# Enantioselective Addition of 2-Lithio-1,3-dithiane to Aldehydes in the Presence of (−)-α-Isosparteine

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In the presence of stoichiometric (−)-α-isosparteine, 2-lithio-1,3-dithiane underwent enantioselective addition to aldehydes with moderate ee's (6-70%).

## Introduction

Asymmetric addition of achiral nucleophiles to prochiral carbonyl compounds has received considerable attention. A prochiral substrate and an achiral reagent may react to give a chiral product if the reaction is conducted in a chiral environment created by chiral solvent, or if chirality is acquired around the achiral reagent from chiral ligand. Thus, most of the successful experiments on the asymmetric addition of achiral nucleophiles usually involve organometallic reagents that are prone to coordinate with ligands, where the resulting optically active complex acts as the reagent. Thus, in a way these reactions are not different from reactions involving optically active reagent.

Since the first investigation was reported by Wright *et al*,[1] various kinds of chiral ligands have been reported by Nozaki,[2] Seebach,[3] Mukaiyama[4] and others.[5] For an example, Nozaki and co-workers reported in 1971 that 1,2-addition of organolithium and Grignard reagents to carbonyl compounds proceeds dissymmetrically in the presence of (−)-sparteine **1**, where *n*-butyllithium and ethylmagnesium bromide reacted with benzaldehyde to afford the corresponding (*R*)-carbinols in 6% and 22% optical purity, respectively.[2]

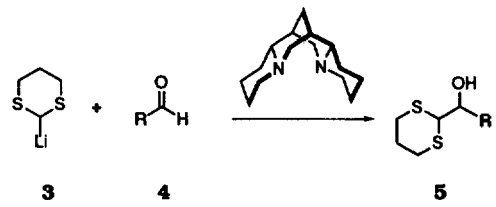
(-)-sparteine **1**

(-)-α-isosparteine **2**

In connection with our studies on the asymmetric reaction of organometallics mediated by a chiral ligand,[6] (−)-sparteine **1** and (−)-α-isosparteine **2** were examined as chiral ligands. Unfortunately, the reaction of benzaldehyde with *n*-butyllithium in the presence of either one of these ligands gave almost racemic product. Therefore, we now report an enantioselective addition of 2-lithio-1,3-dithiane **3**, which has a disubstituted carbanionic center and also ligating sites of the sulfur atom, to aldehydes using more $C_2$-symmetric (−)-α-isosparteine **2** (Scheme 1).

## Results and Discussion

(−)-α-Isosparteine **2**, a chiral ligand required for our studies, was prepared from (−)-sparteine **1** by the method of Leonard,[7] and benzaldehyde **6** as a model substrate was treated with 2-lithio-1,3-dithiane **3** in the presence of (−)-α-isosparteine **2** or (−)-sparteine **1** under various conditions: At first, 1.0 equiv. of benzaldehyde was treated with 1.0 equiv. of 2-lithio-1,3-dithiane in the presence of 1.1 equiv. of (−)-sparteine to give the corresponding alcohol **7** in 84% chemical yield and in 3.0% enantiomeric excess, which was determined by chiral HPLC of the corresponding benzoate ester.



**3** **4** **5**

**Scheme 1.**


**6** 1.0 equiv | **3** 1.0 equiv | **1** 1.1 equiv | **7** 84% (3% ee)

In optimization studies, the following factors were found to be critical: (i) Less coordinating ether was a better solvent than THF. (ii) (−)-α-isosparteine **2** gave better ee's than (−)-sparteine **1**, presumably due to more $C_2$-symmetric nature of the ligand. And (iii) stoichiometric quantity of the ligand was required to achieve any significant asymmetric induction. Thus, in the presence of 1.1 equiv. of (−)-α-isosparteine, 1.0 equiv. of benzaldehyde was treated with 1.0 equiv. of 2-lithio-1,3-dithiane **3** to give the corresponding *sec*-alcohol **7** in 73% chemical yield and in 70.3% ee.


