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On the Origins of Diastereoselectivity in the Alkylation of Enolates Derived from *N*-1-(1′-Naphthyl)ethyl-*O*-*tert*-butylhydroxamates: Chiral Weinreb Amide Equivalents

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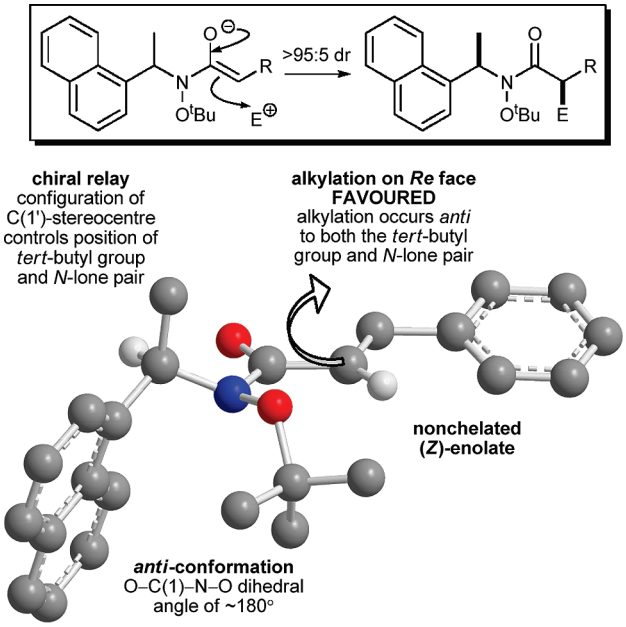

The stereochemical outcome observed upon alkylation of enolates derived from *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxamates (chiral Weinreb amide equivalents) may be rationalized by a chiral relay mechanism. Deprotonation with KHMDS leads to a nonchelated (*Z*)-enolate in which the oxygen atoms adopt an *anti*-periplanar conformation. The configuration of the *N*-1-(1′-naphthyl)ethyl group dictates the conformation of the *O*-*tert*-butyl group and the configuration adopted by the adjacent pyramidal nitrogen atom. Highly diastereoselective enolate alkylation then proceeds *anti* to both the bulky *tert*-butyl group (sterically driven) and the *N*-lone pair (stereoelectronically driven).

Introduction

The use of *N*-methoxy-*N*-methyl amides (Weinreb amides) as acylating agents for the synthesis of aldehydes and ketones was first reported by Nahm and Weinreb in 1981.[1] Since then, these intermediates have enjoyed ever-increasing use and now occupy an important niche in organic synthesis.[2] The main advantage of these compounds over other carboxylic acid derivatives is the lack of overaddition products obtained on reaction with an excess of organometallic and

(1) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(2) For reviews, see: Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. O'Neill, B. T. *Comprehensive Organic Synthesis*; Fleming, I., Trost, B. M., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 1, p 399.

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hydride reducing agents, which is often ascribed to the stabilization of the tetrahedral intermediate through chelation; this property of Weinreb amides allows for a very convenient and efficient synthesis of aldehydes and ketones. Within this area, we have recently reported that *N*-acyl derivatives of *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **1** are able to act as chiral Weinreb amide equivalents.[3,4] Treatment of enantiopure *N*-acyl derivatives **2** with KHMDS followed by an alkyl halide proceeds with high levels of diastereoselectivity (>95:5 dr) to give the corresponding α-substituted derivatives **3** in good yield and as single diastereoisomers (>99:1 dr) after purification. Treatment of **3** with $LiAlH_4$ gives direct access to the corresponding α-stereogenic aldehyde **4** while treatment with MeLi gives the corresponding α-stereogenic ketone **5** in very high enantiopurity (>95:5 er), indicating that the cleavage reaction is accompanied by little competing epimerization or racemization of the α-stereocenter (Figure 1). This sequence of transformations allows for a convenient preparation of α-stereogenic aldehydes and ketones in a single reductive operation and as such is superior to many of the chiral auxiliary based approaches to these compounds using, for instance, Oppolzer's sultam[5] and Evans's oxazolidinones,[6] cleavage of which to generate aldehydes requires at least two synthetic steps.[7,8]

Herein we delineate the design concept of auxiliary **1**, and describe the synthesis and subsequent alkylation of a series of analogues of **2**, incorporating variation in the structure of the chiral auxiliary **1**, that enable the design concept to be validated and the origin of the high alkylation diastereoselectivities to be probed.

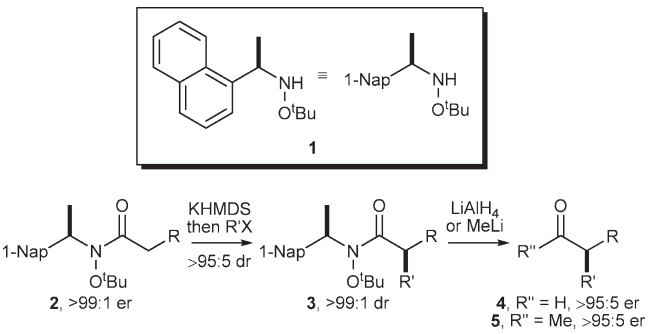


FIGURE 1. Alkylation of chiral Weinreb amide equivalents **2**, derived from *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **1**, and cleavage to give homochiral aldehydes **4** and ketones **5**.

Results and Discussion

Auxiliary Design Concept. A survey of the known solid-state conformations of Weinreb amides **6** within the CCDC revealed some common structural preferences. The N−O bond and carbonyl group generally prefer to adopt an *anti*-periplanar conformation (O═C—N—O dihedral angle ~180°), with the nitrogen atom being pyramidalized. The *N*-lone pair generally prefers to lie *syn*-periplanar to the *O*-methyl group, which is presumably due to a desire to minimize lone pair−lone pair repulsion between the heteroatoms;[9] the *O*-methyl group is therefore located approximately perpendicular to the plane containing the N−O bond and the carbonyl group (O*C*−N−O−*C*H_3 dihedral angle ~90°). Applying Ockham's razor[10] to these observations led to the proposal of the "chiral Weinreb amide" **7**, resulting from the incorporation of an α-arylethyl group on the nitrogen atom (R_1 and R_2 = Me and Ar). Minimization of $A_{1,3}$ strain was expected to place the α-hydrogen atom *syn*-pentane to the carbonyl oxygen, with subsequent minimization of steric interactions between the *N*- and *O*-alkyl groups placing the *O*-*tert*-butyl group preferentially over one of the diastereotopic faces of the carbonyl group (a chiral relay effect).[11] This preference was expected to result in the *N*-lone

(3) Chernega, A. N.; Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Kurosawa, W.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 3254.

(4) Masamune has also reported a benzopyranoisoxazolidine auxiliary that is capable of acting as a chiral Weinreb amide equivalent; see: Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 793. Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1081.

(5) Oppolzer, W.; Chapuis, C.; Bemardiielli, G. *Helv. Chim. Acta* **1984**, *67*, 1397. For reviews, see: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.

(6) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. For reviews, see: Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23. Arya, P.; Quin, H. *Tetrahedron* **2000**, *56*, 917.

(7) For instance, see: Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757. Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613. Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471. Taylor, R. E.; Chen, Y. *Org. Lett.* **2001**, *3*, 2221. Matsushima, Y.; Itoh, H.; Nakayama, T.; Horiuchi, S.; Eguchi, T.; Kakinuma, K. *J. Chem. Soc., Perkin Trans. 1* **2002**, 949. Carter, R. G.; Bourland, T. C.; Campbell, G.; Graves, D. E. *Org. Lett.* **2002**, *4*, 2177. Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2002**, *43*, 3263.

(8) Perhaps the most useful auxiliaries for the direct (one step) preparation of α-chiral aldehydes are Davies's SuperQuat, the ephedrine/pseudoephedrine approach of Larcheveque and Myers, respectively, and Enders's *S*AMP/*R*AMP hydrazone method. For leading references, see: Larcheveque, M.; Ignatova, E.; Cuvigny, I. *Tetrahedron Lett.* **1978**, *19*, 3961. Larcheveque, M.; Ignatova, E.; Cuvigny, I. *J. Organomet. Chem.* **1979**, *177*, 5. Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 549. Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1977**, *18*, 191. Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654. Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 397. Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. M. *Tetrahedron* **1984**, *40*, 1345. Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253. Davies, S. G.; Sanganee, H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 671. Bull, S. D.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Prasad, R. S.; Sanganee, H. J. *Synlett* **1998**, 519. Bach, J.; Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Price, P. D.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2001.

(9) This conformational preference is in accord with hydroxylamine itself, for which the lowest energy conformation has bonds and lone pairs eclipsed; the interconversion of conformers by N−O bond rotation is also considered to be a high-energy process; see: Ali, S. A.; Hassan, A.; Wazeer, M. I. M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1479.

(10) Ockham's razor (also spelled Occam's razor) is a principle attributed to the 14th Century English logician and Franciscan friar William of Ockham. The principle states that the explanation of any phenomenon should make as few assumptions as possible.

(11) Bull, S. D.; Davies, S. G.; Fox, D. J.; Garner, A. C.; Sellers, T. G. R. *Pure Appl. Chem.* **1998**, *70*, 1501. Bull, S. D.; Davies, S. G.; Fox, D. J.; Sellers, T. G. R. *Tetrahedron: Asymmetry* **1998**, *9*, 1483. Bull, S. D.; Davies, S. G.; Epstein, S. W.; Ouzman, J. V. A. *Chem. Commun.* **1998**, 659. Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech, M. A.; Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321. Bull, S. D.; Davies, S. G.; Garner, A. C.; Mujtaba, N. *Synlett* **2001**, 781. Bull, S. D.; Davies, S. G.; Garner, A. C.; O'Shea, M. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3281. Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444. Quaranta, L.; Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 39. Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, M.; Jasperse, C. P.; Sibi, M. P. *Chem.—Eur. J.* **2003**, *9*, 29. Malkov, A. V.; Hand, J. B.; Kocovsky, P. *Chem. Commun.* **2003**, 1948. Hitchcock, S. R.; Casper, D. M.; Vaughn, J. F.; Finefield, J. M.; Ferrence, G. M.; Esken, J. M. *J. Org. Chem.* **2004**, *69*, 714. Sibi, M. P.; Stanley, L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3353. Sibi, M. P.; Prabagaran, N. *Synlett* **2004**, 2421. Clayden, J.; Vassiliou, N. *Org. Biomol. Chem.* **2006**, *4*, 2667. Parrott, R. W. II; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2007**, *18*, 377. Bull, S. D.; Davies, S. G.; Epstein, S. W.; Garner, A. C.; Mujtaba, N.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Tamayo, J. A.; Watkin, D. J. *Tetrahedron* **2006**, *62*, 7911. Bull, S. D.; Davies, S. G.; Garner, A. C.; Parkes, A. L.; Roberts, P. M.; Sellers, T. G. R.; Smith, A. D.; Tamayo, J. A.; Thomson, J. E.; Vickers, R. J. *New J. Chem.* **2007**, *31*, 486.

