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Bridgehead Enolates: Substitution and Asymmetric Desymmetrization of Small Bridged Carbonyl Compounds by Lithium Amide Bases

Gerard M. P. Giblin,[†] **Douglas T. Kirk,**[‡] **Lee Mitchell,**[‡] **and Nigel S. Simpkins***[,‡]

*GlaxoSmithKline, Department of Medicinal Chemistry, Neurology CEDD, The Frythe,
Hertfordshire AL6 9AR, U.K., and School of Chemistry, University of Nottingham,
University Park, Nottingham NG7 2RD, U.K.*

nigel.simpkins@nottingham.ac.uk

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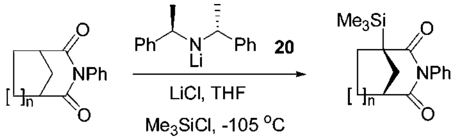
ABSTRACT



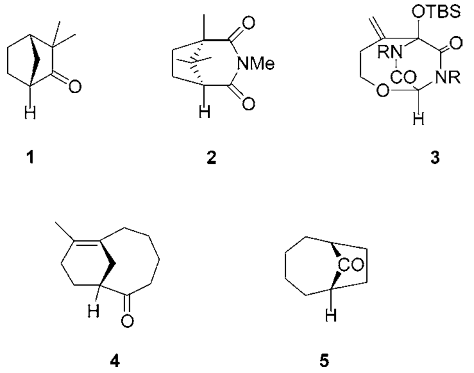
11 n = 2
15 n = 1

(-)-13 n = 2, 74% (98% ee)
(-)-17 n = 1, 63% (70% ee)

Contrary to expectations, a number of bridged carbonyl compounds undergo facile bridgehead metalation with lithium amide bases. Diketone, lactone, lactam, and imide functions are all demonstrated to participate in this type of "bridgehead enolate" chemistry, leading to a range of substituted products. Meso compounds can also be desymmetrized in very high ee by asymmetric bridgehead metalation.

Metalation of ketones such as camphenilone **1** at the bridgehead position is expected to be difficult or impossible because the conventional enolate form of the resulting anion would break Bredt's rule (Figure 1).[1] In fact, ketone **1** is readily metalated by lithium tetramethylpiperidide (LTMP), but the resulting "bridgehead enolate" (perhaps more accurately described as an α-keto carbanion) undergoes such rapid addition to the starting ketone that its interception by alternative electrophiles has not been possible.[2] A number of other bridgehead metalations have also been described, including carboxylation of imide **2** and aldol-type reaction of diketopiperazine **3**.[3,4]

While bridgehead metalation of small-bridge carbonyl compounds is expected to be problematic, with larger systems



1 **2** **3**

4 **5**

Figure 1. Carbonyl compounds known to undergo bridgehead metalation.

[†] GlaxoSmithKline.

[‡] University of Nottingham.

(1) (a) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683. (b) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067. (c) Certain systems are known to undergo base-catalysed bridgehead deuteration; see: Nickon, A.; Covey, D. F.; Huang, F.; Kuo, Y.-N. *J. Am. Chem. Soc.* **1975**, *97*, 904.

(2) (a) Shiner, C. S.; Berks, A. H.; Fisher, A. M. *J. Am. Chem. Soc.* **1988**, *110,* 957. (b) The inability to trap bridgehead enolates has led to the invention of indirect approaches; see, for example: Spitz, U. P.; Eaton, P. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2220.

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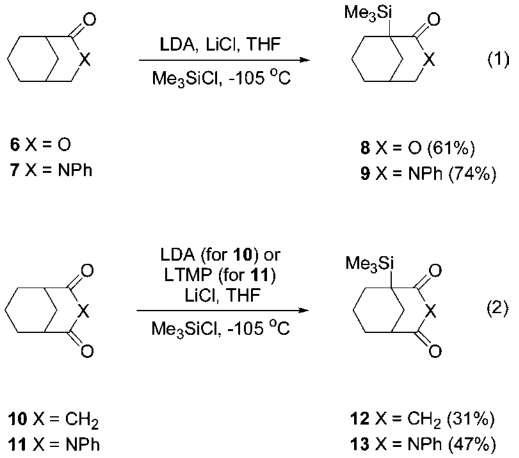
a transition to "normal" enolate chemistry should be evident.[5] Remarkably, ketone **4** undergoes kinetically controlled enolate formation at the bridgehead position despite the availability of an alternative methylene site for deprotonation.[6]

Recently, we demonstrated that bridgehead metalation−substitution of ketones such as **5** is possible in high yield by use of a lithium amide−in situ Me$_3$SiCl quench protocol and that enantioselective desymmetrization was possible using a chiral lithium amide base.[7] However, the scope of such bridgehead metalations remains ill-defined, especially in regard to interesting examples such as imide **2**, which appear to lie between the uncontrolled carbanion-like camphenilone system and the well-behaved large bridge systems.

Here, we demonstrate that a range of bridged systems, having small bridges (one to three atoms), with ketone, imide, lactam, or lactone activating functions undergo lithium amide mediated bridgehead metalation−substitution. We also show that very high levels of enantioselectivity can be achieved in asymmetric desymmetrization of bridged imides using the chiral base method.