**6** 1.0 equiv | **3** 1.0 equiv | **2** 1.1 equiv | **7** 73% (70% ee)

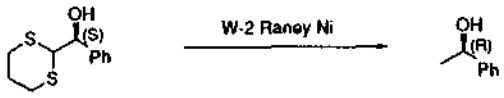
Using this preparative protocol, asymmetric induction in the enantioselective addition of 2-lithio-1,3-dithiane **3** to various aldehydes in the presence of (−)-α-isosparteine **2** was examined. The results are summarized in Table 1. Thus, aromatic aldehydes gave 32-70% ee's, while aliphatic aldehydes gave less than 10% ee's.

**Table 1.** Enantioselective Addition of 2-Lithio-1,3-dithiane to Aldehydes in the Presence of (−)-α-Isosparteine in Ether at −78 ℃.

| Entry | Product (5 : R) | | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | Ph- | 7 | 73 | 70.3 |
| 2 | *p*-Cl-Ph- | 8 | 83 | 39.7 |
| 3 | 2-naphthyl | 9 | 80 | 32.4 |
| 4 | $(Ph)_2CH$- | 10 | 47 | 48.9 |
| 5 | $CH_3(CH_2)_5$- | 11 | 81 | 32.1 |
| 6 | $(CH_3)_3C$- | 12 | 78 | 9.5 |
| 7 | *c*-$C_6H_{11}$- | 13 | 84 | 6.0 |

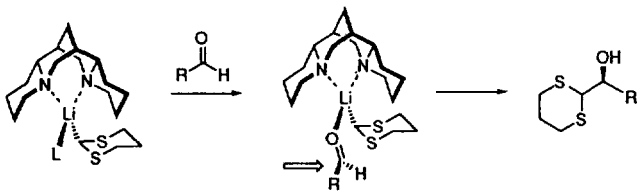
[a]Isolated yield. [b]Enantiomeric excesses were determined as the corresponding benzoate ester by using a chiral HPLC column (Daicel Chiralcel OF, Hexane/*i*-PrOH (4 : 1) as eluent, flow rate 0.5 m*l*/min, UV 254 nm).

In order to obtain the absolute configuration of the resultant alcohols, 1-(1,3-dithian-2-yl)-1-phenylmethanol **7** of 15.0% ee, which had been prepared in the presence of 0.56 equiv. of **2**, was desulfurized with W-2 Raney nickel[7] to afford the known (*R*)-1-phenylethanol **14** in 61% yield, $[\alpha]_D^{20}+8.46$ (*c* 2.6, $CHCl_3$) [lit.[8] for (*S*)-1-phenylethanol: $[\alpha]_D^{20}-53.5$ (*c* 2.6, $CHCl_3$)].




**7** **14**

From these above results, the absolute configuration of the benzylic alcohol **7**, and most probably all the major alcohol enantiomers prepared in the present study, were *S*. Consequently, the schematic transition state (a working hypothesis) for the present reaction can be drawn as the following.




**15** **16** **17**

Thus, upon coordination of the aldehyde through the available space to the lithium atom of the (−)-α-isosparteine complex of 2-ithio-1,3-dithiane **15** to form **16**, the carbinol with (*S*) configuration would result by addition to *re* face of the carbonyl group, which is the same as the results using (−)-sparteine-alkyllithium complexes by Nozaki and co-workers.[2] But the results with (−)-α-isosparteine is better than with (−)-sparteine. This methodology provides the first example of an asymmetric induction in the addition of organolithium compounds to carbonyl group using (−)-α-isosparteine.

Unfortunately, a catalytic version of the reaction with benzaldehyde using (−)-α-isosparteine (0.15 equiv), 2-trimethylsilyl-1,3-dithiane (0.9 equiv) and 2-lithio-1,3-dithiane (0.1 equiv), where C-to-O transsilylation of trimethylsilyl group from 1,3-dithiane to alkoxide was hoped to take place, could not be driven to a synthetically useful level.

