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Stereoselective Alkylations of Chiral Nitro Imine and Nitro Hydrazone Dianions. Synthesis of Enantiomerically Enriched 3-Substituted 1-Nitrocyclohexenes[†]

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Abstract

Dianions of chiral nitro imines (generated by a combination of LDA and *s*-BuLi) underwent diastereoselective alkylation with methyl, butyl, isopropyl, allyl and methallyl iodides. In contrast to the behavior of simple metalloenamines, the most selective auxiliary contained no coordinating groups, but did possess a large steric difference between the two substituents. The yield and selectivity of the alkylations were improved by the addition of HMPA or DMPU. The use of (*S*)-1-naphthylethylamine as the auxiliary afforded the *R* absolute configuration of the alkylation products. This stereochemical outcome could be rationalized by simple steric approach controlled alkylation in a conformationally fixed, internally coordinated dianion. A SAMP nitro hydrazone gave poorer yields and selectivities.

Introduction

Nitroalkenes are an extremely versatile class of organic compounds, serving as substrates for a wide variety of synthetically useful reactions.¹ One of the major themes in this research group over the past two decades is the invention, development and application of tandem [4+2]/[3+2] cycloaddition reactions in which nitroalkenes serve as the 4 π components.² Nitroalkenes undergo smooth cycloaddition reactions with both activated and unactivated olefins in both an intramolecular and intermolecular modes. The nitronates generated by this process serve as useful 1,3-dipoles in [3+2] cycloaddition reactions also in both intermolecular and intramolecular processes. If chiral, non-racemic vinyl ethers are used as dienophiles, the α -hydroxy lactams (formed by hydrogenolytic unmasking) are obtained in high enantiomeric purity. This strategy has been employed in the total syntheses of many representatives of the pyrrolizidine³ and indolizidine⁴ classes of natural products, amino sugars,⁵ sceletium,^{6a} melodinus^{6b} and daphniphyllum alkaloids.^{6c} In addition, the tandem

[†]This paper is dedicated to the memory of Professor Albert I. Meyers for his pioneering contributions to asymmetric synthesis and his inspiring example of passion for organic chemistry.

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Supplementary Material Available. General experimental details and H¹ NMR spectra of all characterized compounds. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

cycloaddition sequence has been employed to prepare 1-azafenestranes, a novel class of strained polycyclic compounds.⁷

In the context of the *intramolecular* nitroalkene cycloaddition studies, an efficient and general synthesis of 3-substituted-1-nitrocyclohexenes was required. This was accomplished (Scheme 1) through the alkylation of the dianion of either a nitro imine or a nitro hydrazone, followed by reduction and elimination to afford the substituted 1-nitrocyclohexene.⁸ This process could also serve as an ideal template for the development of auxiliary-based asymmetric alkylation reactions, using chiral nitro imines or nitro hydrazones. Similar reduction and elimination of the alkylated products would then provide enantiomerically enriched 3-substituted 1-nitrocyclohexenes. The realization of this asymmetric alkylation could have numerous implications. First, it would provide an example of the relatively rare auxiliary-based stereoselective alkylation of a dianion. Secondly, the reduction-elimination sequence would provide access to versatile nitroalkenes in enantiomerically enriched form. Finally, through the use of the Nef reaction,⁹ these 3-substituted cyclohexenes could be transformed into enantiomerically enriched 3-substituted cyclohexanones. This approach to these compounds would complement the well-established asymmetric addition of organocuprates to α,β -unsaturated cyclic ketones.¹⁰

In 1988, we communicated our initial results on the alkylation of chiral nitro imine dianions and the conversion of these alkylated products into enantiomerically enriched nitroalkenes.¹¹ Remarkably, in the intervening 20 years, no new methods for the enantioselective synthesis of such nitroalkenes have been described. Because the foundation of this work is rooted in the pioneering studies of Professor Albert I. Meyers, we felt it a fitting tribute to this great chemist to provide the full details of this work, as well as the results of alkylation studies on the dianion of a chiral nitro hydrazone.

Background

1. Stereoselective Alkylations of Metalloenamines.¹²

The discovery of metalloenamines as enolate equivalents in the early 1960's represented a landmark advance in the development of site selective carbon-carbon bond forming reactions.¹³ In addition to sharing many of the same advantages over classical enolates as their enamine analogs, metalloenamines offered the additional benefit of greater chemical reactivity compared to enamines.^{13a} Moreover, the use of chiral amines as precursors to the metalated imines introduced the ability to carry out these alkylations in a stereoselective manner. Early efforts in this area demonstrated the feasibility of this process, but generally resulted in low levels of stereoselectivity.^{14,15}

In the mid-1970's, the first major breakthrough in the field of stereoselective alkylations of chiral metalloenamines was reported by Albert I. Meyers (Scheme 2).¹⁶ For example the cyclohexanone imine prepared from (*S*)-phenylalaninol methyl ether could be metalated with LDA and alkylated to obtain, after hydrolysis, enantiomerically enriched 2-alkylcyclohexanones **3** with enantiomeric ratios (ers) generally greater than 90:10. The success of the Meyers method was proposed arise from the formation of a lithium chelate in the metalloenamine, the rigidity of which would influence the direction of attack of the approaching electrophile. The poorer selectivities observed in the earlier attempts.^{14,15} was, most likely, due to the absence of an appropriate coordinating group in the chiral amine precursor. Thus, lacking a chelate and its superior orienting properties, the metalloenamines were not effective diastereoface controllers.

2. Stereoselective Alkylations of Hydrazones.¹⁷

In 1976, Enders reported his initial work on the asymmetric alkylation of hydrazones derived from (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP).^{18,19} SAMP hydrazones prepared from ketones and aldehydes can be metalated and alkylated with broad generality, high yield and selectivity (Scheme 3). Removal of the auxiliary from the product hydrazones by hydrolysis or ozonolysis afforded α -alkylated ketones in high enantiomeric purity. As in the case of metalloenamines, the coordination of lithium with the methoxy oxygen is believed to play a major role in controlling the stereoselectivity observed. Further development of the use of SAMP and its enantiomer (RAMP) by the Enders group has resulted in a wide variety of asymmetric alkylation reactions that still in 2008 represent the methods of choice for the asymmetric synthesis of alkylated ketones and aldehydes.^{17,20} Furthermore, modified versions of SAMP have been employed in stereoselective reactions.²¹ Remarkably, asymmetric alkylation remains one of the truly useful synthetic reactions for which a general asymmetric, catalytic process has yet to be developed.²²

3. Stereoselective Alkylations of Dianions

The alkylation of dianions has long been known as a versatile and important way to construct carbon-carbon bonds.²³ In recent years, asymmetric variants of dianion alkylations have become more commonplace. Such asymmetric dianion alkylations can be divided into two main categories depending on whether removable chiral auxiliaries are used. Those dianion alkylations that are simply diastereoselective by nature are much more common.²⁴

In contrast, employment of a chiral auxiliary for asymmetric induction in a dianion alkylation, followed by auxiliary removal to leave behind the newly-created stereogenic center, is rare. Following our initial disclosure¹¹ Bartoli²⁵ reported the alkylation of chiral β -enamino ketones via their dianions (Chart 1). Substrates of this type are derived from 1-phenylethylamine. With the exception of the methyl electrophiles, alkylations generally proceed with diastereoselectivities (drs) greater than 85:15, and these reactions ultimately afforded enantiomerically enriched γ -alkylated chiral 1,3-diketones. Two groups have used 8-phenylmenthol and related compounds as dianionic chiral auxiliaries in the synthesis of α -alkyl amino acid derivatives. Fukumoto²⁶ uses carboxylic acids while Berkowitz²⁷ employs amides to effect the dianionic asymmetric alkylation at the group next to the carboxylic acid or amide nitrogen, respectively. Jenkins²⁸ reported the stereoselective alkylation of cyclohexane-1,2-dicarboxylic acid monomethyl ester to afford, after auxiliary removal, optically active *bis*-hydroxymethyl cyclohexane derivatives. Finally, Myers²⁹ employed pseudoephedrine as a chiral auxiliary in the dianionic diastereoselective alkylation of hydroxy amides. Removal of the auxiliary affords enantiomerically-enriched carboxylic acids, primary alcohols, aldehydes, or ketones.

