ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Asymmetric Lithiation Trapping of *N*-Boc Heterocycles at Temperatures above −78 °C

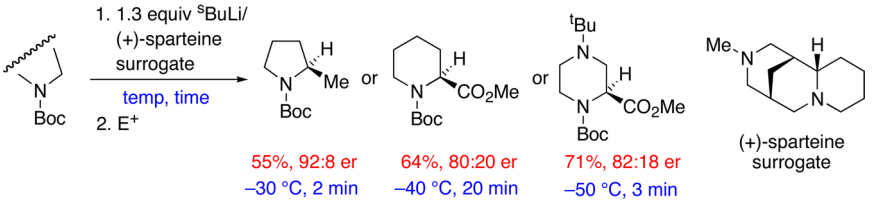
Giacomo Gelardi,[†] Graeme Barker,[†] Peter O'Brien,*[,†] and David C. Blakemore[‡]

Department of Chemistry, University of York, Heslington, York YO10 5DD, U. K., and Neusentis Chemistry, Pfizer Worldwide Research and Development, The Portway Building, Granta Park, Cambridge CB21 6GS, U. K.

peter.obrien@york.ac.uk

Received August 21, 2013

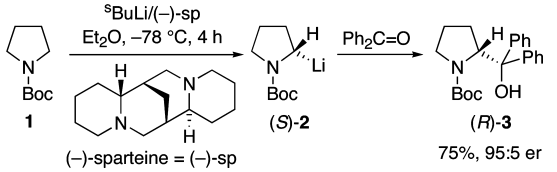
ABSTRACT



The asymmetric lithiation trapping of *N*-Boc heterocycles using *s*-BuLi/chiral diamines at temperatures up to −20 °C is reported. Depending on the *N*-Boc heterocycle, lithiation is accomplished using *s*-BuLi and (−)-sparteine or the (+)-sparteine surrogate in the temperature range −50 to −20 °C for short reaction times (2−20 min). Subsequent electrophilic trapping or transmetalation−Negishi coupling delivered functionalized *N*-Boc heterocycles in 47−95% yield and 77:23−93:7 er. With *N*-Boc pyrrolidine, trapped products can be generated in ∼90:10 er even at −20 °C.

In 1991, Kerrick and Beak reported the first example of the asymmetric α-lithiation and electrophilic trapping of a *N*-Boc heterocycle.[1] Full details were subsequently disclosed in 1994.[2] The methodology was successful for *N*-Boc pyrrolidine **1** and utilized a chiral base comprising *s*-BuLi and (−)-sparteine. A typical example (**1** → (*S*)-**2** → (*R*)-**3** of 95:5 er) is shown in Scheme 1. These types of asymmetric lithiation-trapping reactions are normally conducted at −78 °C for several hours and proceed *via* a configurationally stable lithiated *N*-Boc heterocycle (e.g., (*S*)-**2**). Beak's approach has been extended to a wide range of *N*-Boc heterocycles including piperidine[3,4] and a piperazine.[5] Furthermore, the asymmetric lithiation of *N*-Boc pyrrolidine **1** has been carried out on the kg-scale by researchers at Merck.[6] The use of a reaction temperature of −78 °C for several hours presents a considerable energy cost for multikilogram-scale reactions.[7] A temperature of −20 °C is preferred for process-scale chemistry, as a specialist low-temperature setup is not required. Thus, we asked ourselves the question: is it possible to carry out Beak's α-lithiation-trapping of *N*-Boc heterocycles with high enantioselectivity at temperatures above −78 °C?

Scheme 1. Beak's Asymmetric Lithiation Trapping of *N*-Boc Pyrrolidine **1** Using *s*-BuLi/(−)-Sparteine at −78 °C



In considering this question, we noted two observations from our previous work. In 2010, we disclosed a "high" temperature (−30 °C) *racemic* lithiation trapping of *N*-Boc heterocycles which utilized *s*-BuLi/THF as the reactive base, a protocol which we refer to as "diamine-free".[8]

[†] University of York.
[‡] Neusentis Chemistry, Pfizer.

(1) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.
(2) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
(3) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889.
(4) (a) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260. (b) Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2113.
(5) McDermott, B. P.; Campbell, A. D.; Ertan, A. *Synlett* **2008**, 875.
(6) Klapars, A.; Campos, K. R.; Waldman, J. H.; Zewge, D.; Dormer, P. G.; Chen, C.-y. *J. Org. Chem.* **2008**, *73*, 4986.
(7) Bennie, L. S.; Kerr, W. J.; Middleditch, M. J.; Watson, A. J. B. *Chem. Commun.* **2011**, *47*, 2264.

