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Hydrophobically directed selective reduction of ketones using amine boranes

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Abstract—Amine boranes bearing hydrophobic substituents were used to reduce aryl ketones in competition with a methyl ketone. Their high stability in protic solvents combined with their ease of preparation made amine boranes useful compounds in the study of hydrophobically directed selective reductions. Several characteristics of the reducing agent were found to be important in determining the reaction selectivity, including available hydrocarbon surface area, degree of fluorination, and proximity of the hydrophobic group to the active hydrides.

The hydrophobic effect is the tendency for nonpolar species to aggregate in water so as to minimize the interfacial hydrocarbon–water area.[1–3] We have previously shown that addition reactions involving hydrophobic species, such as the Diels–Alder reaction[4,5] and the benzoin condensation[6] are greatly accelerated when carried out in water due to the packing of hydrocarbon surfaces in the transition state. This principle was further developed as a tool for elucidating the geometries of transition states by determining the extent to which phenyl rings and other hydrophobic surfaces overlap.[7–9]

Although our studies principally involved solutions of the reagents in water, we also saw that the Diels–Alder reaction was promoted even when a simple suspension of reagents in water was used.[1,5] As we pointed out, this effect of water even with poorly soluble substrates made the systems particularly attractive for selective synthesis.

Recently, we have expanded the scope of hydrophobically accelerated reactions to include atom transfer reactions such as hydride reductions.[10] While the magnitude of the rate accelerations in addition reactions in water was dictated by the intrinsic hydrophobicity of the reactants, external reagents bearing substituents of varying hydrophobicity can be used in atom transfer reactions to modulate the rate accelerations. Using $LiC_6F_5BH_3$ in 4 M LiCl (aq), we were able to achieve a 40-fold selective acceleration of the reduction of a naphthoyl group in competition with an acetyl group, compared with the same reaction using $LiBH_4$ in methanol. We also established a trend of increasing selectivity with increasing hydrophobicity of the reducing agent. Our further studies showed that the greatest selective rate accelerations for hydride reductions could be achieved for substrates in which the keto group is locked in a coplanar relationship with the attached hydrophobic aryl group, thus maximizing the potential for hydrophobic packing (structure **A**).[11] In this work, we also showed that we could reverse the normal selectivity of reduction of a steroid 6,17 dione—in which the 17 keto group is normally more reactive for energetic reasons—by using hydrophobic borohydrides in water solution.

All of our previous works in hydrophobically accelerated reductions have involved substituted lithium borohydrides. Although they have demonstrated a remarkable propensity for selective reduction, the lithium arylborohydrides studied often had limited stability in protic solvents, requiring the use of high pH's or excess quantities of the reagent. This susceptibility to solvolysis combined with the limited means for synthesizing substituted

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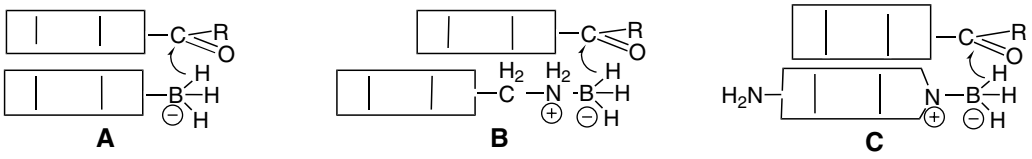
lithium borohydrides contributed to a restricted selection of reagents that could be studied.

We thus undertook the synthesis and use of amine boranes as alternative reducing agents for the hydrophobically directed reduction of ketones. In addition to their ease of preparation, amine borane complexes derived from amines with a pK_a above 5.5 have been generally shown to be stable in protic solvents.[12] We have found them to be useful reagents for investigating the effect of variations in the hydrophobic substituents of the reducing agent on the resulting selectivity.

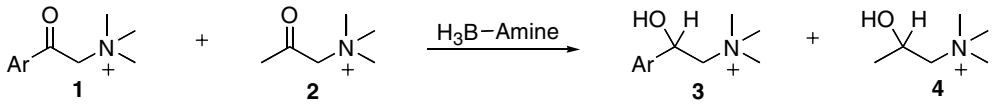


All of the amine boranes used in this study were synthesized in quantitative yield by reaction of the corresponding amine or ammonium chloride salt with BH_3–THF or $LiBH_4$, respectively. The remarkable stability of the amine boranes made them amenable to purification by column chromatography (SiO_2) and capable of being stored in the air at room temperature.

In order to evaluate the ability of a variety of amine boranes to selectively reduce carbonyls with adjacent hydrophobic groups, water-soluble substrates containing aryl ketones (**1a**,**b**) were reacted to 5% conversion in competition with equimolar concentrations of methyl ketone substrate **2** (Table 1). The nonhydrophobic reducing agent, ammonia borane, showed very little selectivity in both methanol and in water, giving product ratios (**3**:**4**) of approximately 50:50. Furthermore, no change in the selectivity was observed as a result of salting out **1a** using 4 M NaCl.