Results

1. Nitro Imines.³⁰

1.1. Preparation and Alkylation of Nitro Imines—Following the Meyers' insight for metalloenamine monalkylation,^{16a} we began our studies by focusing on chiral auxiliaries that contained coordinating groups. Chiral nitro imines were synthesized as indicated in Scheme 4, using the procedure developed in these laboratories for the synthesis of achiral nitro imines.⁸ Accordingly, cyclohexanone was converted into the corresponding enol acetate, which was then transformed into 2-nitrocyclohexanone according to the method of Zajac.³¹ Treatment of this nitro ketone with the acetate salt of the appropriate chiral amine (benzene, reflux) afforded the desired nitro imines. The initial set of alkylation substrates is indicated in Table 1. Chiral methoxy amines used for the synthesis of nitro imines **1** and **2** were derived from (*S*)-phenylalaninol and (*S*)-phenylglycinol, respectively, using the

procedure of Meyers.^{16a,32} The methoxy amine used in the synthesis of **3** was prepared from L-norpseudoephedrine by methyl iodide alkylation of the potassium alkoxide anion. All chiral nitro imines were found to exist exclusively in the *aci*-nitro form as judged by their infrared spectra.^{8,33} For the neutral nitro enamine (nitro ene hydrazine) structure, the C=C (1630–1660 cm⁻¹) and NO₂ (ν_s , 1250–1280 cm⁻¹) IR stretches are most diagnostic.^{33a,b} The dipolar (*aci*-nitronate) structure is characterized by the strong C=N (1590–1605 cm⁻¹) and N-O (1215–1260 and 1120–1180 cm⁻¹) stretches^{33c} also observed in α -keto nitronate salts.^{33d}

The dianions of these nitro imines were generated using the optimized protocol from prior studies (2.0 equiv of *s*-BuLi in THF containing 5.0 equiv of HMPA at –78 °C).⁸ Following dianion formation, the gold-yellow solutions were cooled to –90 °C and treated with various electrophiles. The initial results were disappointing (Table 1). Phenylalaninol-derived substrate **1** provided the highest level of diastereoselectivity in the alkylation reaction (70.5:29.5 with butyl iodide), but this thick oily substrate was operationally difficult to use, and in the alkylations with methyl and allyl halides, the diastereomeric mixture could not be separated chromatographically. On the other hand, the phenylglycinol-derived substrate **2** was crystalline and both the methylation and allylation products were separable by chromatography. Unfortunately, diastereoselectivity in these cases was equally poor. Even the norpseudoephedrine-derived substrate, where presumably the second stereogenic center could align itself much more closely to the alkylation sight than in the case of either **1** or **2**, provided low stereoselectivity in the alkylation step.

Fraser³⁴ has reported that stereoselectivity in certain monoanion metallocenamine alkylations can be improved through the use of magnesium as a counterion. Hence, we treated **3** sequentially with one equivalent of methyl magnesium bromide, one equivalent of *s*-BuLi and allyl iodide. The allylated nitro imine product mixture was obtained in 57% yield, with a dr of only 60:40.

These results revealed substantial differences between the metallocenamine monoanion alkylation reactions and these nitro imine dianion alkylations. Whereas Meyers had found that a coordinating moiety was required for high stereoselectivity for the monoanions, our results with similar auxiliaries suggested that lithium coordination was not playing a major role in the dianion alkylations. To evaluate the requirement for a coordinating ligand, chiral nitro imine **6** derived from (*S*)-1-(naphthyl)ethylamine was synthesized and evaluated. The commercially available, chiral amine was readily transformed into nitro imine **6** in 51% yield using the standard procedure. Treatment of **6** with two equivalents of *s*-BuLi in THF-HMPA followed by addition of allyl iodide afforded the allylated products in 48% chemical yield with a dr of 71.0:29.0 (Scheme 5). The diastereomeric products could be easily separated by silica gel chromatography, and both were highly crystalline in the pure state. Importantly, the diastereoselectivity achieved in this reaction was higher than any that had been achieved with auxiliaries containing coordinating oxygen atoms. This result confirmed that the monoanion and dianion alkylations were fundamentally different and prompted a reexamination of early literature on the stereoselective alkylations of chiral metallocenamines that did not contain coordinating ligands.^{12a} Importantly, in nearly every instance described in this early work, LDA was employed as the base. Accordingly, the alkylation of **6** was repeated (Scheme 5) using one equivalent of LDA (0 °C) and two equivalents of *s*-BuLi at –78 °C (the first equivalent of *s*-BuLi would be needed to deprotonate the diisopropylamine formed). We were delighted to discover that the yield increased to 73%, but more importantly, the dr rose to 93.5:6.5, more than double anything seen previously.

This result immediately prompted the question as to whether a similar improvement in yield and selectivity might be obtained by using LDA with a chiral nitro imine containing a

coordinating group. Thus, phenylglycine-derived substrate **2** was transformed into its dianion using the new LDA (1 equiv)/*s*-BuLi (2 equiv) protocol, followed by alkylation with allyl iodide. The yield did improve substantially from 60% to 83%, but the diastereoselectivity improved only marginally from 67.5:32.5 to 70.5:29.5. Taken together, these results suggest that the difference in size between the groups on the chiral auxiliary is playing the key role in these LDA/*s*-BuLi alkylation reactions.

1.2. Optimization of Alkylation with 6—To gain further insight into the role of the amide base in these asymmetric alkylation reactions, as well as to understand the effect of experimental parameters on outcome, a detailed study of the effect of additives, solvent, amide base and base stoichiometry was carried out with substrate **6**, using allyl iodide as the test electrophile. The results are collected in Table 2. The use of coordinating additives was examined first, since we wished to remove the toxic HMPA from the reaction protocol. Elimination of HMPA from the reaction mixture led to recovery of significant amounts of unreacted starting material (about 40%) along with diminished selectivity (entry 1). The use of warming cycles, up to $-20\text{ }^{\circ}\text{C}$, in the metalation step failed to lead to stoichiometric dianion formation. Substitution of TMEDA for HMPA led to low yields and reduced selectivity (entry 3). We were gratified to discover that the less toxic dimethylpropylene urea (DMPU)³⁵ provided a higher yield and better diastereoselectivity than HMPA (entry 4). The only drawback associated with DMPU was that a small amount of starting material usually remained after the reaction, a situation not generally observed with HMPA. The use of warming cycles in the metalation did not eliminate this problem but did reduce diastereoselectivity. We therefore decided to employ DMPU in the standard metalation protocol since the small amount of starting material could be readily removed by chromatography.

In a brief survey of different solvents, the reduced solubility of the starting material in ether (entry 5) and DME (entry 6) led to poorer results. Because the amide base was essential for good stereoselectivity, a number of amide bases were surveyed (entries 7–9). Lithium diisopropylamide (LDA) was uniformly superior to lithium diethylamide (LDEA), lithium dicyclohexylamide (LDCA), and lithium tetramethylpiperidine (LiTMP) in both yield and selectivity. The diastereoselectivity was not affected by the choice of base as both LDA and LDCA gave comparable results (entries 4 and 8). The low yield and large amount of unreacted starting material seen with the LiTMP (entry 9) suggest that it may be too large to quantitatively deprotonate **6** in the time given, thus obscuring its role in the overall dianion structure.