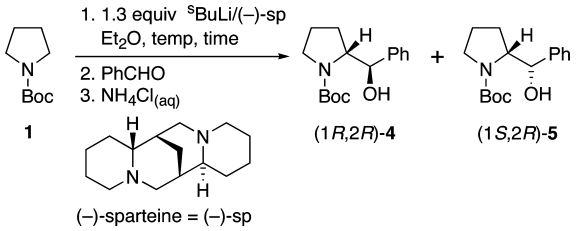
10.1021/ol402395j

At −30 °C, successful reactions required lithiation times with *s*-BuLi/THF of only 5 or 10 min. Subsequently, in 2011, we used *in situ* IR spectroscopic monitoring of the lithiation step to show that the lithiation of *N*-Boc pyrrolidine **1** with *s*-BuLi/(−)-sparteine in Et_2O at −78 °C was complete within 1 h.[9] Hence, with a view to developing a more energy efficient and sustainable asymmetric version of Beak's α-lithiation-trapping of *N*-Boc heterocycles, we decided to explore "high" temperatures (between 0 and −40 °C) and short reaction times (< 1 h). Our aim was to identify the highest temperature for an asymmetric lithiation reaction of ≥80:20 er. This study focused on pyrrolidine, piperidine, and a piperazine due to their prevalence in blockbuster pharmaceuticals.

The four most important issues to consider as the reaction temperature for α-lithiation trapping of *N*-Boc heterocycles is raised above −78 °C are as follows: (i) the time taken for complete lithiation which should be reduced at higher temperatures; (ii) the chemical stability of the lithiated *N*-Boc heterocycle which may be compromised at higher temperatures; (iii) the enantioselectivity (i.e., the kinetic selectivity due to the interaction of the *s*-BuLi/chiral diamine with the *N*-Boc heterocycle) which will be a function of temperature; and (iv) the configurational stability of the intermediate lithiated *N*-Boc heterocycle (e.g., (*S*)-**2**) which will almost certainly be reduced at higher temperatures.[10] Each of these factors could be different for different *N*-Boc heterocycles,[4] and we have previously noted important differences between (−)-sparteine and the (+)-sparteine surrogate.[4a,11,12] Issues (i) and (ii) will affect the yield of the reaction whereas issues (iii) and (iv) will impact the enantioselectivity.

To start with, we explored the "high" temperature lithiation of *N*-Boc pyrrolidine **1** using 1.3 equiv of *s*-BuLi/(−)-sparteine in Et_2O and trapping with benzaldehyde. This gave two known[13] diastereomeric products, (1*R*,2*R*)-**4** and (1*S*,2*R*)-**5**, which were separated and their ers determined using chiral stationary phase (CSP)-HPLC (Table 1). As previously reported, adducts (1*R*,2*R*)-**4** and (1*S*,2*R*)-**5** are each generated with 97:3 er at −78 °C, in 86% total yield (entry 1).[12] The yield and enantioselectivity at −40 °C were evaluated first using reaction times of 1 s, 2 min, 20 min, and 1 h. From these reactions, (1*R*,2*R*)-**4** and (1*S*,2*R*)-**5** were formed in 90:10−93:7 er and, apart from the 1 s reaction, in good total yield (79−87%) (entries 2−5). Clearly, a synthetically useful level of enantioselectivity (≥90:10 er) can be obtained at this elevated temperature of −40 °C. The 1 s reaction time was designed to provide information on the kinetic selectivity at a specific temperature (issue (iii)): with such a short lithiation time, the impact of any configurational instability of the lithiated *N*-Boc pyrrolidine (*S*)-**2** on the er of the trapped products should be minimized. In contrast, the 1 h lithiation time should allow reduction in er due to any configurational instability to be detected (issue (iv)). At −40 °C, the ers of (1*R*,2*R*)-**4** and (1*S*,2*R*)-**5** for a 1 s reaction time (entry 2) were essentially the same as those from the 1 h lithiation (entry 5) suggesting that the (−)-sparteine-complexed lithiated *N*-Boc pyrrolidine (*S*)-**2** is configurationally stable at −40 °C for 1 h. It is also notable that, at −40 °C, a high total yield (84%) can be obtained for lithiation trapping using *s*-BuLi/(−)-sparteine after just 2 min (entry 3). This represents a significant improvement on the 1 h required to attain complete lithiation of *N*-Boc pyrrolidine **1** at −78 °C.[9]