## Experimental

**General.** All reactions involving organometallic reagents were carried out under an inert atmosphere of Nitrogen. Diethyl ether were freshly distilled from sodium benzophenone ketyl prior to use. *n*-Butyllithium solution (Aldrich) were assayed for active alkyl by titration with 2-butanol in tetrahydrofuran using 1, 10-phenanthroline as an indicator. All other reagents and solvents used were reagent grade. Small and medium-scale purifications (20 mg-2 g) were performed by radial chromatography by using a Harrison Research chromatotron on plates of 1-, 2-, or 4-mm thickness made with Merck silica 60 $PF_{254}$ containing gypsum. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and all melting points were uncorrected. $^1H$ NMR spectra were obtained on a Varian Gemini 200 spectrometer. NMR spectra were recorded in ppm (δ) relative to tetramethylsilane (δ 0.00) as an internal standard. Infrared spectra were obtained on a Mattson Galaxy 2000 spectrometer. Mass spectra were taken on a VG Trio 2000 (low resolution) spectrometers with an electron beam energy of 70 eV (EI). High resolution mass spectra were measured on a JEOL JMS-DX303 instrument. Elemental analysis were obtained on a Carlo Erba EA 1180 elemental analyzer. Optical rotations were obtained on a Rudolph Autopol III. digital polarimeter. Data are reported as follow: $[\alpha]_D^{20}$ (concentration g/100 mL, solvent). Enantiomeric excess of secondary alcohols were determined as the corresponding benzoate ester by HPLC using a Daicel Chiralcel OF column (25% isopropanol/*n*-hexane).

**Preparation of 1-(1,3-Dithian-2-yl)-1-phenylmethanol 7 in the Presence of (−)-α-Isosparteine 2.** A solution of (−)-α-isosparteine (515 mg, 2.2 mmol) in 15 m*l* of ether was dried over calcium hydride and transferred using double-ended needle under nitrogen. To the above solution was dropwise added *n*-butyllithium (1.62 m*l* of 1.30 M, 2.1 mmol) at −30 ℃, and the mixture was warmed to 0 ℃ and stirred for 30 min. After cooling to −78 ℃, a solution of 1,3-dithiane (240 mg, 2.0 mmol) in 5 m*l* of ether was dropwise added, and resultant solution was warmed to 0 ℃ and stirred for 30 min. At −78 ℃, benzaldehyde (0.20 m*l*, 2.0 mmol) was dropwise added and the mixture was stirred for 30 min at that temperature. After warming to 0 ℃, the mixture was poured into 6.0 m*l* of 1 *N* HCl. The aqueous phase was extracted with ether and the combined extracts were dried over sodium sulfate, filtered, and concentrate *in vacuo* to give a crude oil, which was chromatographed employing 30% ether in *n*-hexane as an eluent. The yield of the alcohol **7** was 330 mg (73%) as colorless crystal. mp. 50 ℃; TLC $R_f$ 0.21 (50% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.80-2.20 (m, 2H), 2.45-3.00 (m, 5H), 4.07 (d, $J$=7.0 Hz, 1H), 4.89 (d, $J$=7.0 Hz, 1H), 7.38 (s, 5H); IR (neat) 3432 $cm^{-1}$; Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.30; H, 6.44; S, 27.95; $[\alpha]_D^{20}+9.8$ (*c* 3.5, $CHCl_3$).

Likewise, the following chiral alcohols were prepared;

**1-(1,3-Dithian-2-yl)-1-(*p*-chlorophenyl)methanol 8.** Yield 83%; colorless crystal; mp. 54 ℃; TLC $R_f$ 0.13 (30%

ether in *n*-hexane); NMR ($CDCl_3$) δ 1.80-2.15 (m, 2H), 2.55-2.95 (m, 5H), 3.30 (br s, 1H), 4.00 (d, $J$=7.0 Hz, 1H), 4.82 (d, $J$=7.0 Hz, 1H), 7.30 (s, 4H); IR (neat) 3432 $cm^{-1}$; Anal. Calcd for $C_{11}H_{13}OS_2Cl$: C, 50.66; H, 5.02; S, 24.59. Found: C, 50.31; H, 5.38; S, 24.93; $[\alpha]_D^{20}$+4.1 (*c* 3.2, $CHCl_3$).

**1-(1,3-Dithian-2-yl)-1-(2-naphthyl)methanol 9.** Yield 80%; colorless crystal, mp. 115 ℃; TLC $R_f$ 0.38 (50% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.89-2.20 (m, 2H), 2.58-3.20 (m, 4H), 4.20 (d, $J$=7.4 Hz, 1H), 5.09 (d, $J$=7.4 Hz, 1H), 7.40-7.98 (m, 7H); IR (KBr) 3440 $cm^{-1}$; Anal. Calcd for $C_{15}H_{16}OS_2$: C, 65.18; H, 5.83; S, 23.20. Found: C, 65.18; H, 5.83; S, 23.20. Found: C, 65.18; H, 6.25; S, 23.61; $[\alpha]_D^{20}$+4.0 (*c*, 2.4, $CHCl_3$).