Finally, base stoichiometry was examined. Unexpectedly, the use of 1.0 equiv of LDA and 1.0 equiv of *s*-BuLi (entry 10) provided a good yield and high selectivity. In this case, diisopropylamine, and not the lithium amide, must be serving as ligand for the dianion. This implies either that the second pK_{a} of **6** is lower than that of diisopropylamine or that the monoanion of **6** is kinetically more acidic than diisopropylamine and proton transfer is slow. Favorable results in the generation of the dianion of a different nitro imine system (vide infra) prompted us to examine the results of using LDA alone to generate the dianion. Thus, treatment of **6** with 2–3 equiv of LDA alone at $-20\text{ }^{\circ}\text{C}$, followed by alkylation at $-78\text{ }^{\circ}\text{C}$, afforded the desired products in 76–83% yield, but with diminished selectivity (entries 11 and 12).

The scope of this asymmetric alkylation was surveyed with respect to the electrophile, and the results are collected in Table 3. Diastereomeric ratios were determined both by measuring yields of isolated products and by HPLC analysis of the purified but unresolved reaction mixtures, the latter providing a direct comparison of diastereoselectivities. The reaction worked well for allyl, methallyl, and butyl alkylations (entries 1, 2, and 4), both in

terms of yield and selectivity. Alkylation with methyl iodide occurred in good yield (entry 3), but the diastereoselectivity (59%) was lower than with any other electrophile. To address this, dimethyl sulfate was employed, but the yield was unacceptably low (<10%). In contrast, isopropyl iodide (entry 5), gave good selectivity but low yield. In each instance, the diastereomeric products were crystalline and easily separated by chromatography with the exception of the isopropyl adduct **7e** wherein the low yield precluded isolation of a minor diastereomer. A pure sample of the minor isomer of the methyl adduct **7a** was obtained by conducting the alkylation with HMPA instead of DMPU, since the minor isomer of **7a** co-eluted with the starting material on chromatography. Unexpectedly, both benzyl halides and benzyl tosylates gave poor results; benzyl bromide afforded a reasonable dr (95.5:4.5) but low yield (< 40%).

1.3. Assignment of Enantiomeric Purity and Absolute Configuration—The conversion of these alkylated products into enantiomerically enriched nitroalkenes, though obviously the end objective, was also required to determine the absolute configuration and enantiomeric purity of the products. These assessments were accomplished in two independent ways using the major diastereomer from the butyl alkylation **7b** and the methyl alkylation **7a**. The results for **7b** are shown in Scheme 6. Treatment of an ethanol solution of **7b** (major) with 4.0 equiv each of sodium borohydride and cerium trichloride,⁸ added in portions over 8 h, led to formation of nitroalkene **8** in 53% yield ($[\alpha]_D^{27} -20.7$ (CHCl₃, c 3.21)). Basification of the acidic washings from this reaction, followed by extraction and Kugelrohr distillation, allowed for recovery of the (*S*)-1-(naphthyl)ethylamine auxiliary in 52% yield. Conversion of this recovered amine into its 3,5-dinitrobenzoyl amide, followed by analysis on a CSP-HPLC column,³⁶ showed that the amine had an er of 99.8:0.2. This is noteworthy since the starting (*S*)-1-(naphthyl)ethylamine used to form the nitro imine substrate **6** had an er of 95.5:4.5 when similarly analyzed. Apparently, recrystallization of **6** enhanced its enantiomeric purity, and the entire cycle served as a means of purifying the chiral auxiliary!

Treatment of nitroalkene **8** with L-Selectride,³⁷ followed by nitronate hydrolysis afforded 3-butylcyclohexanone **9** in 35% yield (Scheme 6). This ketone was subsequently treated with (2*R*,3*R*)-butanediol (er >99.7:0.3)³⁸ according to the method of Corey³⁹ to generate a diastereomeric mixture of dioxolane ketals **10**. Carbon-13 NMR analysis of this mixture (125 MHz) indicated only the presence of the 3*R* epimer (C(3) = 43.16 ppm).^{39a} None of the C(3)*S* epimer was detected at 44.01 ppm^{39a} with a S/N ratio of 33.2. Hence the *R* enantiomer was formed with an er of > 97:3.⁴⁰

This conclusion was confirmed by studies with the major diastereomer from the methyl alkylation **7a**, and these results are shown in Scheme 7. Treatment of **7a** (major) with 3 equiv of sodium borohydride and cerium trichloride⁸ afforded nitroalkene **11** in 61% yield. Similar transformation into ketone **12** was followed by treatment with semicarbazide hydrochloride to afford the solid semicarbazone **13** ($[\alpha]_D^{27} -18.8$ (EtOH, c 0.42)). A comparison of the optical rotation data for **13** to that in the literature which had been chemically correlated to (*R*)-pulegone indicated that the semicarbazone was of the *R* absolute configuration, with an e.e. of 91%.⁴¹

1.4. Preparation and Alkylation of Nitro Imines 16, 18 and 21—The results from the reactions of nitro imine **6** clearly indicated that the diastereoselectivity of the dianion alkylations was related to the size difference between the two non-hydrogen substituents on the stereogenic center of the amine. Thus, to improve the stereodifferentiation in dianion alkylations, nitro imines **16** and **18** were devised in which the groups on the stereogenic center are sterically quite disparate. These substrates would be synthesized initially in racemic form to evaluate the diastereoselectivities in the alkylation. In those instances where

promising results were obtained, the enantiomerically pure amine would be prepared by resolution or asymmetric synthesis.

The synthesis of racemic **16** is shown in Scheme 8. The known amine **15**⁴² was prepared in two steps, starting from 9-anthrylnitrile. Addition of methylmagnesium bromide to the nitrile in a benzene-ether mixture provided methylimine **14**⁴³ in 78% yield after silica gel chromatography. Reduction of **14** with sodium cyanoborohydride according to the method of Ciganek⁴² afforded the required chiral amine in 66% yield. Simply stirring the acetate salt of this amine with 1.0 equiv of 2-nitrocyclohexanone in benzene provided the crystalline nitro imine **16** in 76% yield. Unfortunately, metalation of **16** by either the usual LDA/*s*-BuLi protocol or through the use of 3.0 equiv of LDA, followed by addition of allyl iodide, resulted in the formation of multiple products and low mass recovery.

Racemic nitro imine **18** was synthesized by the standard procedure from pinacolylamine acetate and cyclohexanone (benzene, reflux) in 56% yield (Scheme 9). Allylation experiments with this compound were also disappointing. Use of the LDA (1.0 equiv)/*s*-BuLi (2.0 equiv) protocol provided an inseparable mixture of diastereomeric products in 44% chemical yield with a 76.0:24.0 dr. Use of 3.0 equiv of LDA provided the same chemical yield, but the dr dropped to 67.0:33.0.

To extend the scope of the dianions derived from the 1-(naphthyl)ethylamine auxiliary, substrate **21** was constructed to assess the feasibility of conducting asymmetric dianion alkylations in the presence of an aromatic ring (Scheme 10). The synthesis of **21** began with the nitration of 5-methoxy-2-tetralone⁴⁴ using the anionic nitration method of Feuer.⁴⁵ Treatment of the tetralone with potassium *t*-butoxide in THF at -50 °C produced a green anion that was treated with isoamyl nitrate to afford the solid potassium nitronate salt **20** in 85% yield. For this transformation to be successful, the potassium *t*-butoxide must be of high purity otherwise the potassium salt would not precipitate out of solution. Attempts to isolate the nitro ketone directly led to very low yields (15%) due to its instability. However, potassium salt **20** could be transformed into nitro imine **21** by first treating the acetate salt of the 1-naphthylethylamine with an additional equivalent of acetic acid in benzene and then adding the solid potassium nitronate salt. This procedure, although low yielding, did provide sufficient quantities of **21** for trial alkylations.

