities and performs equally well for both electron-donating and electron-withdrawing groups with isolated yields >90%. A limitation is found with aryl chlorides which were also reduced in the process. Not unexpectedly, however, aryl fluoride **2j** was resistant to reduction.

Besides producing anilines in high yield, the present method favorably compares to alternate means to reduce nitroaryls in terms of its operationally simple work-up procedure. In fact, in this salt-free, non-aqueous process, the resulting aniline can be isolated from the trimethylamine and trimethylborate by-products by simple concentration.[34] This is in sharp contrast, for example, with the sodium borohydride–Pd/C procedure which requires acidification with aqueous HCl and a series of extractions to isolate the amine.

In conclusion, we have demonstrated that stable borane–amine adducts can be activated through palladium catalysis and act as hydrogen-transfer reagents for the reduction of nitrobenzenes to anilines. The present procedure is high yielding and compatible with various functional groups. More importantly, the safety and handling convenience of borane–amines coupled with an operationally simple and straightforward work-up makes it an attractive procedure. We are currently investigating the synthetic utility of a tandem borane mediated reduction–methanolysis–hydrogenation sequence, a concept which will be exemplified in a forthcoming manuscript.

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33. **General procedure.** To a stirred solution/suspension of nitroaryl (10.0 mmol) and borane–trimethylamine (12.0 mmol) in methanol (20.0 mL) was added Pearlman's catalyst (44 mg, 50% wet, 2.5 dry weight%) and the resulting mixture was heated to reflux. Upon complete consumption of borane–trimethylamine, the solution was cooled, filtered over a pad of Celite and concentrated under vacuum to give the crude aniline, which was further purified by flash chromatography.
34. Boiling point of $MeOH/B(OMe)_3$ azeotrope: 59°C (70% of $B(OMe)_3$ in the azeotropic mixture.