correlation for the substituents *m*- and *p*-CF_3, 3,5-$(CF_3)_2$, *m*- and *p*-$SOCH_3$, *m*- and *p*-SO_2CH_3, *m*- and *p*-SCF_3, *m*-CO_2CH_3, *m*-CH_3CO, *m*-CN, *m*-NO_2, and *m*-SO_2CF_3; (3) there are even larger acidifying SSAR effects in Me_2SO than aqueous solution for the substituents *p*-CO_2CH_3 (0.8), *p*-CN (0.9), *p*-$COCH_3$ (1.1), *p*-SO_2CF_3 (1.3), *p*-NO_2 (2.7), and *p*-NO (4.9). (The figures in parentheses are these obtained from the horizontal deviation lines in Figure 1, in kcal/mol). A comparison plot for phenol acidities, gas vs. aqueous phase, is given in Figure 2, which includes recently obtained results for *m*- and *p*-SO_2CF_3, m- and p-SCF_3, *p*-NO, and 3,5-$(CF_3)_2$ phenols.[7]

The SSAR effects in Me_2SO solution appear to be determined by substituent charge localization, which depends upon a combination of a substituent's ability to attract π electrons (given by its $\sigma_{R^-(g)}$ value[1]) and the degree of localization of negative charge on an oxygen or nitrogen atom at the perimeter of the substituent. The size of the latter effect depends upon the extent of conjugation through the first atom of the substituent (for example, less for S and sp^3 C than for sp^2 C or sp^2 N) as well as the number of N or O atoms that share the charge (for example, less for NO_2 than NO).

The SSAR effects in Me_2SO are roughly 2.5 times *greater* than the corresponding SSSAR effects in H_2O. (The latter were obtained by taking the difference in horizontal deviations in Figure 2 for para substituents minus those for the corresponding meta substituents in order to eliminate SSSAF effects.) This SSAR/SSSAR ratio is approximately the inverse of the ratio of the slopes of the gas vs. Me_2SO and gas vs. H_2O correlation lines in Figures 1 and 2, consistent with the differences in the solvation of the phenoxide ion center.[9]

These comparisons of gas-phase and solution acidities reveal that the solvent plays a dominant role not only in controlling reactivity at the phenoxide ion reaction center but also in modifying the effects of substituents on this reactivity. It is clear from Figures 1 and 2 that modifications due to substituent solvation change significantly the order of substituent effects on acidity (and no doubt on reactivity[2]) from *p*-$SOCH_3$, *p*-CO_2CH_3, *p*-CF_3 < *p*-$COCH_3$, *p*-SCF_3 < *p*-CHO < *p*-CN < *p*-SO_2CH_3 < *p*-NO < *p*-NO_2 < *p*-SO_2CF_3 for nonsolvated substituents (gas phase) to *p*-CF_3, *p*-$SOCH_3$ < *p*-SCF_3 < *p*-CO_2CH_3 < *p*-$COCH_3$ < *p*-SO_2CH_3 < *p*-CN < *p*-NO_2, *p*-SO_2CF_3 < *p*-NO with certain substituents involving SSAR solvation (Me_2SO solution) to *p*-CF_3 < *p*-SCF_3 < *p*-CO_2CH_3 < *p*-$SOCH_3$ < *p*-$COCH_3$, *p*-CN < *p*-SO_2CH_3 < *p*-CHO < *p*-NO_2, *p*-SO_2CF_3 < *p*-NO with SSSAF and SSSAR solvation effects included (aqueous solution, the Hammett σ_p^- order).

These results indicate that we can expect to see SSSAF and SSSAR effects for strong HBA +R substituents[11] in all strong HBD (solvent HBD parameter α[5] $\geq$ 0.5) media and expect to see SSAR effects for charge localized +R para substituents in dipolar nonhydroxylic or non-HBD ("aprotic") solvents[12] for which α = 0 and π^* > 0.75.

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(9) With the more weakly solvated anilide or benzyl ion centers in Me_2SO solution, even larger SSAR effects of appropriate +R para substituents are observed, cf. ref 10 and a preliminary report in ref 2.

