fluoride ions were 1 to 2 mM. The protonation constant of fluoride in water is: $\log K_{HF/F} = 3.15$.

NMR Measurements: ^{1}H NMR spectra were recorded on a Bruker AM500 spectrometer at 500 MHz. Binding constants were obtained by NMR titrations of **L** with fluoride from 25 measurements in D_2O at pD = 5.0 ± 0.1. Initial concentrations were $[\mathbf{L}]^0 = 2$ mM and titrations were performed using aliquots from a 20 mM stock solution of NaF. A solution of the sodium salt of [2,2,3,3-D_4]-3-(trimethylsilyl)propionic acid (TPS) in D_2O in a capillary tube was used as an external reference. The pD value was adjusted with a concentrated solution of TsOH and NaOD in D_2O. All spectra were recorded at room temperature. The association constants K_s were calculated by fitting f to δ_{obs} (consisting of several independent NMR signals) with a 1:1 association model using Sigma Plot software. Equations (1) and (2) were used, where **L** is the ligand and A^- is the anion, and the error limit in K is less than 10%:

$$c = ([A^-]^0 + [\mathbf{L}]^0 + 1/K_s - \{([A^-]^0 + [\mathbf{L}]^0 + 1/K_s)^2 - 4[\mathbf{L}]^0[A^-]^0\}^{1/2})/2 \quad (1)$$

$$f = (\delta_{LA} - \delta_L)c/[\mathbf{L}]^0 + \delta_L \quad (2)$$

The Job's plot was performed by examining different concentration ratios of **L** and NaF in D_2O at pD = 5.0 ± 0.1, while maintaining the total concentration of the ligand plus NaF at 10 mM. The pD value was adjusted with a concentrated solution of TsOH and NaOD in D_2O. NMR measurements were recorded at room temperature.

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Stereoselective Formation of Quaternary Carbon Centers: Alkylation of α,α-Disubstituted Amide Enolates**

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The stereoselective formation of quaternary carbon centers is one of the most challenging tasks in organic chemistry and can only be achieved using methods which employ some form of carbon – carbon bond forming reaction.[1] One of the most straightforward methods for the formation of carbon – carbon bonds is the alkylation of an enolate with an alkyl halide and,

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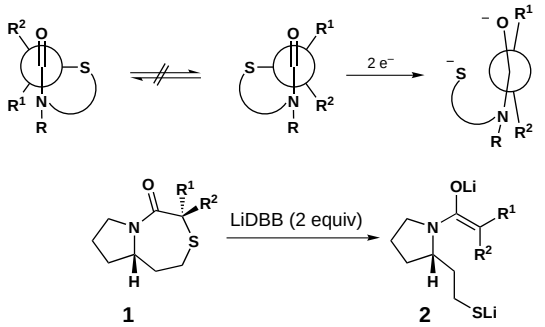
indeed, several methods for the stereoselective formation of quaternary carbon centers have been based on this approach.[2–17] One of the most significant problems in any approach based on enolate alkylation is to control enolate stereochemistry (*E* vs. *Z*). This control is necessary, as it works in tandem with π-facial selectivity to a stereoselective reaction. Many methods solve this problem by employing cyclic enolates or metal chelates.[2–11] Although this works well, the final alkylation products usually contain specific functional group residues that were necessary to form the cyclic enolate. This often limits the scope of these methods.

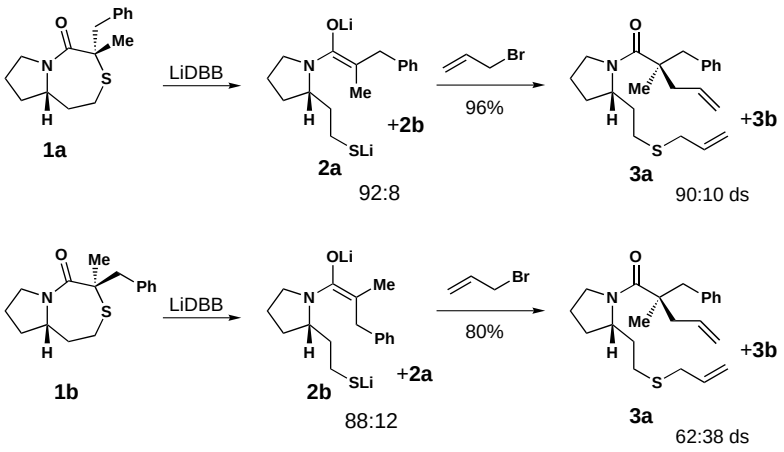
Recently, we reported a method for the preparation of α,α-disubstituted amide enolates by reduction of bicyclic thioglycolate lactams.[18] This method was based on a simple operational model wherein the bicyclic system constrains the sulfur so that it is held rigidly on one face of the carbonyl plane (Scheme 1). Upon two-electron



