Pergamon

Tetrahedron Letters, Vol. 38, No. 6, pp. 957-960, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02489-6

Rate Enhancing Effect of Hydrogen Chloride and Methanesulfonic Acid on the Intramolecular Asymmetric Reduction of *o*-Aminoaceto- and -benzophenones with Diisopinocampheylborane[1]

P. Veeraraghavan Ramachandran, Sanjay V. Malhotra[2], and Herbert C. Brown*

H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907-1393

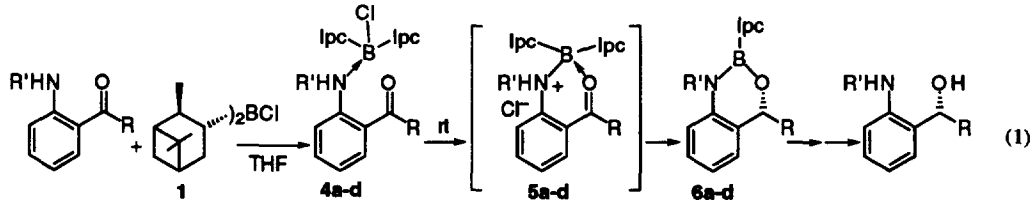
Abstract: While *o*-hydroxyaceto- and -benzophenones undergo reduction with *B*-chlorodiisopinocampheylborane (**1**) and diisopinocampheylborane (**2**) at the same rate, the reduction of *o*-carboxyaceto- and -benzophenones is faster with **2** as compared with **1**. The rate retardation for the reaction of keto acids with **1** was accounted by a competition between an intra- and intermolecular reduction. In contrast, *o*-aminoaceto- and -benzophenone undergo faster reduction with **1** than with **2**. The rate enhancing influence of HCl and $MeSO_3H$ on the intramolecular asymmetric reduction of these amino ketones with **2** has been tested and confirmed.

Our research on asymmetric reductions[3] led to *B*-chlorodiisopinocampheylborane[4] (Ipc_2BCl, DIP-Chloride™, **1**) as an efficient reagent for the reduction of prochiral aralkyl, α-hindered, and α-perfluoroalkyl ketones.[5] While carrying out a study of the compatibility of **1** with various functional groups in the *ortho*, *meta*, and *para* positions of acetophenone, we noted that an *o*-hydroxy group in acetophenone leads to an intramolecular reduction, providing product alcohol of opposite configuration as compared to the product from the reduction of acetophenone itself, or the *o*-methoxy analog.[6,7] Due to the intramolecular nature of this reaction diisopinocampheylborane (Ipc_2BH, **2**)[8] also could be used for the reduction without any difference in the rate of the reaction or the % ee of the product alcohol.[6]

The reaction of *o*-carboxyacetophenone with **1** or **2** also led to the product alcohol of the opposite configuration, as compared to that of the corresponding ester.[9] This observation was exploited for the synthesis of both enantiomers of the biologically important 3-substituted phthalides.[9] However, unlike the case of the *o*-acetylphenols, one molar equiv of HCl liberated from the reaction of *o*-acetylbenzoic acids with **1** exists in equilibrium with the benzoic acids. This results in a retarded reaction rate with competition between intra- and intermolecular reduction, and a lower % ee for the product hydroxy acids. This complication is avoided by using **2** for the reaction.

We observed certain unique features in the reaction of *o*-aminoacetophenones as well. In sharp contrast to the reaction of the *o*-carboxyacetophenones, the reaction of *o*-aminoacetophenone is much faster with **1** than with **2**. Indeed, the presence of HCl in the reaction medium strongly enhances the reduction rate. In this *Letter* we describe some fascinating observations made in the reduction of *o*-aminoaceto- and -benzophenones with **1** and **2**.

The reaction of *o*-aminoacetophenone (**3a**) with **1** in THF, at room temperature (rt) is complete within 30 min (^{11}B NMR δ 32 ppm). The ^{11}B NMR spectrum of an aliquot of the reaction mixture immediately after mixing the substrate with **1** showed two peaks, a major peak (≥95%) at δ 32 ppm and a minor one (≤5%) at δ 9 ppm. The δ 9 peak disappeared in 30 min when the reaction is complete. Alkaline H_2O_2 oxidation provided 86% of the product amino alcohol. Gas chromatographic analysis of the MTPA ester revealed 97% ee (eq 1).