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(11) As substituent–solvent complexing weakens, its acidity effects are expected to suddenly disappear for reasons considered in detail in ref 1 and 2.

(12) Most solvents now commonly referred to as "dipolar aprotic" (Me_2SO, DMF, NMP, HMPA, CH_3CN, CH_3CN, CH_3NO_2, etc.) are *not* aprotic. Since these solvents are frequently used in reactions employing strong bases, it is important that their protic character be recognized. (In Me_2SO solution the pK_a values are, for CH_3NO_2, 17.2, CH_3CN, 31.3, Me_2SO, 35, NMP, ~35, and HMPA, ~45 or above.) For this reason we urge that the "dipolar aprotic" designation for these solvents be abandoned and replaced by "dipolar nonhydroxylic" or "dipolar non-hydrogen-bond donor".

Asymmetric Alkylation of α-Alkyl β-Keto Esters

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The development of new methodologies for asymmetric alkylation and their practical utility in the synthesis of biologically active natural products have been the subjects of intensive investigation,[1] and several approaches have been recently reported.[2] In this communication we report our results for diastereoselective alkylation of lithio enamines **3** derived from α-alkyl β-keto esters **1** (Scheme I).[3] Furthermore, use of various additives have shown that the facial selectivity may be reversed to provide either optical antipode.

Chiral enamines **2a–c** were prepared from the corresponding β-keto esters **1** and (*S*)-valine *tert*-butyl ester.[4,5] By direct analogy with earlier studies of the alkylation of enamines derived from simple ketones,[5] chiral enamine **2a** was lithiated with $LiN(i\text{-}C_3H_7)_2$ (LDA) (1.2 equiv) and methylated with methyl iodide (2 equiv) in tetrahydrofuran (THF) (−78 °C). Subsequent hydrolysis and purification afforded **5a** (R^4 = Me) with an *S* configuration in 58% ee (77% chemical yield).[6] By changing the solvent from THF to toluene (−5 °C),[7] alkylation afforded **4a** (R^4 = Me) with the opposite *R* configuration in 50% ee (57% chemical yield).

The fact that the stereochemical course of the alkylation was strongly influenced by the nature of the solvent[8] led us to the assumption that, if the lithium cation in **3** is ligated to the enamine nitrogen and two ester carbonyl oxygens, its fourth coordination site will be occupied by an external ligand (L in **3**), which may thus affect the stereochemical course of the reaction.[9] For the alkylation studies summarized in Table I, toluene was employed as the solvent and hexamethylphosphoric triamide (HMPT), THF, dioxolane, and trimethylamine were used as the external ligands.

The alkylation conditions involved successive treatment of a 0.1–0.5 M solution of enamine **2** (1–5 mmol) with LDA (1.2 equiv) in toluene at −78 °C for 1 h, then with 1–3 equiv of an additive at −78 °C for 1 h, and finally with 1–5 equiv of an alkylating agent at −55 to −78 °C for 3–25 h. After acidic hydrolysis and purification by silica gel column chromatography (or bulb-to-bulb distillation), the alkylated β-keto ester (**4** or **5**) was obtained. The chiral auxiliary reagent, (*S*)-valine *tert*-butyl ester, was recovered for reuse without any loss of optical purity. Since no keto esters except **4** (R^1 = R^2 = Me, R^3 = Et, R^4 = $CH_2CH{=}CH_2$) were known in optically pure form, the degree of asymmetric induction and the absolute configuration were determined by converting them into known compounds[6] and also

(1) For recent reviews, see: (a) Meyers, A. I. *Pure Appl. Chem.* **1979**, *51*, 1225. (b) ApSimon, J. W.; Seguin, R. P. *Tetrahedron* **1979**, *35*, 2797. (c) "*Asymmetric Reactions and Process in Chemistry*"; Eliel, E. L., Otsuka, S., Eds.; American Chemical Society: Washington, DC, 1982.