Scheme 1. Operational model for the stereocontrolled synthesis of α,α-disubstituted amide enolates **2** by reduction of bicyclic thioglycolate lactams **1**.

reduction, carbon–sulfur bond cleavage occurs to form an enolate dianion and the *E*/*Z* stereochemistry of the enolate is governed by the relative locations of the α-alkyl groups in the starting lactam. Good to excellent levels of stereocontrol are observed and both *E* and *Z* amide enolates **2** may be prepared (Scheme 1). Importantly, this method removes the requirement for a cyclic enolate or chelating functionality to control enolate stereochemistry; any alkyl groups may be present at the R^1 and R^2 positions. A feature of our design is that the reduction step liberates a chiral auxiliary which is reminiscent of a prolinol amide. Prolinol amides have been used to control stereochemistry in alkylations which form tertiary carbon stereocenters.[19] Here, we report that high stereoselectivities may be achieved for the formation of quaternary carbon centers by the alkylation of our α,α-disubstituted enolates, which in many cases even exceed the stereoisomer ratio of the intermediate enolates.

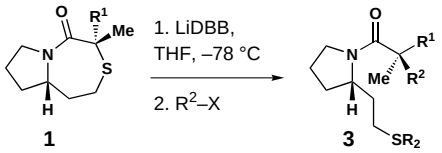
As previously reported, reduction of diastereomeric lactams **1a** and **1b** with lithium di-*tert*-butyldiphenylide (LiDBB)[20] in THF at −78 °C affords the corresponding *Z* and *E* enolates with 92:8 and 88:12 selectivity, respectively (Scheme 2).[18] Addition of allyl bromide to the enolates



Scheme 2. Alkylation to form quaternary carbon stereocenters.

resulted in the formation of C,S-dialkylated products in high yields.[21] Intriguingly, alkylation of either enolate, **2a** or **2b**, afforded *the same major product* **3a**. The alkylation of *Z* enolate **2a** showed good stereoselectivity (90:10) which was roughly in line with the ratio of the intermediate enolates. Alkylation of *E* enolate **2b** was only poorly selective (62:38).[22] Additives had only a modest effect on the alkylation selectivity of the *E* enolate. Conducting the reaction in the presence of 20% hexamethylphosphoramide (HMPA) reversed the stereoselectivity slightly (39:61 ratio), while addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 45%) or LiCl (10 equiv) had minimal effects. The addition of HMPA had no discernable effect on either the yield or the stereoselectivity in the alkylation of the *Z* enolate.

A significant and practical improvement in the stereoselectivity of the alkylation was observed when the *Z* enolates are allowed to react with unactivated alkyl halides [Eq. (1), Table 1]. For instance, reaction of enolate **2a** with ethyl iodide instead of allyl bromide afforded the corresponding product **3c** with 96.5:3.5 diastereoselectivity (93% *de*). Similar selec-



(1)

Table 1. Alkylations using unactivated electrophiles [Eq. (1)].

Lactam	R^1	*Z*/*E* Ratio of **2**[a]	*de* [%] of **2**	R^2X	Product	Yield [%]	de [%][a]
1a	Bn	92:8	84	EtI	**3c**	89	93
1a	Bn	92:8	84	*n*BuI	**3d**	76	> 95
1c	*n*Pr	87:13	74	EtI	**3e**	85	89
1c	*n*Pr	87:13	74	*n*BuI	**3f**	71	95
1c	*n*Pr	87:13	74	*i*BuI	**3g**	59[b]	87
1d	Et	90:10	80	*n*PrI	**3h**	83	> 95
1e	allyl	87:13	74	EtI	**3i**	84	88
1e	allyl	87:13	74	BuI	**3j**	80	91
1f	*n*Bu	–[c]	–	*n*PrI	**3k**	88	> 95

[a] Determined by ^{13}C NMR spectroscopy. [b] HMPA (23%) was added during the alkylation step. [c] Not determined.