Table 1. Asymmetric Lithiation Trapping of *N*-Boc Pyrrolidine **1** Using *s*-BuLi/(−)-Sparteine at Temperatures above −78 °C



entry	temp/°C	time	yield (%), er of (1*R*,2*R*)-**4**[a]	yield (%), er of (1*S*,2*R*)-**5**[a]	total yield (%)[b]
1[c]	−78	3 h	63, 97:3	23, 97:3	86
2	−40	1 s	6, 92:8	4, 91:9	10[d]
3	−40	2 min	58, 93:7	26, 91:9	84
4	−40	20 min	58, 92:8	29, 92:8	87
5	−40	1 h	52, 92:8	27, 90:10	79
6	−30	1 s	12, 89:11	7, 89:11	19[e]
7	−30	2 min	58, 90:10	34, 89:11	92
8	−30	20 min	49, 88:12	28, 87:13	77
9	−30	1 h	42, 87:13	30, 84:16	72
10	−20	1 min	53, 86:14	33, 85:15	86
11	−20	2 min	51, 87:13	31, 85:15	82
12	−10	30 s	43, 80:20	29, 80:20	72
13	0	10 s	40, 75:25	27, 75:25	67
14	0	1 min	35, 65:35	25, 62:38	60

[a] Yield after purification by chromatography; Enantiomer ratio (er) determined by CSP-HPLC (see Supporting Information (SI)). [b] Total yield of (1*R*,2*R*)-**4** and (1*S*,2*R*)-**5** after purification by chromatography. [c] See ref 12. [d] 73% recovered starting material. [e] 51% recovered starting material.

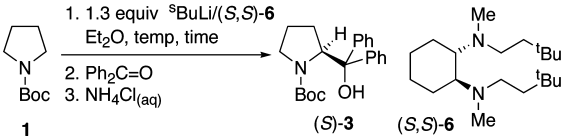
With interesting enantioselectivity at −40 °C, our attention switched to even higher temperatures. The results at −30 °C (1 s, 2 min, 20 min, and 1 h lithiation times) (entries 6−9) were similar to those at −40 °C. Reaction times of ≤20 min at −30 °C generated (1*R*,2*R*)-**4** and (1*S*,2*R*)-**5** in 87:13−90:10 er (entries 6−8). The slightly reduced enantioselectivity for a 1 h lithiation at −30 °C ((1*S*,2*R*)-**5** of 84:16 er, entry 9) suggests that configurational instability becomes an issue at −30 °C over extended times (≥1 h). At higher temperatures (−20, −10, or 0 °C), the enantioselectivity was more significantly eroded despite the use of short lithiation times (10 s to 2 min, entries 10−14).

(8) Barker, G.; O'Brien, P.; Campos, K. R. *Org. Lett.* **2010**, *12*, 4176.
(9) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P. *J. Org. Chem.* **2011**, *76*, 5936.
(10) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716.
(11) McGrath, M. J.; Bilke, J. L.; O'Brien, P. *Chem. Commun.* **2006**, 2607.
(12) Carbone, G.; O'Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445.
(13) Bilke, J. L.; Moore, S. P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935.

The lower enantioselectivity at these higher temperatures is presumably due to a combination of reduced kinetic selectivity and a greater degree of configurational instability. Despite this, lithiation of *N*-Boc pyrrolidine **1** using *s*-BuLi/(−)-sparteine at 0 °C for just 10 s and subsequent trapping gave a total 67% yield of adducts (1*R*,2*R*)-**4** and (1*S*,2*R*)-**5**, each in 75:25 er (entry 13).

Next, the use of diamine (*S*,*S*)-**6**, which we have previously shown to be a useful (+)-sparteine surrogate,[14] was explored. With (*S*,*S*)-**6**, trapping with benzophenone was carried out to give (*S*)-**3** and reactions at −78, −40, and −30 °C were evaluated (Table 2). At −78 °C, an 82% yield of (*S*)-**3** of 95:5 er was obtained (entry 1). However, 1 s reactions at −40 and −30 °C led to a reduced enantioselectivity of 86:14 er and 80:20 er respectively (entries 2 and 4). This reduction in kinetic selectivity was far more pronounced than that seen with (−)-sparteine (Table 1). Synthetic reactions at −40 and −30 °C for 2 min gave (*S*)-**3** in 49% yield (86:14 er) and 45% yield (81:19 er) respectively (entries 3 and 5). Thus, no further work was carried out with diamine (*S*,*S*)-**6**.

