JOC Article

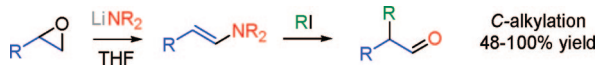
Synthesis and *C*-Alkylation of Hindered Aldehyde Enamines

David M. Hodgson,* Christopher D. Bray,[⊥] Nicholas D. Kindon,[†] Nigel J. Reynolds, Steven J. Coote,[‡] Joann M. Um,[§] and K. N. Houk[§]

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

david.hodgson@chem.ox.ac.uk

Received September 12, 2008

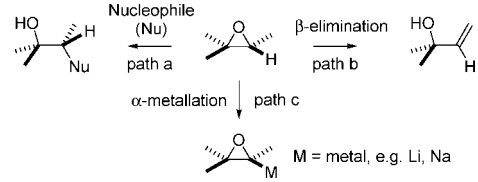


A new reactivity mode of hindered lithium amides with terminal epoxides is described whereby aldehyde enamines are produced via a previously unrecognized reaction pathway. Some of these aldehyde enamines display unprecedented *C*-alkylation reactivity toward unactivated primary and secondary alkyl halides. For comparison, the reactivity of aldehyde enamines synthesized via a traditional condensation method was examined. *C*- rather than *N*-alkylation was the dominant reaction pathway found with a range of electrophiles, making this route to α-alkylated aldehydes more synthetically useful than previously reported.

Introduction

Epoxides are widely utilized as synthetic intermediates, and the epoxide functional group is also found in a number of interesting natural products.[1] Much of the chemistry of epoxides involves nucleophilic cleavage of the strained heterocyclic ring (Scheme 1, path a); however, another aspect of epoxide chemistry is that which occurs upon reaction with a strong base, typically an organolithium or hindered lithium amide. As well as simple ring-opening,[2] abstraction of a β-proton can occur, which leads to the formation of allylic alcohols (path b), a process known as β-elimination.[3,4] As a result of the electron-withdrawing effect of the oxygen and the acidifying nature of the strained ring, abstraction of an α-proton can also occur (path c) to give an α-metallated epoxide (oxiranyl anion).[5]

SCHEME 1. Reaction Pathways of Epoxides



Since α-metallated epoxides were first proposed[6] and evidence for their existence first presented,[7] their place in organic chemistry has evolved from initially being viewed as uncontrollable transient species[4b,5b] to that of useful synthetic intermediates.[5g,h,8] For example, we have reported an experimentally straightforward method for the synthesis of α,β-epoxysilanes (e.g., **2**) from simple terminal epoxides (**1**) via direct deprotonation using lithium 2,2,6,6-tetramethylpiperidide (LTMP) as base in combination with an in situ silylating agent (Me_3SiCl) (Scheme 2).[9]

During this program of work we uncovered a new reactivity mode of terminal epoxides with hindered lithium amides that

[†] AstraZeneca R&D Charnwood, Medicinal Chemistry, Bakewell Road, Loughborough LE11 5RH, U.K.

[‡] GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, U.K.

[§] Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095-1569.

[⊥] Present address: Queen Mary University of London, School of Biological and Chemical Sciences, Mile End Road, London E1 4NS, U.K.

(1) (a) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006. (b) *Comprehensive Heterocyclic Chemistry III*; Padwa, A., Ed.; Elsevier: Oxford, 2008; Vol. 1.

(2) Harris, C. E.; Fisher, G. B.; Beardesley, D.; Lee, L.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 7746–7751.

(3) Haynes, L. J.; Heilbron, I. M.; Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc., Abstr.* **1947**, 1583–1585.

(4) For recent reviews, see: (a) Eames, J. *Eur. J. Org. Chem.* **2002**, 393–401. (b) Magnus, A.; Bertilsson, S. K.; Andersson, P. G. *Chem. Soc. Rev.* **2002**, *31*, 223–229. (c) Eames, J. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Snieckus, V., Majewski, M., Eds.; Thieme: Stuttgart, Germany, 2005; Vol. 8a, pp 171−242. (d) Hodgson, D. M.; Humphreys, P. G. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Clayden, J. P., Ed.; Thieme: Stuttgart, Germany, 2007; Vol. 36, pp 583−665.

(5) For reviews, see: (a) Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345–443. (b) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325. (c) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337–343. (d) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625–1642. (e) Hodgson, D. M.; Tomooka, K.; Gras, E. In *Topics in Organometallic Chemistry*; Hodgson, D. M., Ed.; Springer: Berlin/Heidelberg, Germany, 2003; pp 217−250. (f) Chemla, F.; Vrancken, E. In *The Chemistry of Organolithium Reagents*; Rappoport, Z., Marek, I., Eds.; J. Wiley and Sons: New York, 2004; pp 1165−1242. (g) Reference 1a, pp 145−184. (h) Capriati, V.; Florio, S.; Luisi, R. *Chem. Rev.* **2008**, *108*, 1918–1942.

(6) Cope, A. C.; Tiffany, B. D. *J. Am. Chem. Soc.* **1951**, *73*, 4158–4161.

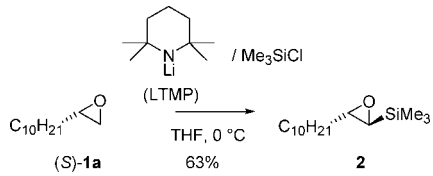
(7) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428–2433.

(8) (a) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, 1–22. (b) Hodgson, D. M.; Humphreys, P. G.; Hughes, S. P. *Pure Appl. Chem.* **2007**, *79*, 269–279.

(9) Hodgson, D. M.; Reynolds, N. J.; Coote, S. J. *Tetrahedron Lett.* **2002**, *43*, 7895–7897.

10.1021/jo802016t CCC: $40.75
Published on Web 12/23/2008

SCHEME 2. α,β-Epoxysilane Synthesis from Terminal Epoxides[9]

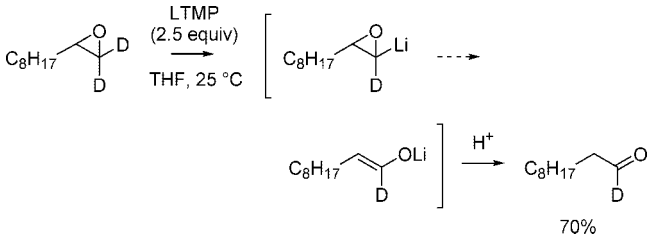


leads to aldehyde enamines.[10] In the present paper, we present full details of these findings, including a comparison of reactivity toward simple alkyl halides of the aldehyde enamines generated by this newly identified process with that of aldehyde enamines synthesized via a traditional condensation route.

Results and Discussion

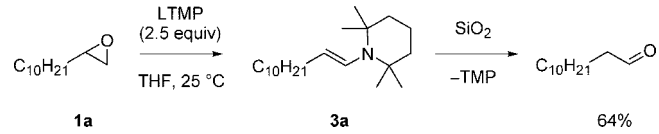
In 1994, Yamamoto and co-workers reported the selective and high-yielding isomerization of a variety of terminal epoxides to aldehydes using sterically hindered lithium amides.[11] LTMP, generated from commercially available 2,2,6,6-tetramethylpiperidine (TMP) using *n*-BuLi, was found to provide the best results (LTMP (2.5 equiv), 20 °C, 12 h) for aldehyde formation (75−83% yields). With evidence from experiments using deuterium-labeled epoxides, Yamamoto et al. suggested a reaction pathway for this transformation (Scheme 3).

SCHEME 3. Originally Proposed Reaction Pathway for Isomerization of Epoxides to Aldehydes[11]



This report was of interest in connection with our studies on the direct-deprotonation/electrophile trapping of simple epoxides[9,12] and initially led to our development of a method for the straightforward synthesis of α,β-epoxysilanes from terminal epoxides (Scheme 2). During the development of this latter procedure, we had recourse to examine the LTMP-induced isomerization of 1,2-epoxydodecane **1a** as a prior check of experimental technique. Intriguingly, we found that the crude product of this reaction was not dodecanal, as expected. Analysis of the ^{1}H NMR spectrum of the reaction mixture following aqueous workup (NH_4Cl) but prior to column chromatography indicated that all of the starting epoxide had been consumed. However, it showed only a trace of the characteristic aldehyde proton signal [9.72 (t, $J = 1.8$ Hz, CHO)]. Instead, two mutually coupled resonances in the ^{1}H NMR spectrum were displayed, consistent with an *E*-olefin [5.66 (1 H, dt, $J = 13.6$ and 1.0 Hz) and 5.16 (1 H, dt, $J = 13.6$ and 7.2 Hz)]. Combining this information with the molecular ion observed by mass spectrometry led us to conclude that enamine **3a** was in fact the initial product of the reaction (Scheme 4). Upon column chromatography, the wet and slightly acidic nature of silica gel led to the expected hydrolysis product dodecanal, in 64% yield.