The bicyclo[3.3.1]nonane systems **6**, **7**, **10**, and **11**, having various carbonyl functions in one of the three-atom bridges, provide interesting preliminary observations concerning the viability of bridgehead substitution. Under our usual low-temperature in situ quench conditions using Me$_3$SiCl as the electrophile, modest to good yields of the desired products were obtained, Scheme 1 (eqs 1 and 2).

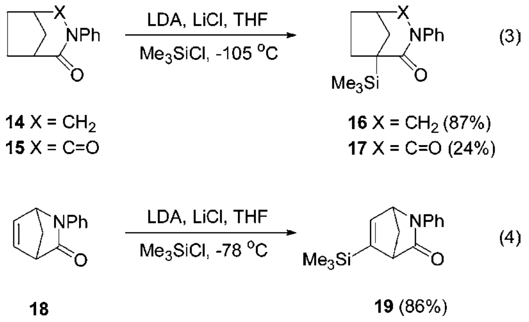
Scheme 1



The lactone **6** and lactam **7** underwent surprisingly smooth bridgehead silylation, using excess (1.2−1.8 equiv) LDA−LiCl as base (eq 1). In the diketone and imide cases (**10** and **11**), the desired product was accompanied by lesser amounts of disilylated product (typically 10−20%) and unidentified byproducts, which could be minimized by the use of LTMP in place of LDA (eq 2).[8] In the case of diketone **10**, we employed 2.5 equiv of base in the expectation that bridgehead substitution might occur via a dianion[9] although the reaction most likely proceeds via initial formation of an enol silane.

In the next phase of exploration, we examined metalation of lactam and imide compounds having shorter bridges, Scheme 2 (eqs 3 and 4).

Scheme 2



The bicyclo[3.2.1]octane lactam **14** underwent high-yielding silylation using LDA−LiCl, and we found that the use of ^{s}BuLi, as employed in metalations of the rather more hindered imide **2**, gave none of the desired product. Silylation of the corresponding imide **15** proved more problematic, with bis-silylation predominating. The unsaturated bicyclo[2.2.1]-heptane lactam **18** gave no products of bridgehead substitution, but instead gave a high yield of silylated alkene **19**. When we removed the double bond from **18**, either by hydrogenation or by dihydroxylation-acetonide formation, none of the desired mode of substitution could be achieved. This system is related to the classical camphenilone example **1**, and in line with previous work we were unable to intercept the anion from this ketone, even using a large excess of Me$_3$SiCl at low temperature. Thus, it seems that successful metalations of these very small rigid systems still present a problem.

Asymmetric desymmetrization of the *meso*-imides **11** and **15** was carried out by use of chiral lithium amide base **20** or the bis-lithiated base **21**, Scheme 3.[10,11]

The use of (*R*,*R*)-bisphenylethylamide **20** enabled the synthesis of (−)-**13** in high yield and enantiomeric excess, the process being considerably more efficient than the corresponding reaction with LDA or LTMP. In the silylation

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(3) Wanner, K. T.; Paintner, F. F. *Liebigs Ann*. **1996**, 1941.

(4) (a) Yamaura, M.; Nakayama, T.; Hashimoto, H.; Shin, C.; Yoshimura, J.; Kodama, H. *J. Org. Chem*. **1988**, *53*, 6035. (b) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc*. **1984**, *106*, 5748. (c) Eastwood, F. W.; Gunawardana, D.; Wernert, G. T. *Aust. J. Chem*. **1982**, *35*, 2289.

(5) (a) Khan, F. A.; Czerwonka, R.; Zimmer, R.; Reissig, H.-U. *Synlett* **1997**, 995. (b) Magnus, P.; Parry, D.; Iliadis, T.; Eisenbeis, S. A.; Fairhurst, R. A. *J. Chem. Soc., Chem. Commun*. **1994**, 1543. (c) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc*. **1992**, *114*, 5878. (d) Rigby, J. H.; Moore, T. L. *J. Org. Chem*. **1990**, *55*, 2959.

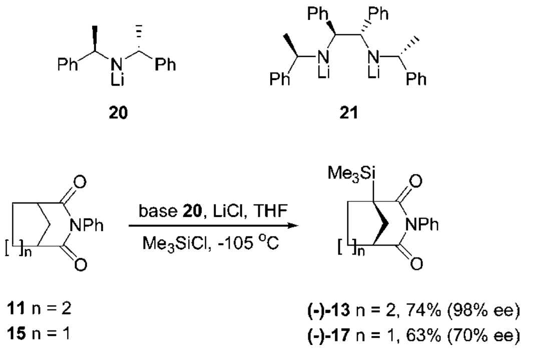
(6) Gwaltney, S. L., II; Sakata, S. T.; Shea, K. L. *J. Org. Chem*. **1996**, *61*, 7438.

(7) Blake, A. J.; Giblin, G. M. P.; Kirk, D. T.; Simpkins, N. S.; Wilson, C. *Chem. Commun*. **2001**, 2668.