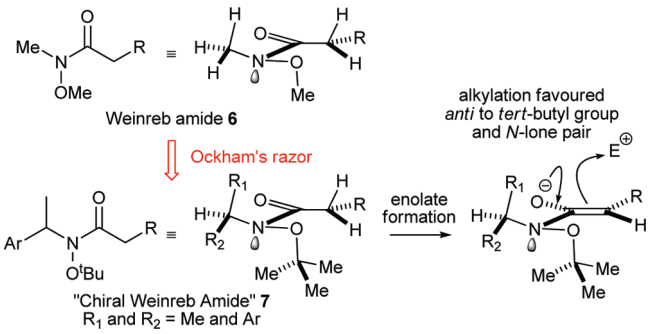
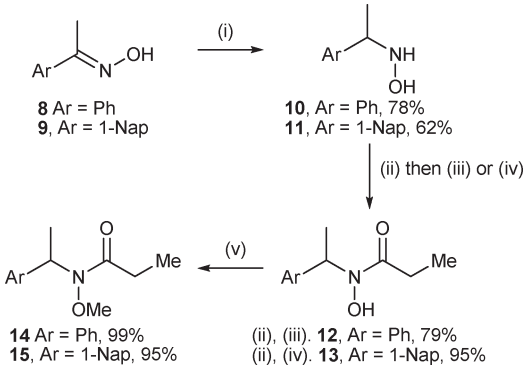


FIGURE 2. Conformational preferences of a generic Weinreb amide **6** and proposed structure of the chiral Weinreb amide **7**.

pair being orientated over the same face as the *O*-*tert*-butyl group. It was envisaged that deprotonation of hydroxamate **7** would give rise to the corresponding (*Z*)-enolate.[12] If either the enolate counterion was of low Lewis acidity (e.g., K^+) or a "naked" enolate was generated (e.g., addition of 12-crown-4 to the lithium enolate) then it was anticipated that the conformational preference shown by the parent hydroxamate for an *anti*-periplanar arrangement of the two oxygen atoms would also be present within the enolate due to the desire to minimize electrostatic repulsions. The presence of an *O*-*tert*-butyl group within the hydroxamate structure was also anticipated to confer enhanced stability on the enolate: the decomposition of Weinreb amide enolates via a retro-ene type process resulting in the elimination of formaldehyde is known,[13] and is impossible for enolates derived from *O*-*tert*-butyl hydroxamates.[13b] Subsequent enolate alkylation *anti* to both the *tert*-butyl group and *N*-lone pair[14] was expected to be favored on both steric and stereoelectronic grounds, respectively (Figure 2).

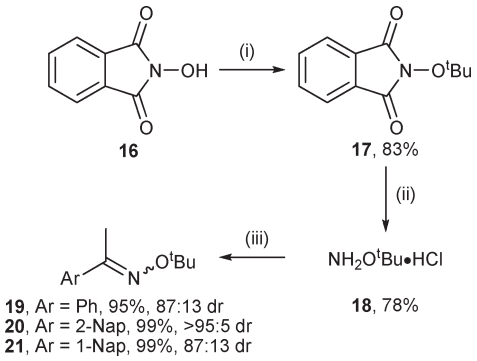
Synthesis of a Range of *N*-1-Arylethyl-*O*-alkylhydroxamates. A range of racemic[15] hydroxamates of the general structure **7** was prepared for subsequent investigation in their enolate alkylation reactions. Treatment of commercially available acetophenone oxime **8** with sodium cyanoborohydride at pH 3 afforded the known racemic hydroxylamine **10**[16] in 78% yield, while condensation of 1-acetylnaphthalene with hydroxylamine hydrochloride and subsequent reduction of the resultant oxime **9**[16] afforded the known hydroxylamine **11**[16] in 62% yield (Scheme 1). Highly selective *N*-acylation of hydroxylamine **10** was achieved by the method of Nakonieczna and Chimiak,[17] upon treatment with TMSCl in pyridine followed by the mixed anhydride

SCHEME 1[a]



[a]Reagents and conditions: (i) $NaBH_3CN$, MeOH, HCl, 1 h, rt; (ii) TMSCl, pyridine, −10 °C, 30 min; (iii) $CH_3CH_2CO_2CO_2{}^tBu$, CH_2Cl_2, −10 °C to rt, 14 h; (iv) $(CH_3CH_2CO)_2O$, CH_2Cl_2, −10 °C to rt, 2 days; (v) MeI, K_2CO_3, $CHCl_3$, reflux, 48 h. 1-Nap = 1-naphthyl.

SCHEME 2[a]



[a]Reagents and conditions: (i) ${}^tBuOAc$, dioxane, TfOH, rt, 24 h; (ii) 40% hydrazine hydrate, EtOH, reflux, 3 h, then Et_2O, HCl; (iii) ArCOMe, NaOAc, EtOH, rt, 24 h. 2-Nap = 2-naphthyl; 1-Nap = 1-naphthyl.

reagent formed by the reaction of propanoic acid with isobutyl chloroformate, to give hydroxamic acid **12**[18] in 79% yield. The 500 MHz ^1H NMR spectrum of **12** was exceptionally broad in $CDCl_3$ at rt; even recording the spectrum at 80 °C in d_8-PhMe failed to fully resolve all the signals. The origin of line broadening observed in the ^1H NMR spectra of hydroxylamine and hydroxamate derivatives has been the subject of some debate in the literature,[19] and is often ascribed to either slow inversion of configuration at the nitrogen atom[20] or slow rotation about the N−O bond;[21] it is generally accepted that interconversion of the two conformers occurs by a combined inversion−rotation process. The 1-naphthyl derivative **13** was produced in a similar manner to **12**, except that propanoic anhydride was used as the acylating agent. *O*-Methylation of hydroxamic acids **12** and **13** was readily achieved upon treatment with

(12) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(13) (a) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269. (b) Labeeuw, O.; Phansavath, P.; Genêt, J. P. *Tetrahedron Lett.* **2004**, *45*, 7107.

(14) (a) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146. (b) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105. (c) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603. (d) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (e) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.

(15) To assess the ability of a chiral auxiliary to promote diastereoselective reactions, it is not necessary to employ enantiomerically pure materials as racemates give the required information. Having identified *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **1** as the optimum chiral auxiliary in this reaction we subsequently developed a facile resolution procedure that provides access to both enantiomers of **1** on a multigram scale; see ref 3.

(16) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464.

(17) Nakonieczna, L.; Chimiak, A. *Synthesis* **1987**, 418.

(18) da Costa, M. R. G.; Curto, M. J. M.; Davies, S. G.; Sanders, J.; Teixeira, F. C. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2850.

(19) Raban, M. D.; Kost, D. *Acyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: Cambridge, UK, 1992; p 78.

(20) Griffith, D. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 4089.

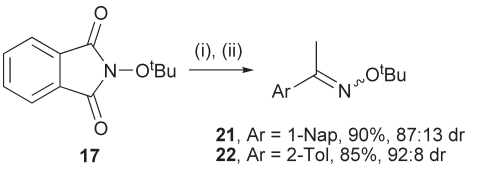
(21) Fletcher, J. R.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1970**, 687. Griffith, D. L.; Olson, B. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 1648. Riddell, F. G.; Turner, E. S. *J. Chem. Soc., Perkin Trans. 2* **1978**, 707.

methyl iodide in the presence of K_2CO_3. The reaction was conveniently followed by using the iron(III) chloride test for hydroxamic acids;[22] once complete, filtration of the reaction mixture and bulb-to-bulb distillation afforded pure samples of **14**[18] and **15** in good yield (Scheme 1). The ^{1}H NMR spectra of hydroxamates **14** and **15** were much sharper than those of the hydroxamic acid precursors **12** and **13**. Unfortunately, attempted production of the corresponding *O*-*tert*-butyl hydroxamates via *O*-*tert*-butylation of hydroxamic acids **12** and **13** employing all the common conditions gave no or very low isolated yields of the desired hydroxamates.[23]

A more efficient route for the production of *O*-*tert*-butyl hydroxamates involved the formation and subsequent reduction of oxime ethers derived from *O*-*tert*-butylhydroxylamine. Treatment of *N*-hydroxyphthalimide **16** with *tert*-butyl acetate and a small quantity of triflic acid[24,25] gave *N*-*tert*-butoxyphthalimide **17**[24] in 83% yield, which upon treatment with hydrazine liberated *O*-*tert*-butylhydroxylamine that was isolated as the HCl salt **18**[24,26] in 78% yield.[27] Condensation of acetophenone and 1-acetylnaphthalene with **18** gave oxime ethers **19**[18,28] and **21** as 87:13 mixtures of geometric isomers in both cases. The 2-naphthyl derivative **20** was formed in an analogous manner from 2-acetylnaphthalene as a single geometrical isomer (>95:5 dr), although ^{1}H NMR NOE analysis did not permit assignment of its configuration as no enhancements either to or from the *tert*-butyl group were observed (Scheme 2).

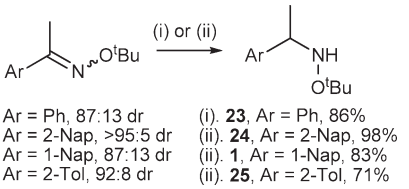
Alternatively, addition of a stoichiometric amount of methylhydrazine, which is soluble in organic solvents and readily available in anhydrous form,[29] to a solution of *N*-*tert*-butoxyphthalimide **17** in CH_2Cl_2 resulted in the rapid precipitation of *N*-methylphthalhydrazide; subsequent introduction of either 1-acetylnaphthalene or 2-methylacetophenone and an equivalent of acetic acid[30] to the reaction flask gave the corresponding oxime ethers **21** and **22** (as mixtures of geometrical isomers) in good yield (≥85%) after chromatographic purification. However, the crude material obtained from these reactions was usually sufficiently pure to be used in the following steps without the need for purification and as such this method represents a more convenient preparation of *O*-*tert*-butyl oxime ethers that avoids the need to isolate *O*-*tert*-butylhydroxylamine[3] (Scheme 3).

SCHEME 3[a]



[a]Reagents and conditions: (i) $MeNHNH_2$, CH_2Cl_2, rt, 12 h; (ii) ArCOMe, EtOH, AcOH, CH_2Cl_2, reflux, 12 h. 1-Nap = 1-naphthyl; 2-Tol = 2-tolyl.

SCHEME 4[a]



[a]Reagents and conditions: (i) BH_3·pyridine, EtOH, HCl (10% aq), 0 °C to rt, 1 h; (ii) BH_3·pyridine, EtOH, HCl, 0 °C to rt, 1−12 h. 2-Nap = 2-naphthyl; 1-Nap = 1-naphthyl; 2-Tol = 2-tolyl.

Treatment of oxime ether **19** with borane−pyridine complex and 10% aq HCl in EtOH afforded hydroxylamine **23**. *O*-*tert*-Butyl oxime ethers **20**−**22** were reduced in high yield by treatment with borane−pyridine and ethanolic HCl.[31] The reductions of oxime ethers **21** and **22** resisted attempts to drive the reaction to completion. For example, the reduction of **21** ran consistently to ∼90% conversion but not beyond, even upon addition of excess borane reagent. It is plausible that once the oxime ether concentration has dropped to a low level, the rate of consumption of the reducing agent by the solvent may begin to dominate over oxime ether reduction for these more hindered substrates. Nevertheless, good yields of hydroxylamines **1** and **25** were obtained from these reactions (Scheme 4).

A range of conditions was investigated for the acylation of hydroxylamines **1** and **23**−**25**, furnishing the dersired hydroxamates **26**−**33** in reasonable to good yield. The 1-naphthyl and 2-tolyl derivatives showed much more significant line broadening in their ^{1}H NMR spectra than their phenyl and 2-naphthyl counterparts. To obtain well-resolved spectra, heating to 70 °C at 250 MHz or 90 °C at 500 MHz was required (Scheme 5).

N-Neopentyl amides **36** and **37** (analogues of hydroxamates **28** and **32**, respectively, in which the oxygen atom has been replaced with a methylene group) were also prepared. Reductive amination of pivalaldehyde with (*RS*)-1-(1′-naphthyl)-ethylamine **34** gave secondary amine **35** in 65% isolated yield.