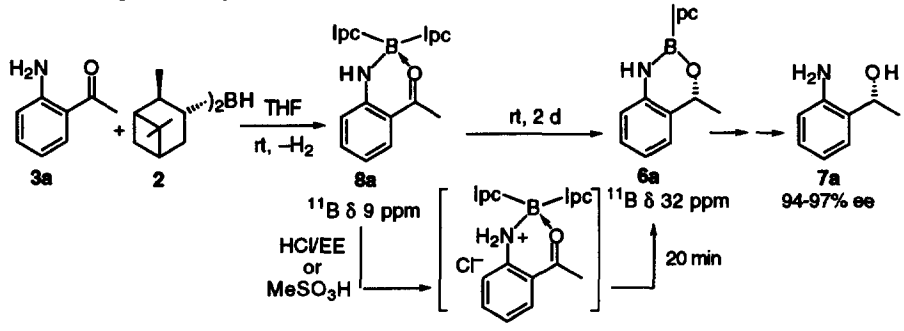


(1)

3a R = Me, R' = H
3b R = Ph, R' = H
3c R =R' = Me
3d R = Ph, R' = Me

7a R = Me, R' = H, 97% ee
7b R = Ph, R' = H, 70% ee
7c R = R' = Me, 69% ee
7d R = Ph, R' = Me, 64% ee

In contrast, the reaction of **3a** with **2** in THF at rt liberated one molar equiv of H_2 within 1 h and formed a violet intermediate **8a**. The ^{11}B NMR spectrum showed a peak at δ 9 ppm suggesting a coordination between the lone pair of the carbonyl oxygen and the boron atom. This intermediate underwent a slow reduction to oxazaborole **6a** in 48 h, which upon oxidation with alkaline H_2O_2, followed by the usual workup, provided the product amino alcohol of the same configuration in 85% yield and 94% ee (eq 2). The "pseudoaromatic" oxazaborole, which is stable to air and moisture, was isolated and characterized using ^1H NMR and mass spectrometry.



(2)

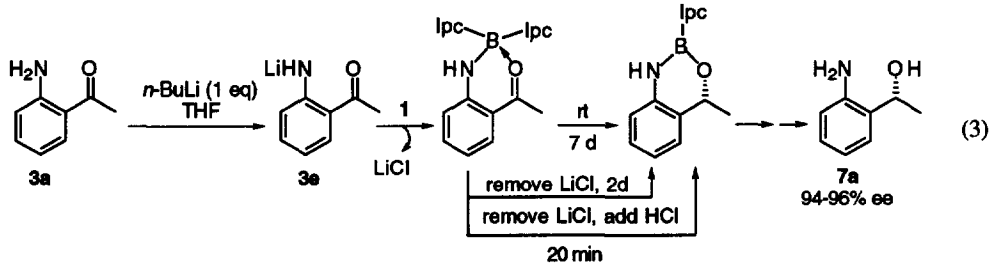
We believe that **1** forms an initial complex with the nitrogen atom of **3a**, followed by ionization of chloride to form the HCl salt of the intermediate (**5a**). The loss of the lone pair on the nitrogen for salt formation probably makes the boron atom more Lewis acidic, thereby facilitating the reduction. Similar reactions of dialkylhaloboranes with amines are known in the literature.[10] We carried out a blank reaction of aniline with **1** and **2**. We observed that in both cases we obtained the same intermediate, as shown by the ^{11}B NMR spectral peak at δ 48 ppm. However, while the reaction of aniline with **1** forms a solid HCl salt, the reaction mixture with **2** is a clear solution. Treatment of N-lithioaniline with **1** in THF provided a clear solution and the same intermediate (^{11}B NMR δ 48 ppm). Consequently, we believe that the initial reaction of **3a** with **1** and **2** is the formation of the B–N bond. The peak in the ^{11}B NMR spectrum, expected to be at δ 48 ppm is shifted upfield to δ 9 due to the formation of a six-membered chelate. Salt formation with HCl, in the reaction with **1**, facilitates the hydride transfer reaction so it takes place within 20 min. In the absence of HCl, it requires 48 h for completion of the reaction.