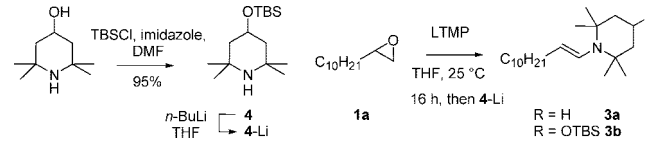
SCHEME 4. Initial Observation of the Epoxide-Enamine Transformation



Evidently, enamine formation had not been recognized by Yamamoto and his co-workers, since they made no comment as to the nature of the crude products obtained from treating terminal epoxides with LTMP. Similarly, in a subsequent (and as yet only other) reported application of this methodology for terminal epoxide isomerization (the synthesis of 3,3-dimethylbutyraldehyde from *tert*-butyloxirane) by Katritzky et al., no mention of enamine formation was made.[13]

The workup for this reaction involved addition of saturated aqueous NH_4Cl. Enamine **3a** could, in principle, simply have been formed during workup by condensation of dodecanal with the TMP generated in situ. However, adding dodecanal to a solution of LTMP in THF, which had already been quenched by the addition of saturated aqueous NH_4Cl, did not generate enamine **3a**. Similarly, azeotropic distillation of dodecanal with TMP in the presence of catalytic *p*-TSA, a standard method for synthesizing enamines, failed to give enamine **3a**. Carlson and Nilsson have described the synthesis of aldehyde enamines using $TiCl_4$ as both a Lewis acid and dehydrating agent;[14] however, even application of these forcing condition failed to give enamine **3a**. These results imply that enamine **3a** was formed during the reaction, rather than during the aqueous workup. To test this hypothesis, a crossover experiment was designed: 4-hydroxy-2,2,6,6-tetramethylpiperidine was protected as its *tert*-butyldimethylsilyl ether and subsequently deprotonated with *n*-BuLi to give lithium amide **4**-Li. The isomerization of 1,2-epoxydodecane **1a** was conducted as described above; however, prior to aqueous workup, lithium amide **4**-Li (2.5 equiv) was added. Enamine **3b** was not observed as a product,[15] indicating that enamine **3a** was generated during the reaction and not as a result of a subsequent condensation (Scheme 5).

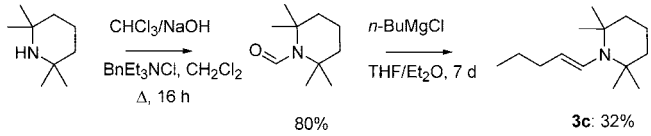
SCHEME 5. Crossover Experiment To Discount a Condensation Route to Enamine 3a



It was possible to independently synthesize an example of such a highly hindered enamine via the method described by Hannson and Wickberg.[16] *N*-Formyl-2,2,6,6-tetramethylpiperidine was obtained in 80% yield from TMP according to the procedure of Blum and Nyberg (Scheme 6).[17] Prolonged reaction of this amide with excess *n*-BuMgCl gave enamine **3c** in 32% yield (unoptimized).

(10) Preliminary communication: Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870–6871.
(11) Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1994**, 2103–2104.
(12) (a) Hodgson, D. M.; Reynolds, N. J.; Coote, S. J. *Org. Lett.* **2004**, *6*, 4187–4189. (b) Hodgson, D. M.; Kirton, E. H. M.; Miles, S. M.; Norsikian, S. L. M.; Reynolds, N. J.; Coote, S. J. *Org. Biomol. Chem.* **2005**, *3*, 1893–1904.
(13) Katritzky, A. R.; Fang, Y.; Prakash, I. *J. Indian Chem. Soc.* **2000**, *77*, 635–636.
(14) Carlson, R.; Nilsson, A. *Acta Chem. Scand., Ser. B* **1984**, *38*, 49–53.
(15) Use of **4**-Li with epoxide **1a** gave **3b**, as expected.
(16) Hansson, C.; Wickberg, B. *J. Org. Chem.* **1973**, *38*, 3074–3076.
(17) Blum, Z.; Nyberg, K. *Acta Chem. Scand., Ser. B* **1981**, *35*, 743–745.

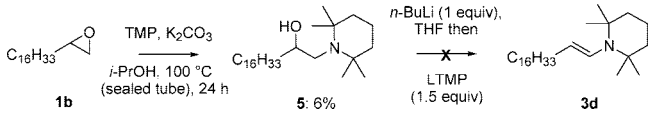
SCHEME 6. Synthesis of Enamine 3c from an *N*-Formyl Piperidine



Unequivocal proof that enamines (**3**) were being formed by a new reactivity mode of lithium amides with epoxides and not by simple condensation of an aldehyde with TMP was obtained by in situ ^{1}H NMR monitoring of the reaction between 1,2-epoxypentane and LTMP in THF-d_8. After only 5 min, complete consumption of the starting material was observed and the resonances due to the vinylic protons of **3c** could clearly be seen in the ^{1}H NMR spectrum.

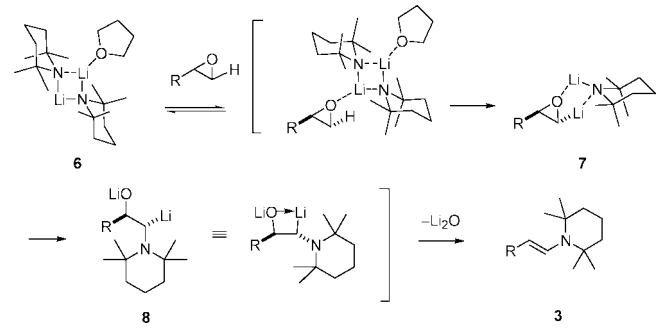
A possible reaction pathway leading to enamines from terminal epoxides could involve direct epoxide ring-opening with LTMP,[2] followed by α-amino lithiation and subsequent elimination of Li_2O. However, this was shown to be unlikely by the following experiments. Direct ring-opening of 1,2-epoxyoctadecane (**1b**) with 2,2,6,6-tetramethylpiperidine (TMP) (3 equiv, *i*-PrOH, 100 °C, 24 h) gave aminoalcohol **5** (Scheme 7). Treatment of the lithium alkoxide of **5** (generated by deprotonation with *n*-BuLi (1 equiv)) with LTMP (1.5 equiv, THF, 25 °C, 1 h) returned **5** quantitatively following aqueous workup; enamine **3d** was not observed.

SCHEME 7. Evidence To Disprove a Direct Ring-Opening/ Elimination Pathway



A new reactivity mode of lithium amides with epoxides is therefore proposed that could explain the formation of enamines. Collum et al. have demonstrated that α-lithiation of cyclooctene oxide by LTMP in THF proceeds predominantly via a monosolvated dimer **6** (Scheme 8).[18] Coordination of a terminal epoxide to this monosolvated dimer **6** could precede α-*trans*-deprotonation using one molecule of LTMP. The second, proximal molecule of LTMP could then add to the electrophilic[19] α-lithiated epoxide **7**, either in an S_N2 manner or via a 1,2-metallate shift,[20] to give the dianion **8**. It should be noted that Yamamoto et al. reported that the use of only 1 equiv of LTMP in the isomerization of terminal epoxides led to yields of aldehydes <50%.[11] Finally, *syn*-elimination of Li_2O from the dianion **8** gives enamine **3**. It cannot be assumed that the elimination of Li_2O, which is highly ionic, occurs like the elimination of a typical organic fragment. The high lattice enthalpy of Li_2O (calculated to be 2799 kJ mol^{-1}) would suggest that co-ordination between lithium and oxygen would be highly favorable.[21] This process represents a fundamentally new strategy for the synthesis of enamines, formally constituting the addition of a lithium amide to a vinyl cation equivalent.[22]

SCHEME 8. Proposed Reaction Pathway for the Epoxide-Enamine Transformation



The process proposed above is analogous to that described by Crandall and Lin for the reductive alkylation of epoxides with organolithiums.[23,20b−f] Supporting evidence for this analogy came through comparison of the ^{7}Li NMR spectra of the reactions between 1,2-epoxypentane and LTMP (1.95 equiv, THF, 25 °C, 1 h) and of that between 1,2-epoxypentane and *n*-BuLi (1.95 equiv, THF, 25 °C, 1 h).[24] They contain the same lithium byproduct, presumably Li_2O.[25]

Though the first chemistry of enamines dates back to 1884,[26] the name itself was not coined until 1927 when Wittig emphasized the analogy of this class of compounds with enols.[27] Even so, the synthetic potential of the reaction of enamines with electrophiles was not realized until 1954 when the pioneering work of Stork et al. demonstrated their use for α-alkylations and α-acylations of carbonyl compounds.[28] With this method, enamines react with such electrophiles to give iminium ions, which are subsequently hydrolyzed to yield α-alkylated carbonyl or 1,3-dicarbonyl compounds. Reactions of enamines with electrophiles have been extensively reviewed.[29] Unfortunately, reactions of aldehyde enamines with simple alkyl halides are generally problematic; competing N- over C-alkylation often

(18) Wiedemann, S. H.; Ramírez, A.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15893–15901.

(19) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697–756.