Results of the alkylation experiments with **21** are shown in Scheme 11. Use of the established protocol of LDA (1 equiv) and *s*-BuLi (2 equiv) led to a complex mixture, with low yields of the desired products. We hypothesized that the highly reactive *s*-BuLi might be reacting with the methoxy-containing aromatic ring; therefore, we repeated the alkylation using exclusively LDA as the base (entries 2 and 3). In both instances, much cleaner reactions ensued, with best results being obtained using 2 equiv of LDA (entry 2). However, in this instance, diastereoselectivity was less than half of that observed in the simple cyclohexyl system, indicating that structural changes distant from the reaction sight can influence the dianion structure and affect the stereochemical outcome of the reaction.

2. Nitro Hydrazones

The successes achieved in SAMP hydrazone asymmetric alkylation reactions,^{17e} coupled with the general and efficient alkylations of achiral nitro hydrazone dianions described previously,⁸ made evaluation of the 2-nitrocyclohexanone SAMP hydrazone (**23**) a logical next step (Scheme 12). Like nitro imines, nitro hydrazones can be easily doubly deprotonated and their subsequent alkylations proceed in generally higher yields than those of nitro imines. The disadvantage of nitro hydrazones lies in the fact that their transformations to nitroalkenes require harsher conditions (sodium borohydride, then acetic anhydride at 120 °C) than nitro imines.⁸ We sought initially to evaluate alkylations of the

dianion of **23**. If higher yields and selectivities could be achieved than in the nitro imine cases, we would reevaluate methods of achieving mild conversion to nitroalkenes.

The synthesis of SAMP nitro hydrazone **23** is shown in Scheme 12 and begins with *N*-formyl prolinol.⁴⁶ Direct application of the Enders sequence of methylation, hydrolysis, urea formation and Hofmann degradation afforded crude SAMP, which was treated directly with 2-nitrocyclohexanone/acetic acid in benzene to provide pure **23** in 15% overall yield from formyl prolinol.

The results of alkylation experiments with **23** are collected in Scheme 13. The dianions were formed using the optimized protocol from the achiral nitro hydrazone series,⁸ namely by forming with *s*-BuLi in THF/HMPA. Unlike the nitro imines however, a reasonable level of stereoselection was achieved in the alkylation despite the absence of amide bases in the deprotonation. The two diastereomeric products could not be separated by chromatography, so drs were determined by integration of the *aci*-proton signals in the ¹H NMR spectrum. DMPU did *not* serve as a suitable replacement additive for HMPA in the nitro hydrazone alkylations. The fact that a reasonable level of stereoselectivity was achieved despite the absence of an amide base suggested that, unlike the nitro imines, an internal chelation of the lithium ion by the methoxy oxygen, as suggested by Enders,^{17a} may be of critical importance in the dianion structure. However, if this is the case, it might be unreasonable to expect any significant improvement with lithium amide bases. Indeed, the use of the LDA (1.0 equiv)/*s*-BuLi (2.0 equiv) protocol produced only a marginal increase in selectivity with a concurrent reduction in yield. The use of LDA alone (3.0 equiv) led to a decrease in both yield and selectivity.

Discussion

1. Dianion Generation and Structure

The use of polymetalated derivatives of functionalized organic molecules has been extensively developed²³ since the pioneering work of Hauser and Harris.⁴⁷ Di- and even trianions have been generated from hydrazones, again following initial studies by the Hauser group.⁴⁸ These polyanions, however, have additional stabilizing groups on the terminal nitrogen (aryl, arylSO₂ or arylCO) wherein NH deprotonation constitutes one of the anions. In contrast, the dianions described herein possess the general structure **i** which have been reported on only two previous occasions, first by Hauser in the alkylation the phenylimine of acetylacetophenone (**i**: Z=PhCO, R=Ph).⁴⁸ In a second, more related example, Fuchs⁴⁹ has reported the formation and trapping of β -keto ester tosylhydrazone trianions, **ii**.

By comparison, there exists considerable precedent in the chemistry of polymetalated derivatives of nitro aliphatic compounds from the work of Seebach.⁵⁰ Both, α,α' -dianions, and α,β -dianions (super-enamines) **iii**, have been generated with and without additional anion stabilizing groups. Because these structures described herein are secondary nitro compounds only α,β -dianions are possible. The α,β -dianion of 1-nitrocyclohexane is generated at -90 °C with *n*-BuLi and *t*-BuLi in the presence of HMPA,^{50a} conditions similar to those employed for nitro imines. Thus, the question of gross dianion structure is understood in terms of the relative kinetic acidifying effects of a hydrazone/imine moiety (by loss of H_a) to form **v** versus the nitronate moiety (by loss of H_b) to form **vi** from the

monoanion **iv**. In all cases studied the products arose from alkylation of the dianion **vi** exclusively. However, we cannot rule out partial formation of **v** since the documented instability of such species may account for lower yields with α -nitro imines.

The detailed structures of the α -nitro imine ($2\text{Li}^+\cdot\mathbf{6}^{2-}$) and α -nitro hydrazone ($2\text{Li}^+\cdot\mathbf{23}^{2-}$) dianions have not been elucidated, but it is nonetheless instructive at this point to speculate on reasonable possibilities based on the known structures of the isolated nitro, hydrazone and imine anions. The solution structures of metalated hydrazones and imines derived from both ketones and aldehydes have been extensively investigated by the groups of Newcomb and Bergbreiter,^{12a} Enders,^{17a} Fraser,^{12b} Knorr,⁵¹ Meyers⁵² and Collum.⁵³ Direct observation of lithioenamines and lithiohydrazones coupled with stereochemical analysis of kinetic trapping experiments has provided a wealth of information on the carbon-carbon and carbon-nitrogen double bond geometries. These studies are primarily concerned with the origin of the "syn effect"^{12c} and effects of deprotonation conditions on anion structure in acyclic and macrocyclic frameworks. In $2\text{Li}^+\cdot\mathbf{6}^{2-}$ and $2\text{Li}^+\cdot\mathbf{23}^{2-}$, the geometries of the carbon-carbon and carbon-nitrogen bonds are assured ($E\text{ C}=\text{C}/Z\text{ C}-\text{N}$, **vi**, Scheme 14) by both structural constraints and the observed syn disposition of the nitrogen substituent in the products.

The more relevant question is the location and role of the counterion and overall aggregation state. These questions have been addressed in an ongoing series of elegant studies by Collum using a combination of $^6\text{Li}/^{15}\text{N}$ NMR spectroscopy, X-ray crystallography, molecular weight determinations and reaction kinetics.⁵³ For the structure of $2\text{Li}^+\cdot\mathbf{6}^{2-}$ the closest analogies are found in the X-ray structures of lithio cyclohexanone phenylimine (**25**)^{53c} and lithio cyclohexanone cyclohexylimine (**26**)⁵³ⁱ which both exist as solvated dimers in the solid state. These structures represent the limits of η^1 and η^3 bonding motifs that are characteristic of these species. Moreover, Collum has clearly shown that these different modes (and aggregation states) are strongly solvent dependent; in pure THF, **26** exists as a highly solvated monomer and in THF containing HMPA, the analogous lithio cyclohexanone isopropyl imine (**27**) also exists as a solvated monomer.⁵³ⁱ

2. Rationalization of Stereoselectivity

Any attempt to rationalize the stereochemical outcome of the dianion alkylations must be tempered with the caveat that the solution structures and transitions structure stoichiometries are not known. That said, from empirical observation of the stereochemical outcome, three significant contributions to the alkylation selectivity can be identified: (1) the difference in steric bulk between the substituents on the chiral auxiliary, (2) the use of an amide base in the deprotonation and (3) the use of a strongly coordinating additive (HMPA or DMPU). The lack of a requirement for a coordinating appendage on the auxiliary contradicts the lessons from Meyers, Koga and Enders who introduced oxygen and nitrogen groups to improve the selectivity of metalloenamine alkylations. Apparently, the conformation-controlling features of those coordinating groups in the monoanion structures are not needed in the dianions. This behavior suggests that the dianions take up defined conformations in structures that are dependent on the presence of an amide base⁵⁴ and a coordinating ligand. Curiously however, the size of base has little influence on the selectivity of alkylation, but both HMPA and DMPU improved the selectivity.