This interpretation was examined by the addition of one equiv of HCl in EE to the intermediate **8a** from the reaction of **3a** with **2**. Indeed, the reaction was complete in 20 min (eq 2)! Oxidation provided the product amino alcohol in 84% yield and 95% ee.

We observed that the rate enhancement is significant only with a stoichiometric amount of HCl. Addition of 10 and 20 mol% of HCl did not show any significant increase in the rate. Addition of 40 mol% of HCl altered the rate from 48 h to 22 h for completion. These results are in agreement with our interpretation.

A similar rate enhancement was observed for the addition of one equiv of methanesulfonic acid to the intermediate **8** from the reaction of **3a** and **2**, with completion of reaction in 20 min. Oxidation provided the product amino alcohol in 81% yield and 97% ee. Consequently, it appears that other strong acids would be also effective.

The effect of HCl was also demonstrated by avoiding the formation of HCl. This was achieved by conducting the reaction of **1** with *N*-lithio-*o*-aminoacetophenone (**3e**), prepared by treating **3a** with *n*-butyllithium. The ^{11}B NMR spectrum revealed the expected peak at δ 9 ppm and the intermediate underwent slow reaction, within 7 d. The presence of LiCl in the reaction mixture apparently retards the rate, possibly by the formation of a tetra-coordinated boron. Removal of LiCl from the medium by transferring the intermediate by a cannula to another flask enhances the reaction rate, so it goes to completion within 2 d. In this case also, the reaction rate was strongly enhanced by the addition of one equiv of HCl (eq 3).



(3)

All of these observations were also applicable to the reduction of *o*-aminobenzophenones. Thus, the reaction of **3b** with **1** was essentially complete in 5 h, whereas the reaction of **3b** with **2** required 24 h for completion.[11, 12] Addition of HCl to the intermediate **8b** from the reaction of **3b** and **2** enhances the rate. The product alcohol was obtained in 80-82% yield and 65-70% ee.

Table. Intramolecular Asymmetric Reduction of *o*-Aminoaceto- and -benzophenones, *o*-NHR'PhCOR, with (–)-Ipc$_2$BX in THF at RT

o-NHR'PhCOR			Ipc$_2$BX	reactn	product amino alcohol		
	R	R'	X	time, h[a]	isol. yield, %	ee[b] %	config.[c]
3a	Me	H	Cl	0.5	86	97	*R*
3a	Me	H	H	48	86	94	*R*
3a	Me	H	H	0.3[d]	84	95	*R*
3a	Me	H	H	0.3[e]	81	97	*R*
3b	Ph	H	Cl	5	82	70[f]	*R*
3b	Ph	H	H	24	80	65[f]	*R*
3b	Ph	H	H	5[d]	84	69[f]	*R*
3c	Me	Me	Cl	7 d	70	69[f]	*R*
3d	Ph	Me	Cl	30 d	40	64[f]	*R*
3e	Me	Li	Cl	7 d	80	96	*R*
3e	Me	Li	Cl	48[g]	76	94	*R*
3e	Me	Li	Cl	0.3[h]	79	94	*R*
3f	Ph	Li	Cl	7 d	80	66[f]	*R*
3f	Ph	Li	Cl	24[g]	78	66[f]	*R*

[a]Determined by ^{11}B NMR spectroscopy. [b]Determined as the MTPA ester on a SPB-5 capillary column, unless otherwise stated. [c]On the basis of analogy with the product from intramolecular reductions, ref. 6. [d]For a reaction following the addition of one equiv HCl to the intermediate. [e]For a reaction following the addition of one equiv of methanesulfonic acid. [f]Ee determined by ^{19}F NMR spectroscopy of the MTPA esters. [g]For a reaction following the removal of LiCl. [h]For a reaction following the removal of LiCl and addition of one equiv of HCl.

The study was then extended to *N*-methyl-*o*-aminoaceto- and -benzophenones. The reactions with 1 were slower than that of the corresponding primary amino compounds. Probably, the presence of the methyl group on the nitrogen makes it more difficult for the boron atom to coordinate, reducing the reaction rate.