Table 2. Asymmetric Lithiation Trapping of *N*-Boc Pyrrolidine **1** Using *s*-BuLi/Diamine (*S*,*S*)-**6** at Temperatures above −78 °C

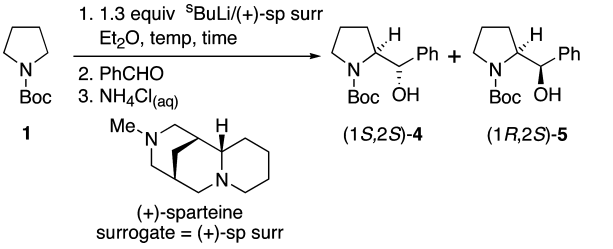


entry	temp/° C	time	yield of (*S*)-**3** (%)[a]	er of (*S*)-**3**[b]	yield of recov. **1** (%)[c]
1	−78	1 h	82	95:5	–
2	−40	1 s	15	86:14	50
3	−40	2 min	49	86:14	–
4	−30	1 s	14	80:20	55
5	−30	2 min	45	81:19	15

[a] Yield after purification by chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC (see SI). [c] Yield of recovered starting material **1** after purification by chromatography.

Much better results were obtained with the more "sparteine-like" (+)-sparteine surrogate.[15] Here, trapping with benzaldehyde was deployed, and the results with the (+)-sparteine surrogate (Table 3) were generally comparable to those obtained with (−)-sparteine (Table 1), but with the opposite sense of induction. At −78 °C, adducts (1*S*,2*S*)-**4** and (1*R*,2*S*)-**5** are generated with 95:5 er and 94:6 er respectively (81% total yield, entry 1).[12] Reaction times of 2 min at −40, −30, and −20 °C each gave (1*S*,2*S*)-**4** and (1*R*,2*S*)-**5** in ∼90:10 er, in good overall yields (73−95%) (entries 2, 4, and 6). The (+)-sparteine complexed lithiated *N*-Boc pyrrolidine (*R*)-**2** is configurationally stable over 1 h at −40 or −30 °C (entries 3 and 5). In contrast, at −20 °C for 1 h, adducts (1*S*,2*S*)-**4** and (1*R*,2*S*)-**5** are formed with <90:10 er due to partial configurational instability.[16] Leaving the lithiated *N*-Boc pyrrolidine (*S*)-**2** or (*R*)-**2** at −40 °C or higher temperatures for 1 h leads to a reduction in overall yield which is likely due to chemical instability of the organolithium (Table 1, compare entries 3/5 and 7/9; Table 2, compare entries 2/3, 4/5 and 6/7) (issue (ii)).

Table 3. Asymmetric Lithiation Trapping of *N*-Boc Pyrrolidine **1** Using *s*-BuLi/(+)-Sparteine Surrogate at Temperatures above −78 °C



entry	temp/ °C	time	yield (%), er of (1*S*,2*S*)-**4**[a]	yield (%), er of (1*R*,2*S*)-**5**[a]	total yield (%)[b]
1[c]	−78	3 h	58, 95:5	23, 94:6	81
2	−40	2 min	65, 90:10	30, 92:8	95
3	−40	1 h	46, 90:10	20, 91:9	66
4	−30	2 min	67, 90:10	27, 90:10	92
5	−30	1 h	41, 89:11	23, 90:10	64
6	−20	2 min	50, 89:11	23, 91:9	73
7	−20	1 h	40, 83:17	20, 85:15	60

[a] Yield after purification by chromatography; Enantiomer ratio (er) determined by CSP-HPLC (see SI). [b] Total yield of (1*S*,2*S*)-**4** and (1*R*,2*S*)-**5** after purification by chromatography. [c] See ref 12.

Based on the results in Tables 1 and 3, the best compromise of highest temperature, highest total yield, and ∼90:10 er for *N*-Boc pyrrolidine **1** was obtained using *s*-BuLi and (−)-sparteine or the (+)-sparteine surrogate at −30 °C for a 2 min lithiation time. Using these optimized conditions with the (+)-sparteine surrogate, C−C bond forming electrophiles were explored (Scheme 2). Direct trapping with benzophenone, dimethyl sulfate, and phenylisocyanate gave (*S*)-**3** (86:14 er), (*R*)-**7** (92:8 er), and (*S*)-**8** (89:11 er) respectively. Similarly, allylation (using a Li/Cu transmetalation protocol[17]) or Negishi coupling with bromobenzene (*via* Li/Zn/Pd transmetalation[6,8,9,18]) generated (*S*)-**9** (84:16 er) and (*S*)-**10** (92:8 er) respectively.

