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Palladium and Raney Nickel Catalyzed Methanolic Cleavage of Stable Borane–Amine Complexes

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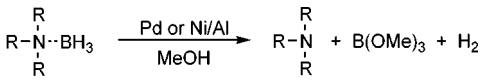
ABSTRACT



R = H, alkyl, aromatic

Palladium and Raney nickel were found to catalyze the methanolysis of borane–amine adducts. Hence, strongly complexed amines can now be liberated by simple treatment with Pd/C or Raney Ni in methanol. The method is applicable to primary, secondary, tertiary, and aromatic amines, and the mildness of the reaction conditions allows preservation of otherwise labile functional groups.

Borane−amine adducts are widely encountered in modern synthetic organic chemistry[1] and industrial processes.[2] Notable examples of their applications include aqueous reductions of aldehydes and ketones,[3] reductive aminations,[4] olefin hydroborations,[5] and amide reductions.[5b,c] Recently, borane−amine adducts were employed in palladium-catalyzed systems such as epoxide openings,[6] aryl triflate reductions,[7] and *N*-alloc deprotections.[8] Complexes of amine−boranes have also been utilized as chiral transfer agents,[9] as activators for α-deprotonation of benzylamines,[10] and as a protective device against nitrogen lone pair oxidation.[11]

Usually, borane−amine complexes are readily formed by reduction of amides, imides, and imines or by treatment of the corresponding amine with diborane or borane carriers such as THF,[12] DMS,[13] and amines.[5,14] Tertiary amine−boranes have also been prepared from benzyl halides and lithium aminoborane (LAB) reagents.[15] An attractive feature of these complexes is they are usually air-stable, crystalline compounds, and therefore are easily handled.[16] A limitation is they can be difficult to cleave (vide infra).

In the course of developing a drug candidate, we required

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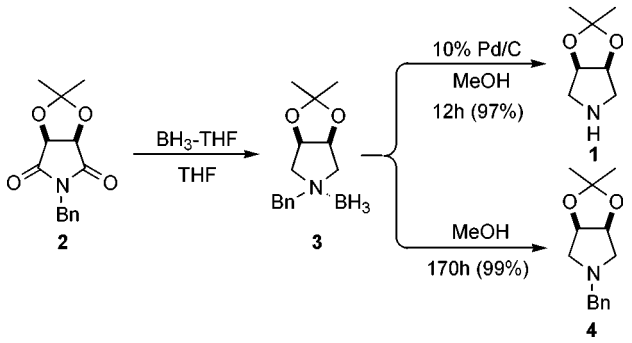
an efficient, large-scale synthesis of pyrrolidine **1** from readily available *N*-benzymaleimide. For this purpose, borane reduction of imide **2** using commercial BH_3−THF led to the stable borane−amine adduct **3** (Scheme 1). It is noteworthy

Scheme 1. Tandem Methanolysis−Hydrogenolysis of a Borane−Benzylamine Adduct



that the latter is a crystalline material and provides a purification handle otherwise not possible with the known liquid free-amine **4**.[17]

At this stage, we envisioned an atom economical use of the borane adduct as an internal hydrogen transfer reagent for the impending hydrogenolysis of the *N*-benzyl protective group. Indeed, treatment of the amine−borane adduct in methanol with 10% palladium on carbon led to the desired debenzylated pyrrolidine **1** in 97% yield. More importantly, the reaction took place in only 12 h, whereas the sole decomplexation in methanol in the absence of palladium required over 170 h. This observation suggests that the palladium not only affected the hydrogenolysis of the *N*-benzyl moiety but also catalyzed the decomplexation of the borane−amine adduct.[18]