By contrast, benzylamine borane, bearing a hydrophobic phenyl ring, showed enhanced selectivity for the

Table 1. Ratios of products (3:4) formed in the competition reactions of quaternized β-ketoamines with amine boranes[a,b,c]



1a: Ar = Phenyl
1b: Ar = 2-Naphthyl

Amine	Substrate **1**	D_2O	4 M NaCl/D_2O	CD_3OD
Ammonia	**1a**	53:47 (−0.07)	53:47 (−0.07)	39:62 (+0.26)
	1b	59:41 (−0.22)	59:41 (−0.22)	43:57 (+0.17)
Benzylamine	**1a**	56:44 (−0.14)	61:39 (−0.26)	45:55 (+0.12)
	1b	64:36 (−0.34)	68:32 (−0.45)	48:52 (+0.05)
Dibenzylamine	**1a**	65:35 (−0.37)	—[d]	47:53 (+0.07)
	1b	69:31 (−0.47)	—[d]	53:47 (−0.07)
1-Aminoindan	**1a**	59:41 (−0.22)	64:34 (−0.34)	43:57 (+0.17)
	1b	65:35 (−0.37)	70:30 (−0.50)	49:51 (+0.02)
1-Naphthylmethylamine	**1a**	58:42 (−0.19)	67:33 (−0.42)	41:59 (+0.22)
	1b	66:34 (−0.39)	82:18 (−0.90)	45:55 (+0.12)
2-Naphthylmethylamine	**1a**	64:36 (−0.34)	67:33 (−0.42)	43:57 (+0.17)
	1b	75:25 (−0.65)	81:19 (−0.86)	41:59 (+0.22)
4-Fluorobenzylamine	**1a**	59:41 (−0.22)	62:38 (−0.29)	47:53 (+0.07)
	1b	67:33 (−0.42)	70:30 (−0.50)	50:50 (+0.00)
3,5-Difluorobenzylamine	**1a**	62:38 (−0.29)	66:34 (−0.39)	44:56 (+0.14)
	1b	69:31 (−0.47)	72:28 (−0.56)	50:50 (+0.00)
3,4,5-Trifluorobenzylamine	**1a**	60:40 (−0.24)	67:33 (−0.42)	44:56 (+0.14)
	1b	64:36 (−0.34)	73:27 (−0.59)	49:51 (+0.02)
2,3,5,6-Tetrafluorobenzylamine	**1a**	60:40 (−0.24)	69:31 (−0.47)	46:54 (+0.09)
	1b	71:29 (−0.53)	74:26 (−0.62)	48:52 (+0.05)
Pentafluorobenzylamine	**1a**	64:36 (−0.34)	68:32 (−0.45)	46:54 (+0.09)
	1b	71:29 (−0.53)	78:22 (−0.75)	51:49 (−0.02)
4-Aminopyridine	**1a**	72:28 (−0.56)	76:24 (−0.68)	46:54 (+0.09)
	1b	89:11 (−1.24)	85:15 (−1.03)	55:45 (−0.12)
9-Aminoacridine	**1a**	75:25 (−0.65)	74:26 (−0.62)	44:56 (+0.14)
	1b	85:15 (−1.03)	79:21 (−0.78)	55:45 (−0.12)

[a] All reactions were carried to ca. 5% conversion with substrate concentrations of 5.0 mM.
[b] Reported ratios are within an error of ±1% in at least duplicate runs.
[c] $\Delta\Delta G^{\ddagger}$ (kcal/mol) for each reaction is in parentheses.
[d] Dibenzylamine borane was not sufficiently soluble in 4 M NaCl/D_2O to observe a reaction.

reduction of aryl ketones (cf. structure **B**), and greater selective rate accelerations were observed for reduction of the more hydrophobic 2-naphthoyl group, **1b**, as compared to the benzoyl group, **1a**. Salting out resulted in a further increase in selectivity, which implicates the hydrophobic effect in the observed product ratios.