(20) The concept of a 1,2-metallate shift follows related suggestions; see: (a) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 5275–5280. (b) Hodgson, D. M.; Stent, M. A. H.; Wilson, F. X. *Org. Lett.* **2001**, *3*, 3401–3403. (c) Hodgson, D. M.; Stent, M. A. H.; Wilson, F. X. *Synthesis* **2002**, 1445–1453. (d) Hodgson, D. M.; Fleming, M. J.; Stanway, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 12250–12251. (e) Hodgson, D. M.; Fleming, M. J.; Stanway, S. J. *J. Org. Chem.* **2007**, *72*, 4763–4773. (f) Hodgson, D. M.; Humphreys, P. G.; Fleming, M. J. *Org. Synth.* **2008**, *85*, 1–9.

(21) (a) Jenkins, H. D. B. In *CRC Handbook of Chemistry and Physics 1999−2000*; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 1998. (b) Bouyacoub, A.; Hadjadj-Aoul, R.; Volatron, F. *Eur. J. Org. Chem.* **2008**, 4466–4474.

(22) For an approach based on an amino-Cope rearrangement, see: (a) Allin, S. M.; Button, M. A. C.; Shuttleworth, S. J. *Synlett* **1997**, 725–727. For cross-coupling based approaches, see: (b) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Commun.* **2002**, 2362–2363. (c) Willis, M. C.; Brace, G. N. *Tetrahedron Lett.* **2002**, *43*, 9085–9088. (d) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2004**, *10*, 494–507. For routes based on hydroamination of alkynes, see: (e) Seayad, A. M.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5615–5619.

(23) (a) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4527–4528. See also: (b) Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 7943–7946.

(24) See Supporting Information.

(25) Attempts to obtain the ^{7}Li NMR spectrum of commercial Li_2O, for direct comparison, failed because of its complete insolubility in THF.

(26) Collie, J. N. *Liebigs Ann. Chem.* **1884**, *226*, 294–322.

(27) Wittig, G.; Blumenthal, H. *Ber.* **1927**, *60B*, 1085–1094.

(28) (a) Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029–2030. (b) Stork, G.; Landesman, H. K. *J. Am. Chem. Soc.* **1956**, *78*, 5128–5129. (c) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222.

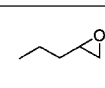
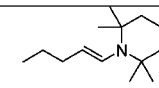
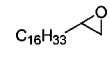
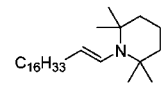
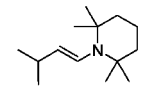
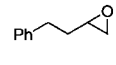
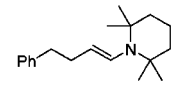
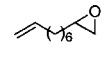
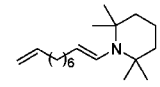
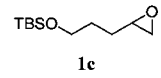
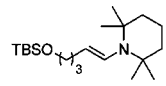
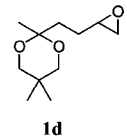
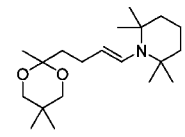
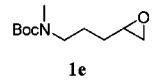
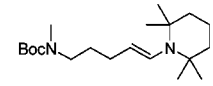
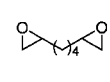
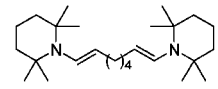
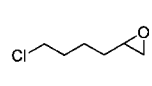
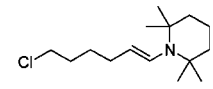
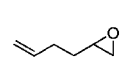
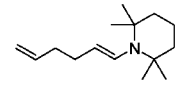
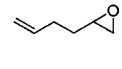
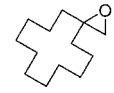
(29) (a) *Enamines: Synthesis, Structure, and Reactions*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1987. (b) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975–2050. (c) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 3363–3446. (d) Dyke, S. F. *The Chemistry of Enamines*; Cambridge University Press: Cambridge, 1973. (e) *The Chemistry of Enamines*, Pt. 1; Rappoport, Z., Ed.; Wiley: Chichester, 1994. (f) Adams, J. P. *Perkin Trans. 1* **2000**, 125–139. (g) Sammakia, T.; Abramite, J. A. Sammons, M. F. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Molander, G., Ed.; Thieme: Stuttgart, Germany, 2006; Vol. 33, pp 405−441.

leads to poor yields of α-substituted aldehydes. Reports by Curphey[30] and later by Allin[22a] have demonstrated that C-alkylation is promoted over N-alkylation if the aldehyde enamines are sterically encumbered around the nitrogen. Nevertheless, reactions with simple alkyl iodides (e.g., *n*-BuI) are reported to give low yields (24−34%)[30b] of α-alkylated product, and there are relatively few examples of such reactions.

The direct mono-α-alkylation of aldehydes is not a trivial task.[31] For the most part, methods routinely employed to achieve this transformation are indirect and usually involve alkylation of a substrate at a higher oxidation state (e.g., an amide or ester) followed by a subsequent reduction to give an aldehyde, either directly or via reduction to the alcohol and subsequent oxidation. Paradoxically, there has been a great deal of interest in the area of organocatalysis, where catalytic quantities of chiral amines react with aldehydes to generate chiral enamines.[32] Even so, organocatalytic intermolecular alkylations of aldehydes using simple alkyl halides are not currently possible.[33] In light of this, we were intrigued to examine the scope for the synthesis of highly hindered aldehyde enamines by this newly identified process from epoxides and to discover whether the products obtained would undergo efficient C-alkylation.

Up until this point, the enamines **3a**−**c** isolated had been contaminated with small proportions (5−10%) of the corresponding aldehydes as a result of hydrolysis. Under reaction conditions otherwise identical to those employed by Yamamoto et al.[11] (LTMP (2.5 equiv), THF, 0−25 °C, 1 h), various other aqueous workup procedures were examined (pH 7 buffer solution, 0.5 M HCl, saturated aqueous $NaHSO_3$, or water). Unfortunately, contamination by hydrolysis products was always observed (3−30%, as judged by ^{1}H NMR spectroscopy). Attempted purification by column chromatography (NEt_3 doped silica (∼1%), basic alumina, or Florisil) also resulted in further hydrolysis, whereas attempted distillation resulted in decomposition. These results indicated that the use of an aqueous workup was incompatible with the isolation of such enamines. However, it was found that a rapid filtration of the reaction mixture through a short pad of silica that had been deactivated by stirring with *neat* NEt_3 overnight (∼16 h), followed by removal of all volatile compounds under high vacuum gave spectroscopically pure samples of enamines **3**. Using this isolation procedure, 1,2-epoxypentane gave enamine **3c** in 75% yield (Table 1, entry 1). A brief survey of alternative solvents in the epoxide-enamine transformation gave less satisfactory results: using Et_2O, enamine **3c** was obtained in 32% yield, whereas in hexane a yield of 33% was observed. Returning to THF as solvent, 1,2-epoxyoctadecane gave the corresponding enamine **3d** in 78% yield (entry 2). In comparison, isomerization of this epoxide according to the procedure of Yamamoto et al. gave octadecanal in 77% yield (lit.[11] 79%), indicating that this operationally simple method of isolation of the enamine was as efficient as the more traditional one used to isolate the corresponding aldehydes. The scope of this new, previously unrecognized process was further explored. Isopropyl oxirane gave enamine **3e** in 60% yield (entry 3), which demonstrated that increased substitution in the γ-position is tolerated. 1,2-Epoxy-4-phenylbutane[24] gave enamine **3f** in 72% yield (entry 4), whereas 1,2-epoxy-9-decene gave enamine **3g** in 83% yield (entry 5). These latter results demonstrate that benzylic and allylic protons, which are potentially labile,[34] do not compromise the process. To further demonstrate the utility of this protocol for enamine formation over pre-existing acid-catalyzed meth-

TABLE 1. Substrate Scope in Enamine Formation

Entry	Substrate	Product	Yield (%)[a]
1			**3c** 75
2			**3d** 78
3			**3e** 60
4			**3f** 72
5			**3g** 83
6	 **1c**		**3h** 77
7	 **1d**		**3i** 76
8	 **1e**		**3j** 69
9			**3k** 69[c]
10			**3l** 71[d]
11			**3m** 33
12			**9** 52[e]
13		-	- 0[f]

[a] Isolated yields. [b] Observed by ^{1}H NMR but not isolatable. [c] 5.0 equiv of LTMP. [d] 8:1 **3l**:**3m** mixture. [e] Et_2O as solvent. [f] Starting material returned.

(30) (a) Curphey, T. J.; Hung, J. C. Y. *Chem. Commun.* **1967**, 510. (b) Curphey, T. J.; Hung, J. C. Y.; Chu, C. C. C. *J. Org. Chem.* **1975**, *40*, 607–614.

(31) (a) Caine, D. In *Comprehensive Organic Synthesis*; Pattenden, G., Ed.; Pergamon: New York, 1991; Vol. 3, pp 1−63. (b) Göttlich, R. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Brückner, R., Ed.; Thieme: Stuttgart, Germany, 2006; Vol. 25, pp 355−366.

(32) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

(33) (a) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450–451. See also: (b) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952–1956. (c) Beeson, T. D.; Mastracchio, A.; Hong, J. B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582–585. (d) Jang, H.; Hong, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004–7005. (e) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539–7542. (f) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80.

odology, silyloxyepoxide[24] **1c**, dioxolane-containing epoxide **1d**,[24] and 5-(*N*-Boc-*N*-methylamino)-1,2-epoxypentane[9] **1e** were each converted to the corresponding enamines in good yield (entries 6−8). During a traditional acid-catalyzed condensation of an aldehyde with a secondary amine, these protecting groups could well be labile, and so the present route is complimentary to that approach. Yamamoto et al. described the conversion of 1,2,7,8-diepoxyoctane into octanedial in 71% yield.[11] Pleasingly, formation of bis-enamine **3k** from this epoxide proceeded in 69% yield (entry 9).