(22) *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Furniss, B. S., Hannaford, A. J., Smith, P. W. G., Tatchell, A. R., Eds.; Wiley: New York, 1989.

(23) Reaction with isobutene and *tert*-butyl acetate with strong acid catalysis produced only trace quantities of hydroxamate **26**, as did the use of *tert*-butyl trichloroacetimidate (Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett*. **1988**, *29*, 2483.). Treatment with DMF-dineopentylacetal (Buchi, H.; Steen, K.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl*. **1964**, *3*, 62. Baldwin, J. E.; Farthing, C. N.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett*. **1996**, *37*, 3761. Widmer, H. *Synthesis* **1983**, 135.) and application of *tert*-butyl bromide under phase transfer conditions (Chevallet, P.; Garrouste, P.; Malawska, B.; Martinez, J. *Tetrahedron Lett*. **1993**, *34*, 7409.) gave none of the desired product at all. The most successful method attempted employed excess *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea (Mathias, L. J. *Synthesis* **1979**, 561.) over an extended reaction time of 7 days, which gave *O*-*tert*-butyl hydroxamate **26** in 22% yield. Reaction of 1-naphthyl hydroxamic acid **13** under the same conditions produced **28** in 31% yield.

(24) Chimiak, A.; Kolasa, T. *Rocz. Chem*. **1974**, *48*, 139.

(25) The use of triflic acid is a modification from those of the original report, which employed $HClO_4$. The reaction time of 24 h seems to be critical for success. Shorter reaction times prevent full conversion being achieved; longer times result in lower yields, perhaps due to product decomposition. The reaction also seems to be sensitive to the purity of *N*-hydroxyphthalimide **16** employed. Commercially available material is often of low quality and is best recrystallized from ethanol prior to use.

(26) Chimiak, A.; Kolasa, T. *Bull. Acad. Pol. Sci*. **1974**, *22*, 195. Koening, T.; Deinzer, M. *J. Am. Chem. Soc*. **1968**, *90*, 7014.

(27) During the acidification, a trace of methyl orange indicator was added to the hydroxylamine solution, in order to monitor the pH and prevent it from dropping too low by the overaddition of hydrogen chloride. The original report suggests that decomposition, possibly through loss of the *tert*-butyl group, may occur in very acidic solutions.

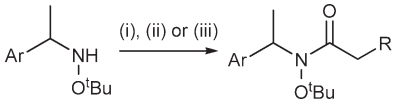
(28) de Lijser, H. J. P.; Tsai, C.-K. *J. Org. Chem*. **2004**, *69*, 3057.

(29) Smith, A. L.; Hwang, C.-K.; Pitsinos, E.; Scarlato, G. R.; Nicolaou, K. C. *J. Am. Chem. Soc*. **1992**, *114*, 3134.

(30) Jencks, J. *J. Am. Chem. Soc*. **1959**, *81*, 475.

(31) Aqueous HCl could not be employed in these instances due to the insolubility of oxime ethers **20**−**22**.

SCHEME 5[a]



23, Ar = Ph
24, Ar = 2-Nap
1, Ar = 1-Nap
25, Ar = 2-Tol

26-33
Ar = Ph, 2-Nap, 1-Nap or 2-Tol
R = Me or Bn

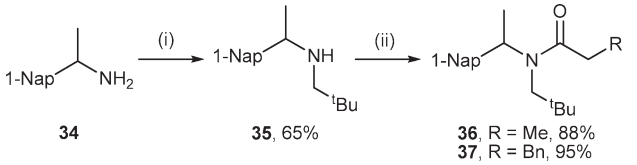
	Ar	conditions	R	product	yield %
23	Ph	(i)	Me	**26**	61
24	2-Nap	(ii)	Me	**27**	73
1	1-Nap	(ii)	Me	**28**	85
25	2-Tol	(i)	Me	**29**	68
23	Ph	(iii)	Bn	**30**	94
24	2-Nap	(ii)	Bn	**31**	60
1	1-Nap	(ii)	Bn	**32**	72
25	2-Tol	(iii)	Bn	**33**	98

[a]Reagents and conditions: (i) propanoyl chloride, pyridine, 0 °C to rt, 12 h; (ii) RCH_2COCl, $^i Pr_2NEt$, CH_2Cl_2, 0 °C to rt, 12 h; (iii) hydrocinnamoyl chloride, NaOH (1 M, aq), CH_2Cl_2, 0 °C to rt, 12 h. 2-Nap = 2-naphthyl; 1-Nap = 1-naphthyl; 2-Tol = 2-tolyl.

N-Acylation of **35** with propanoyl chloride and hydrocinnamoyl chloride gave amides **36** and **37**, respectively, in good yield. The ^1H and ^{13}C NMR spectra of **36** and **37** showed distinct sets of peaks, consistent with the presence of two rotamers. Recording the NMR spectra at high temperature did not result in peak coalescence (Scheme 6).

Alkylation of *N*-(1-Arylethyl)-*O*-*tert*-butylhydroxamates. Given the reported decomposition of Weinreb amides and other hydroxamates under strongly basic conditions,[13] the stability of the enolates derived from hydroxamates **14** and **26** was investigated. Treatment of *O*-methyl hydroxamate **14** with LDA at −78 °C gave a bright orange solution. After being stirred for 30 min the reaction was quenched and subjected to an aqueous workup, which gave a 55:40:5 ratio of the starting hydroxamate **14**, vinylamide **40**, and amide **41**. Chromatography gave **14** in 46% yield and **40** in 27% yield; **41** was not isolated although its identity was confirmed by independent chemical synthesis from α-methylbenzylamine and propanoyl chloride (Scheme 7). The formation of **40** and **41** in this reaction is not unexpected and is consistent with the known decomposition pathways available to hydroxamates upon treatment with strong bases: competing deprotonation α to nitrogen (the benzylic center within **14**), elimination of methoxide and imine−enamine tautomerization leads to **40**,[32] while a retro-ene type fragmentation of enolate **38**,[13] to give **39**, followed by subsequent protonation accounts for the formation of **41** (Scheme 7). However, when **14** was treated with KHMDS at −78 °C, to form the potassium enolate, aqueous workup gave a mixture of products which contained a 95:5 mixture of **14**:**41**, indicating that the benzylic deprotonation pathway had been suppressed.[33] To block the retro-ene fragmentation, the behavior of the *O*-*tert*-butyl hydroxamate **26** upon treatment with KHMDS was investigated. The enolate derived from **26** proved to be stable, even when the reaction mixture was allowed to warm to 0 °C and, after quenching and aqueous workup, 98% mass return of **26** was obtained. Thus, by careful choice of both the base (KHMDS) and the O-substituent on the chiral auxiliary (*O*-*tert*-butyl) both enolate decomposition pathways were effectively blocked (Scheme 7).

SCHEME 6[a]



34 **35**, 65% **36**, R = Me, 88% **37**, R = Bn, 95%

[a]Reagents and conditions: (i) pivalaldehyde, EtOH, rt, then $NaBH_4$, EtOH, rt, 12 h; (ii) RCH_2COCl, NaOH (1 M, aq), CH_2Cl_2, 0 °C to rt, 12 h. 1-Nap = 1-naphthyl.

The alkylation reactions of *O*-*tert*-butyl hydroxamates **26**−**33** were next investigated. Treatment of the *N*-propanoyl derivatives **26**−**29** with KHMDS afforded, in all cases, pale yellow solutions that faded rapidly upon addition of benzyl bromide, to give **42**−**45** as the major diastereoisomeric products. The reaction diastereoselectivities were assessed by peak integration of the ^1H NMR spectra of the crude reaction mixtures, with purification furnishing diastereoisomerically pure samples of **42**−**45** (Scheme 12). To verify the levels of diastereoselectivity obtained in these benzylation reactions, the alternative diastereoisomeric products **46**−**49** were prepared by methylation of the *N*-hydrocinamoyl derivatives **30**−**33**. The relative configurations within **43** (resulting from benzylation of **27**, Ar = 2-Nap)[34] and **48** (resulting from methylation of **32**, Ar = 1-Nap)[35] were unambiguously established by single-crystal X-ray analysis. The preferred solid state conformations of **43** and **48** revealed analogous conformational preferences to standard Weinreb amides, in that the oxygen atoms adopt an *anti*-periplanar conformation, and that the *O*-*tert*-butyl group is approximately perpendicular to this plane; the nitrogen atom is pyramidalized, and the nitrogen lone pair lies *syn*-periplanar to the *O*-*tert*-butyl group. These solid-state investigations also allowed the relative configurations of **44** and **47** to be unambiguously assigned. The relative configurations within **42** and **45** (resulting from enolate benzylation of **26** and **29**, respectively) and **46** and **49** (resulting from enolate methylation of **30** and **33**, respectively) were thus assigned by analogy. These assignments could be made with some confidence as comparison of the ^1H NMR spectra of **42**−**45** revealed significant similarities in the 2.00−3.50 ppm region, which contained the resonances associated with the C(2)*H* and CH_2Ph protons; the ^1H NMR spectra of **46**−**49** also revealed distinct similarities in the 2.00−3.50 ppm region and these spectra were notably different from those of **42**−**45**. These observations allowed confident assignment of the configurations within all the diastereoisomers **42**−**49**. Thus,

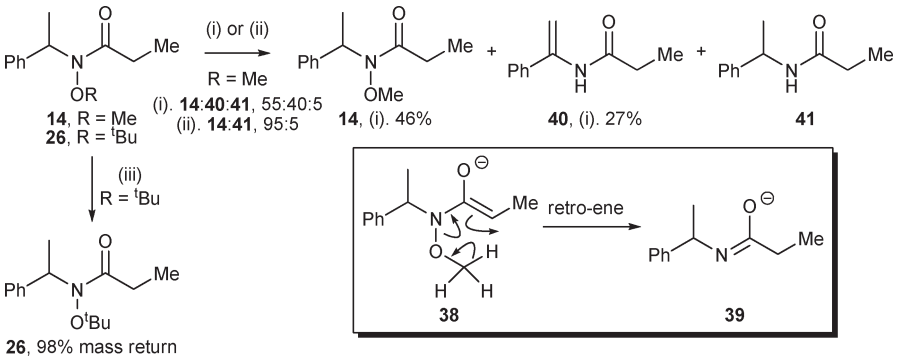
(32) Meyers, A. I.; Kunnen, K. B.; Still, W. C. *J. Am. Chem. Soc.* **1987**, *109*, 4405. Fray, A. H.; Meyers, A. I. *Tetrahedron Lett.* **1992**, *33*, 3575. Davies, S. G.; Doisneau, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2513. Snyder, L.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 7507.

(33) The retro-ene reaction could be driven to 100% conversion by allowing the enolate solution to warm to 0 °C; amide **41** was isolated from this reaction in 41% yield.

(34) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 739479.

(35) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 733577; see ref 3.

SCHEME 7[a]



[a]Reagents and conditions: (i) LDA, THF, −78 °C, 30 min; (ii) KHMDS, THF, −78 °C, 30 min; (iii) KHMDS, THF, −78 to 0 °C, 30 min.