The discovery of catalysis by palladium is significant since the aforementioned, widely encountered amine−borane adducts are usually stable. Their cleavage often requires harsh reaction conditions, most commonly performed by refluxing in aqueous HCl.[3,4b,c,12,13a] In fact, such forcing conditions have been shown recently to promote side reactions which significantly depress the quality and physical yield of product on an industrial scale.[19] Other methods involve treatment with BF_3−OEt_2[4c,13a] and extended reflux in aqueous trifluoroacetic acid,[20] methanolic HCl,[15,21] methanolic Na_2CO_3,[22] and ethanol.[23] Acidic workup procedures are further complicated by the need to basify in order to release the free amine. Dissociations are also accomplished through ligand exchange with a better complexing amine such as TMEDA[13a] and usually require extended reaction times at higher temperature than ambient.[24] Hall recently reported a method applicable to both solution- and solid-phase synthesis using molecular iodine in acetic acid and methanol.[25] On the basis of our success in the palladium-catalyzed cleavage of the amine−borane complex **3**, we decided to study the generality of our method as a mild, nonaqueous, and neutral decomplexation procedure.

To gain insight into the scope and limitations of this procedure, the decomplexation rates of several commercial borane−amine adducts were compared in the presence and absence of 10% palladium on carbon. As shown in Table 1,

Table 1. Reaction Times for Complete Methanolysis of Borane−Amine Adducts at Room Temperature with Pd/C and Raney Ni[a]

amine··BH_3 $\xrightarrow[\text{MeOH}]{\text{catalyst}}$ amine + $B(OMe)_3$ + H_2

amine-borane	time (h)			
	uncatalyzed[c]	1M HCl[d]	10% Pd/C[c,e]	Raney Ni[c,f]
ammonia	(24)[b]	0.01	0.2	5.5
methylamine	(7.2)[b]	0.01	0.2	2.0
t-butylamine	(8.5)[b]	0.01	0.2	4.0
dimethylamine	unreactive	8.0	0.1	3.0
morpholine	(7.6)[b]	72	0.1	2.0
trimethylamine	(21)[b]	(99)[b]	20.0	140.0
triethylamine	(76)[b]	200	16.0	6.0
diisopropyethylamine	30	45	5.5	3.5
4-methylmorpholine	290	(94)[b]	23.0	62.0
4-ethylmorpholine	160	1400	8.0	4.5
pyridine	1200	35	0.2	260.0
2,6-lutidine	55	60	0.1	18.0

[a] All reactions were performed at room temperature and monitored by ^{1}H NMR and iodometric titration. [b] Percentage of hydride consumed after 60 days, based on iodometric titration. [c] 1 M solution in MeOH. [d] 0.4 M solution in 1:1 MeOH/1 M aqueous HCl. [e] 1 mol % of 10% Pd/C. [f] 5 mol % of Raney nickel.

the decomplexation rates are greatly increased by the action of palladium. In fact, the method is generally applicable to ammonia and primary, secondary, tertiary, and aromatic amine−borane adducts, all of which were cleaved within a day using 1 mol % of 10% Pd/C. Whereas secondary amine−boranes were relatively unreactive with methanol, *reactions in the presence of Pd were highly exothermic and led to rapid hydrogen evolution. Care should, therefore, be exercised in*

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(18) It is noteworthy that a similar observation was made during a chemical electroplating process producing nickel− and cobalt−boron alloy plates using amine−boranes as reducing agents: Berzins, T. U.S. Patent 3 338 726, 1967; *Chem. Abstr.* **1967**, *67*, 119784g.
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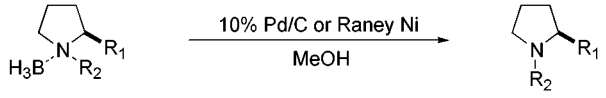
undertaking such decomplexations. Even the rather acid stable trimethylamine borane was cleaved in 20 h, reaction conditions which favorably compare to 21% conversion after 60 days in 1 M aqueous HCl.

Raney Ni was also found to catalyze the methanolysis of amine−borane adducts. With the exception of trimethylamine and pyridine, all the amine−boranes tested were cleaved in a matter of hours using 5 mol % of catalyst. Compared to palladium, Raney Ni offered a slower, more controlled rate of methanolisis for primary, secondary, and aromatic amines.

We also sought a trend in the relative rates of decomplexation. It is well documented[26] that the steric bulk and the basicity of the amine influence the strength of the amine−borane bond. Although the uncatalyzed system does show these trends, no such parallel exists for the catalyzed versions. This could be attributed to the ligating properties of the resulting free-amine on the metal, thereby reducing the activity of the catalyst.