(2) For example, see: (a) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *Ibid.* **1982**, *104*, 1737. (c) Saigo, K.; Kasahara, A.; Ogawa, S.; Nohira, H. *Tetrahedron Lett.* **1983**, *24*, 503. (d) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117.

(3) Leading references for asymmetric alkylation reactions of β-keto esters: (a) Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547. (b) Cram, J. D.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. (c) Yamamoto, K.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 3089. (d) Enders, D., "*Asymmetric Synthesis*"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 225.

(4) Satisfactory analytical and spectral data were obtained for all new compounds.

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(6) For the absolute configuration and enantiomeric excess, see Table I.

(7) In toluene **3a** does not react with methyl iodide below −55 °C.

(8) Enders also reported a similar influence of the solvent in the diastereoselective alkylation reactions of chiral hydrazones.[3d]

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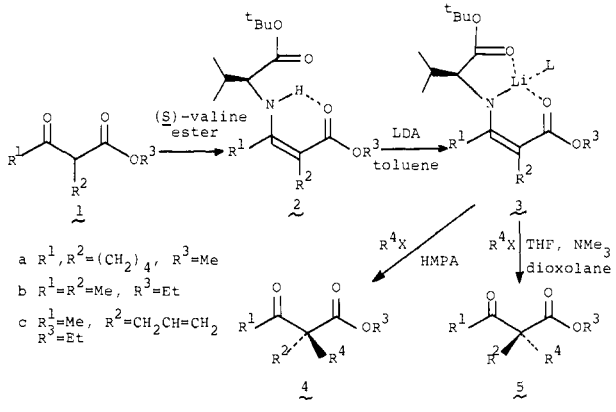
Table I. Asymmetric Alkylation of **2** Leading to **4** or **5** (Scheme I)[a]

entry	enamine[b]	R^4X (equiv)	ligand[c] (equiv)	4/5	isolated yield, %	$[\alpha]_D$,[d] deg	ee, %[e] (confn)
1	**2a**	MeI (1.2)	HMPT (1.0)	**4a**	57	−108	≥99 (R^f)
2	**2a**	MeI (5.0)	THF (2.0)	**5a**	63	−100	92 (S^f)
3	**2a**	CH_2=$CHCH_2Br$ (1.3)	HMPT (1.0)	**4a**	71	−102	76 (S^g)
4	**2a**	CH_2=$CHCH_2Br$ (5.0)	dioxolane (1.2)	**5a**	56	+75.2	56 (R^g)
5	**2a**	$PhCH_2Br$ (2.0)	HMPT (1.0)	**4a**	77	−111	≥99 (S^h)
6	**2a**	$PhCH_2Br$ (5.0)	dioxolane (1.6)	**5a**	48	+77.0	71 (R^h)
7	**2a**	$BrCH_2CO_2Me$ (2.0)	HMPT (1.0)	**4a**	59	−64.9	70 (S^h)
8	**2a**	$BrCH_2CO_2Me$ (2.0)	TMA (3.0)	**5a**	78	+69.2	74 (R^h)
9	**2b**	CH_2=$CHCH_2Br$ (2.0)	HMPT (1.0)	**4b**	68	−27.9	94 (S^i)
10	**2b**	CH_2=$CHCH_2Br$ (2.0)	dioxolane (2.0)	**5b**	20	+14.0	47 (R^i)
11	**2b**	$PhCH_2Br$ (2.0)	HMPT (1.0)	**4b**	90	−58.2	92 (S^j)
12	**2b**	$PhCH_2Br$ (5.0)	dioxolane (2.0)	**5b**	83	−57.0	90 (R^j)
13	**2b**	$BrCH_2CO_2Me$ (2.0)	HMPT (1.0)	**4b**	81	−30.6	76 (S^j)
14	**2b**	$BrCH_2CO_2Me$ (2.0)	TMA (3.0)	**5b**	76	+17.7	44 (R^j)
15	**2c**	MeI (2.0)	HMPT (1.0)	**4c**	54	+28.2	95 (R^i)
16	**2c**	MeI (2.0)	THF (1.6)	**5c**	66	−23.2	78 (S^i)