An epoxide bearing a chloro substituent was also examined to see if it was compatible with the epoxide-enamine transformation. Treatment of 1-chloro-5,6-epoxyhexane[24] with LTMP using the typical procedure gave an 8:1 mixture of the desired chlorine containing enamine **3l** (entry 10) and an enamine identifiable [^{13}C NMR δ 139.0 and 115.0] as that derived from additional elimination of HCl, **3m**. Conclusive proof of the structure of this elimination product was sought by attempted formation of enamine **3m** (entry 11) from commercially available 1,2-epoxy-5-hexene. Enamine formation from this epoxide proceeded in only 33% yield; however, the spectral characteristics of the product obtained matched that of the elimination product obtained previously. The poor yield obtained for enamine **3m** was initially surprising given that it had already been shown that tethered olefins are tolerated in this process (entry 5). With 1,2-epoxy-5-hexene, it was found that the formation of bicyclic alcohol **9** was a competitive process; indeed changing to Et_2O as solvent (since such conditions had been found earlier to reduce enamine formation) gave the bicyclic alcohol **9** in 52% yield. Ultimately, this latter observation led to the development of the intramolecular cyclopropanation of unsaturated terminal epoxides.[35] All of the successful enamine-forming reactions that had been carried out thus far had functionality in rather a remote position. In order to probe whether functionality could be tolerated much closer to the epoxide moiety, two substrates were examined. Initially, it seemed that 3-morpholinopropylene oxide had produced the desired enamine; however, closer inspection of the ^{1}H NMR spectrum of the product, which was not pure, revealed that in fact the initially formed enamine had likely isomerized to give a morpholino-enamine [δ 5.98 (d, 1H, J = 14 Hz, NCH), 4.73 (dt, 1H, J = 14 and 7 Hz, =CH); the larger difference in chemical shift between the olefinic protons (1.25 ppm) being diagnostic; see later discussion]. Similarly, under identical reaction conditions, reaction of *tert*-butylglycidyl ether with LTMP likely initially formed an enamine, which then isomerized to a *tert*-butylvinyl ether [δ 6.08 (d, 1H, J = 14 Hz, OCH), 4.90 (dt, 1H, J = 14 and 7 Hz, =CH)]. Finally, methylenecyclododecane oxide was examined as a substrate; however, as has previously been observed,[9,36] this material was unreactive toward LTMP at least under the conditions examined here,[20d−f] and the starting material was returned (entry 13).

Having examined the mechanistic details and the scope of this new enamine-forming reaction, our attention turned toward synthetic applications of the highly hindered aldehyde enamines we had prepared, specifically, their α-alkylation.

Enamine **3c** (1.0 mmol), which was readily prepared on a multigram scale, was heated to reflux with MeI (2.0 equiv) in MeCN-d_3, and the progress of the reaction was followed by in situ ^{1}H NMR spectroscopy. After 3 h, the starting enamine was completely consumed, as judged by the disappearance of the olefinic signals and the appearance of a signal presumably due to an iminium ion [8.51 (d, 1H, J = 11 Hz, N=CH)]. However, after hydrolysis with acidic buffer (1:1:2 NaOAc/AcOH/H_2O)[30b] and subsequent aqueous workup, 2-methylvaleraldehyde was isolated in only 30% yield following column chromatography. Under similar conditions employing benzyl bromide as electrophile, a 1:1 mixture of valeraldehyde and 2-benzylvaleraldehyde was obtained. Reaction with allyl bromide, propargyl bromide and methyl α-bromoacetate led to similar mixtures of alkylated and unalkylated products. Re-examination of the in situ ^{1}H NMR spectra of the reaction between enamine **3c** and MeI revealed, after 1 h, the presence of a series of unexpected olefinic signals that were not due to the starting material.

The possibility was considered that enamine **3c** was not thermally stable. However when a solution of this enamine was heated to 100 °C for 3 h (MeCN-d_3, sealed tube), the in situ ^{1}H NMR spectrum revealed no appreciable decomposition. Enamine **3c** could also have been unstable with respect to reaction with the iminium ion generated through its own alkylation. Indeed, when enamine **3c** was heated (82 °C) with a deficiency of MeI (0.5 equiv, MeCN-d_3, 3 h), in situ ^{1}H NMR monitoring revealed complete consumption of the starting material. The signal due to the iminium ion was very weak, and there were spurious vinylic signals reminiscent of the starting enamine **3c**. These observations led us to speculate that the activation energy required for enamine **3c** to abstract the α-iminium proton from its alkylated product is competitive with that for MeI alkylation itself. With this inherent instability, although one could potentially increase the number of equivalents of electrophile to improve the selectivity for alkylated products, the ultimate aim of LTMP derived enamines (**3**) reacting with unactivated alkyl halides was unfortunately unlikely to be realized.

In hindsight, the problematic reactivity of enamines such as **3c** with electrophiles might have been anticipated on the basis of the difference in chemical shift in the ^{1}H and ^{13}C NMR spectra between the vinylic protons.[37] For a typical aldehyde enamine, one would expect this difference to be ∼1.5−2 ppm in the ^{1}H NMR and >30 ppm in the ^{13}C NMR spectra.[29] For enamine **3c** these differences were only $\Delta\delta_H$ 0.48, $\Delta\delta_C$ 6.0. These values are similar to those observed for the structurally related alkene (*E*)-1-pentenylcyclohexane [$\Delta\delta_H$ 0.19, $\Delta\delta_C$ 9.1],[38] which indicates minimal n → π* donation for enamine **3c**. It was surmised that enamine **3c** may preferentially adopt a conformation whereby the nitrogen lone pair and the π* orbital of the olefin are orthogonal. Such a conformation would likely minimize the steric interaction between the *gem*-dimethyl groups on the piperidine ring and the vinylic protons (H_a, Figure 1) Quantum mechanical studies support this hypothesis. Density functional calculations at the B3LYP[39]/6-31G(d)[40] level show that the lowest energy conformation of enamine **3***[41] is indeed one where the nitrogen lone pair and π* orbital of the olefin

(34) Mordini, A.; Peruzzi, D.; Russo, F.; Valacchi, M.; Reginato, G.; Brandi, A. *Tetrahedron* **2005**, *61*, 3349–3360.

(35) (a) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 8664–8665. (b) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *Synthesis* **2005**, 2264–2266. (c) Hodgson, D. M.; Chung, Y. K.; Nuzzo, I.; Freixas, G.; Kulikiewicz, K. K.; Cleator, E.; Paris, J.-M. *J. Am. Chem. Soc.* **2007**, *129*, 4456–4462. (d) Alorati, A. D.; Bio, M. M.; Brands, K. M. J.; Cleator, E.; Davies, A. J.; Wilson, R. D.; Wise, C. S. *Org. Process Res. Dev.* **2007**, *11*, 637–641.

(36) Yasuda, A.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1705–1708.

(37) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9*, 2209–2218.

(38) Pelter, A.; Smith, K.; Elgendy, S. M. A. *Tetrahedron* **1993**, *49*, 7119–7132.

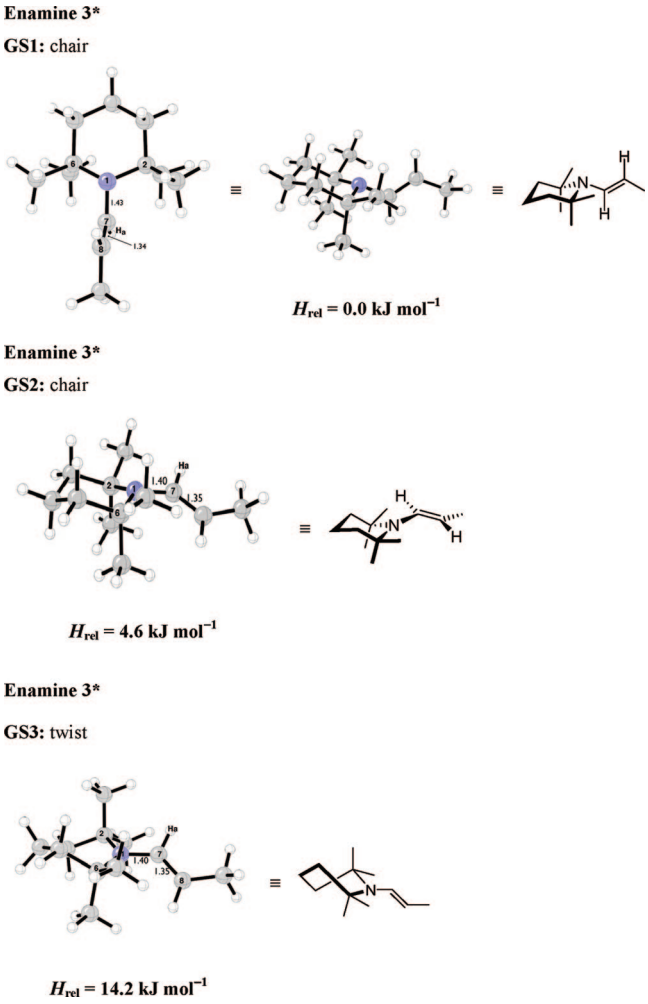
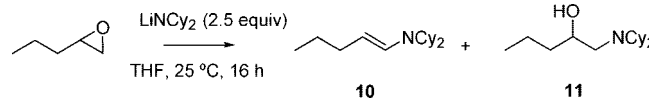


FIGURE 1. Predicted ground state conformations of enamine **3***.

are orthogonal to each other (cf. **GS1**, chair).[42] Moreover, the energy difference between the latter (**GS1**) and the conjugated chair conformer **GS2** was calculated to be +4.6 kJ mol^{-1}. An additional conjugated twist conformer **GS3** was found to be 14.2 kJ mol^{-1} higher in energy than **GS1**. For both of the conjugated conformers there was minimal contraction in the *N*-alkene bond length compared to the nonconjugated conformer, which provides further evidence for the nonclassical nature of the enamines (**3**).