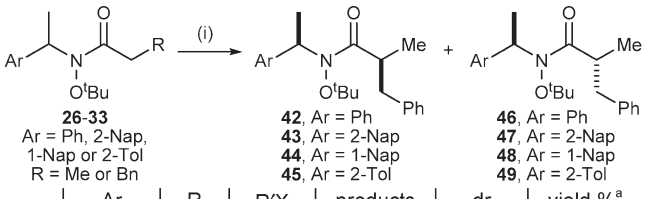
an increase in alkylation diastereoselectivity was noted when the bulk of the aromatic group was increased from phenyl to 2-naphthyl. Alkylation of the 1-napthyl and the 2-tolyl derivatives results in very high levels of diastereoselectivity, which are nearly identical. These studies suggest that the presence of an ortho-substituent on the aromatic ring is a key feature for obtaining high levels of diastereoselectivity in these alkylation reactions (Scheme 8).

Further Investigations: Probing the Origin of Diastereoselectivity. Having identified hydroxamates **28** and **32**, derived from hydroxylamine **1**, as offering high levels of alkylation diastereoselectivity, the origin of this selectivity was further probed. Treatment of **28** with KHMDS gave a pale yellow solution. Addition of TMSCl caused rapid fading of the yellow coloration; after trituration of the product from pentane (to remove KCl and other insoluble material), ^{1}H NMR spectroscopic analysis was indicative of the rotameric (*Z*)-silyl enol ether **50** being present as a single major product[36] in >95:5 dr (Scheme 9). Assignment of the double bond geometry within **50** was possible by a somewhat complex NOE difference experiment. Due to the practical difficulties of performing such an experiment at high temperature (where the rotameric room temperature ^{1}H NMR spectrum had coalesced into a single set of peaks), the NOE experiment was performed at rt, with irradiation of each set of peaks corresponding to *both* rotameric forms. The enhancements thus obtained provided strong evidence in favor of a (*Z*)-enolate geometry: strong mutual enhancements were observed between the trimethylsilyl group and the C(3)H_3 protons, and between the *O*-*tert*-butyl group and the C(2)*H* vinylic proton, and crucially no enhancements were observed between the trimethylsilyl group and the C(2)*H* vinylic proton, or between the C(3)H_3 and *O*-*tert*-butyl groups. The generation of the corresponding (*Z*)-enolate upon deprotonation of **28** with KHMDS is consistent with the known preference of amides, *N*-acyl oxazolidinones, and hydroxamates to give (*Z*)-enolates upon treatment with a range of bases.[12]

To investigate the role of the potassium ion in these enolate reactions, the benzylation of **28** in the presence of 18-crown-6 was performed. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed that both the sense and magnitude of the diastereoselectivity (98:2 dr) was

(36) Returned starting material **28** was also present.

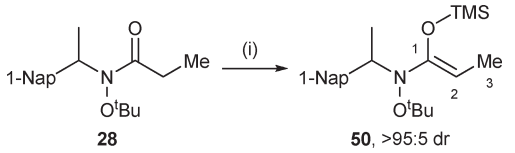
SCHEME 8[b]



	Ar	R	R′X	products	dr	yield %[a]
26	Ph	Me	BnBr	**42**:**46**	93:7	70
27	2-Nap	Me	BnBr	**43**:**47**	96:4	71
28	1-Nap	Me	BnBr	**44**:**48**	98:2	68
29	2-Tol	Me	BnBr	**45**:**49**	97:3	97
30	Ph	Bn	MeI	**42**:**46**	22:78	32
31	2-Nap	Bn	MeI	**43**:**47**	12:88	63
32	1-Nap	Bn	MeI	**44**:**48**	3:97	79
33	2-Tol	Bn	MeI	**45**:**49**	5:95	79

[a]Isolated yield of major diastereoisomer (>99:1 dr). [b]Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then R′X, −78 °C, 6−12 h. 2-Nap = 2-naphthyl; 1-Nap = 1-naphthyl; 2-Tol = 2-tolyl.

SCHEME 9[a]

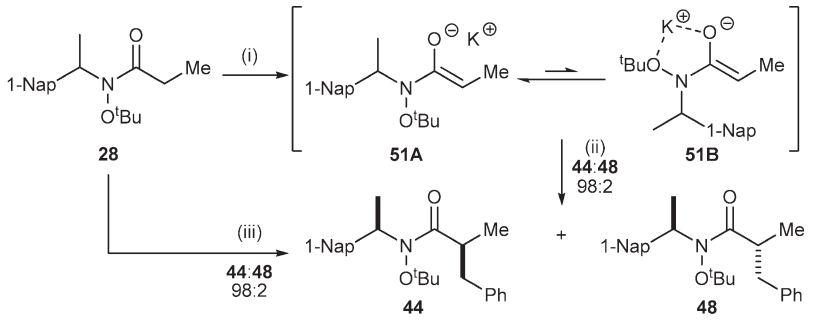


[a]Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then TMSCl, −78 °C to rt, 30 min. 1-Nap = 1-naphthyl.

the same as in the absence of this additive; the yield of the reaction also remained high (95% isolated yield of **44** after chromatography). This result strongly suggests that the potassium counterion does not promote formation of the chelated enolate **51B** (in accordance with the known low Lewis acidity of potassium ions) and that enolate aggregation is unimportant in influencing the diastereoselectivity in these reactions. It can therefore be inferred that the alkylation reaction proceeds from the enolate in the nonchelated, *anti*-conformation **51A** (Scheme 10).

The importance of the *O*-*tert*-butyl group was next probed. Treatment of *N*-propanoyl amide **36** with KHMDS in THF at −78 °C afforded a violet solution. After the addition of benzyl bromide, the reaction was maintained at

SCHEME 10[b]



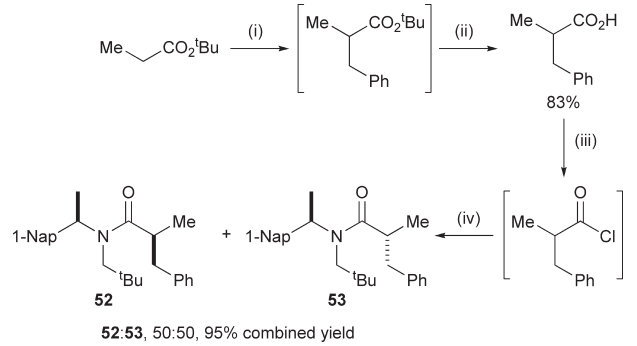
conditions	dr **44**:**48**	yield **44** %[a]
(i) then (ii)	98:2	68
(iii)	98:2	95

[a]Isolated yield of major diastereoisomer (> 99:1 dr). [b]Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min; (ii) BnBr, −78 °C, 6 h; (iii) KHMDS, 18-crown-6, THF, −78 °C, then BnBr, −78 °C, 1 h. 1-Nap = 1-naphthyl.

−78 °C for 18 h. The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of both diastereoisomers **52** and **53**, together with some unreacted starting material **35**. Due to the highly complex nature of this NMR spectrum (two sets of peaks for each amide) the diastereoisomeric ratio was estimated as ∼85:15,[37,38] although the relative stereochemistry of the major diastereoisomer was not assigned. Enolate methylation of *N*-hydrocinnamoyl amide **37** under the same conditions, using KHMDS and MeI, proceeded to only very low conversion (ca. 5%) even after 24 h. Flash column chromatography allowed the isolation of a slightly impure sample of amides **52** and **53** in 4% yield, in approximately 85:15 dr[37] (Scheme 11).

(37) The reaction diastereoselectivity was estimated by peak integration of the ^{1}H NMR spectra of the crude reaction mixture and pure products recorded in d_8-PhMe at rt.

(38) Authentic samples of the expected diastereoisomeric products **52** and **53** resulting from the alkylation reactions of the *N*-neopentyl amides **36** and **37** were prepared. Deprotonation of *tert*-butyl propanoate with LDA followed by addition of benzyl bromide and hydrolysis of the resulting ester with TFA gave 2-benzylpropanoic acid in 83% isolated yield. Conversion to the corresponding acid chloride was effected with oxalyl chloride, and subsequent reaction with *N*-neopentyl amine **35** gave the chromatographically inseparable diastereoisomeric products **52** and **53** in 95% isolated yield. The ^{1}H and ^{13}C NMR spectra for this mixture were highly complex, as both **52** and **53** showed separate sets of peaks for each amide rotamer. High-temperature ^{1}H NMR spectroscopy failed to effect peak coalesce.



Reagents and conditions: (i) LDA, THF, −78 °C, 30 min, then BnBr, −78 °C to rt, 2 h; (ii) TFA, CH_2Cl_2, 30 °C, 30 min; (iii) $(COCl)_2$, pentane, DMF (cat.), rt, 1 h; (iv) **35**, NaOH (2 M, aq), CH_2Cl_2, 0 °C to rt, 12 h.

Alkylations of the *O*-methyl hydroxamates **14** and **15** were next performed. Although partial decomposition of the enolate of **14** via a retro-ene reaction had already been noted, it was anticipated that if the benzylation reaction was sufficiently rapid then a clean reaction may still be possible, the diastereoselectivity of which would yield the required information. Thus, benzylation of hydroxamate **14** (Ar = Ph) upon treatment with KHMDS and benzyl bromide at −78 °C for 3 h gave a 72:28 mixture[39] of the diastereoisomers **54** and **55**, of undetermined stereochemistry, which were isolated as a 72:28 mixture in 78% combined yield after flash chromatography. Enolate benzylation of **15**[40] (Ar = 1-Nap) also gave a 72:28 mixture of the diastereoisomers **56** and **57**, which were isolated as a 72:28 mixture in 78% combined yield after chromatography (Scheme 12).

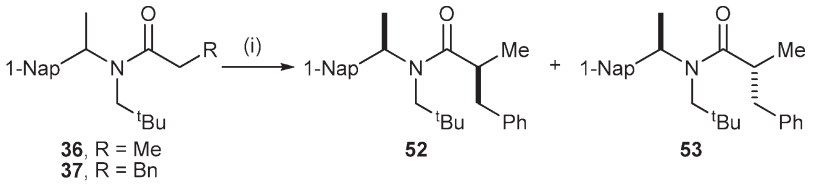
These studies suggest that, as predicted, the *O*-*tert*-butyl group is a pivotal structural feature that enhances the efficacy of the auxiliary, with both the oxygen atom *and* the *tert*-butyl group being important. *N*-Neopentyl amides **36** and **37** behave in a very different manner to hydroxamates **28** and **32**. While the enolate alkylations were not completely lacking in stereoselectivity, the values obtained were very much lower than those obtained with use of the *O*-*tert*-butyl hydroxamate analogues. Furthermore, the alkylations of amides **36** and **37** were found to be significantly slower than those of the corresponding hydroxamates **28** and **32**. In the case of methylation of **37**, the reaction was prohibitively slow at −78 °C. The higher reactivity of the enolates derived from the hydroxamates **28** and **32** relative to those derived from amides **36** and **37** may be due to the so-called "kinetic α-effect",[41] resulting from the presence of the oxygen atom within auxiliary **1**. Lone pair−lone pair repulsions between the nitrogen and oxygen atoms may increase the energy of

(39) The reaction diastereoselectivity was estimated by peak integration of the ^{1}H NMR spectra of the crude reaction mixture and pure products recorded in d_8-PhMe at 70 °C.

(40) Treatment of **15** with KHMDS at −78 °C gave a pale yellow solution, consistent with enolate formation. After 30 min the reaction mixture was quenched, resulting >95% mass return of the starting hydroxamate **15**, and thus demonstrating that the enolate is stable at −78 °C (i.e., that the 1′-naphthyl system **15** behaves in a similar fashion to the 1′-phenyl analogue **14**).

(41) Fleming, I. *Frontier Orbital Effects in Organic Chemical Reactions*; Wiley: Chichester, UK, 1976; p 77.

