magnitudes of these slopes cannot be explained if only the effects on the radicals are considered. However, they are consistent with electronegativity differences between O–H and O–C in the bonds undergoing homolysis. In fact, a plot of the Hammett slopes for bond homolysis in the phenols,[5] anisoles,[20] toluenes,[14] and the benzyl bromides versus the electronegativity difference, ΔV_X,[21] appears to be linear with a slope of 2.0. While there is no reason to expect a linear relationship a priori, these trends clearly support the simple substituent–dipole interaction mechanism in Figure 2. The generality of this relationship is currently being explored.

The conclusion that remote substituent effects on bond energies reflect the interaction of the substituent with the dipole of the bond that is undergoing homolysis raises the following question. Is it possible to define radical stabilization energy so that it is both meaningful (i.e., a property of the radical only) and experimentally accessible?

Acknowledgment. The authors thank Professor J. M. Saveant for stimulating our interest in this work and Dr. K. U. Ingold for helpful discussions.

Registry No. 4-$MeC_6H_4CH_2Br$, 104-81-4; 4-*t*-$BuC_6H_4CH_2Br$, 18880-00-7; 4-$FC_6H_4CH_2Br$, 459-46-1; 4-$BrC_6H_4CH_2Br$, 589-15-1; 4-$CF_3C_6H_4CH_2Br$, 402-49-3; 4-$CNC_6H_4CH_2Br$, 17201-43-3.

(21) V_X is a new electronegativity scale proposed recently by Luo and Benson.[22] ΔV_X is the difference between the electronegativity of the atoms in the bond that undergoes homolysis (e.g., $V_C - V_{Br}$ for the benzyl bromides and $V_O - V_C$ for the anisoles).

(22) Luo, Y.-R.; Benson, S. W. *J. Phys. Chem.* **1989**, *93*, 4643, 3791, 3306, 3304, 1674. (b) Luo, Y.-R.; Benson, S. W. *J. Phys. Chem.* **1988**, *92*, 5255. (c) Luo, Y.-R.; Benson, S. W. *J. Am. Chem. Soc.* **1989**, *111*, 2480.

New Catalysts for the Asymmetric Aldol Reaction: Chiral Boranes Prepared from α,α-Disubstituted Glycine Arenesulfonamides

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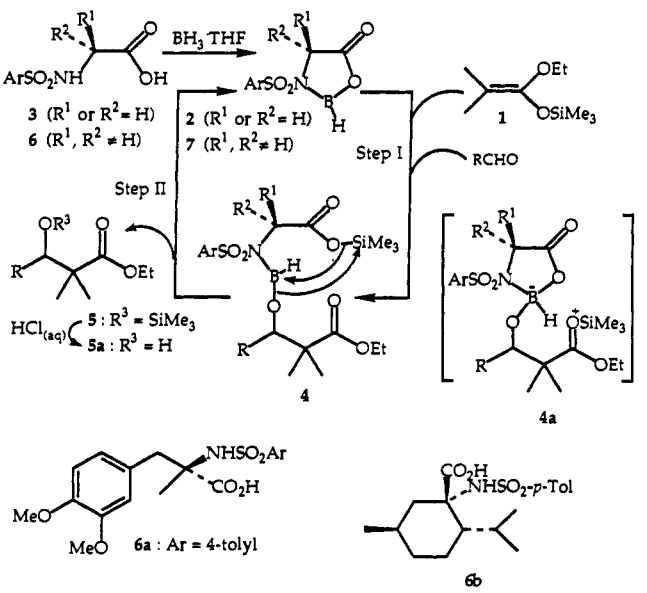
Received August 1, 1991