(8) In cases such as **6** or **7**, excess base can be used to ensure smooth conversion to product, whereas with substrates such as imide **11** the possibility for double bridgehead substitution dictates the use of close to stoichiometric amounts of base (usually 1.1 equiv). In typical metalations, we added a solution of 1.1−1.2 equiv of base to a mixture of 1.0 equiv of substrate and 3.0 equiv of electrophile in THF at −105 °C. The mixture was then allowed to warm to room temperature before standard workup and chromatography. Further details can be found in the Supporting Information.

(9) Berry, N. M.; Darey, M. C. P.; Harwood, L. M. *Synthesis* **1986**, 476 and references therein.

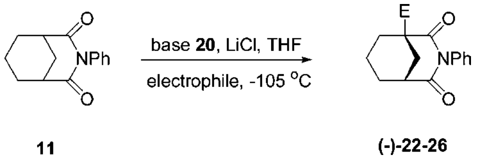
Scheme 3



of **15**, base **20** proved less selective, providing (−)-**17** in 70% ee. In this case we utilized the bis-lithium amide base **21**,[12] which then provided (+)-**17** in 47% yield and 94% ee.

Although the Me_3SiCl in situ quench procedure had provided some remarkable new bridgehead silylation results, we were interested in probing the possibilities for achieving alternative bridgehead alkylation, acylation, etc. At present, it appears that treatment of most of the aforementioned substrates with lithium amide bases, *followed* by addition of electrophiles in the conventional way, provides very low levels of substitution product. However, by addition of chiral base **20** to a mixture of imide **11** and an appropriate electrophile, asymmetric *C*-alkylation or acylation is possible (Table 1).[13]

Table 1. Asymmetric Bridgehead Substitution of Imide **11**



product	electrophile	E	yield (%)	ee (%)
(−)-**22**	methyl iodide	Me	57	97
(−)-**23**	allyl bromide	$CH_2CH{=}CH_2$	42	95
(−)-**24**	prenyl bromide	$CH_2CH{=}C(Me)_2$	50	98
(−)-**25**	benzyl bromide	CH_2Ph	52	95
(−)-**26**	pivaloyl chloride	CO^tBu	56	98

Although yields are somewhat modest at present, this being in part due to bis-alkylation, in all cases the enantiomeric excess of the product was excellent. We have not yet ascertained the full scope of this procedure in terms of substrate or electrophile, but we expect that similar substitutions will be possible on other systems.

The highly enantioselective silylation of imides **11** and **15** enables further selective transformations with synthetic potential. First, it was interesting to note that silylimide (−)-**13** undergoes rather facile and high-yielding substitution at the remaining bridgehead site, using the type of in situ quenching procedure outlined above and with LTMP as base, e.g., to give **27** and **28** (Figure 2).

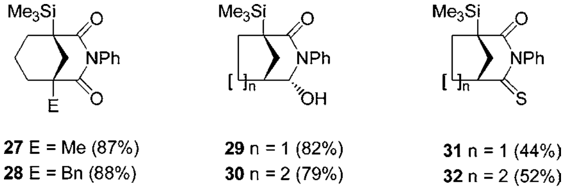


Figure 2.

Second, the bridgehead silicon substituent in chiral imides such as (−)-**13** and (−)-**17** exerts impressive control of the regiochemistry of subsequent reactions of the imide function. For example, completely regioselective reduction of these compounds was possible using DIBAL in CH_2Cl_2 at −78 °C to give **29** and **30**, which could be further reduced to **16** (88%) and **9** (83%), respectively, using Et_3SiH and Me_3SiOTf.[14]

Similarly, regioselective thionation to give **31** and **32** was possible using Lawesson's reagent,[15] and again no minor regioisomers could be detected. Although we have not checked the ee of these lactam and thioimide products they should correspond to the initial values achieved in the chiral base reactions.

In conclusion, we have demonstrated the unexpectedly wide scope of bridgehead substitution via lithium amide metalation of carbonyl compounds having relatively short bridges. The chiral lithium amide mediated desymmetrizations of *meso*-imide substrates further adds to the repertoire of these versatile reagents, and enables highly enantioselective access to certain bridged imides and lactams. Further explorations of the scope and limitations of such bridgehead metalations are ongoing, along with applications to bioactive target molecules.

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Supporting Information Available: Typical procedures for metalations, NMR data for all compounds, and HPLC data for ee determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For previous chiral base desymmetrisation of imides, see: (a) Adams, D. J.; Blake, A. J.; Cooke, P. A.; Gill, C. D.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4603. (b) Greenhalgh, D. A.; Simpkins, N. S. *Synlett* **2002**, 2074.

(11) The absolute configurations of the chiral silylimides **13** and **17** were determined by X-ray crystallography and the *C*-alkylated compounds are assumed to belong to the same enantiomeric series; full details will be published elsewhere.

(12) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391.

(13) At this time, it is not clear why this procedure is required, and we have been unable to satisfactorily monitor the course of the metalations using deuterium-quenching experiments.

(14) For contributions to the area of regioselective imide reduction, see: (a) Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(15) Milewska, M. J.; Gdaniec, M.; Polonski, T. *J. Org. Chem.* **1997**, *62*, 1860.