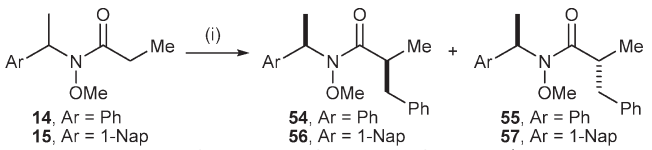
SCHEME 11[b]



R	R'X	dr	yield %[a]
Me	BnBr	~85:15	73
Ph	MeI	~85:15	4

[a]Combined isolated yield for mixture of diastereoisomers. [b]Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then R′X, −78 °C, 18−24 h. 1-Nap = 1-naphthyl.

SCHEME 12[c]



Ar	products	dr[a]	yield %[b]
Ph	**54**, **55**	72:28	78
1-Nap	**56**, **57**	72:28	78

[a]Diastereoisomeric ratio of both the crude reaction mixture and purified product. [b]Combined isolated yield for mixture of diastereoisomers. [c]Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then BnBr, −78 °C, 3 h. 1-Nap = 1-naphthyl.

the lone pair of the former so that it is closer in energy to the enolate LUMO. This may mean these electrons are more readily donated into the enolate π-system, thus increasing its electron density and hence its nucleophilicity. The poor diastereoselectivity obtained upon alkylation of *O*-methyl hydroxamate **15** supports the hypothesis that the *tert*-butyl group acts as a steric block toward alkylation.

Molecular Modeling Studies. Experimental evidence supporting several of the control elements originally predicted in the chiral relay mechanism had now been obtained; namely, the enolate is (*Z*)-configured and an *anti* (nonchelated) conformation seems most likely, and the *tert*-butyl group is at least partially responsible for hindering attack at one of the diastereotopic enolate faces. The origin of the chiral relay mechanism, that is, the transfer of stereochemical information from the asymmetric carbon center to the conformation of the *tert*-butyl group and the adjacent nitrogen center, remained to be explained, although the ortho-substitution patterns present in the 1-naphthyl and 2-tolyl hydroxamates appeared to be important. To provide answers to these remaining questions, molecular mechanics calculations were performed using the CAChe program with MM2 force field parameters. The atomic coordinates from the X-ray crystal structure of 1-naphthyl derivative **48** were imported into the modeling program. The 2-benzylpropanoyl group was replaced with a (*Z*)-enolate derived from a propanoyl group, with the O−C(1)−N−O dihedral angle being fixed at 180°. A "naked" enolate, carrying a full negative charge on the oxygen atom, was used given that alkylation reactions of **28** were equally stereoselective in the absence or presence of 18-crown-6. The insignificant role of the counterion also ruled out any complications which may have resulted due to enolate aggregation and/or solvent co-ordination. The C(1)—N—O—CMe_3 dihedral angle was restrained to the value observed in the X-ray crystal structure (107°). The nitrogen atom of an amide enolate is usually considered to be pyramidalized,[42] and therefore the nitrogen atom in the enolate model was fixed as sp^3-hybridized. Energy minimization of the initial enolate model **58** led to little change in structure. This result appeared to establish a correlation between the structural preferences of the enolate and that of the parent hydroxamate. Rotation about each of the N−C(1′) and C(1′)−Ar bonds in 7.5° increments was performed and the results were plotted as an energy surface. A sharp minimum (much lower in energy than any other conformations) corresponded to **58A**, which is almost identical with that obtained from the initial minimization. This result provided evidence that the initially minimized structure was indeed a genuine energy minimum (Figure 3). It is important to note that the assumptions utilized to generate the initial model render the nitrogen atom a stereogenic center and the N−O bond a chiral axis. The remaining three possible diastereoisomeric enolate structures resulting from these assumptions were therefore next considered. The conformation about the N−O bond was altered so that the *tert*-butyl group was positioned on the opposite face to the nitrogen lone pair. This was achieved by simply reflecting its position in the plane of the enolate. The energy of this structure was allowed to minimize by rotation about the N−C(1′) and C(1′)−Ar bonds, but a large increase in the energy of all conformations of the enolate (> 400 kJ mol^{-1}) was noted. This is not surprising: as well as the effects of lone pair−lone pair repulsions, simple inspection of this structure shows a big increase in steric crowding around the chiral auxiliary. Due to the large increase in energy upon making this structural alteration, further consideration of similar conformations was not undertaken. This experiment provides further support for the hypothesis that the position of the *tert*-butyl group controls the configuration adopted by the nitrogen center; a similar effect is observed in Oppolzer's

(42) In the enolate of an amide, interaction between the nitrogen lone pair and the enolate π-system may be expected to be significantly lower than that between the lone pair and the carbonyl π^*-orbital in the parent amide. Thus, the nitrogen atom is usually considered to be sp^3-hybridized; see: Brisse, F.; Thoraval, D.; Chan, T. H. *Can. J. Chem.* **1986**, *64*, 739. Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61. Seebach, D.; Maetzke, T.; Petter, W.; Kloetzer, B.; Plattner, D. *J. Am. Chem. Soc.* **1991**, *113*, 1781. This prediction has been vindicated by X-ray crystallographic studies; see: Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373.

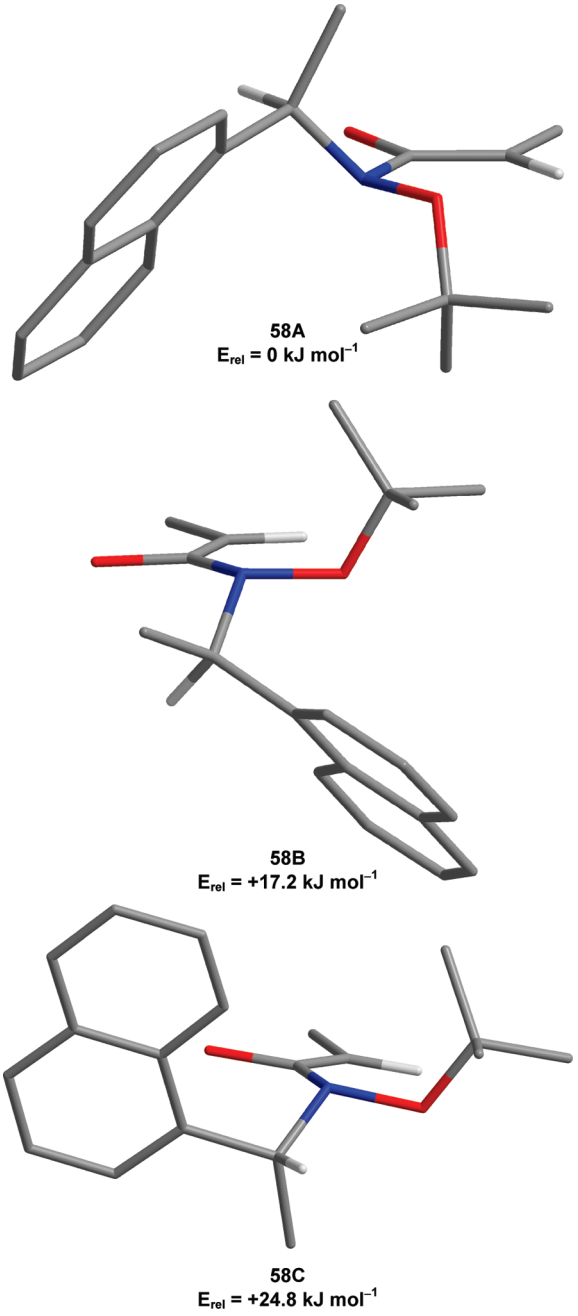


FIGURE 3. Energy minimized enolate structures **58A**, **58B**, and **58C**.

sultam-derived enolates.[14c] The final modification investigated was therefore alteration of *both* the configuration at the nitrogen center and the position of the *tert*-butyl group. Thus, the nitrogen center was inverted, and the *tert*-butyl group was reflected in the plane of the enolate. Generation of an energy surface by rotation about the N−C(1′) and C(1′)−Ar bonds revealed two minima corresponding to **58B** and **58C**, although both minima were higher in energy than **58A** (Figure 3).

Thus, evidence for the final link in the chiral relay has been gained. If the configuration at the stereogenic C(1′)-stereocenter is fixed as (*R*), then the *tert*-butyl group, which may choose its conformation by bond rotation, will prefer to lie over the *Si* face of the enolate. The nitrogen atom, which may choose its configuration by inversion, will prefer to adopt the

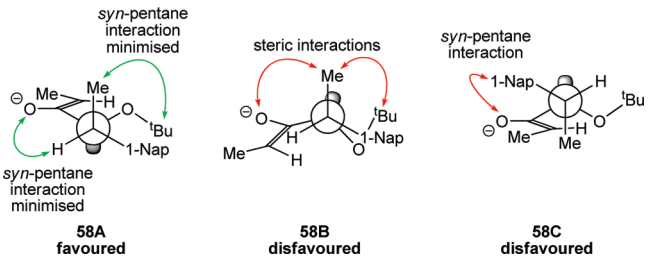


FIGURE 4. Newman projections (viewed along the C(1′)−N bond) of energy minimized enolate structures **58A**, **58B**, and **58C**.

(*S*)-configuration to minimize lone pair−lone pair repulsions, and this gives rise to conformation **58A**, which is expected to undergo alkylation on the *Re* face, opposite to both the nitrogen lone pair and the bulky *tert*-butyl group. Such a reaction gives a product with the correct relative configuration, as has been unambiguously determined by X-ray crystallography. The preference for **58A** over **58B** and **58C** is readily explained by examination of Newman projections along the C(1′)−N bond. In **58A**, a fully staggered arrangement is adopted, with the sterically demanding C(1′)-methyl and *O*-*tert*-butyl groups in a conformation that minimizes their mutual steric interaction. This leaves the sterically undemanding C(1′)-hydrogen and enolate oxygen atoms eclipsing, minimizing *syn*-pentane interactions. Although an analogous conformation is present in **58C**, an unfavorable *syn*-pentane interaction between the enolate oxygen and the naphthyl group is unavoidable. In **58B**, a nearly eclipsed conformation is adopted, and the C(1′)-methyl group occupies a position where it experiences unfavorable steric interactions with both the *tert*-butyl group and the enolate oxygen atom (Figure 4).

In addition to understanding the origins of the diastereoselectivities with use of the 1-naphthyl auxiliary **1**, it was also of interest to consider why this hydroxylamine was much more effective than its phenyl and 2-naphthyl analogues **23** and **24**, and displayed comparable levels of diastereoselectivity to the 2-tolyl analogue **25**. Models of enolate structures **59**−**61** derived from the phenyl, 2-naphthyl, and 2-tolyl hydroxamates **26**, **27**, and **29**, respectively, were built in the modeling program by simple alteration of the aryl group within **58**. In each case, energy minimization of this structure led to very little change in conformation. Energy surfaces were generated for **59**−**61** in the same manner as for the 1-naphthyl derivative **58**. The resulting energy surfaces displayed energy minima which corresponded to conformations **59A**, **60A**, and **61A**. The near symmetrical nature of the energy surface for **60** (Ar = 2-naphthyl) and the close resemblance to the (completely) symmetrical energy surface for **59** (Ar = Ph) were notable.[43] Conformations **59A**−**61A** correlated

(43) The near-symmetrical nature of the surface is due to the further distance of the "second ring" in the 2-naphthyl system from the rest of the structure when compared to the 1-naphthyl system. Thus, there is little difference between a rotation through +180° and −180° about the C(1′)−Ar bond. In the phenyl system, there is no difference between a rotation through +180° and −180° about the C(1′)−Ar bond, and this gives rise to the completely symmetrical energy surface.