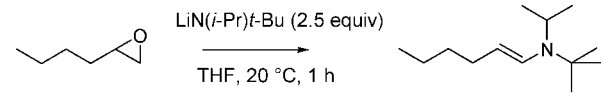
Next, we examined the reactivity of lithium amides slightly less hindered than LTMP with terminal epoxides. It was hoped that we might discover enamines that were accessible via this new epoxide-enamine transformation but that displayed more classical enamine character in terms of their reactivity toward electrophiles. Yamamoto et al. had previously reported that, as well as LTMP, terminal epoxides can be "isomerized" to aldehydes with lithium dicyclohexylamide ($LiNCy_2$) (1,2-epoxyoctadecane gave octadecanal in 63% yield).[11] 1,2-Epoxypentane was therefore treated with $LiNCy_2$ (2.5 equiv, THF, 25 °C, 1 h), and following filtration and evaporation to dryness, the signals due to the desired enamine **10** (Scheme 9) were clearly present in the ^{1}H and ^{13}C NMR spectra of the residue [δ_H 5.97 (dt, 1H, J = 14 and 1 Hz, NCH), 4.06 (dt, 1H, J = 14 and 7 Hz, NCH=C*H*); δ_C 132.5 (NCH), 93.9 (NCH=*C*H)]. The difference in chemical shift between the two olefinic protons was now much larger (1.91 ppm), indicating greatly increased n → π^* donation compared to enamine **3c**. However, it was also apparent that amino alcohol **11**, the result of direct ring-opening of the epoxide with the base, was also present [δ_C 67.9 and 55.0]. This was expected, since Yamamoto et al. reported a similar byproduct (17% isolated yield) in their isomerization.[11] Attempted reduced pressure distillation of this mixture resulted in decomposition, presumably due to the high boiling point of enamine **10**.

SCHEME 9. Epoxide-Enamine Transformation using $LiNCy_2$



Following on from this, we examined the reactivity of lithium *tert*-butylisopropylamide (LTBIPA) toward terminal epoxides. Although this lithium amide had not been employed by Yamamoto et al. in their isomerizations, it was considered that it would be sterically more encumbered than $LiNCy_2$ but would give an enamine that was more volatile. In the event, treatment of 1,2-epoxyhexane with LTBIPA (2.5 equiv, THF, 1 h, 20 °C) gave enamine **12** in 42% yield following reduced pressure distillation (Scheme 10). The double bond geometry was assigned as *trans* on the basis of the 14 Hz coupling constant observed between the two olefinic signals in the ^{1}H NMR spectrum. Traces of the corresponding amino alcohol, as well as 2-ene-1,4-diols resulting from α-lithiated epoxide dimerization,[43] were also observed but not isolated. Again, the use of other solvents (Et_2O, hexane) resulted in greatly diminished yields, whereas the inclusion of additives (e.g., LiCl, TMEDA) did not result in an increase in yield for enamine **12**.

SCHEME 10. Epoxide-Enamine Transformation using LTBIPA



The yield of enamine **12** was lower than what might have been anticipated on the basis of the yields obtained by Yamamoto et al. when using $LiNCy_2$ as base. To test whether this was due to partial enamine hydrolysis during the isolation, the isomerization of 1,2-epoxyoctadecane with LTBIPA (2.5 equiv, THF, 16 h, 20 °C) was carried out. This produced octadecanal in 42% yield, indicating that the isolation technique used was highly efficient. This isomerization was also carried out using $LiNCy_2$ (2.5 equiv, THF, 16 h, 20 °C); however, this proceeded in only 40% yield, and despite numerous attempts

(39) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

(40) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724–728. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257–2261. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213–222.

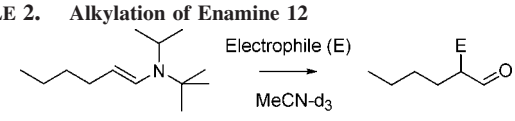
(41) Replacement of the experimentally used *n*-propyl group with a methyl group in the calculations should still provide an accurate indication of the relative energies of the various conformations, since the energy differences mainly arise from (1) strain between the vinyl protons and the *gem*-dimethyl groups (GS1 versus GS2) and (2) differing ring stabilities (GS2 versus GS3). Truncating the alkyl chain by two carbons reduces the number of possible conformations 9-fold and makes the computational study feasible.

(42) All calculations were carried out for the gas phase using the Gaussian 03 suite of programs: Frisch, M. J. *Gaussian 03*, rev. C02; Gaussian Inc.: Wallingford, CT, 2004. See Supporting Information for full reference.

on a variety of reaction scales, this could not be improved upon. In the present work when using $LiNCy_2$ as base, yields comparable to that reported by Yamamoto et al. for the isomerization of 1,2-epoxyoctadecane to octadecanal (lit.[11] 63%) were not attainable.

Returning to α-alkylation, enamine **12** was found to demonstrate unprecedented reactivity toward a range of electrophiles.[10] Reaction with benzyl bromide, allyl bromide, propargyl bromide, methyl α-bromoacetate, and MeI (2 equiv) proceeded smoothly at 15 °C to give the corresponding α-branched aldehydes **13a**−**e** in excellent yields (Table 2, entries 1−5) following aqueous workup and column chromatography. More than 40 years after its introduction in the mid 1950s, Stork noted that enamine alkylation (of unsubstituted α-methylene aldehydes) is "the only method for the controlled alkylation of such aldehydes with electrophilic olefins";[44] therefore, it was pleasing that reaction of enamine **12** with acrylonitrile and methyl acrylate proceeded well to give aldehydes **13f** and **13g** (entries 6 and 7). Enamine addition reactions using such Michael acceptors are known to lead to different intermediates (cyclobutanes and/or more substituted enamines), compared with the iminium ions formed in substitution reactions using organohalides.[29] For example, direct ^{1}H NMR analysis at the end of the reaction of enamine **12** with acrylonitrile tentatively indicated that an approximately equal mixture of the corresponding cyclobutane and substituted enamine were present.[24] Enamine **11** also reacted with simple alkyl halides. Reaction with iodoethane occurred on moderate heating to give aldehyde **13h** in quantitative yield (entry 8); this is impressive given the potential for competing elimination of HI with liberation of ethene.[45] In addition, reaction with 1-iodobutane and 1-iododecane proceeded in excellent yield (entries 9 and 10), further demonstrating that increased steric bulk around the nitrogen favors *C*- over *N*-alkylation. Enamine **12** also reacted with 2-iodopropane in good yield (entry 11), although three equivalents of electrophile needed to be employed in order that the reaction went to completion within a reasonable time scale. To the best of our knowledge,[29] this is the first example of an α-alkylated aldehyde being generated from an enamine by substitution of a secondary alkyl halide. Enamine **12** was then reacted with *tert*-BuI, but unfortunately the iminium ion that was observed in situ was a triplet [δ_H 8.44 (t, 1H, J = 7 Hz, CH=N$^+$)], likely due to protonation of **12** following elimination of HI from the electrophile; the desired alkylation did not occur (entry 12).

TABLE 2. Alkylation of Enamine 12



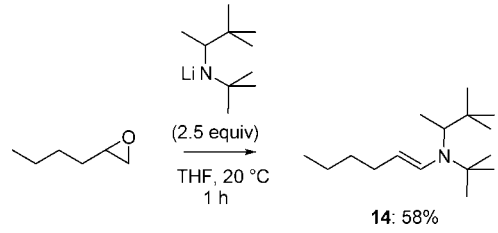
12 **13**

entry	electrophile (E)[a]	temp (°C)	time (h)	yield (%)[b]	
1	$PhCH_2Br$	15	18	**13a**	>99
2	CH_2=$CHCH_2Br$	15	18	**13b**	96
3	HC≡CCH_2Br	15	15	**13c**	>99
4	MeO_2CCH_2Br	15	16	**13d**	91
5	MeI	15	18	**13e**	86
6	acrylonitrile	84	19	**13f**	91
7	methyl acrylate	84	22	**13g**	70
8	EtI	50	18	**13h**	99
9	*n*-BuI	75	23	**13i**	97
10	$C_{10}H_{21}I$	84	22	**13j**	95
11	*i*-PrI[c]	84	40	**13k**	80
12	*t*-BuI	84	<1	**13l**	0

[a] 2 equiv unless otherwise stated. [b] Isolated yield (%). [c] 3 equiv.