**1-(1,3-Dithan-2-yl)-2,2-diphenylethan-1-ol 10.** Yield 47%; colorless crystal, mp. 159-161 ℃; TLC $R_f$ 0.25 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.78-2.15 (m, 2H), 2.50-3.05 (m, 4H), 3.38-3.69 (m, 2H), 4.20-4.50 (m, 2H), 6.90-7.40 (m, 10H); IR (KBr) 3450 $cm^{-1}$; HRMS (EI) calcd for $C_{18}H_{20}OS_2$; 316.4754. Found: 316.4772; $[\alpha]_D^{20}$+0.8 (*c* 2.0, $CHCl_3$).

**1-(1,3-Dithian-2-yl)-1-heptanol 11.** Yield 81%; colorless oil; TLC $R_f$ 0.19 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 0.70-2.20 (m, 15H), 2.50 (s, 1H), 2.70-3.00 (m, 4H), 3.70-4.00 (m, 2H); IR (neat) 3448 $cm^{-1}$; HRMS (EI) calcd for $C_{11}H_{22}OS_2$ 234.4142. Found: 234.4144; $[\alpha]_D^{20}$−9.7 (*c* 3.0, $CHCl_3$).

**1-(1,3-Dithian-2-yl)-2,2-dimethylpropan-1-ol 12.** Yield 78%; colorless crystal, mp. 54 ℃; TLC $R_f$ 0.27 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.00 (s, 9H), 1.90-2.25 (m, 2H), 2.30 (br s, 1H), 2.72-3.05 (m, 4H), 3.46 (d, $J$=4.0 Hz, 1H), 4.29 (d, $J$=4.0 Hz, 1H); IR 3405 $cm^{-1}$; HRMS (EI) calcd for $C_9H_{18}OS_2$ 206.3606. Found: 206.3599; $[\alpha]_D^{20}$+6.3 (*c* 1.4, $CHCl_3$).

**1-(1,3-Dithian-2-yl)-1-cyclohexylmethanol 13.** Yield 84%; colorless crystal, mp. 65 ℃; TLC $R_f$ 0.18 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 0.90-2.30 (m, 14H), 2.65-3.02 (m, 4H), 3.48-3.72 (m, 1H), 4.12 (d, $J$=6.0 Hz, 1H); IR 3454 $cm^{-1}$; HRMS (EI) calcd for $C_{11}H_{20}OS_2$ 232.3984, Found: 232.3977; $[\alpha]_D^{20}$−1.6 (*c* 1.7, $CHCl_3$).

**Preparation of 1-(1,3-Dithian-2-yl)-1-phenylmethyl Benzoate 7.** To a solution of the alcohol 7 (110 mg, 0.49 mmol) in 1.5 m*l* of pyridine at 0 ℃, was added benzoyl chloride (0.14 m*l*, 1.18 mmol). The mixture was warmed to *rt* and stirred for 5h. After cooling to 0 ℃, a solution of 15 m*l* of 2 N hydrochloric acid was added. The aqueous layer was extracted with ether, and the combined extracts were dried and evaporated. Chromatography gave the corresponding chiral benzoate ester (110 mg, 70%). TLC $R_f$ 0.33 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.78-2.20 (m, 2H), 2.65-2.98 (m, 4H), 4.40 (d, $J$=7.0 Hz, 1H), 6.25 (d, $J$=7.0 Hz, 1H), 7.20-7.58 (m, 8H), 7.95-8.20 (m, 2H); IR 1719 $cm^{-1}$; MS m/e 330 ($M^+$); $[\alpha]_D^{20}$+0.88 (*c* 3.0, $CHCl_3$); retention time: 20.80 (major), 27.90 (minor).

Likewise, the following benzoates were prepared.