The aldol reaction continues to attract the interest of synthetic organic chemists. One of the most recent versions involves the reaction of aldehydes with silyl ketene acetal **1**, using the chiral Lewis acid mediator **2** prepared from BH_3·THF and the sulfonamide derivative **3** of a natural α-amino acid such as valine.[1] The efficient completion of this reaction with high enantioselectivity, however, requires a stoichiometric amount of **2**, as we observed earlier, and efforts have been directed to the construction of a catalytic process[2] on the basis of the hypothetical Scheme I. Scheme I consists of steps I and II which involve (1) carbon–carbon bond formation to provide the initial aldol product **4** via **4a** and (2) release of the silylated product **5** with simultaneous regeneration of **2**, respectively.[3] Step II likely represents the slowest process and must be accelerated. Two obvious devices appear effective. (1) Use of synthetic α,α-disubstituted glycine arenesulfonamides **6** (neither R^1 nor R^2 is H) as shown in **7** would facilitate ring closure of **4** (as indicated by the arrows), a phenomenon commonly attributed to the Thorpe–Ingold effect.[4] (2) Slow addition of aldehydes to a mixture of **1** and **7** would reduce the accumulation of **4**, a species which might also catalyze the aldol reaction but with a lesser enantioselectivity than that of **1**. An enhancement of product enantiopurity is anticipated. Our investigation along this line of reasoning has resulted in catalytic asymmetric aldol processes which provide β-hydroxy esters **5a** of >97% ee with typical primary aldehydes and 84–96% with secondary aldehydes.[5] The specific catalysts used are the borane complexes of **6a** and **6b**.

Scheme I



The first set of experiments concerned the α-substituent effect of various ligands on the turnover capability of their borane complexes, as judged by the yield of the aldol reaction using a *substoichiometric* amount of the mediator. Thus, the *p*-toluenesulfonamides of several simple α-amino acids provided the following results [the numbers in parentheses indicate the yields of **5a** in the reaction using benzaldehyde (1 equiv), ketene acetal **1** (1.2 equiv), and mediators (20 mol %) prepared from BH_3·THF and the *p*-toluenesulfonamides of amino acids]:[6] valine (54%), *tert*-leucine (46%), α-methylalanine (95%), and α-phenylalanine (98%). α-Hydroxy carboxylic acids chosen for comparison gave similar results: malic acid (21%), mandelic acid (19%), α-methyllactic acid (55%), and atrolactic acid (96%). The trend is consistent with the argument that disubstitution at the α-carbon enhances the catalytic activity of the complexes, as outlined above.

(1) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276.

(2) Chiral Lewis acids related to **2** are capable of catalyzing typical Diels–Alder reactions with good enantioselection. (a) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (b) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197.

(3) Earlier we observed that the neutral aqueous workup of the reaction mixture that resulted with 1 equiv of **2** (R^1 = isopropyl, R^2 = H) led to the isolation of the β-hydroxy ester **5a** as the major product, indicating that the hydroxyl group of **5a** was linked with B rather than Si. On prolonged standing, however, the reaction mixture became enriched in the silyl ether **5** of **5a** as evidenced by its isolation.

(4) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, 1080.

(5) For catalytic asymmetric aldol processes, see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 235. (c) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455. (d) Kobayashi, S.; Ohtsubo, A.; Mukaiyama, T. *Chem. Lett.* **1991**, 831 and references quoted therein. (e) Mukaiyama, T.; Inubushi, A.; Suda, S.; Hara, R.; Kobayashi, S. *Chem. Lett.* **1990**, 1015. (f) Mukaiyama, T.; Takashima, T.; Kusaka, H.; Shimpuku, T. *Chem. Lett.* **1990**, 1777. (g) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041; (h) Furuta, K.; Maruyama, T.; Yamamoto, H. *Synlett* **1991**, 439. (i) Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. *Chem. Ind.* (*London*) **1986**, 824.

(6) Procedures as outlined in the text, except that the aldehyde was added neat over 1 min, followed by stirring at −78 °C (30 min) before quenching.

0002-7863/91/1513-9365$02.50/0

Table I. Catalytic Aldol Reactions of Silyl Ketene Acetal 1 with Aldehydes Mediated by Borane Complexes of **6a** and **6b**[a]

entry	aldehyde	ligand	yield of **5a**, %	ee,[b] % (confign)
1	PhCHO	**6a**	80	84 (*R*)[c]
2	PhCHO	**6b**	83	91 (*R*)[c]
3	c-C_6H_{11}CHO	**6a**	68	91 (*R*)[d]
4	c-C_6H_{11}CHO	**6b**	59	96 (*R*)[d]
5	$CH_3(CH_2)_2CHO$	**6a**	81	>98[e]
6	$CH_3(CH_2)_2CHO$	**6b**	82	>98[e]
7	$(CH_3)_2CHCH_2CHO$	**6a**	87	97[e]
8	$(CH_3)_2CHCH_2CHO$	**6b**	89	>98[e]
9	$Ph(CH_2)_2CHO$	**6a**	83	>98[e]
10	$Ph(CH_2)_2CHO$	**6b**	83	>98[e]
11	$BnO(CH_2)_2CHO$	**6a**	86	99[e]