These empirical observations, taken together with the absolute stereochemical course of the reaction allow the formulation of hypothetical structures for the chiral dianions, Scheme 15. Under the assumption that the dianion $2\text{Li}^+\cdot\mathbf{6}^{2-}$ is monomeric in solution, two limiting

structures are suggested that incorporate the structural features of individual lithio metalloenamines (vide supra) and nitronates.⁵⁵ To explain the high selectivity without chelating groups on the auxiliary implies that the metalloenamines adopts a highly preferred conformation that provides significant levels of facial differentiation. Structures **vii** and **viii** feature a metalloenamine that is internally coordinated to the lithio nitronate moiety in such away as to fix the position of the C-N bond to the 1-naphthylethyl group synplanar to the enamine C-C double bond. This feature provides the primary diastereoface differentiation for the approach of the alkylating agent to the metalloenamine carbon. The difference between these two structures is the η^3 or η^1 coordination motifs for the second lithium atom which is suggested to be controlled by the solvating power of the medium. The η^3 -coordination of the second lithium atom in **vii** could be preferred in pure THF, i.e. wherein the enamine C-C double bond can compete with the solvent for the lithium ion. The η^1 -coordination of both lithium atoms in **viii** would be preferred in a medium containing stronger donor solvents (HMPA or DMPU). The slight increase in diastereoselectivity seen with HMPA or DMPU could arise from removing the η^3 -coordinated lithium atom from the *Re* face of the dianion (assuming that is its preferred location on steric grounds). Neither of these models explains the enhanced selectivity afforded by the use of amide bases in combination with *s*-BuLi. Presumably the amide plays an important role as a ligand for the one of the lithium atoms by influencing aggregation state or the conformational preferences of the auxiliary.⁵⁶

Conclusion

The dianions of nitro imines derived from chiral amines could be generated by the combination an amide base (LDA) and *s*-BuLi. These dianions underwent alkylation in moderate yields and good diastereoselectivities with methyl, butyl, isopropyl, allyl and methallyl iodides. DMPU improved the yield and selectivity of the alkylation. The nitro imine **6** derived from (*S*)-1-(naphthyl)ethylamine afforded the *R* configuration of the alkylation products. The nitro hydrazone gave poorer results compared to the nitro imines including inferior yields and selectivities. Also, HMPA was required with the nitro hydrazones, while the safer DMPU could be used with nitro imines. Although empirical models could rationalize the stereochemical outcome, the well-established structural variability of simple metalloenamines discourages a too-literal interpretation of these models.

Experimental Section

General Methods

See Supporting Information.

General Procedure 1. Preparation of Chiral Nitro Imines. 2-[*S*-(1-Naphthyl)ethylimino]-*aci*-1-nitrocyclohexane (**6**)

Freshly distilled (130–140 °C (ABT), 0.5 mm Hg) (*S*)-(naphthyl)ethylamine (7.66 g, 44.8 mmol) was dissolved in benzene (150 mL) and cooled in ice. Acetic acid (2.68 g, 2.55 mL, 44.8 mmol) was added dropwise. After cooling in ice 10 min, the salt precipitated from solution, stopping the stir bar. 2-Nitrocyclohexanone (6.1 g, 42.6 mmol) in benzene (75 mL) was added dropwise over 25 min with external shaking required in the beginning until the stir bar was shaken free of the precipitated salts. After addition, the mixture was heated to reflux with water removal (Dean Stark trap) for 1 h. The cooled solution was poured into 1% aqueous HOAc (220 mL) and extracted with EtOAc (1 × 200 mL, then 2 × 100 mL). The combined organic layers were washed with water (1 × 200 mL), brine (1 × 200 mL), dried (Na_2SO_4) and evaporated to a solid that was recrystallized from EtOAc to afford 6.38 g of

pale yellow needles (51%). Data for **6**: mp 203–204 °C; $[\alpha]_D^{30} +1032.9$ (c 1.02, CH₂Cl₂); ¹H NMR (300 MHz) 11.75 (br d, 1 H), 8.02–7.75 (m, 3 H), 7.60–7.40 (m, 4 H), 5.58 (m, 1 H), 2.67–2.40 (m, 3 H), 2.10–1.90 (m, 1 H), 1.75–1.30 (m, 4 H), 1.74 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (75.5 MHz) 158.6, 138.6, 133.9, 129.5, 129.3, 128.3, 126.7, 125.9, 125.8, 122.3, 121.6, 119.3, 49.5, 26.9, 25.6, 23.8, 21.8, 21.2; IR (CCl₄) 2946 (w), 1593 (s), 1373 (s); MS (70 eV) 298 (M⁺ + 2, 2), 297 (M⁺ + 1, 11), 297 (M⁺, 57), 250 (100); *R*_f 0.28 (hexane/EtOAc, 2:1); HPLC *t*_R = 23.68 min (Supelco LC-Si, hexane/EtOAc, 9:1); Anal. Calcd for C₁₈H₂₀N₂O₂ (MW 296.37): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.83; H, 6.91; N, 9.43.

Nitro Imine Alkylations: 1 Equiv LDA/2 Equiv *s*-BuLi Protocol. 2-[*S*-(1-Naphthyl)ethylimino]-3*S*-2-propenyl-*aci*-1-nitrocyclohexane (**7c**)

The following alkylation of **6**, using 1 equiv of LDA and 2 equiv of *s*-BuLi, is representative of all nitro imine alkylations using this base combination: *n*-BuLi (2.4 M, 0.281 mL, 0.675 mmol) was added to a solution of diisopropylamine (68 mg, 0.094 mL, 0.675 mmol) in THF (4 mL) at 0 °C in a 25-mL, three-necked, round-bottomed flask equipped with a stir bar, thermometer, nitrogen inlet and septum. The solution was stirred at 0 °C for 25 min and then DMPU (518 mg, 0.489 mL, 4.05 mmol) was added. After stirring for 5 min at 0 °C, a solution of nitro imine **6** (200 mg, 0.675 mmol) in THF (6 mL) was added rapidly, forming a reddish solution which faded to orange-yellow after the addition was complete. The solution was stirred at 0 °C for 30 min, cooled to –78 °C and *s*-BuLi (1.3 M, 1.1 mL, 1.42 mmol) was added dropwise, forming a reddish solution. The solution was stirred at –78 °C for 2.5 h, cooled to –90 °C (methanol/liquid nitrogen) and allyl iodide (295 mg, 0.161 mL, 1.75 mmol) was added neat. A brownish-yellow solution formed rapidly which was allowed to warm to 0 °C over 1 h. The clear tan solution was poured into 1% aqueous HOAc (22 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water, brine, dried over Na₂SO₄ and evaporated to a dark oil, which solidified. Silica gel chromatography (hexane/EtOAc, 3:1) provided the major diastereomer (158.35 mg) and minor diastereomer (8.65 mg) of **7c**, along with starting material (20.8 mg). Yield: 73%; dr 95.0:5.0.