(44) Although these results are in accord with **58A** and the X-ray crystal structure of the 1-naphthyl derivative **48**, conformation **60A** (Ar = 2-Nap) does not match that found in the X-ray crystal structure of **43**; however, this difference is likely to be caused by crystal-packing effects. Indeed, inspection of the energy surface revealed that the conformation corresponding to that adopted in the X-ray crystal structure of **43** is relatively low in energy.

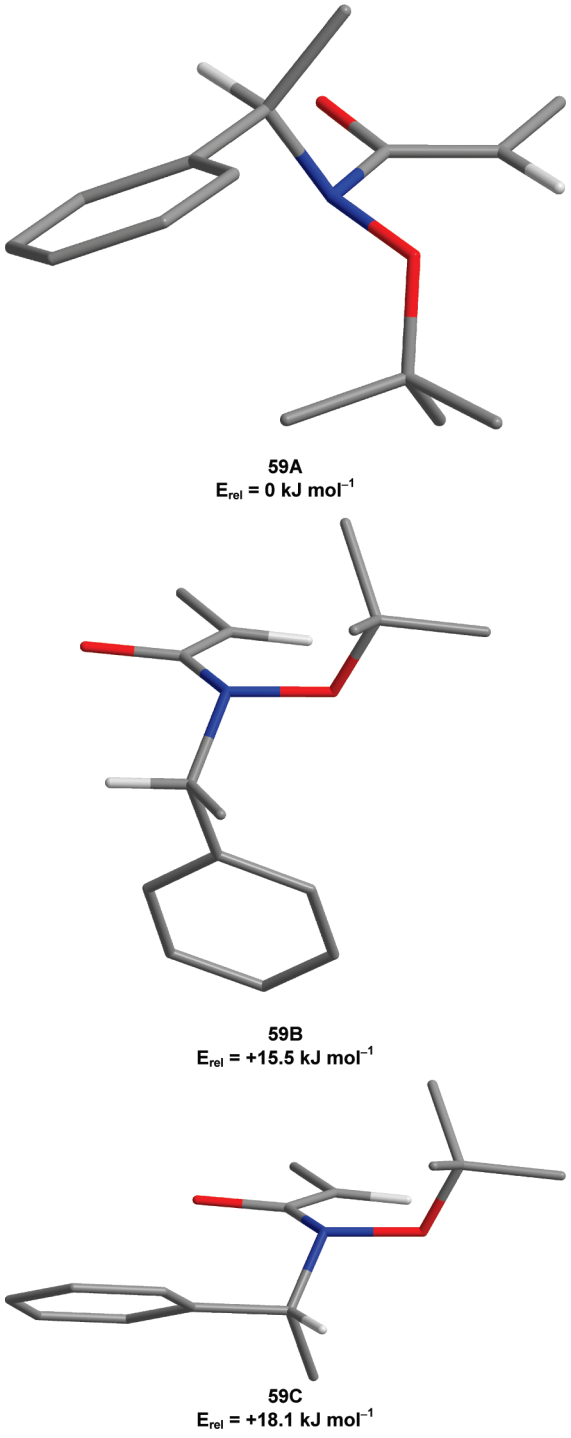


FIGURE 5. Energy minimized enolate structures **59A**, **59B**, and **59C**.

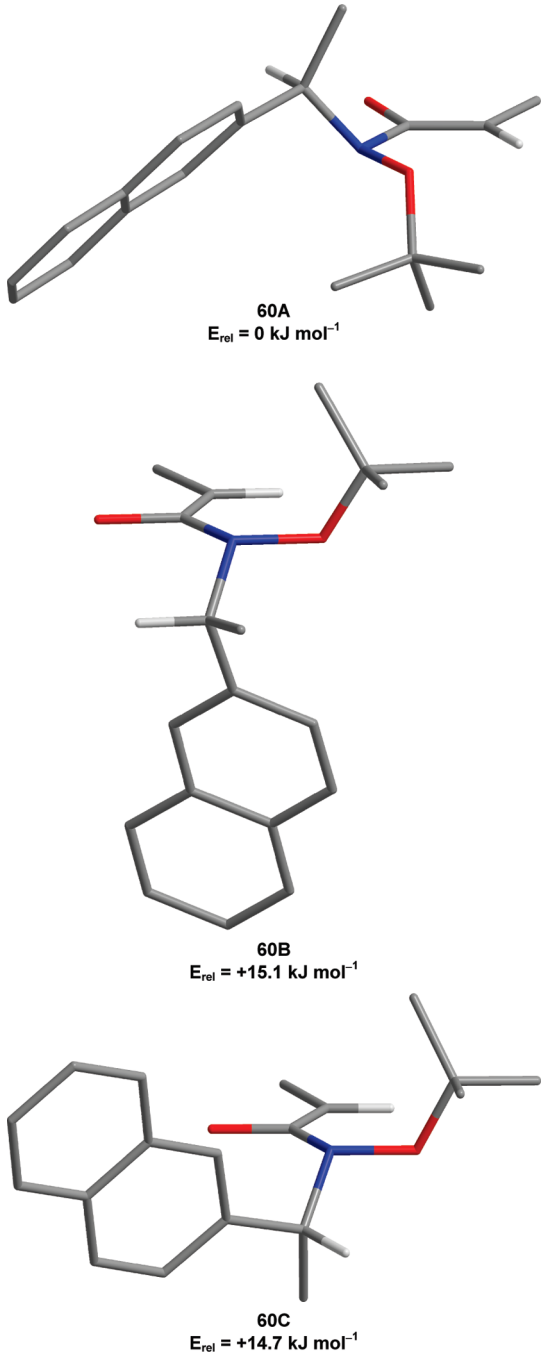


FIGURE 6. Energy minimized enolate structures **60A**, **60B**, and **60C**.

closely with the initially inputted structures in each case, and are equivalent to the 1-naphthyl analogue **58A**.[44] Reflection of the tert-butyl group in the plane of the enolate and inversion of the nitrogen center was performed for the phenyl, 2-naphthyl, and 2-tolyl enolate models (as for the 1-naphthyl case), and a new energy surface was generated. The minima on the resulting energy surfaces corresponded to the enolate conformations 59B, **59C**, **60B**, **60C**, **61B**, and **61C**, which are analogous to conformations **58B** and **58C** for the 1-naphthyl derivative (Figures 5−7).

Alkylation of enolates **59**−**61** with benzyl bromide (as a representative electrophile) in conformations **59A**−**61A** would be expected to occur from the *Re* face of the enolate in each case, opposite to both the *tert*-butyl group and the *N*-lone pair, giving rise to the corresponding major diastereoisomeric products, which is borne out by experiment. In conformations **58B**, **59B**, **60B**, and **61B**, the *tert*-butyl group appears to block the *Re* face of the enolate while approach to the *Si* face is hindered by the aromatic group; this is particularly pronounced in **58B** due to the strong conformational preference of the 1-naphthyl group to lie, as nearly as possible, such that the $C(8''a)-C(1'')-C(1')-C(1')CH_3$ dihedral angle is ∼180°. This avoids an unfavorable steric

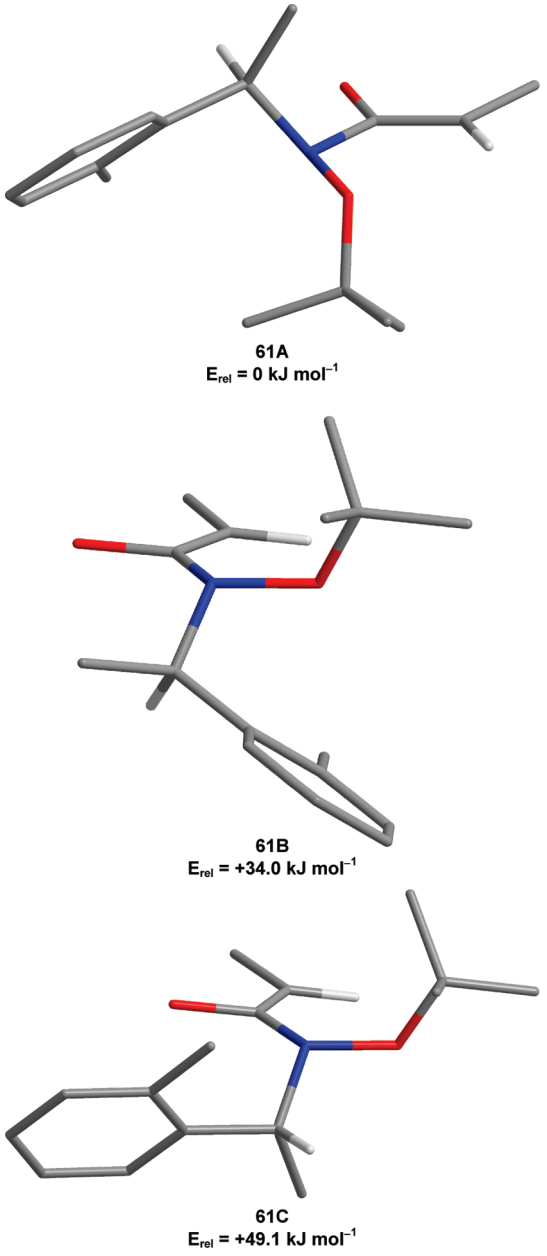


FIGURE 7. Energy minimized enolate structures **61A**, **61B**, and **61C**.

interaction between the C(1′)-methyl group and the peri-hydrogen atom at C(8″). Rotation about the N−C(1′) bond within **58B** is able to move the aryl ring to a position more removed from the *Si* face of the enolate; further inspection of the energy surfaces reveals that any such rotation of **58B** is accompanied by a rapid increase in energy, due to the resulting unfavorable steric interactions between the peri-hydrogen atom and the N−O bond of the hydroxamate, while rotation of **59B** and **60B** demands very little energy due to the absence of any such interaction. The 2-tolyl group within **61B** is able to mimic the conformational properties of the 1-naphthyl group due to the desire to avoid interactions with the aromatic methyl group. Erosion of the alkylation diastereoselectivity is more likely to occur through conformation **B** in the cases of **59** and **60**; meanwhile it seems unlikely that **58B** represents a reactive conformation, although in comparison the smaller size of the 2-tolyl group means that the *Si* face of **61B** is less well shielded, and reaction to give the minor diastereoisomer may potentially occur through this conformer. Adoption of the higher energy structure **58C** (in which the *tert*-butyl group and the *N*-lone pair both lie over the *Re* face of the enolate and therefore promote alkylation on the *Si* face) is therefore required for leakage to produce the minor diastereoisomer. Consequently, the highest diastereoselectivities are obtained with use of the 1-naphthyl hydroxylamine auxiliary **1**.

Conclusion

In conclusion, a combination of evidence gained through experimental observations (including modification of the auxiliary structure), physical measurements (including X-ray crystal structure analysis), and molecular mechanics calculations has given an insight into the origin of diastereoselectivity in alkylation reactions of enolates derived from *N*-1-(1′-naphthyl)-ethyl-*O*-*tert*-butylhydroxamates (chiral Weinreb amide equivalents). A chiral relay mechanism to rationalize the observed stereochemical outcome was proposed and validated. It has been shown that deprotonation leads to a nonchelated (*Z*)-enolate with the oxygen atoms adopting an *anti*-periplanar conformation. The configuration of the *N*-1-(1′-naphthyl)ethyl group dictates the position of the *O*-*tert*-butyl group and the configuration adopted by the pyramidal *N*-atom. Subsequent enolate alkylation occurs on the face *anti* to both the *O*-*tert*-butyl group (steric control) and *N*-lone pair (stereoelectronic control). The identical diastereoselectivities observed upon alkylation of the potassium enolate and the "naked" enolate in both the racemic and enantiopure series suggest that the effect of enolate aggregation is unimportant in these reactions. It is hoped that *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine will prove a valuable addition to the field of asymmetric synthesis and that the mechanistic insight gained from the experiments described herein will assist in the further development of chemistry in this important area.