[a] Experimental conditions as in text. [b] Enantiomeric excesses determined by chiral Daicel OD HPLC column (entries 1 and 2) or ^1H (300 MHz) and ^{19}F NMR analysis of the (*S*)-MTPA esters derived from **5a**. [c] Absolute configuration determined by hydrolysis of the β-hydroxy ester to the corresponding carboxylic acid and comparison of optical rotations with literature values.[11] [d] Absolute configuration determined by comparison with authentic material derived from reduction (H_2/Rh-Al_2O_3) of (*R*)-(-)-**5a** (R = Ph). [e] Absolute configuration undetermined.

Complete consumption of benzaldehyde using α,α-disubstituted glycine derivatives has led to the selection of ligands **6a** and **6b**, both of which are readily available in enantiopure form from known amino acids.[7] Slow addition of benzaldehyde over a 3.5-h period resulted in an increase in the enantioselectivity from 57 to 84% ee for the catalytic (20 mol %)[8] reaction using ligand **6a**, and hence a standard procedure was established as defined below. Furthermore, modification of the *p*-tolylsulfonyl moiety of ligand **6a** provided the following enantiomeric excesses with varying Ar: Ar = 3,5-bis(trifluoromethyl)phenyl (52%), mesityl (53%), α-naphthyl (67%), β-naphthyl (78%), 4-*tert*-butylphenyl (81%), phenyl (83%), 4-methoxyphenyl (86%), 4-acetamidophenyl (86%). Since these modifications did not offer a substantial improvement in ee over **6a**, the *p*-toluenesulfonamide derivatives were selected as ligands.[9] Aldol reactions with **6a** and **6b** indeed proceeded smoothly, with high chemical yields and, pleasingly, with high enantioselection as well, for a number of typical aldehydes (Table I). Note that the reactions of primary aldehydes led to the exclusive formation of a single enantiomer through the use of either ligand **6a** or **6b** (entries 5 and 6 and 8-10).

Although the hypothetical Scheme I has served as a guide for successfully designing the catalytic process, its mechanistic course is undoubtedly complicated, and even the structure of the catalyst tentatively formulated as **7** is yet to be established.[10] Preliminary results, however, indicate that an *intramolecular* B/Si-exchange reaction features in the catalytic cycle, and the same holds true for the asymmetric aldol reaction reported by the Yamamoto group.[5g] In the past we have attempted in vain to construct cycles with an *intermolecular* metal-exchange reaction, and the success outlined above hints at the direction of future catalyst design.

A standard procedure for aldol reactions is as follows. The ligand **6** (0.1 mmol, 0.2 equiv) in propionitrile (1.5 mL) was treated with BH_3·THF complex (100 μL of a 1 M solution in THF, 0.1 mmol, 0.2 equiv). The solution was warmed to 45 °C for 1 h and cooled to -78 °C before the addition of the ketene acetal (126 μL, 0.6 mmol, 1.2 equiv). The aldehyde (0.5 mmol) was then added as a solution in propionitrile (1 mL) over 3.5 h (syringe pump) and the reaction mixture stirred a further 1 h at the same temperature before being poured into pH 7 buffer at 0 °C. Usual workup, yielding silyl ether **5** accompanied by a small amount of β-hydroxy ester **5a**, was followed by hydrolysis (1 N HCl/THF) and column chromatography to give pure **5a**.

Acknowledgment. This work was supported by a grant from the NIH (GM35879). E.R.P. and O.T. are holders of SERC/NATO postdoctoral and Merck Fellowships, respectively.

Supplementary Material Available: Experimental details of the synthesis of **6a** and **6b** (5 pages). Ordering information is given on any current masthead page.