Data for **7c (major)**: mp 158–159 °C; $[\alpha]_D^{28} +1070.6$ (c 0.91, CH₂Cl₂); ¹H NMR (300 MHz) 11.75 (br d, 1 H), 8.01–7.77 (m, 3 H), 7.60–7.33 (m, 4 H), 5.80–5.55 (m, 2 H), 5.20–5.00 (m, 2 H), 2.90–2.30 (m, 5 H), 1.80–1.00 (m, 4 H), 1.72 (d, *J* = 6.7 Hz, 3 H, CH₃); ¹³C NMR (75.5 MHz, CDCl₃) 161.4, 139.4, 134.7, 133.8, 129.5, 129.2, 128.1, 126.7, 125.9, 125.8, 122.1, 121.4, 119.3, 117.8, 49.0, 36.9, 34.6, 24.9, 23.6, 23.4, 16.0; IR (CCl₄) 2946 (w), 1593 (s), 1450 (w), 1383 (s), 1229 (w), 1171 (m), 1132 (s), 1074 (m), 1016 (w), 920 (w), 816 (s); MS (70 eV) 338 (M⁺ + 2, 1), 337 (M⁺ + 1, 11), 336 (M⁺, 43), 291 (80), 290 (100), 277 (10), 276 (35), 156 (73), 155 (100), 154 (37), 136 (11); *R*_f 0.57 (hexane/EtOAc, 2:1); HPLC *t*_R = 8.57 min (Supelco LC-Si, hexane/EtOAc, 9:1); Anal. Calcd for C₂₁H₂₄N₂O₂ (MW 336.44): C, 74.97; H, 7.19; N, 8.33. Found: C, 74.85; H, 7.28; N, 8.25.

2-[*S*-(1-Naphthyl)ethylimino]-3*R*-2-propenyl-*aci*-1-nitrocyclohexane (**7c**, minor)

Data for **7c (minor)**: mp 132–135 °C; $[\alpha]_D^{28} +683.9$ (c 0.33, CH₂Cl₂); ¹H NMR (300 MHz) 12.45 (br d, 1 H), 8.10–7.80 (m, 3 H), 7.61–7.42 (m, 4 H), 5.75 (m, 1 H), 5.35 (m, 1 H), 4.80 (br d, 1 H), 4.50 (br d, 1 H), 3.00–2.72 (m, 2 H), 2.60 (m, 1 H), 1.90–1.40 (m, 6 H), 1.73 (d, *J* = 6.6 Hz, 3 H); IR (CCl₄) 2946 (w), 1593 (s), 1381 (s), 1123 (s); MS (70 eV) 336 (M⁺, 1), 155 (100); *R*_f 0.38 (hexane/EtOAc, 2:1); HPLC *t*_R = 17.84 min (Supelco LC-Si, hexane/EtOAc, 9:1); Anal. Calcd for C₂₁H₂₄N₂O₂ (MW 336.44): C, 74.97; H, 7.19; N, 8.33. Found: C, 75.06; H, 7.34; N, 8.14.

3*R*-*n*-Butyl-1-nitrocyclohexene (8)

To the pure major diastereomer of **7d** (525 mg, 1.49 mmol) in ethanol (23 mL) was added cerium trichloride heptahydrate (1.11 g, 2.98 mmol), followed by sodium borohydride (113 mg, 2.98 mmol). After 1.5 h, an additional 0.5 equiv of each reagent was added. This was repeated three times until, after 8 h, a total of 4 equiv each of NaBH₄/CeCl₃ had been added. Acetone (5 mL) was added, and the milky suspension was poured into a separatory funnel containing 1 N HCl (54 mL) and hexane (54 mL). The funnel was shaken, and the layers were separated. The aqueous layer was further extracted with hexane (2 × 50 mL) and saved for recovery of the auxiliary (see below). The combined organic layers were washed with water, brine, backwashed with hexane (20 mL), dried (Na₂SO₄) and evaporated to a residue which was purified by flash chromatography (hexane/EtOAc, 15:1) to afford 143 mg of a green oil (53%). Data for **8**: bp 100 °C (0.1 mm Hg); [α]_D²⁹ −20.7 (c 3.21, CHCl₃); ¹H NMR (300 MHz) 7.22 (s, 1 H), 2.65–2.36 (m, 3 H), 1.95–1.76 (m, 2 H), 1.70–1.16 (m, 8 H), 0.91 (t, 3 H, *J* = 7.0 Hz); IR (CCl₄) 2932 (s), 2861 (m), 1522 (s), 1337 (s); *R*_f 0.61 (hexane/EtOAc, 2:1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Berner OM, Tedeschi L, Enders D. Eur. J. Org. Chem. 2002:1877. (b) Ono, N., editor. The Nitro Group in Organic Synthesis. New York: Wiley; 2001. (c) Perekalin, VV.; Lipina, ES.; Berestovitskaya, VM.; Efremov, DA. Nitroalkenes, Conjugated Nitro Compounds. Chichester: Wiley; 1994. (c) Barrett AGM. Chem. Soc. Rev. 1991; 20:95–127. (d) Kabalka GW, Varma RS. Org. Prep. Proc. Int. 1987; 19:283–328. (e) Barrett AGM, Grabowski GG. Chem. Rev. 1986; 86:751–762. (f) Corey EJ, Estreicher H. J. Am. Chem. Soc. 1978; 100:6294.
2. (a) Denmark SE, Thorarensen A. Chem. Rev. 1996; 96:137–165. [PubMed: 11848747] (b) Denmark, SE.; Cottell, JJ. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products. New Jersey: John Wiley & Sons; 2003. Chapter 2.
3. (a) Denmark SE, Hurd AR. J. Org. Chem. 2000; 65:2875–2886. [PubMed: 10814173] (b) Denmark SE, Herbert B. J. Org. Chem. 2000; 65:2887–2896. and references cited therein. [PubMed: 10814174]
4. Denmark SE, Martinborough EA. J. Am. Chem. Soc. 1999; 121:3046–3056.
5. Denmark SE, Juhl M. Helv. Chim. Acta. 2002; 85:3712–3736.
6. (a) Denmark SE, Marcin LR. J. Org. Chem. 1997; 62:1675–1686. (b) Denmark SE, Cottell JJ. Adv. Synth. Cat. 2006; 348:2397–2402. (c) Denmark SE, Baiazitov RY. J. Org. Chem. 2006; 71:593–605. [PubMed: 16408969]
7. Denmark SE, Montgomery JJ, Kramps L. J. Am. Chem. Soc. 2006; 128:11620–11630. [PubMed: 16939287]
8. Denmark SE, Sternberg JA, Lueoend R. J. Org. Chem. 1988; 53:1251.
9. For a review on the Nef reaction, see Noland WE. Chem. Rev. 1955; 55:137..
10. (a) Feringa BL. Acc. Chem. Res. 2000; 33:346. [PubMed: 10891052] (b) Perlmutter, P. Conjugate Addition Reactions in Organic Synthesis. Oxford: Pergamon; 1992. (c) Schmalz, H-G. Chapt. 1.5. In: Trost, BM.; Fleming, I., editors. Comprehensive Organic Synthesis. Vol. Vol. 4. Oxford: Pergamon; 1991. (c) Rossiter BE, Swingle NM. Chem. Rev. 1992; 92:771.
11. Denmark SE, Ares JJ. J. Am. Chem. Soc. 1988; 110:4432.