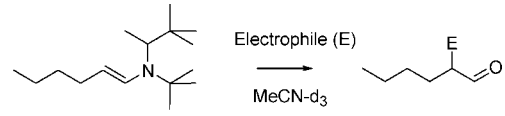
As efficient (for the most part) as the alkylations described above were, they were based on an enamine (**12**) that could only be formed in 42% yield. A lithium amide was therefore sought whose steric encumbrance was intermediate in nature between LTMP and LTBIPA. Lithium *N*-*tert*-butylpinacoylamide was selected as a potential candidate, since the parent amine could be readily prepared in multigram quantities by reductive amination of pinacolone with *t*-$BuNH_2$.[24] Reaction of this lithium amide (2.5 equiv, THF, 1 h, 20 °C) with 1,2-epoxyhexane gave enamine **14** in 58% yield (Scheme 11). It should be noted that the increasing yields obtained for the formation of enamines **12**, **14**, and **3c** (42%, 58%, and 75%, respectively) bear a near linear relationship with the decreasing differences in chemical shift observed in the ^{1}H NMR spectra for the vinylic protons of these compounds ($\Delta\delta_H$ 1.45, 0.89, and 0.48, respectively).

SCHEME 11. Epoxide-Enamine Transformation using Lithium *N*-*tert*-Butylpinacoylamide



Enamine **14** retained its ability to act as a *C*-nucleophile. Reaction with 1-iodobutane gave aldehyde **13i** in 84% yield (Table 3, entry 1); moreover reaction with *i*-PrI gave aldehyde **13k** in 49% yield (entry 2). Unfortunately, reaction with 1-iododecane was less efficient; this reaction never became homogeneous as was usually observed as the iminium ion formed, and the isolated yield of aldehyde **13j** was only 33% (entry 3).

TABLE 3. Alkylation of Enamine 14



14 **13**

entry	electrophile (E)	temp (°C)	time (h)	yield (%)[a]	
1	*n*-BuI (2 equiv)	84	96	**13i**	84
2	*i*-PrI (3 equiv)	94	96	**13k**	49
3	*n*-$C_{10}H_{21}I$ (2 equiv)	82	96	**13j**	33

[a] Isolated yield.

The reactivity of two other hindered lithium amides toward terminal epoxides was examined. Reaction between lithium 2,2,5,5-tetramethylpyrrolidide[24] (2.5 equiv, THF) and 1,2-epoxyoctadecane returned the starting material after 1 h at 25 °C. The starting material was consumed, however, when the same reaction was heated to reflux for 16 h. Following aqueous workup, ^{1}H NMR spectroscopy revealed that as well as octadecanal, a small amount of enamine [δ_H 5.83 (dt, 1H, J =

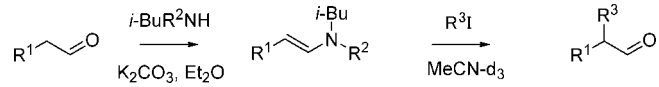
(43) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *Org. Lett.* **2005**, *7*, 6870–6871.

14 and 1 Hz, =CH), 4.18 (dt, 1H, J = 14 and 7 Hz, NCH)] remained unhydrolyzed. The difference in chemical shift observed in the ^{1}H NMR spectrum between the two olefinic protons was 1.65 ppm. However, following purification by column chromatography (SiO_2), octadecanal was obtained in only 25% yield. This was perhaps unsurprising since it would be expected that the intermediate α-lithiated epoxide would be labile in refluxing THF. At ambient temperature this reaction proved unworkably sluggish, proceeding to less than 50% conversion in 7 days. Lithium *N*-trityl-*N*-*tert*-butylamide[46] was also examined as base for the formation of enamines from terminal epoxides. Treatment of 1,2-epoxyoctadecane with LiN(*t*-Bu)Tr (2.5 equiv, THF, 25 °C, 16 h) returned the starting material in quantitative yield. Repeating this reaction at reflux (16 h) gave the same result. The lack of reactivity of this base with a terminal epoxide could be due to its highly hindered nature, or because it is simply not basic enough to abstract a proton from the epoxide ring.

Finally, the possibility of using a mixture of lithium amides for enamine formation from terminal epoxides was examined. It was considered that a highly basic and hindered lithium amide could deprotonate the terminal epoxide and a second less hindered/more nucleophilic lithium amide could act as a nucleophile with the resulting α-lithiated epoxide. It was anticipated that the products of such a reaction would display more classical enamine character, but could be formed in high yield. However, even when employing a highly nucleophilic lithium amide such as lithium pyrrolidide alongside LTMP, mixtures of enamines were observed along with considerable amounts of amino alcohols. The fact that LTMP is able to compete as a nucleophile with such a powerful nucleophile serves to indicate the high electrophilicity of α-lithiated epoxides.[19] In addition, it might also indicate that the use of a lithium amide dimer is crucial in obtaining good yields of enamine such that the nucleophilic lithium amide is intimately bound in aggregate during the deprotonation step and is then nearby to intercept the transient lithiated epoxide as soon as it is formed (cf. Scheme 8). Though it is known that the α-lithiation of cyclooctene oxide proceeds via a monosolvated LTMP dimer (vide supra),[18] it is not clear how this mechanism would translate on replacing that epoxide with a terminal one or how the structure of other dimeric lithium amides would be affected.[20d−f,43]

In order that we could accurately compare the yields for the synthesis of α-alkylated aldehydes via our new method with those obtained via a traditional condensation route, it was considered prudent to repeat some of the early results of Curphey.[30] As a prior check of experimental technique, the base-catalyzed (K_2CO_3) condensation of *n*-butylisobutylamine with valeraldehyde was carried out as previously described by Curphey;[30] this gave enamine **15** in 66% yield (Table 4, entry 1; lit.[30b] 71%).[47] Interestingly however, reaction of enamine **15** with *n*-BuI (2 equiv, MeCN, Δ, 20 h) gave 2-*n*-propylhexanal **13m** in 54% isolated yield, whereas the reported yield for this reaction was considerably lower (lit.[30b] 24% (GC)). In light of this unusually high yield, we sought to synthesize aldehydes **13i**−**k** in order that we could compare the yields obtained in this manner with those achieved via our route from terminal epoxides and lithium amides. Base-catalyzed (K_2CO_3) condensation of *n*-butylisobutylamine with hexanal proceeded in 64% yield to give enamine **16a**. Reaction of enamine **16a** with *n*-BuI (2 equiv, MeCN, Δ, 20 h) gave aldehyde **13i** in 74% yield, and although reaction with *n*-$C_{10}H_{21}$I was less facile, aldehyde **13j** was obtained in 57% yield. Given these unexpectedly high yields, we attempted to alkylate enamine **16a** with *i*-PrI, which gave aldehyde **13k** in 48% yield. The amine employed thus far, *n*-butylisobutylamine, was prepared via the inelegant reaction between *i*-$BuNH_2$ (3 equiv) and *n*-BuBr (55% yield, lit.[30b] 69%); therefore the use of a commercial amine, namely, *i*-Bu_2NH, was also examined. Base-catalyzed (K_2CO_3) condensation of hexanal with this amine gave enamine **16b** in 73% yield. Reaction of enamine **16b** with *n*-BuI (2 equiv, MeCN, Δ, 20 h) gave 2-butylhexanal **12i** in 62% yield and with i-PrI gave aldehyde **13k** in 50% yield.

TABLE 4. Alkylation of Enamines Synthesized via a Classical Condensation



entry	R^1	R^2	enamine	yield (%)	R^3	aldehyde	yield (%)
1	*n*-Pr	*n*-Bu	**15**	66	*n*-Bu	**13m**	54
2	*n*-Bu	*n*-Bu	**16a**	64	*n*-Bu	**13i**	74
3	*n*-Bu	*n*-Bu	**16a**		$C_{10}H_{21}$	**13j**	57
4	*n*-Bu	*n*-Bu	**16a**		*i*-Pr	**13k**	48
5	*n*-Bu	*i*-Bu	**16b**	73	*n*-Bu	**13i**	62
6	*n*-Bu	*i*-Bu	**16b**		*i*-Pr	**13k**	50

The realization that this traditional method is significantly higher yielding than previously thought should promote a re-evaluation of current thinking concerning the reactivity of such enamines toward simple haloalkane electrophiles. Despite this, the two-step synthesis of aldehyde **13i** from hexanal via enamine **16a** is achieved in 47% overall yield, and for aldehyde **13k** the yield is 31%.[30b,48] In comparison, our newly developed method starting from 1,2-epoxyhexane gives aldehyde **13i** in 49% and aldehyde **13k** in 29% overall yields, which indicates our new method is of comparable efficiency.