**1-(1,3-Dithian-2-yl)-1-(*p*-chlorophenyl)methyl Benzoate 8.** Yield 64%; TLC $R_f$ 0.32 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.80-2.20 (m, 2H), 2.62-3.02 (m, 4H), 4.40 (d, $J$=7.0 Hz, 1H), 6.25 (d, $J$=7.0 Hz, 1H), 7.25-7.60 (m, 7H), 7.90-8.20 (m, 2H); IR 1721 $cm^{-1}$; MS m/e 242 ($M^+$-$C_7H_6O_2$); $[\alpha]_D^{20}$−1.8 (*c* 2.4, $CHCl_3$); retention time: 17.20 (major), 20.92 (minor).

**1-(1,3-Dithian-2-yl)-1-(2-naphthyl)methyl Benzoate 9.** Yield 60%; TLC $R_f$ 0.41 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.80-2.20 (m, 2H), 2.65-3.05 (m, 4H), 4.55 (d, $J$=7.8 Hz, 1H), 6.44 (d, $J$=7.8 Hz, 1H), 7.40-8.19 (m, 12H); IR 1706 $cm^{-1}$; MS m/e 258 ($M^+$-$C_7H_6O_2$); $[\alpha]_D^{20}$ −10.3 (*c* 2.2, $CHCl_3$); retention time; 18.64 (major), 26.56 (minor).

**1-(1,3-Dithian-2-yl)-2,2-diphenyl-1-ethyl Benzoate 10.** Yield 68%; TLC $R_f$ 0.41 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.75-2.10 (m, 2H), 2.50-3.00 (m, 4H), 3.96 (d, $J$=6.0 Hz, 1H), 4.80-5.02 (m, 1H), 6.20-6.50 (m, 1H), 7.10-7.60 (m, 13H), 7.80-8.10 (m, 2H); IR 1718 $cm^{-1}$; MS m/e 298 ($M^+$-$C_7H_6O_2$) $[\alpha]_D^{20}$+2.6 (c 1.8, $CHCl_3$); retention time: 15.88 (major), 26.96 (minor).

**1-(1,3-Dithian-2-yl)-1-heptyl Benzoate 11.** Yield 43 %; TLC $R_f$ 0.48 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 0.70-2.20 (m, 15H), 2.70-3.00 (m, 4H), 4.23 (d, $J$=6.0 Hz, 1H), 5.22-5.60 (m, 1H), 7.30-7.60 (m, 3H), 7.95-8.20 (m, 2H), IR (neat) 1720 $cm^{-1}$; MS m/e 216 ($M^+$-$C_4H_7S_2$); $[\alpha]_D^{20}$+0.83 (c 2.4, $CHCl_3$); retention time: 13.09 (major), 16.88 (minor).

**1-(1,3-Dithian-2-yl)-2,2-dimethyl-1-propyl Benzoate 12.** Yield 40%; TLC $R_f$ 0.50 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.83-2.12 (m, 2H), 2.70-3.00 (m, 4H), 4.45 (d, $J$=4.0 Hz, 1H), 5.06 (d, $J$=4.0 Hz, 1H), 7.37-7.60 (m, 3H), 8.02-8.25 (m, 2H); IR 1720 $cm^{-1}$; MS m/e 310 ($M^+$); $[\alpha]_D^{20}$+4.2 (c 2.0, $CHCl_3$); retention time: 11.85 (major), 17.37 (minor).

**1-(1,3-Dithian-2-yl)-1-cyclohexylmethyl Benzoate 13.** Yield 62%; TLC $R_f$ 0.47 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 0.90-2.20 (m, 13H), 2.65-3.00 (m, 4H), 4.23 (d, $J$=6.0 Hz, 1H), 5.25-5.50 (m, 1H), 7.40-7.60 (m, 3H), 8.00-8.25 (m, 2H); IR 1714 $cm^{-1}$; MS m/e 336 ($M^+$); $[\alpha]_D^{20}$+0.9 (*c* 2.0, $CHCl_3$); retention time: 11.93 (major), 11.84 (minor).