12. For reviews of metalloenamine chemistry see: (a) Bergbreiter DE, Newcomb M. Morrison JD. Chapt. 9. Asymmetric Synthesis. 1983; Vol. 2 New York Academic Press (b) Fraser RR. Buncl E, Durst T. Part B, Chapt. 2. Comprehensive Carbanion Chemistry. 1984 Amsterdam Elsevier (c) Martin SF. Heathcock CH. Chapt. 1.16. Comprehensive Organic Synthesis, Vol. 2, Additions to C-X Bonds, Part 2. 1991 Oxford Pergamon Press (c) Mangelinckx S, Guibellina N, De Kimpe N. Chem. Rev. 2004; 104:2353–2399. [PubMed: 15137794].
13. (a) Stork G, Dowd S. J. Am. Chem. Soc. 1963; 85:2178. (b) Wittig G, Frommelt HD, Suchanek P. Angew. Chem. 1963; 75:978.
14. Mea-Jacheet D, Horeau A. Bull. Soc. Chim. Fr. 1968:4571.
15. Kitomoto M, Hiroi K, Terashima S, Yamada S. Chem. Pharm. Bull. 1974; 22:459.
16. (a) Meyers AI, Williams DR, Druelinger M. J. Am. Chem. Soc. 1976; 98:3032. (b) Meyers AI, Williams DR, Erickson GW, White S, Druelinger M. J. Am. Chem. Soc. 1981; 103:3081.. For a personal, historical account see: (c) Meyers AI. J. Org. Chem. 2005; 70:6137–6151. [PubMed: 16050670].
17. For reviews on the chemistry of hydrazone anions see: (a) Enders D. Morrison JD. Chapt. 4. Asymmetric Synthesis. 1984; Vol 3 New York Academic Press (b) Bergbreiter DE, Momongan M. Heathcock CH. Chapt. 1.17. Comprehensive Organic Synthesis, Vol. 2, Additions to C-X Bonds, Part 2. 1991 Oxford Pergamon Press (c) Fey P. Helmchen G, Hoffman RW, Schaumann E. Stereoselective Synthesis, Houben-Weyl, Methods of Organic Chemistry. 1995; Vol. E21a Stuttgart Theime:994–1015. (d) Enders D, Peters R, Wortmann L. Acc. Chem. Res. 2000; 33:157–169. [PubMed: 10727205] (e) Job A, Janeck CF, Bettray W, Peters R, Enders D. Tetrahedron. 2002; 58:2253–2429..
18. Enders D, Eichenauer H. Angew. Chem. Int. Ed. Engl. 1976; 15:549. [PubMed: 823841]
19. Enders D, Kipphardt H, Fey P. Org. Synth. 1987; 65:183.
20. (a) Enders D, Schubert H, Nubling C. Angew. Chem. Int. Ed. Engl. 1986; 25:1109. (b) Enders D, Bhushan V. Tetrahedron Lett. 1988; 29:2437. (c) Enders D, Schafer T, Piva O, Zamponi A. Tetrahedron. 1994; 50:3349. (d) Enders D, Gatzweiler W, Jegelka U. Synthesis. 1991:1137. (e) Enders E, Zamponi A, Raabe G. Synlett. 1992:897.
21. (a) Lohray BB, Enders D. Synthesis. 1993:1092. (b) Enders D, Bettray W, Raabe G, Runsink J. Synthesis. 1994:1322.
22. For notable exceptions see: (a) List B. J. Am. Chem. Soc. 2004; 126:450–451. [PubMed: 14719926] (b) Doyle AG, Jacobsen EN. J. Am. Chem. Soc. 2005; 127:62–63. [PubMed: 15631449] (c) Beeson TD, Mastracchio A, Hong J-B, Ashton K, MacMillan DWC. Science. 2007; 316:582–585. [PubMed: 17395791]. Asymmetric phase transfer alkylations must also be included. See (d) Maruoka K. Asymmetric Phase Transfer Reactions. 2007 Weinheim Wiley-VCH.
23. (a) Kaiser EM, Detty JD, Knutson PLA. Synthesis. 1977:509. (b) Bates, RB. Part A, Chapt. 1. In: Buncl, E.; Durst, D., editors. Comprehensive Carbanion Chemistry. Amsterdam: Elsevier; 1980. (c) Seebach D, Pohmakotor M. Tetrahedron. 1981; 37:4047. (d) Thompson CM, Green DLC. Tetrahedron. 1991; 47:4223. (e) Thompson, CM. Dianion Chemistry in Organic Synthesis. Boca Raton: CRC Press; 1994.
24. For recent examples, see the following: (a) Neeland EG, Ounsworth JP, Sims RJ, Weiler L. J. Org. Chem. 1994; 59:7383. (b) Micouin L, Schanen V, Riche C, Chiaroni A, Quirion J-C, Husson H-P. Tetrahedron Lett. 1994; 35:7223. (c) Wittenberger SJ, Baker WR, Donner BG. Tetrahedron. 1993; 49:1547. (d) Avery MA, Chong WKM, Jennings-White C. J. Am. Chem. Soc. 1992; 114:974. (e) Dugger RW, Ralbovsky JL, Bryant D, Commander J, Massett SS, Sage NA, Selvidio JR. Tetrahedron Lett. 1992; 33:6763. (f) Rao AVR, Singh AK, Varaprasad CVNS. Tetrahedron Lett. 1991; 32:4393..
25. Bartoli G, Bosco M, Cimarelli C, Dalpozzo R, De Munno G, Palmieri G. Tetrahedron: Asymmetry. 1993; 4:1651.
26. Ihara M, Takahashi M, Taniguchi N, Yasui K, Niitsuma H, Fukumoto K. J. Chem. Soc Perkin Trans. I. 1991:525.
27. Berkowitz DB, Smith MK. J. Org. Chem. 1995; 60:1233.
28. Hulme SJ, Jenkins PR, Fawcett J, Russell DR. Tetrahedron Lett. 1994; 35:5501.
29. Myers AG, Yang BH, Chen H, Gleason JL. J. Am. Chem. Soc. 1994; 116:9361.