Conclusions

In summary, the reactivity modes of hindered lithium amides with epoxides have been explored. Furthermore, some of the enamines derived by this process react with activated and simple alkyl halides in synthetically useful yields.[49] A re-examination of the alkylation of "traditional" enamines (synthesized by condensation of secondary amines with aldehydes) has revealed that these reactions are significantly more efficient than previously reported.

Experimental Section

General experimental details are described in Supporting Information. General Procedure for LTMP-Induced Epoxide-Enamine Transformation. 2,2,6,6-Tetramethyl(octadec-1-en-1-yl)piperidine (3d). To a solution of 2,2,6,6-tetramethylpiperidine (0.50 cm^3, 2.96 mmol) in THF (6 cm^3) at 0 °C was added *n*-BuLi (1.6 mol dm^{-3} in hexanes; 1.85 cm^3, 2.96 mmol) dropwise. The solution was allowed to warm to 25 °C over 15 min before a solution of 1,2-epoxyoctadecane (318 mg, 1.19 mmol) in THF (1.5 cm^3) was added in one portion. The reaction mixture was stirred at 25 °C for 1 h before being filtered through a pad of silica (∼5 cm^2 × 5 cm, deactivated by stirring for 16 h in neat NEt_3). The pad

(44) Stork, G. *Med. Res. Rev.* **1999**, *19*, 370–387.
(45) For a recent example of this problem in synthesis, see: Hodgson, D. M.; Galano, J.-M. *Org. Lett.* **2005**, *7*, 2221–2224.
(46) Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **2000**, *41*, 2515–2518.
(47) See also Bélanger, G.; Doré, D.; Ménard, F.; Darsigny, V. *J. Org. Chem.* **2006**, *71*, 7481–7484.

was washed with 5% NEt_3 in light petrol (250 cm^3). The solvent and amines were removed in vacuo (down to 0.1 mbar, 50 °C) to give enamine **3d** (361 mg, 78%) as a glassy solid; IR (cm^{-1}) 2924s, 2853s, 1641w (C═C), 1465m, 1376w, 1382w, 1265w, 1246w, 1174w, 1131w, 1080w, 1033w; ^{1}H NMR (500 MHz, C_6D_6) δ 5.79 (d, 1H, J = 14 Hz), 5.32 (dt, 1H, J = 14 and 7 Hz), 2.08 (dt, 2H, J = 7 and 7 Hz), 1.51−1.18 (m, 34H), 1.13 (s, 12H), 0.91 (t, 3H, J = 7 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 131.8 (NCH═), 126.2 (═*C*H), 53.7 (2 × *C*Me_2), 41.6 (2 × CMe_2*C*H_2), 32.4 (═CH*C*H_2), 32.1 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 30.2−29.7 (10 × CH_2), 28.0 (2 × NC*Me*$_2$), 23.1 (CH_2), 18.1 (CH_2), 14.4 (Me); HRMS *m*/*z* (M + H^+) found 392.4254. $C_{27}H_{54}N$ requires 392.4251.

***tert*-Butyl(hex-1-en-1-yl)isopropylamine (12).** To a solution of *N*-*tert*-butylisopropylamine (1.50 cm^3, 9.46 mmol) in THF (15 cm^3) at −78 °C was added *n*-BuLi (1.6 mol dm^{-3} in hexanes; 5.91 cm^3, 9.46 mmol) dropwise. The solution was allowed to warm to 25 °C over 15 min before a solution of 1,2-epoxyhexane (378 mg, 3.78 mmol) in THF (5 cm^3) was added in one portion. The reaction was stirred at 25 °C for 1 h before being filtered through a pad of celite (∼5 cm^2 × 5 cm). The pad was washed with Et_2O (250 cm^3). The solvent was removed in vacuo, and the residue was purified by bulb-to-bulb distillation to give enamine **12** (314 mg, 42%) as a colorless oil; bp 90 °C/0.1 mbar; IR (cm^{-1}) 2970s, 2925s, 2873s, 1645s (C═C), 1465w, 1377m, 1363m, 1302m, 1220m; ^{1}H NMR (400 MHz) δ 5.93 (dt, 1H, J = 14 and 1 Hz), 4.48 (dt, 1H, J = 14 and 7 Hz), 3.56 (dsept, 1H, J = 14 and 1 Hz), 1.99−1.93 (m, 2H), 1.35−1.30 (m, 4H), 1.23−1.18 (m, 15H), 0.91 (t, 3H, J = 7 Hz); ^{13}C NMR (100 MHz) δ 129.9 (NCH═), 105.3 (═*C*H), 55.5 (NC), 46.1 (NC), 33.8 (CH_2), 31.5 (CH_2), 29.0 (C*Me*$_3$), 22.1 (CH_2), 20.9 (C*Me*$_3$), 14.0 (Me); HRMS *m*/*z* (M + H^+) found 198.2228. $C_{13}H_{28}N$ requires 198.2222.

***tert*-Butyl(hex-1-en-1-yl)(3,3-dimethylbut-2-yl)amine (14).** To a solution of *N*-*tert*-butylpinacoylamine[24] (1.00 g, 6.37 mmol) in THF (15 cm^3) at −78 °C was added *n*-BuLi (1.6 mol dm^{-3} in hexanes; 3.98 cm^3, 6.37 mmol) dropwise. The solution was allowed to warm to 25 °C over 15 min before a solution of 1,2-epoxyhexane (255 mg, 2.55 mmol) in THF (5 cm^3) was added in one portion. The reaction was stirred at 25 °C for 1 h before being filtered through a pad of celite (∼5 cm^2 × 5 cm). The pad was washed with Et_2O (250 cm^3). The solvent was removed in vacuo, and the residue was purified by bulb-to-bulb distillation to give enamine **14** (353 mg, 58%) as a colorless oil; bp 125 °C/0.03 mbar; IR (cm^{-1}) 2957s, 2924s, 1646 (C═C), 1457m, 1370m, 1259w, 1195w; ^{1}H NMR (500 MHz, C_6D_6) δ 5.83 (dt, 1H, J = 14 and 1 Hz), 4.94 (dt, 1H, J = 14 and 7 Hz), 2.92 (q, 1H, J = 7 Hz), 2.05 (dt, 2H, J = 7 and 7 Hz), 1.42−1.35 (m, 4H), 1.15 (s, 9H), 1.05 (d, 3H, J = 7 Hz), 0.96 (s, 9H), 0.91(t, 3H, J = 7 Hz); ^{13}C NMR δ 133.0 (NCH═), 117.3 (═CH), 58.6 (NCH), 55.5 (NC), 36.3 (CH*C*Me_3), 33.5 (═CH*C*H_2), 31.5 (CH_2), 29.3 (CMe_3), 28.6 (CMe_3), 22.7 (CH_2), 14.2 (Me), 14.2 (Me); HRMS *m*/*z* (M + H^+) found 240.2692. $C_{16}H_{34}N$ requires 240.2691.

Butyl(hex-1-en-1-yl)isobutylamine (16a). Prepared by analogy to the procedure reported by Curphey.[30b] To a stirred solution of *n*-butylisobutylamine (11.19 g, 86.7 mmol) in dry Et_2O (22 cm^3) at 0 °C under argon was added anhydrous K_2CO_3 (12.12 g) followed by freshly distilled hexanal (8.67 g, 86.7 mmol) dropwise. The reaction was stirred at room temperature for a further 16 h before being filtered through an oven-dried sintered glass filter. The filtrate was fractionally distilled to give enamine **16a** (11.68 g, 64%) as a colorless oil; bp 106 °C/17 mbar; IR (cm^{-1}) 3049m, 2955s, 2926s, 2870s, 1651s (C═C), 1466m, 1378m, 1290m, 1262w, 1225m, 1202m, 1113m; ^{1}H NMR (400 MHz) δ 5.88 (d, 1H, J = 14 Hz), 4.02 (dt, 1H, J = 7 and 7 Hz), 2.87 (t, 3H, J = 7 Hz), 2.63 (d, 2H, J = 7 Hz), 1.93 (dt, 2H, J = 7 and 7 Hz), 1.80 (sept. 1H, J = 7 Hz), 1.59−1.08 (m, 8H) 1.04−0.77 (m, 12H); ^{13}C NMR (100 MHz) δ 138.5 (NCH), 95.8 (═CH), 60.3 (NCH_2*i*-Pr), 51.8 (NCH_2), 34.4, 30.7, 29.5, 27.4, 22.3, 20.7, 20.6, 14.3 (Me), 14.2 (Me); HRMS *m*/*z* (M + H^+) found 212.2381. $C_{14}H_{30}N$ requires 212.2378.

(Hex-1-en-1-yl)diisobutylamine (16b). Prepared in the same manner as described for **16a**: K_2CO_3 (14.00 g), diisobutylamine (17.3 cm^3, 100 mmol), and hexanal (10.0 g, 100 mmol) gave enamine **16b** (15.39 g, 73%) as a colorless oil; bp 102 °C/18 mbar; IR (cm^{-1}) 3049w, 2954s, 2926s, 2869s, 1651s (C═C), 1467s, 1383m, 1366m, 1333w, 1294w, 1227m, 1208w, 1102m; ^{1}H NMR (500 MHz, C_6D_6) δ 5.89 (d, 1H, J = 14 Hz), 4.15 (dt, 1H, J = 14 and 7 Hz), 2.60 (d, 4H, J = 7 Hz), 2.10 (dt, 2H, J = 7 and 7 Hz), 1.85 (sept. 2H, J = 7 Hz), 1.42−0.85 (m, 19H); ^{13}C NMR (125 MHz, C_6D_6) δ 138.9 (NCH), 95.8 (═CH), 61.0 (NCH_2), 34.7 (CH_2), 31.2 (CH_2), 27.4 (2 × C*H*Me_2), 22.5 (CH_2), 20.6 (2 × CH*Me*$_2$), 14.3 (Me); HRMS *m*/*z* (M + H^+) found 212.2384. $C_{14}H_{30}N$ requires 212.2378.