Experimental Section

General Experimental Details. All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere, using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[45] KHMDS was titrated according to an amalgamation of the procedures reported by Duhamel and Plaquevent[46] and Lin and Paquette.[47] Other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminum plates coated with 60 F_{254} silica. Plates were visualized by using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. IR spectra were recorded as either a thin film on NaCl plates (film) or a KBr disk (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Spectra were recorded at rt unless otherwise stated. The ^{13}C

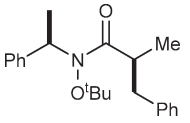
(45) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
(46) Duhamel, L; Plaquevent, J.-C. *J. Organomet. Chem.* **1993**, *448*, 1.
(47) Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.

NMR spectra of many of the hydroxamate derivatives contained peaks that were very broad (in some cases absent); the chemical shifts of these peaks are reported in *italics*. $^1H-^1H$ COSY and $^1H-^{13}C$ HMQC analyses were used to establish atom connectivity.

General Procedure for the Alkylation of Hydroxamate Derivatives. Alkylation Procedure. KHMDS in PhMe (ca. 0.5 M) was added dropwise to a solution of an accurately weighed sample of menthol (ca. 150 mg in 3 mL of PhMe), containing a trace of (*E*)-*N*-benzylidenebiphenyl-4-amine as an indicator, at 0 °C. A single drop of excess KHMDS caused the formation of an intense blue coloration.[48] The titration was repeated twice more by the addition of a further aliquot of menthol.

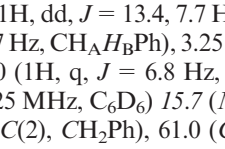
Alkylation Procedure. A solution of the requisite substrate in THF at −78 °C was added dropwise to a solution of KHMDS (prepared by the addition of THF to solid KHMDS). The reaction was stirred at this temperature for 30 min before the addition of the requisite alkyl halide. The reaction mixture was stirred at −78 °C for the duration indicated before being quenched by the addition of pH 7 phosphate buffer solution. The reaction mixture was concentrated in vacuo, and the residue was redissolved in Et_2O and filtered through a short silica/$MgSO_4$ plug (eluent Et_2O). The filtrated was concentrated in vacuo to give the crude reaction product.

(2*RS*,1′*SR*)-*N*-*tert*-Butoxy-*N*-1′-phenylethyl 2-Benzylpropanamide, 42.



26 (505 mg, 2.0 mmol) in THF (10 mL) was treated with KHMDS (2.2 mmol) in THF (10 mL) and BnBr (723 μL, 6.1 mmol) according to the General Procedure. The reaction was held at −78 °C for 8 h before being quenched by the addition of pH 7 phosphate buffer (1 mL). ^1H NMR spectroscopic analysis of the crude reaction mixture (500 MHz, d_8-PhMe, 70 °C) showed the presence of **42** and **46** in a 93:7 ratio. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 10:1) gave a mixed fraction containing **42** and **46** in a 10:90 ratio (112 mg, 16%). Further elution gave **42** a colorless oil (485 mg, 70%, >99:1 dr): found C, 77.55; H, 8.8; N, 4.2, $C_{22}H_{29}NO_2$ requires C, 77.8; H, 8.6; N, 4.1; ν_{max} (film) 1666 (C═O), 1605; δ_H (500 MHz, d_8-PhMe, 90 °C) 0.97 (9H, s, CMe_3), 1.08 (3H, d, J = 6.8 Hz, C(3)H_3), 1.53 (3H, d, J = 6.8 Hz, C(1′)*Me*), 2.38 (1H, dd, J = 13.4, 7.7 Hz, CH_AH$_B$Ph), 2.97 (1H, dd, J = 13.4, 6.7 Hz, CH$_A$$H_B$Ph), 3.25 (1H, app septet, J = 7.0 Hz, C(2)*H*), 5.10 (1H, q, J = 6.8 Hz, C(1′)*H*), 6.95−7.38 (10H, m, *Ph*); δ_C (125 MHz, C_6D_6) *15.7* (*Me*), *16.1* (*Me*), 27.6 (CMe_3), *38.5*, *39.0* (*C*(2), *C*H$_2$Ph), 61.0 (*C*(1′)), 82.2 (*C*Me$_3$), 126.3, 127.3, 127.7, 128.2, 129.5 (*o*-, *m*-, *p*-*Ph*), 140.2 141.6 (*i*-*Ph*), 182.1 (*C*(1)); m/z (CI$^+$) 340 ([M + H]$^+$, 100%). Further elution gave unreacted **26** (70 mg, 14%).

(2*RS*,1′*SR*)-*N*-*tert*-Butoxy-*N*-1′-(2″-naphthyl)ethyl 2-Benzylpropanamide, 43.



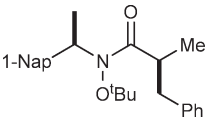
27 (64 mg, 0.21 mmol) in THF (1 mL) was treated with KHMDS (0.24 mmol) in THF (1 mL) and BnBr (76 μL, 0.64 mmol) according to the General Procedure. The reaction was held at −78 °C for 8 h before being quenched by the addition of pH 7 phosphate buffer (1 mL). ^1H NMR spectroscopic analysis of the crude reaction mixture (500 MHz, d_8-PhMe, 70 °C) showed the presence of **43** and **47** in a 96:4 ratio. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 10:1) gave **43** as a colorless oil that solidified on standing (59 mg, 71%, >99:1 dr). Recrystallization of an aliquot from MeOH gave colorless needles: found C, 80.1; H, 7.9; N, 3.4, $C_{26}H_{31}NO_2$ requires C, 80.2; H, 8.0; N, 3.6; mp 110−111 °C; ν_{max} (film) 1663 (C═O), 1602; δ_H (250 MHz, d_8-PhMe, 90 °C) 0.93 (9H, s, CMe_3), 1.12 (3H, d, J = 6.8 Hz, C(3)H_3), 1.62 (3H, d, J = 7.2 Hz, C(1′)*Me*), 2.38 (1H, dd, J = 13.2, 7.6 Hz, CH_AH$_B$Ph), 3.02 (1H, dd, J = 13.2, 6.8 Hz, CH$_A$$H_B$Ph), 3.28 (1H, app septet, J = 6.9 Hz, C(2)*H*), 5.31 (1H, q, J = 7.2 Hz, C(1′)*H*), 6.88−7.29 (8H, m, *Ar*), 7.50−7.84 (4H, m, *Ar*); δ_C (50 MHz, $CDCl_3$) *16.0* (*Me*), 27.7 (CMe_3), *38.0*, *39.0* (*C*(2), *C*H$_2$Ph), *60.0* (*C*(1′)), 82.2 (*C*Me$_3$), 125.6, 125.7, 125.9, 126.1, 127.5, 127.7, 128.2, 129.3, 132.5, 133.1, 139.1, 139.9 (*Ar*, *Ph*), *181.9* (*C*(1)); m/z (CI$^+$) 390 ([M + H]$^+$, 100%).

X-ray Crystal Structure Determination for 43. Data were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo Kα radiation, using standard procedures at 190 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined by using CRYSTALS.[49]

X-ray crystal structure data for **43** [$C_{26}H_{31}NO_2$]: M = 389.54, monoclinic, space group $P2_1/c$, a = 11.5977(9) Å, b = 16.253(2) Å, c = 11.883(5) Å, β = 90.64(2)°, V = 2240(1) Å^3, Z = 4, μ = 0.067 mm^{-1}, colorless prism, crystal dimensions = 0.12 × 0.25 × 0.53 mm^3. A total of 3296 unique reflections were measured for $5 < \theta < 27$ and 2437 reflections were used in the refinement. The final parameters were wR_2 = 0.059 and R_1 = 0.049 [$I > 3.0\sigma(I)$].

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 739479. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223−336033 or e-mail deposit@ccdc.cam.ac.uk].

(2*RS*,1′*SR*)-*N*-*tert*-Butoxy-*N*-1′-(1″-naphthyl)ethyl 2-Benzylpropanamide, 44.



Method A. 28 (75 mg, 0.25 mmol) in THF (1 mL) was treated with KHMDS (0.28 mmol) in THF (1 mL) and BnBr (89 μL, 0.75 mmol) according to the General Procedure. The reaction mixture was held at −78 °C for 6 h before being quenched by the addition of pH 7 phosphate buffer solution (0.5 mL). ^1H NMR spectroscopic analysis of the crude reaction mixture (250 MHz, d_8-PhMe, 70 °C) showed the presence of **44** and **48** in a 98:2 ratio. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 10:1) gave **44** as a colorless oil (66 mg, 68%, >99:1 dr); found C, 80.3; H, 8.1; N, 3.4, $C_{26}H_{31}NO_2$ requires C, 80.2; H, 8.0; N, 3.6; ν_{max} (film) 1663 (C═O), 1601; δ_H (250 MHz, d_8-PhMe, 70 °C) 0.71 (9H, s, CMe_3), 1.16 (3H, d, J = 6.8 Hz, C(3)H_3), 1.58 (3H, d, J = 7.0 Hz, C(1′)*Me*), 2.46 (1H, dd, J = 13.2, 8.3 Hz, CH_AH$_B$Ph), 3.08 (1H, dd, J = 13.2, 6.1 Hz,

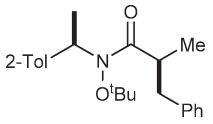
(48) Use of PhMe as the solvent provided a sharper end-point than THF.

(49) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. CRYSTALS, 2001, Issue 11; Chemical Crystallography Laboratory, University of Oxford, Oxford, UK.

CH_AH_BPh), 3.28−3.42 (1H, m, C(2)*H*), 6.25 (1H, br m, C(1′)*H*), 6.96−7.62 (11H, m, *Ar*, *Ph*), 8.37 (1H, br m, *Ar*); δ_C (50 MHz, $CDCl_3$) *18.0* (*C*(3)), 27.7 (CMe_3), *38.0* (*C*(2)), *39.2* (CH_2Ph), *55.0* (*C*(1′)), 82.5 (CMe_3), *124.4*, *125.2*, 125.8, 126.3, 126.6, 128.5, 128.9, 129.6, 133.8, *137.0*, *140.0* (*Ar*, *Ph*); *m*/*z* (CI^+) 390 ($[M + H]^+$, 100%).

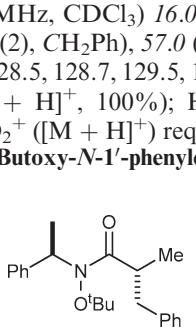
Method B. 28 (351 mg, 1.17 mmol) in THF (6 mL) was treated with KHMDS (1.29 mmol) and 18-crown-6 (511 mg, 1.94 mmol)[50] in THF (6 mL) and benzyl bromide (1.28 mL, 10.8 mmol) according to the General Procedure. The reaction was held at −78 °C for 1 h before being quenched by the addition of pH 7 buffer solution (1 mL). ^{1}H NMR spectroscopic analysis of the crude reaction mixture (250 MHz, d_8-PhMe, 70 °C) showed the presence of **44** and **48** in a 98:2 ratio. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 10:1) gave **44** as a colorless oil (433 mg, 95%, >99:1 dr).