**Reduction of 1-(1,3-Dithian-2-yl)-1-phenylmethanol 7 to 1-Phenylethanol 14.** A mixture of alcohol 7 (820 mg, 3.62 mmol) prepared in the presence of 0.56 equiv. of 2, 7.2 m*l* of ethanol, and 15 teaspoons of W-2 Raney nickel was stirred at 25 ℃ for 5h, and the ethanolic solution was decanted from the catalyst. The catalyst was then washed with one 10 m*l* portion of absolute ethanol and one 20 m*l* portion of dichloromethane, the solvent being removed by decanting in each case. The organic solution was combined and concentrated on a rotary evaporator to give a crude liquid, which was chromatographed empolying 30% ether in *n*-hexane as an eluent. The yield of the phenethyl alcohol **14** was 270 mg (61%). TLC $R_f$ 0.20 (30% ether in *n*-hexane); NMR ($CDCl_3$) δ 1.45 (d, $J$=6.0 Hz, 3H), 2.05 (s, 1H), 4.83 (q, $J$=6.0 Hz, 1H), 7.30 (s, 5H); $[\alpha]_D^{20}$+8.46 (*c* 2.6, $CHCl_3$) [lit.[8] (*S*)-1-phenylethanol: $[\alpha]_D^{20}$−53.5 (*c* 2.6, $CHCl_3$)].

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# Limitations of the Linear Solvation Energy Relationships in Reversed Phase Liquid Chromatography

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We have re-examined the linear solvation energy relationships in reversed phase liquid chromatography by considering various solutes including quite a number of compounds of strong hydrogen bond capability. We observed that solutes of strong hydrogen bond ability should be excluded in order to obtain resonable correlations between ln $k'$ and solute polarity parameters and that inclusion of one or two such solutes causes severe distortions of correlation results. This anomaly may be due to existence of residual silanol groups in the stationary phase, that is, their specific interactions with solutes.

## Introduction

Linear solvation energy comparison methods based on Kamlet/Taft polarity scales[1-5] have been known to be very useful in exploring linear solvation energy relationships (LSER) in reversed phase liquid chromatography.[6-12] The basic idea of this approach is that a distribution of a solute between two immiscible phases is governed by the cavity formation energy of the solute and by the solute-solvent interaction energies in each phase and that the solute-solvent interaction energies are the linear sum of several independent terms each of which corresponds to a characteristic solute-solvent interaction. Each interaction energy is proportional to the product of the semiempirical polarities of the solute and the solvent.

According to the LSER formalism, when applied to chromatographic retention, a logarithmic capacity factor, the solute-solvent specific property for a given chromatographic column, can be related to solute and solvent(phase) solvatochromic properties as follows[6-12]:

$$\ln k' = I + M\ (\delta_m^2 - \delta_s^2)\ V_{12}/100 + S\ (\pi^*_s - \pi^*_m) + B\ (\alpha_s - \alpha_m)\ \beta_2 + A(\beta_s - \beta_m)\ \alpha_2 \quad (1)$$

Retention in reversed phase liquid chromatography is determined by the difference in various types of solute-solvent interactions in the mobile and stationary phases. Each solute property is multiplied by a term that represents the difference in complementary solvent properties for the two phases. In Eq. (1), subscript s denotes the stationary phase, m, the mobile phase respectively, and subscript 2 designates a solute property. $\pi^*$ represents a polarizability-dipolarity of a solvent(phase) or a solute, $\alpha$, hydrogen bond donating acidity, and, $\beta$, hydrogen bond accepting basicity. $\delta$ is a solvent solubility parameter and $V_{1,2}/100$ is a normalized solute intrinsic volume.[13] $I$ is the intercept of regression, and $M$, $S$, $B$, and $A$, the regression coefficients of positive value.

When a system with a fixed pair of mobile and stationary phases is considered, Eq. (1) is reduced to

$$\ln k' = I' + m\ V_{12}/100 + s\pi^*_2 + b\ \beta_2 + a\ \alpha_2 \quad (2)$$

The coefficients $m$, $s$, $b$, and a are determined by multiple linear regression of ln $k'$ against the solute parameters and are measures of the difference of each specific polarity between the mobile and stationary phases. In reversed phase liquid chromatography, each polarity of the mobile phase is greater than that of the stationary phase, thus $m$ (representing $\delta_m^2 - \delta_s^2$) is positive and $s$ ($\pi^*_s - \pi^*_m$), $b$ ($\alpha_s - \alpha_m$), and $a(\beta_s - \beta_s)$ are negative (See Eq. (1)).

## Experimental

The retention data of solutes on a Shodex (Tokyo, Japan) C18-5B column (250×4.6 mm, 5 μ) were measured with methanol/water mixtures as eluents at various compositions.