General Procedure for Enamine Alkylation. 2-Benzylhexanal[10] (13a). A solution of enamine **12** (227 mg, 1.15 mmol) and BnBr (273 μL, 2.30 mmol) in MeCN-d_3 (1.0 cm^3) was allowed to stand (with occasional shaking) at 15 °C (rt) in a NMR tube fitted with a PTFE valve, until consumption of enamine **12** was judged complete by ^{1}H NMR spectroscopy (18 h). Acidic buffer solution (made up of AcOH (0.5 g), AcONa (0.5 g), and water (1.0 g)) (0.5 cm^3) was added, and the mixture was allowed to stand at the same temperature as before, for 1 h with occasional shaking before being separated between H_2O (10 cm^3) and Et_2O (10 cm^3). The aqueous phase was washed with Et_2O (10 cm^3), the combined organic layers were washed with brine (20 cm^3), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. Purification by column chromatography (SiO_2, 5% Et_2O/light petrol) gave 2-benzylhexanal **13a** (217 mg, quant) as a colorless oil; R_f 0.26 (5% Et_2O/light petrol); IR (cm^{-1}) 3086w, 3063w, 3028m, 2957s, 2931s, 2859s, 2711m, 2360w, 2340w, 1725s (C═O), 1604w, 1496m, 1466m, 1454s, 1392w, 1379w, 1030w; ^{1}H NMR (400 MHz) δ 9.67 (d, 1H, J = 3 Hz), 7.33−7.26 (m, 2H), 7.25−7.15 (m, 3H), 2.99 and 2.73 (AB-part of ABX, 2H, J_{AX} = 7, J_{BX} = 7, J_{AB} = 14 Hz), 2.67−2.58 (m, 1H), 1.72−1.22 (m, 6H), 0.89 (t, 3H, J = 7 Hz); ^{13}C NMR (100 MHz) δ 204.8 (CHO), 138.9 (ArC), 129.0 (2 × ArC -H), 128.5 (2 × ArC -H), 126.3 (ArC -H) 53.4 (*C*HCHO), 35.0 (*C*H_2Ph), 29.1 (CH_2), 28.3 (CH_2) 22.7 (CH_2), 13.8 (Me).

2-*n*-Butylhexanal (13i). According to the procedure described for 2-benzylhexanal **13a**, a solution of enamine **12** (144 mg, 0.73 mmol) and *n*-BuI (166 μL, 1.46 mmol) at 75 °C for 23 h gave 2-*n*-butylhexanal **13i** (110 mg, 97%) as a colorless oil; R_f 0.21 (1% Et_2O/light petrol); IR (cm^{-1}) 2958s, 2931s, 2873s, 2860s, 2693w, 1727s (C═O), 1467m, 1379w; ^{1}H NMR (400 MHz) δ 9.54 (d, 1H, J = 3 Hz), 2.26−2.16 (m, 1H), 1.66−1.55 (m, 2H), 1.48−1.37 (m, 2H), 1.36−1.19 (m, 8H), 0.88 (t, 6H, J = 7 Hz); ^{13}C NMR (100 MHz) δ 205.6 (CHO), 51.9 (*C*HBu_2), 29.2 (2 × CH_2), 28.6 (2 × CH_2) 22.7 (2 × CH_2), 13.8 (2 × Me).

Similarly, a solution of enamine **14** (119 mg, 0.50 mmol) and *n*-BuI (113 μL, 1.00 mmol) at 82 °C for 96 h gave 2-*n*-butylhexanal **13i** (65 mg, 84%) as a colorless oil; data as above.

A solution of enamine **16a** (198 mg, 0.94 mmol) and *n*-BuI (214 μL, 1.88 mmol) at 82 °C for 20 h gave 2-*n*-butylhexanal **13i** (108 mg, 74%) as a colorless oil; data as above.

A solution of enamine **16b** (160 mg, 0.76 mmol) and *n*-BuI (170 μL, 1.51 mmol) at 82 °C for 22 h gave 2-*n*-butylhexanal **13i** (73 mg, 62%) as a colorless oil; data as above.

2-*n*-Butyldodecanal (13j). According to the procedure described for 2-benzylhexanal **13a**, a solution of enamine **12** (212 mg, 1.07 mmol) and $C_{10}H_{21}I$ (458 μL, 2.14 mmol) at 82 °C for 22 h gave 2-*n*-butyldodecanal **13j** as a colorless oil (244 mg, 95%); R_f 0.29 (2% Et_2O/light petrol); IR (film) (cm^{-1}) 3434w, 2926s, 2855s, 2692m (CHO), 1728s (C═O), 1466s, 1378m, 1239m, 1143w, 1016w; ^{1}H NMR (400 MHz) δ 9.54 (d, 1H, J = 3 Hz), 2.26−2.16 (m, 1H), 1.67−1.16 (m, 24H), 0.92−0.83 (m, 6H); ^{13}C NMR (100 MHz) δ 205.7 (CHO), 51.9 (*C*HCHO), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.9

(48) For a one-pot procedure, see: Ho, T.-L.; Wong, C. M. *Synth. Commun.* **1974**, *4*, 147–149.

(49) For a recent asymmetric development of this process, see: Hodgson, D. M.; Kaka, N. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 9958–9960.

(CH_2), 28.6 (CH_2), 27.0 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.0 (Me), 13.8 (Me); HRMS *m*/*z* (M + NH_4^+) found 258.2801. $C_{16}H_{36}NO$ requires 258.2797.

A solution of enamine **16a** (200 mg, 0.95 mmol) and $C_{10}H_{21}I$ (400 μL, 1.90 mmol) at 82 °C for 44 h gave 2-*n*-butyldodecanal **13j** (131 mg, 57%) as a colorless oil; data as above.

2-Isopropylhexanal (13k). According to the procedure described for 2-benzylhexanal **13a**, a solution of enamine **12** (136 mg, 0.69 mmol) and *i*-PrI (135 μL, 1.38 mmol) at 82 °C for 40 h gave 2-isopropylhexanal **13k** as a colorless oil (79 mg, 80%); R_f 0.29 (2% Et_2O/light petrol); IR (cm^{-1}) 2961s, 2873s, 1725s (C═O), 1466w, 1371w, 1264w, 1128w, 1066w; ^{1}H NMR (400 MHz) δ 9.61 (d, 1H, J = 3 Hz), 2.06−1.91 (m, 2H), 1.69−1.57 (m, 1H), 1.51−1.40 (m, 1H), 1.37−1.13 (m, 4H), 0.96 (d, 6H, J = 7 Hz), 0.89 (t, 3H, J = 7 Hz); ^{13}C NMR (100 MHz) δ 206.1 (CHO), 58.3 (*C*HCHO), 29.8 (CH_2), 28.3 (*C*Me_2), 25.8 (CH_2), 22.8 (CH_2), 20.2 (C*Me*(Me)), 19.8 (CMe(*Me*)), 13.9 (Me); HRMS *m*/*z* (M + NH_4^+) found 160.1700. C_9H_2NO requires 160.1701.

Similarly, a solution of enamine **14** (198 mg, 0.83 mmol) and *i*-PrI (248 μL, 2.49 mmol) at 82 °C for 96 h gave 2-isopropylhexanal **13k** as a colorless oil (58 mg, 48%); data as above.

A solution of enamine **16a** (201 mg, 0.95 mmol) and *i*-PrI (190 μL, 1.90 mmol) at 82 °C for 20 h gave 2-isopropylhexanal **13k** as a colorless oil (65 mg, 48%); data as above.

A solution of enamine **16b** (183 mg, 0.87 mmol) and *i*-PrI (190 μL, 1.90 mmol) at 82 °C for 20 h gave 2-isopropylhexanal **13k** as a colorless oil (62 mg, 50%); data as above.

Acknowledgment. We thank the EPSRC and AstraZeneca for an Industrial CASE award, Wadham College for a Keeley Senior Scholarship (to C.D.B.), the EPSRC and Glaxo-Smith-Kline for a CASE award (to N.J.R.), the EPSRC for a research grant (GR/S46789/01), the National Institutes of General Medical Sciences, National Institutes of Health (G36700), N. S. Kaka (Oxford) for additional data and helpful discussion, and the EPSRC National Mass Spectrometry Service Centre for mass spectra.

Note Added after ASAP Publication. A previous version of the Supporting Information file was published ASAP on December 23, 2008. The correct version was published ASAP on January 13, 2009.

Supporting Information Available: Spectra for compounds, experimental details of compounds prepared via routine methods, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802016T