These results are summarized in the Table. We believe that the (*R*)-alcohol is produced in all of the above intramolecular reactions with the reagents prepared from (+)-α-pinene, analogous to the behavior of the corresponding *o*-hydroxy derivatives.

In conclusion, we have shown that the reduction of *o*-aminoaceto- and -benzophenone with *B*-chlorodiisopinocampheylborane is faster than that with diisopinocampheylborane. A rate enhancing effect of added hydrogen chloride or methanesulfonic acid to the reaction intermediate has been established. This reaction sequence[13] provides an efficient procedure for the preparation of optically active amino alcohols in very high ee. This methodology should be especially valuable for the synthesis of pharmaceuticals with similar structures.[14] Currently we are studying the efficacy of the optically active oxazaborole intermediates as catalysts in asymmetric reduction. Preliminary results are encouraging.

Acknowledgement. Financial assistance from the United States Army Research Office (Grant No. DAAH-94-G-0313) is gratefully acknowledged.

REFERENCES AND NOTES

1. Paper #101 presented at the 29th ACS Great Lakes Regional Meeting, Normal, IL, May 20, 1996.
2. Postdoctoral Research Associate on a grant from the U. S. Army Research Office.
3. *Reductions in Organic Synthesis*, Abdel-Magid, A. F.; Ed. American Chemical Society, Washington, DC, 1996.
4. Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. DIP-Chloride is a trademark of the Aldrich Chemical Company.
5. Ramachandran, P. V.; Brown, H. C. in ref. 3. Chapter 5.
6. Ramachandran, P. V.; Gong, B.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 2141.
7. This reaction of **1** was applied by a Ciba-Geigy group for the synthesis of both enantiomers of a potent LDL cholesterol lowering agent, CGS-26214. However, they have utilized a 100% excess of the reagent, probably not necessary according to the reaction mechanism.[6] Shieh, W. C.; Cantrell, Jr., E. R.; Carlson, J. A. *Tetrahedron Lett.* **1995**, *36*, 3797.
8. Ipc_2BH by itself is not an efficient reducing agent. Brown, H. C.; Mandal, A. K. *J. Org. Chem.* **1977**, *42*, 2996.
9. Ramachandran, P. V.; Chen, G. M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205.
10. (a) Lockart, J. C. *J. Chem. Soc.* **1962**, 1197. (b) Cragg, R. H.; Miller, T. J. *J. Organometal. Chem.* **1982**, *232*, 201.
11. A rate difference (10 min vs 12 d) in the reduction of **3a** and **3b** with sodium borohydride-acetic acid (1:3) has been reported. Nieminen, T. E. A.; Hase, T. A. *Tetrahedron Lett.* **1987**, *28*, 4725.
12. The Ciba-Geigy group reported 72 h for the reduction of **3b** with 2 equiv of **1**.[7] Evidently, in this reaction also 2 equiv of the reagent is not necessary.
13. All of the operations were carried out under nitrogen.[15] An oven-dried, 50 mL round-bottom flask equipped with a side-arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. Ipc_2BH (4.3 g, 15 mmol) was transferred to the flask in a glove bag and suspended in THF (15 mL). The flask was cooled to 0 °C and the amino ketone (15 mmol) was added using a syringe. One equiv of hydrogen evolved when all of **2** dissolved (1 h) and the solution turned violet. The ^{11}B NMR spectrum of an aliquot showed a singlet at δ 9 ppm. One equiv of hydrogen chloride in EE was added at this time and the mixture was stirred at rt. The reaction was complete within 20 min (^{11}B NMR δ 32 ppm). Workup using alkaline H_2O_2 provided a crude product which was chromatographed through silica (*n*-pentane:ethyl acetate = 2:1 as eluent) and concentrated to obtain the amino alcohol in 84% yield, whose structure was confirmed by ^1H and ^{13}C NMR. The MTPA ester of this alcohol was prepared and analyzed using a gas chromatograph fitted with a SPB-5 capillary column, which showed an ee of 95%.
14. Boting, N. P. *Chem. Soc. Rev.* **1995**, *24*, 401.
15. Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes* Wiley-Interscience: New York, **1975**; Chapter 9.

(*Received in USA* 12 *November* 1996; *revised* 12 *December* 1996; *accepted* 16 *December* 1996)