(2*RS*,1′*SR*)-*N*-*tert*-Butoxy-*N*-1′-(2″-methylphenyl)ethyl 2-Benzylpropanamide, 45.



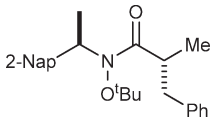
29 (114 mg, 0.43 mmol) in THF (2 mL) was treated with KHMDS (0.48 mmol) in THF (2 mL) and BnBr (154 μL, 1.30 mmol) according to the General Procedure. The reaction was stirred for 6 h at −78 °C before being quenched by the addition of pH 7 phosphate buffer solution (0.5 mL). ^{1}H NMR spectroscopic analysis of the crude reaction mixture (250 MHz, d_8-PhMe, 70 °C) showed the presence of **45** and **49** in a 97:3 ratio. Purification via flash chromatography (eluent 30−40 °C petroleum ether/Et_2O, 3:1) gave **45** as a colorless oil (149 mg, 97%, >99:1 dr); ν_{max} (film) 1668 (C=O), 1605; δ_H (500 MHz, d_8-PhMe, 70 °C) 0.87 (9H, s, CMe_3), 1.11 (3H, d, *J* = 6.7 Hz, C(3)H_3), 1.52 (3H, d, *J* = 6.8 Hz, C(1′)*Me*), 2.26 (3H, s, Ar*Me*), 2.44 (1H, dd, *J* = 13.3, 7.9 Hz, CH_AH_BPh), 3.05 (1H, dd, *J* = 13.3, 6.3 Hz, CH_AH_BPh), 3.27 (1H, app septet, *J* = 6.7 Hz, C(2)*H*), 5.40 (1H, br q, *J* = 6.8 Hz, C(1′)*H*), 6.92−7.11 (8H, m, *Ar*), 7.55 (1H, d, *J* = 6.9 Hz, *Ar*); δ_C (50 MHz, $CDCl_3$) *16.0* (*Me*), *19.6* (Ar*Me*), 27.6 (CMe_3), *39.0* (*C*(2), CH_2Ph), *57.0* (*C*(1′)), 82.3 (CMe_3), 125.9, 126.3, 127.7, 128.5, 128.7, 129.5, 130.5, *140.0* (*Ar*, *Ph*); *m*/*z* (CI^+) 354 ($[M + H]^+$, 100%); HRMS (CI^+) found 354.2443, $C_{23}H_{32}NO_2^+$ ($[M + H]^+$) requires 354.2428.

(2*RS*,1′*RS*)-*N*-*tert*-Butoxy-*N*-1′-phenylethyl 2-Benzylpropanamide, 46.



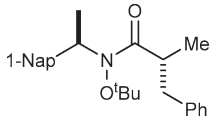
30 (105 mg, 0.32 mmol) in THF (2 mL) was treated with KHMDS (0.36 mmol) in THF (2 mL) and MeI (60 μL, 0.96 mmol) according to the General Procedure. The reaction was held at −78 °C for 8 h before being quenched by the addition of pH 7 phosphate buffer (1 mL). ^{1}H NMR spectroscopic analysis of the crude reaction mixture (500 MHz, d_8-PhMe, 70 °C) showed the presence of **42** and **46** in a 22:78 ratio. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 10:1) gave **46** as a colorless oil (35 mg, 32%, >99:1 dr); found C, 77.6; H, 8.8; N, 4.45, $C_{22}H_{29}NO_2$ requires C, 77.8; H, 8.6; N, 4.1; ν_{max} (film) 1667 (C=O), 1605; δ_H (250 MHz, d_8-PhMe, 70 °C) 0.90 (9H, s, CMe_3), 0.96 (3H, d, *J* = 6.7, Hz C(3)H_3), 1.58 (3H, d, *J* = 7.2 Hz, C(1′)*Me*), 2.45−2.55 (1H, m), 3.12−3.23 (2H, m), 5.11 (1H, q, *J* = 7.2 Hz, C(1′)*H*), 6.88−7.40 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) *16.0* (*Me*), 27.5 (CMe_3), *39.0* (CH_2Ph), *62.0* (C(1′)), 82.1 (CMe_3), 126.3, 127.2, 127.7, 128.2, 128.5, 129.5 (*o*-, *m*-, *p*-*Ph*), 140.5, 141.6 (*i*-*Ph*), 179.5 (C(1)); *m*/*z* (CI^+) 340 ($[M + H]^+$, 100%). Further elution gave a mixed fraction containing **42** and **46** in a 50:50 ratio (30 mg, 27%). Further elution gave unreacted **30** (40 mg, 38%).

(2*RS*,1′*RS*)-*N*-*tert*-Butoxy-*N*-1′-(2″-naphthyl)ethyl 2-Benzylpropanamide, 47.



31 (95 mg, 0.25 mmol) in THF (1.5 mL) was treated with KHMDS (0.24 mmol) in THF (2 mL) and MeI (47 μL, 0.76 mmol) according to the General Procedure. The reaction was held at −78 °C over 12 h before being quenched by the addition of pH 7 phosphate buffer (1 mL). ^{1}H NMR spectroscopic analysis of the crude reaction mixture (500 MHz, d_8-PhMe, 70 °C) showed the presence of **43** and **47** in a 12:88 ratio. Purification via flash chromatography (eluent 30−40 °C petroleum ether/Et_2O, 10:1) gave **47** as a colorless oil, which was crystallized from pentane upon prolonged standing at −30 °C (62 mg, 63%, >99:1 dr); found C, 80.4; H, 7.9; N, 3.5, $C_{26}H_{31}NO_2$ requires C, 80.2; H, 8.0; N, 3.6; mp 92−93 °C; ν_{max} (film) 1669 (C=O), 1603; δ_H (250 MHz, d_8-PhMe, 70 °C) 0.89 (9H, s, CMe_3), 0.98 (3H, d, *J* = 6.7 Hz, C(3)H_3), 1.69 (3H, d, *J* = 7.2 Hz, C(1′)*Me*), 2.46−2.56 (1H, m, CH_AH_BPh), 3.15−3.31 (2H, m, C(2)*H*, CH_AH_BPh), 5.32 (1H, q, *J* = 7.2 Hz, C(1′)*H*), 6.87−7.27 (8H, m, *Ar*), 7.50−7.77 (4H, m, *Ar*); δ_C (50 MHz, $CDCl_3$) *16.4* (*Me*), 27.7 (CMe_3), *39.0* (*C*(2), CH_2Ph), 82.2 (CMe_3), 125.6, 125.8, 126.0, 126.1, 126.4, 127.6, 127.7, 128.2, 128.3, 129.4, 132.6, 133.1, 139.0, 140.4 (*Ar*, *Ph*), *182.0* (*C*(1)); *m*/*z* (CI^+) 390 ($[M + H]^+$, 100%).

(2*RS*,1′*RS*)-*N*-*tert*-Butoxy-*N*-1′-(1″-naphthyl)ethyl 2-Benzylpropanamide 48.

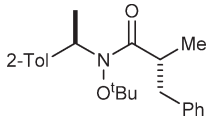


32 (103 mg, 0.27 mmol) in THF (1.5 mL) was treated with KHMDS (0.3 mmol) in THF (1.5 mL) and MeI (51 μL, 0.76 mmol) according to the General Procedure. The reaction mixture was held at −78 °C for 6 h before being quenched by the addition of pH 7 phosphate buffer solution (0.5 mL). ^{1}H NMR spectroscopic analysis of the crude reaction mixture (250 MHz, d_8-PhMe, 70 °C) showed the presence of **44** and **48** in a 3:97 ratio. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 10:1) gave **48** as

(50) 18-Crown-6 was dissolved in THF and the reaction mixture was allowed to stand over activated 4Å molecular sieves for 12 h. This solution was added to solid KHMDS and the alkylation reaction carried out according to the General Procedure.

a colorless oil, which solidified on standing (85 mg, 79%, >99:1). Recrystallization of an aliquot from MeOH gave colorless tiles; found C, 79.9; H, 8.1; N, 3.9, $C_{26}H_{31}NO_2$ requires C, 80.2; H, 8.0; N, 3.6; mp 94−95 °C; ν_{max} (film) 1661 (C=O), 1601; δ_H (250 MHz, d_8-PhMe, 70 °C) 0.58 (9H, s, CMe_3), 1.07 (3H, d, J = 6.7 Hz, C(3)H_3), 1.61 (3H, d, J = 6.9 Hz, C(1′)*Me*), 2.53−2.63 (1H, m, CH_AH$_B$Ph), 3.19−3.35 (2H, m, C(2)*H*, CH$_A$$H_B$Ph), 6.32−6.35 (1H, br m, C(1′)*H*), 6.96−7.60 (11H, m, *Ar*, *Ph*), 8.35−8.41 (1H, br m, *Ar*); δ_C (50 MHz, $CDCl_3$) *16.0* (*C*(3)), 27.6 (CMe_3), *39.0* (*C*H$_2$Ph), *39.5* (*C*(2)), 82.3 (*C*Me$_3$), *125.1*, 125.8, 126.3, 126.5, 128.5, 128.8, 129.5, 133.8, *140.6* (*Ar*, *Ph*); m/z (CI$^+$) 390 ([M + H]$^+$, 100%).

(2*RS*,1′*RS*)-*N*-*tert*-Butoxy-*N*-1′-(2″-methylphenyl)ethyl 2-Benzylpropanamide 49.



33 (140 mg, 0.41 mmol) in THF (2 mL) was treated with KHMDS (0.45 mmol) in THF (2 mL) and MeI (77 μL, 1.24 mmol) according to the General Procedure. The reaction was stirred for 6 h at −78 °C before being quenched by the addition of pH 7 phosphate buffer solution (0.5 mL). ^{1}H NMR spectroscopic analysis of the crude reaction mixture (250 MHz, d_8-PhMe, 70 °C) showed the presence of **45** and **49** in a 5:95 ratio. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et$_2$O, 3:1) gave **49** as a colorless oil (113 mg, 79%, >99:1 dr); ν_{max} (film) 1667 (C=O), 1605; δ_H (250 MHz, d_8-PhMe, 70 °C) 0.79 (9H, s, CMe_3), 1.04 (3H, d, J = 6.7 Hz, C(3)H_3), 1.50 (3H, d, J = 6.7 Hz, C(1′)*Me*), 2.26 (3H, s, Ar*Me*), 2.47−2.57 (1H, m, CH_AH$_B$Ph), 3.31−3.17 (2H, m, C(2)*H*, CH$_A$$H_B$Ph), 5.55 (1H, br q, J = 6.7 Hz, C(1′)*H*), 6.92−7.19 (8H, m, *Ar*), 7.50 (1H, d, J = 6.9 Hz, *Ar*); δ_C (125 MHz, $CDCl_3$) *16.6* (*Me*), *19.5* (Ar*Me*), 27.6 (CMe_3), *39.5* (*C*(2), *C*H$_2$Ph), *56.0* (*C*(1′)), 82.1 (*C*Me$_3$), *125.6*, 126.1, *127.4*, 128.3, 129.3, 130.2, 138.5, *140.3* (*Ar*, *Ph*), *182.0* (*C*(1)); m/z (APCI$^+$) 376 ([M + Na]$^+$, 50%), 354 (100); HRMS (CI$^+$) found 354.2438, $C_{23}H_{32}NO_2^+$ ([M + H]$^+$) requires 354.2428.

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Supporting Information Available: Full details of all experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.