[a] For the reaction procedures, see the text. Reaction temperature: −55 °C (entries 1 and 3), −78 °C (entries 2, 4–16). [b] **2a**, $[\alpha]^{25}_D$ +139° (benzene); **2b**, $[\alpha]^{25}_D$ +153° (benzene); **2c**, $[\alpha]^{25}_D$ +132° (benzene). [c] HMPT, hexamethylphosphoric triamide; THF, tetrahydrofuran; TMA, trimethylamine. [d] Optical rotations were taken in ethanol at 25 °C for entries 1–8 and in chloroform at 22 °C for entries 9–16. [e] These values were determined by the LIS-NMR technique ($Eu(hfc)_3$). [f] Absolute configuration was determined by correlating **4a** (R^4 = Me) with (+)-(1*R*,2*R*)-(2-methyl-2-carboxycyclohexyl)acetic acid. Bachman, W. E.; Kushner, S. *J. Am. Chem. Soc.* **1943**, *65*, 1963. Gautschi, F.; Jeger, O.; Prelog, V.; Woodward, R. B. *Helv. Chim. Acta* **1955**, *38*, 296. [g] Absolute configuration was determined by correlation with the corresponding ethyl ester (NaOEt in ethanol). Frater, G. *Helv. Chim. Acta* **1980**, *63*, 1383. [h] Absolute configuration was determined by correlating **4a** ($R^4 = CH_2CH{=}CH_2$) and **4a** ($R^4 = CH_2Ph$) with **4a** ($R^4 = CH_2CO_2Me$) (ozonolysis, then methylation with diazomethane). [i] Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. [j] Absolute configuration was determined by correlating **4b** ($R^4 = CH_2CH{=}CH_2$) and **4b** ($R^4 = CH_2Ph$) with **4b** ($R^4 = CH_2CO_2Me$) (ozonolysis, then methylation with diazomethane).

Scheme I



by the LIS-NMR technique ($Eu(hfc)_3$).

A number of general trends are evident from the data in the table. First, an opposite sense of asymmetric induction is found in the solvent system of toluene–HMPT on the one hand and systems toluene–THF, –dioxolane, or –trimethylamine on the other, with the former system exhibiting a somewhat greater selectivity. For example, in the reaction of **3a** with methyl iodide (entries 1 and 2), the enantiomeric excess was found to be over 99% in favor of **4a** (R^4 = Me) for the toluene–HMPT system and 92% in favor of **5a** (R^4 = Me) for the toluene–THF system. Second, in the synthesis of **5**, the appropriate combination of alkylating agent and ligand is of great importance in realizing a high level of asymmetric induction. For example, utilization of THF, dioxolane, and trimethylamine as the ligands in the methylation of **3a** with methyl iodide led to **5a** (R^4 = Me) (92% ee), **5a** (R^4 = Me) (64% ee), and **4a** (R^4 = Me) (3% ee), respectively. The appropriate combinations were found to be THF for methyl iodide, dioxolane for allyl bromide and benzyl bromide, and trimethylamine for methyl bromoacetate, but the reason for this is not yet clear. Third, asymmetric alkylation to each enantiomer can be realized regardless of whether cyclic or acylic β-keto esters are involved.[10]

In general, alkylation in toluene in the presence of HMPT as the ligand takes place preferentially from the top face of **3** to yield **4**, while in the presence of THF, dioxolane, or trimethylamine as the ligand it takes place from the bottom face of **3** to yield **5**. Further studies are in progress to elucidate this behavior.

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Reactions of Transition-Metal Carbonyl Anions with Dioxygen in the Gas Phase

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Molecular metal oxides have provided a key source of fundamental information regarding oxidation-state stabilities,[1-3] metal-oxygen bonding,[4-8] combustion,[9] corrosion processes,[10] and catalytic oxidation mechanisms.[8,11,12] Mononuclear transition-metal polyoxides and their partially ligated derivatives are often kinetically unstable as discrete molecules, however, and methods involving extremes of temperature and/or fast spectroscopic probes are frequently necessary for their formation and characterization.[13-27] We wish to report here the formation of several novel

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