30. For a review on the chemistry of nitroenamines see: Rajappa S. *Tetrahedron*. 1981; 37:1453..
31. Dampawan P, Zajac WW. *Synthesis*. 1983:545.
32. Meyers AI, Poindexter GS, Brich Z. *J. Org. Chem.* 1978; 43:892.
33. (a) Ostercamp DL, Taylor PJ. *J. Chem. Soc., Perkin Trans 2*. 1985:1021.(b) Fetell AI, Feuer H. *J. Org. Chem.* 1978; 43:497.(c) Feuer H, McMillan RM. *J. Org. Chem.* 1979; 44:3410.(d) Feuer H, Sarides C, Rao CNR. *Spectrochim. Acta*. 1963; 19:431.
34. Fraser RR, Akiyama F, Banville J. *Tetrahedron Lett.* 1979:2929.
35. Mukhopadhyay T, Seebach D. *Helv. Chim. Acta*. 1982; 65:385.
36. Pirkle WH, Mahler G, Hyun MH. *J. Liquid Chromatog.* 1986; 9:443.
37. Mourad MS, Varma RS, Kabalka GW. *Synthesis*. 1985:654.
38. The enantiomeric purity of this diol was determined in the following way: Treatment of the diol with 1.0 equiv of 3,5-dinitrophenylisocyanate (generated *in situ* from the corresponding acyl azide) produced the monocarbamate, which was analyzed by CSP-HPLC; t_R (*R,R*), 8.82 min; t_R (*S,S*), min (Pirkle L-naphthylleucine, hexane/isopropanol, 85/15; 0.75 mL/min, 254 nm).
39. Corey EJ, Naef R, Hannon FJ. *J. Am. Chem. Soc.* 1986; 108:7114.(b) Hiemstra H, Wynberg H. *Tetrahedron Lett.* 1977:2183.
40. Seebach has correlated 3-butyl- and 3-methylcyclohexanone (both dextrorotatory isomers are *R*) by chiroptical methods, the latter of which has been chemically correlated to (*R*)-pulegone.⁴¹ Langer W, Seebach D. *Helv. Chim. Acta*. 1979; 62:1710..
41. Allinger NL, Riew CK. *J. Org. Chem.* 1975; 40:1316.
42. Ciganek, E. U. S. Patent. 4,076,830. 1978.
43. Martynoff M, Chauvin M, Grumez M, Lefevre N. *Bull. Soc. Chim. France*. 1958:164.
44. Aristoff PA, Johnson PD, Harrison AW. *J. Am. Chem. Soc.* 1985; 107:7967.
45. Feuer H, Pivawer PM. *J. Org. Chem.* 1966; 31:3152.
46. Enders D, Fey P, Kipphardt H. *Org. Prep. Proc. Int.* 1985; 17:1.
47. (a) Hauser CR, Harris TM. *J. Am. Chem. Soc.* 1958; 80:6360.(b) Harris TM, Harris CM. *Org. React.* 1969; 17:155. (22). (a) Hensch FE, Hampton KG, Hauser CR. *J. Am. Chem. Soc.* 1967; 89:463.(b) Beam CF, Sandifer RM, Foote RS, Hauser CR. *Synth. Commun.* 1976; 6:5.(c) Sandifer RM, Davis SE, Beam CF. *Synth. Commun.* 1976; 6:339.
48. Boatman S, Hauser CR. *J. Org. Chem.* 1966; 31:1758.
49. Bunnell CA, Fuchs PL. *J. Am. Chem. Soc.* 1977; 99:5184.
50. (a) Brandli U, Eyer M, Seebach D. *Chem. Ber.* 1986; 119:575.(b) Seebach D, Henning R, Mukhopadhyay T. *Chem. Ber.* 1982; 115:1705.(c) Seebach D, Henning R, Gonnermann J. *Chem. Ber.* 1979; 112:234.(d) Seebach D, Henning R, Lehr F. *Angew. Chem. Int. Ed. Engl.* 1978; 17:458.
51. (a) Knorr R, Low P. *J. Am. Chem. Soc.* 1980; 102:3241.(b) Knorr R, Weiss A, Low P, Rapple E. *Chem. Ber.* 1980; 113:2462.
52. Meyers AI, Williams DR, White S, Erickson DW. *J. Am. Chem. Soc.* 1981; 103:3088.
53. (a) Collum DB, Kahne D, Gut SA, DePue RT, Mohamadi R, Wanat RA, Clardy J, VanDuyne G. *J. Am. Chem. Soc.* 1984; 106:4865.(b) Wanat RA, Collum DB. *J. Am. Chem. Soc.* 1985; 107:2078. (c) Wanat RA, Collum DB, VanDuyne G, Clardy J, DePue RT. *J. Am. Chem. Soc.* 1986; 108:3415.(d) Bernstein MP, Romesberg FE, Fuller DJ, Harrison AT, Williard PG, Liu QY, Collum DB. *J. Am. Chem. Soc.* 1992; 114:5100.(e) Bernstein MP, Collum DB. *J. Am. Chem. Soc.* 1993; 115:789.(f) Bernstein MP, Collum DB. *J. Am. Chem. Soc.* 1993; 115:8008.(g) Romesberg FE, Collum DB. *J. Am. Chem. Soc.* 1995; 117:2166.(h) Liao S, Collum DB. *J. Am. Chem. Soc.* 2003; 125 15114-1527. (i) Zuend SJ, Ramirez A, Lobkovsky E, Collum DB. *J. Am. Chem. Soc.* 2006; 128:5839-5848.(j) Ma Y, Collum DB. *J. Am. Chem. Soc.* 2007; 129:14818-14825. [PubMed: 17985891]
54. The special role of LDA has already been demonstrated in selective alkylations of chiral oxazolines. Meyers AI, Knaus G, Kamata K, Ford ME. *J. Am. Chem. Soc.* 1976; 98:567..
55. Klebe G, Bohn KH, Marsch M, Boche G. *Angew. Chem. Int. Ed. Engl.* 1987; 26:78.
56. A referee has suggested that a Li- π -naphthalene coordination might be responsible for the preferred conformation of the stereocontrolling group. In a simple calculation it was found that the

cyclohexene ring in the dianion is not planar and pseudo axial hydrogens may also contribute to the direction of electrophilic attack. We thank the referee for this suggestion.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.

Scheme 11.

Scheme 12.

s-BuLi (2.0 equiv)

70% (dr: 89.0:11.0)

1. LDA (1.0 equiv)
2. *s*-BuLi (2.0 equiv)

61% (dr: 91.0:9.0)

LDA (3.0 equiv)

56% (dr: 86.0:14.0)

Scheme 13.

Scheme 14.

Scheme 15.

Chart 1.

Table 1

Alkylation of Dianions from Nitro Imines 13–15

entry	substrate	R ¹	R ²	R ³	product	yield ^a , %	dt ^b
1	1	CH ₂ OCH ₃	CH ₂ Ph	CH ₃	4a	53	59.0:41.0 ^c
2	1	CH ₂ OCH ₃	CH ₂ Ph	CH ₃ (CH ₂) ₃	4b	55	70.5:29.5
3	1	CH ₂ OCH ₃	CH ₂ Ph	CH ₂ CH=CH ₂	4c	66	65.0:35.0 ^c
4	2	CH ₂ OCH ₃	Ph	CH ₃	5a	47	54.0:46.0
5	2	CH ₂ OCH ₃	Ph	CH ₂ CH=CH ₂	5c	60	67.5:32.5
6	3	CH(OCH ₃)Ph	CH ₃	CH ₂ CH=CH ₂	5c	60	67.5:32.5

^a Combined yield of chromatographically homogeneous diastereomers.^b Determined by yields of separated isolated products.^c Determined by integration in the ¹H-NMR spectrum of an unresolved mixture.

Table 2

Optimization of Alkylation of **6**.

entry	amide base	amide base, equiv	s-BuLi, equiv	additive	solvent	yield ^a (%) ^b	dr ^c
1	LDA	1.0	2.0	none	THF	34 (58)	89.5:10.5
2	LDA	1.0	2.0	HMPA	THF	73	93.5:6.5
3	LDA	1.0	2.0	TMEDA	THF	19 (27)	82.0:18.0
4	LDA	1.0	2.0	DMPU	THF	74 (82)	95.0:5.0
5	LDA	1.0	2.0	DMPU	Et ₂ O	15	74.0:26.0
6	LDA	1.0	2.0	DMPU	DME	56 (60)	90.5:9.5
7	LDEA	1.0	2.0	DMPU	THF	78 (82)	89.0:11.0
8	LDCA	1.0	2.0	DMPU	THF	59 (68)	91.0:9.0
9	LiTMP	1.0	2.0	DMPU	THF	41 (64)	91.5:8.5
10	LDA	1.0	1.0	DMPU	THF	68 (77)	91.5:8.5
11	LDA	2.0	0	DMPU	THF	76	87.0:13.0
12	LDA	3.0	0	DMPU	THF	83	89.0:11.0

^a Combined yield of chromatographically homogeneous diastereomers.^b Yield based on converted starting material.^c Determined by yields of separated isolated products.

Table 3Survey of Electrophile in Alkylations of **6**.

entry	R	product	yield ^a () ^b , %	dr ^c () ^d , %
1	CH ₃	7a	63 (70)	80.5:20.5 (80.5:20.5)
2	CH ₃ (CH ₂) ₃	7b	59 (62)	98.0:2.0 (99.0:1.0)
3	CH ₂ CH=CH ₂	7c	74 (82)	95.0:5.0 (90.0:10)
4	CH ₂ C(CH ₃)=CH ₂	7d	56 (64)	92.5:7.5 (93.0:7.0)
5	(CH ₃) ₂ CH	7e	16 (34)	97.5:2.5 (95.0:5.0)

^a Combined yield of chromatographically homogeneous diastereomers.^b Yield based on converted starting material.^c Determined by yields of separated isolated products.^d Determined by HPLC analysis of purified but unresolved mixtures.