Table 2. Decomplexation of Functionalized Amine−Boranes



5a-d	R_1 =	R_2 =	yield (%)[a] Pd	yield (%)[a] Ni/Al	**6**a-d
a	CO_2t-Bu	H	97	96	a
b	H	CH_2CH_2OTHP	84	95	b
c	CH_2OTBS	H	94	96	c
d	CH_2OTBS	Bn	45[b]	96[b]	d
e	CH_2OMOM	Bn	52[b]	95[b]	e

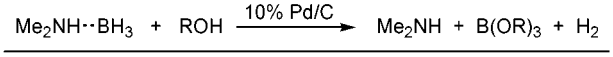
[a] Isolated yields. [b] Decomplexation performed in the presence of 1-hexene as hydrogen scavenger.

Aside from the rate acceleration in decomplexation, the present procedure is simple and highly practical compared to the alternative known methods. The palladium-catalyzed methanolysis produces trimethylborate and hydrogen, which evolves directly from the reaction as a byproduct. Although amines are known to form "onium" tetramethylborate salts in the presence of the trimethylborate and methanol,[27] the amine can be released from "ate" complex by simple evaporation of the methanol−trimethylborate azeotrope.[28]

To illustrate the mildness of the present method, the borane−amine complexes[29] **5a**−**d** bearing acid sensitive protective devices such as OTHP, OMOM, OTBS, and *tert*-butyl ester were cleaved with methanol in the presence of 10% Pd/C or Raney Ni (Table 2).[30] Both catalysts worked well for secondary amines (**5a**−**c**) whereas Raney Ni was superior in the tertiary series (**5d**,**e**). It is noteworthy that *N*-benzyl groups of pyrrolidines **5d**,**e** remained intact when the decomplexation was performed in the presence of 1-hexene as hydrogen scavenger, thereby broadening the scope of this method.[31] Overall, Raney nickel offered the best reaction profiles with excellent yields and exhibited compatibility with all the acid labile functional groups tested.

The effect of the protic source was also investigated in the palladium-catalyzed alcoholysis of dimethylamine−borane (Table 3). Not unexpectedly, the decomplexation rates

Table 3. Reaction Times[a] for Decomplexations of Dimethylamine−Borane Using 10% Pd/C in Various Protic Solvents



entry	R =	time (min)
1	H	25
2	Me	5
3	Et	6
4	n-Pr	7
5	i-Pr	13
6	t-Bu	190

[a] Indicated times relate to decomplexation, and alkoxyborohydrides intermediates may still be present.

decreased with an increase in the steric bulk of the alcohol, albeit not to an appreciable extent in the primary alcohol series. However, for practical purposes, methanol was deemed the protic source of choice since it offers the most volatile borate, which can be easily removed by evaporation.

In conclusion, we have discovered a mild decomplexation procedure for borane−amine adducts which is neutral, rapid, and operationally simple. Additionally, this method is compatible with acid labile protective groups such as acetonides, OMOM, OTHP, OTBS, and *t*-Bu esters. The palladium-catalyzed methanolysis of borane−amines should find wide use in academic and industrial processes and may lead to future applications of the latter class of reducing agents.

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Supporting Information Available: Experimental details for the synthesis of compounds **1**, **3**, **4**, **5a**−**e**, **6b**, and **6c** with corresponding ^1H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Prerared from corresponding amide reduction and/or amine complexation with borane−THF.

(30) **General Procedure.** To a magnetically stirred solution of borane−amine complex (5.0 mmol) and, optionally, 1-hexene (25.0 mmol) in methanol (10 mL) was added Raney nickel (5.0 mol %) or 10% palladium on charcoal (1.0 mol %). Upon completion, the reaction mixture was filtered over a small pad of Celite and the latter was rinsed with methanol (5.0 mL). The concentrated residue was purified by "flash" silica chromatography to yield the desired amine.

(31) Olefins and alkynes containing substrates might be prone to hydrogenation under these reaction conditions.