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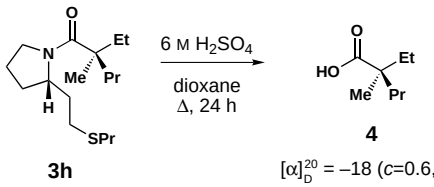
tivities were observed for a series of *Z* enolates and unactivated *n*-alkyl halides. The yields were high and in most cases the reactions proceeded to completion within 4 h at −78 °C without added polar co-solvents.[23] Branched alkyl halides such as isobutyl iodide were slower to react, but gave acceptable yields at −78 °C in the presence of HMPA.[24] Importantly, in all cases explored with unactivated alkyl iodides the alkylation selectivities were higher than the *Z*/*E* ratios of the intermediate enolates. This selectivity enhancement presumably has its origin in the low alkylation selectivity of the minor *E* enolates (1:1 selectivity was observed for reaction of **2b** with EtI). From a practical standpoint, the poor selectivity of the *E* enolates is not a significant issue, as a judicious choice of the alkylation sequence can allow stereoisomeric products to be prepared. For example, alkylation products **3f** and **3k** were prepared with high diastereoselectivity by simply inverting the overall alkylation sequence. These molecules are not true diastereomers, as they have different alkyl groups on sulfur. However, upon cleavage of the amide auxiliary (vide infra), the final products were isolated as a pair of enantiomers.

Hydrolysis of the alkylation products proved to be difficult. Heating **3h** in a 1:1 mixture of 6 M H_2SO_4 and dioxane for 24 h resulted in formation of the acid **4** [Eq. (2)] in 18% yield



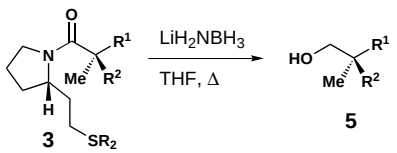
3h

$[\alpha]_D^{20}$ = –18 (*c*=0.6, EtOH)

(2)

along with recovery of 71% of the starting material. Although this direct hydrolysis was not practical, it did allow the stereochemistry of the alkylation process to be elucidated. Comparison of the optical rotation of **4** with literature data established that the *S* isomer was formed in the alkylation step.[25] Thus, the alkylation occurs from the top face of the enolate [as drawn in Eq. (2)]. Similar facial selectivity was observed by Evans and Takacs in the reactions of O-alkylated prolinol *Z* amide enolates.[19a] In the latter case, masking the prolinol hydroxyl group as an ether resulted in a switch in facial selectivity, presumably due to a loss of chelation. Given the similar facial selectivity and that chelation here would require an eight-membered ring, our results seem most consistent with an unchelated enolate.

An effective method for removal of the chiral auxiliary proved to be reductive cleavage. Treatment of the amides with lithium amidotrihydroborate[26] in THF at reflux [Eq. (3)] afforded the corresponding primary alcohols in high yields (Table 2). The enantiomeric excess of the products was assessed either directly or on the corresponding carboxylic acids (see Table 2 and Supporting Information). In all cases, the enantiomeric excess of the products was consistent with the diastereomeric excess of the alkylation products, indicating that no significant kinetic resolution occurred during the reductive cleavage of the chiral auxiliary.



3 **5**

(3)

Table 2. Reductive cleavage of the chiral auxiliary with lithium amidotrihydroborate [Eq. (3)].

Amide	R^1	R^2	Product	Yield [%]	*ee* [%]
3c	Bn	Et	**5a**	96	94[a]
3d	Bn	*n*Bu	**5b**	97	96[a]
3f	*n*Pr	*n*Bu	**5c**	99	96[b]
3k	*n*Bu	*n*Pr	**5d**	87	95[b]
3j	allyl	*n*Bu	**5e**	74	93[b]

[a] Determined by HPLC analysis (Chiracel OD column). [b] Determined by capillary GC analysis (ChirasilDex column) on the corresponding carboxylic acid. Due to peak tailing, the GC analyses are accurate to within ±2%.

In conclusion, we have developed a highly stereoselective enolate alkylation process for the generation of quaternary carbon centers. The stereoselectivities are highest for reactions of α,α-disubstituted *Z* amide enolates with unactivated *n*-alkyl iodides. The method is notable in that high selectivities are obtained without the need for cyclic enolates or metal chelates, thus allowing any alkyl group to be incorporated into the final product. The resulting alkylation products may be cleaved in high yield to the corresponding primary alcohols using lithium amidotrihydroborate. Finally, enantiomeric pairs of molecules may be formed simply by inverting the order of alkylation followed by cleavage of the chiral auxiliary. Further studies in this area will focus on the extension of the method to other carbon–carbon bond forming reactions.