(7) (a) Slates, H. L.; Taub, D.; Kuo, C. H.; Wendler, N. L. *J. Org. Chem.* **1964**, *29*, 1424. (b) Cremlyn, R. J. W.; Chisholm, M. *J. Chem. Soc. C* **1967**, 1762. (c) Munday, L. *J. Chem. Soc.* **1961**, 4372. (d) Stereochemistry of **6b**: Sacripante, G.; Edward, J. T. *Can. J. Chem.* **1982**, *60*, 1982. (e) For general and specific synthetic procedures, see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. (f) Galdecki, Z.; Karolak-Wojciechowska, J. *J. Crystallogr. Spectrosc. Res.* **1986**, *16*, 467.

(8) The use of 10 mol % catalyst derived from ligand **6a** did not result in a significant loss of enantioselectivity or reactivity.

(9) The ligands are recoverable.

(10) The ^{11}B NMR spectra of the borane complexes derived from **6a** and α-methylalanine sulfonamide exhibit a single broad peak centered at ≈+6 ppm (reference = BF_3·OEt_2).

(11) (a) Matell, M. *Ark. Kemi* **1949**, *1*, 455. (b) Guette, M.; Capillon, J.; Guette, J.-P. *Tetrahedron* **1973**, *29*, 3659. (c) Kende, A. S.; Kawamura, K.; Orwat, M. J. *Tetrahedron Lett.* **1989**, *30*, 5821.

Induced Stereoselectivity and Substrate Selectivity of Bio-Imprinted α-Chymotrypsin in Anhydrous Organic Media

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Received June 7, 1991

In recent years much work has focused on attempts to change the properties of antibodies[1] or of proteins and enzymes in water-poor media where rigidity of conformation is the basis for the new properties.[2] In this communication we describe how precipitation of α-chymotrypsin with 1-propanol in the presence of *N*-acetyl-D-tryptophan, *N*-acetyl-D-phenylalanine, or *N*-acetyl-D-tyrosine, followed by drying of the precipitate, appears to induce a new conformation of the active site. In an anhydrous solvent α-chymotrypsin prepared in this way exhibits high selectivity in the synthesis of the D-form of the ethyl ester of the N-acetylated amino acid present during precipitation. This is not possible with α-chymotrypsin precipitated in the presence of the L-form or in the absence of the D-isomer. We have coined this method, leading to a change of the conformation of the active site, "bio-imprinting", in analogy to molecular imprinting in synthetic polymers.[3]

To gain a better understanding of the underlying mechanism, α-chymotrypsin was bio-imprinted with *N*-acetyl-D-tryptophan and *N*-acetyl-L-tryptophan, and the synthesis of *N*-acetyl-D-tryptophan ethyl ester and *N*-acetyl-L-tryptophan ethyl ester, as influenced by small additions of water to the reaction solution, was investigated. The activity of the enzyme in the synthesis of *N*-acetyl-L-tryptophan ethyl ester increased rapidly as the water concentration was increased (Figure 1A), whereas the opposite was the case in the synthesis of *N*-acetyl-D-tryptophan ethyl ester (Figure 1B). The effects of water on catalysis described in Figure 1A have been observed earlier[6] and was interpreted as an effect

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(2) (a) Ståhl, M.; Månsson, M. O.; Mosbach, K. *Swedish patent application no. 89040215-4* **1989**. (b) Braco, L.; Dabulis, K.; Klibanov, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 274-277. (c) Ståhl, M.; Månsson, M. O.; Mosbach, K. *Biotechnol. Lett.* **1990**, *12*, 161-166. (d) Zaks, A.; Klibanov, A. M. *J. Biol. Chem.* **1988**, *263*, 3194-3201.

(3) Ekberg, B.; Mosbach, K. *TIBTECH* **1989**, *7*, 92-96.

(4) Initial water content of the reaction mixture was 10 mM and after equilibration with the enzyme 20 mM, indicating that water had been removed from the enzyme and into the solvent (measured using the Fisher method). Water content of the dried enzyme (measured gravimetrically) was 12.2% (w/w).

0002-7863/91/1513-9366$02.50/0