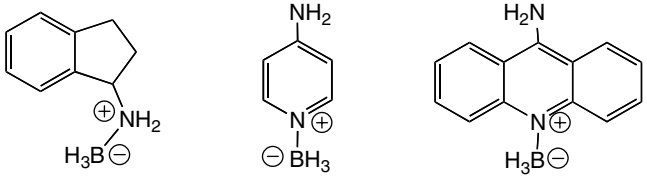
In an attempt to improve the selectivity of ketone reduction, amine boranes bearing groups of greater hydrophobic surface area were synthesized. Indeed, both 1-naphthylmethylamine borane and 2-naphthylmethylamine borane proved to be more selective for hydrophobic substrates than benzylamine borane. The available area for hydrophobic packing was also increased by incorporating an additional hydrophobic aryl group in the reducing agent; greater selectivity was observed for dibenzylamine borane than for benzylamine borane. The trends in selectivity observed using various amine boranes were thus consistent with those we had previously obtained using analogous lithium aryl borohydrides, suggesting that the ability to exploit hydrophobic packing in order to achieve the selective reduction of aryl ketones was a general one, not restricted to the particular class of substituted lithium borohydride reducing agents.

Previously, the greatest selectivities for reduction of hydrophobic ketones were obtained using $LiC_6F_5BH_3$, which benefits from increased hydrophobicity as a result of fluorination as well as the possibility for favorable quadrupolar interaction with nonfluorinated aryl rings. Building on this observation, we synthesized a series of fluorinated benzylamine boranes in order to assess the effect of varying numbers of fluorine substituents on the reaction selectivity. We found that as the number of fluorine atoms on benzylamine borane was increased, there was a corresponding trend of increasing selectivity for reactions conducted under solvent conditions suitable for hydrophobic packing. Pentafluorobenzylamine borane proved to be the most selective reducing agent in the fluorinated series.

Nevertheless, the selectivity exhibited by pentafluorobenzylamine borane fell short of that previously obtained using the analogous $LiC_6F_5BH_3$, which gave a product ratio of 95:5 for reduction of 2-naphthoyl substrate **1b** in competition with the acetyl substrate **2** in 4 M LiCl (aq).[5] We believe that the lower selectivities obtained with pentafluorobenzylamine borane were in part due to the greater distance between the hydrophobic group and the hydrides being delivered as well as to the entropic cost of additional rotational degrees of freedom intrinsic to the amine boranes (structure **B**); both of these factors may contribute to the decreased ability of the amine boranes to achieve hydrophobic packing with the ketone substrates in the transition state of the reaction.

The importance of minimizing rotational freedom is effectively demonstrated by the higher selectivity of 1-aminoindan borane **5** compared with benzylamine borane. Although the number of atoms between the phenyl ring and the reactive hydrides are the same in both reducing agents, the cyclic structure of 1-aminoindan effectively freezes the orientation of the phenyl ring relative to the boron atom. We have previously shown that saturated carbons such as those found in the framework of 1-aminoindan are not suitable for packing with aryl rings and are thus not expected to contribute to the observed selectivity.

Finally, 4-aminopyridine borane **6** and 9-aminoacridine borane **7** were studied in order to determine the effect of the proximity of the hydrophobic aryl ring and the active hydrides on the resulting selectivities (structure **C**). 4-Aminopyridine indeed proved to be more selective than benzylamine borane, presumably because the geometry permits greater hydrophobic overlap (cf. structure **C** with structure **B**). In fact, **6** exhibited significantly greater selectivity than the analogous $LiPhBH_3$,[5] suggesting additional contributions to the observed rate acceleration. These contributions almost certainly include cation–π interactions between the positively charged nitrogen of pyridine ring and the aryl ring of the ketone substrate. Such interactions may also account for the slight decrease in selectivity observed under the salting-out condition, which is expected to decrease the strength of cation–π interactions by increasing the dielectric constant of the medium. Steric effects appear to contribute to the lower selectivities for the reduction of the naphthyl ketone using 9-aminoacridine. The large selectivity decreases observed for reactions in methanol nevertheless underscore the importance of the hydrophobic effect in the selectivity of the reductions. The selective hydrophobic rate accelerations observed for 4-aminopyridine borane **6** are the highest we have been able to achieve using a single aryl ring substituent without fluorination.



5 **6** **7**

We have thus demonstrated that amine boranes are capable of being used as selective reagents for the reduction of aryl ketones under conditions favorable for hydrophobic packing. As with substituted lithium borohydrides, a direct relationship was established between the hydrophobicity of the amine borane and the selectivity of the reaction. The highest selectivities were obtained for amine boranes in which the hydrophobic aryl substituents were in close proximity to the hydrides being delivered. However, amine boranes, convenient as they are, have not yet shown hydrophobically directed selectivities as high as those we have achieved previously with our best aryl borohydrides.

The substrate selectivities we report here will also be translated into positional selectivities with appropriate diketones, as we have demonstrated with aryl borohydrides and steroidal diketones.[11] Perhaps more

important, the well-defined transition states in these hydrophobically packed reduction processes should be translatable into enantioselectivity with appropriate chiral amines. We have already seen some modest effects of this type; our exploration of such enantioselective reductions will be published in due course.

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