Experimental Section

Reduction/alkylation procedure [Eq. (1)]: A solution of LiDBB in THF was added dropwise with a glass syringe to a solution of lactam **1a** (243 mg, 882 μmol, 1 equiv) in THF (8.8 mL) in a Schlenk flask at −78 °C until the green color of LiDBB briefly persisted. *n*-Butyl iodide (402 μL, 3.53 mmol, 4.0 equiv) was added dropwise and the solution was stirred at −78 °C for 4 h. Saturated ammonium chloride solution (10 mL) was added and the resulting mixture was warmed to room temperature and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 3% ethyl acetate in hexanes to afford 260 mg of **3d** as a colorless oil in 76% yield. The product was determined to have >95% *de* by ^{13}C NMR analysis. ^1H NMR ($C_6D_5CD_3$, 105 °C): δ = 6.95–7.08 (m, 5H), 4.24 (m, 1H), 2.93–3.11 (m, 3H), 2.38–2.51 (m, 5H), 1.97–2.16 (m, 2H), 1.07–1.60 (m, 14H), 1.13 (s, 3H), 0.76–0.88 ppm (m, 6H); ^{13}C NMR ($C_6D_5CD_3$, 105 °C): δ = 173.8, 138.8, 130.3, 127.7, 126.0, 58.8, 48.2, 46.9, 46.3, 41.3, 34.3, 31.9, 31.8, 29.3, 28.8, 27.0, 25.0, 23.2, 22.6, 21.8, 13.6, 13.2 ppm. C,H,N analysis calcd for $C_{24}H_{39}NOS$: C 73.98, H 10.09, N 3.59; found: C 74.31, H 9.98, N 3.60.

Reductive cleavage of the chiral auxiliary [Eq. ((3)]: A solution of *n*-butyllithium in hexanes (2.27 M, 2.39 mL, 5.42 mmol, 3.90 equiv) was slowly added to a stirred solution of diisopropylamine (799 μL, 5.70 mmol, 4.10 equiv) in THF (2.5 mL) at 0 °C. After stirring for 10 min, borane–ammonia complex (90%, 191 mg, 5.56 mmol, 4.0 equiv) was added in one portion. After stirring at 0 °C for 15 min the mixture was warmed to 23 °C and after 10 min a solution of **3c** (464 mg, 1.39 mmol, 1 equiv) in THF (5 mL) was added with a cannula. The mixture was heated at reflux for

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24 h, then cooled to 0 °C, and quenched with aqueous hydrochloric acid (3 M, 5 mL). The resulting mixture was warmed to 23 °C and stirred for 30 min, at which point aqueous sodium hydroxide (3 M, 10 mL) was added. The mixture was stirred at 23 °C for 30 min and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Column chromatography on silica gel eluting with 30 % diethyl ether in pentane afforded (*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl alcohol **5a** (239 mg, 1.34 mmol, 96 %) as a colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.19 - 7.31$ (m, 5H), 3.33 (s, 2H), 2.61 (AB, 2H, $J = 24.6$ Hz), 1.58 (bs, 1H), 1.27 – 1.40 (m, 2H), 0.93 (t, 3H, $J = 7.5$ Hz), 0.82 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 139.0$, 130.8, 128.1, 126.2, 68.4, 42.8, 39.1, 29.1, 21.0, 8.3 ppm. High-resolution FAB-MS: m/z (M+H): 179.14359 ($C_{12}H_{19}O^+$ requires 179.14359). $[\alpha]_D^{25} = -5.9$ (c = 14.2, CH_2Cl_2). The product was determined to have 94 % *ee* by HPLC (Chiralcel OD column, eluting with 1 % 2-propanol in hexanes at 0.7 mL min^{-1}; $R_t = 20.5$ min (major enantiomer), 22.8 min (minor enantiomer)).

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The Chemistry of the Oxychlorination Catalyst: an In Situ, Time-Resolved XANES Study**

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Almost all of the world production of vinyl chloride today is based on cracking of 1,2-dichloroethane. For many decades, this compound has been produced by catalytic oxychlorination of ethylene with hydrochloric acid and oxygen [Eq. (1)]. The reaction is performed at 490 – 530 K and 5 – 6 atm (1 atm ≈ 1.01×10^5 Pa) using both air and oxygen in fluid- or fixed-bed reactors.[1]

$$C_2H_4 + 2\,HCl + \tfrac{1}{2}O_2 \rightarrow C_2H_4Cl_2 + H_2O \quad (1)$$

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