Extension of this "high" temperature asymmetric lithiation-trapping protocol to *N*-Boc piperidine and a *N*-Boc piperazine was then investigated. It is well-known that *N*-Boc piperidine **11** is harder to lithiate than *N*-Boc pyrrolidine **1**.[3,4] At −78 °C, the reactive *s*-BuLi/(+)-sparteine

(14) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.
(15) (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870. (b) O'Brien, P.; Wiberg, K. B.; Bailey, W. F.; Hermet, J.-P. R.; McGrath, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15480. (c) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789. (d) Dixon, A. J.; McGrath, M. J.; O'Brien, P. *Org. Synth.* **2006**, *83*, 141. (e) O'Brien, P. *Chem. Commun.* **2008**, 655.

(16) (a) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515. (b) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Patel, J. J.; Sanchez-Jiminez, G. *J. Am. Chem. Soc.* **2006**, *128*, 10943.
(17) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076.
(18) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538.

Scheme 2. Scope of the Asymmetric Lithiation Trapping of *N*-Boc Pyrrolidine **1** Using *s*-BuLi/(+)-Sparteine Surrogate at −30 °C

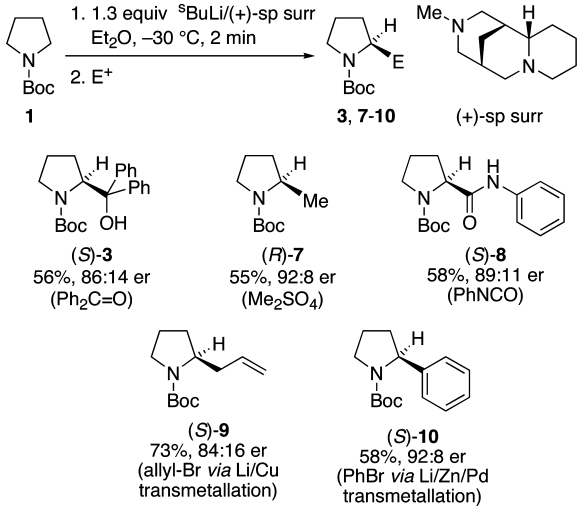
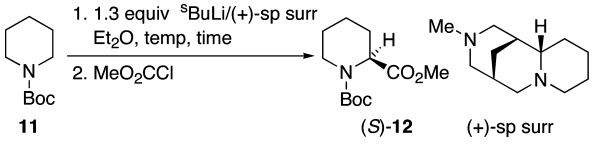


Table 4. Asymmetric Lithiation Trapping of *N*-Boc Piperidine **11** Using *s*-BuLi/(+)-Sparteine Surrogate at Temperatures above −78 °C



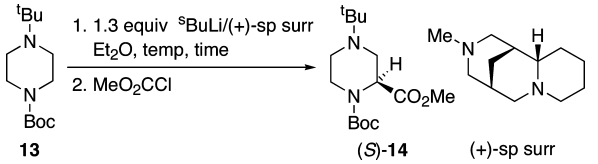
entry	temp/°C	time	yield of (*S*)-**12** (%)[a]	er of (*S*)-**12**[b]	yield of recov. **11** (%)[c]
1[d]	−78	6 h	78	88:12	–
2[d]	−78	3 h	83	87:13	–
3[d]	−78	1 h	24	86:14	–
4	−50	30 min	46	79:21	21
5	−40	20 min	64	80:20	15
6	−30	5 min	47	77:23	26

[a] Yield after purification by chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC (see SI). [c] Yield of recovered starting material **11** after purification by chromatography. [d] See ref 4.

complex is required to obtain satisfactory yields although a 3 h lithiation time is necessary (Table 4, entries 1−3).[4a] We therefore explored higher temperatures (−50 °C, −40 and −30 °C) and 5−30 min lithiation times (entries 4−6), trapping with methyl chloroformate to give (*S*)-**12**. At each temperature, lithiation using the *s*-BuLi/(+)-sparteine surrogate was not complete as judged by the isolation of some recovered starting material (15−26%). At −50 °C for 30 min and −40 °C for 20 min, satisfactory yields (46% and 64% respectively) of ester (*S*)-**12** of ~80:20 er were obtained (entries 4 and 5).

A similar set of results was obtained with *N*-Boc piperazine **13** using the *s*-BuLi/(+)-sparteine surrogate (Table 5). There is only one previous report on the

Table 5. Asymmetric Lithiation Trapping of *N*-Boc Piperazine **13** Using *s*-BuLi/(+)-Sparteine Surrogate at Temperatures above −78 °C



entry	temp/°C	time	yield of (*S*)-**14** (%)[a]	er of (*S*)-**14**[b]
1	−78	1 h	91	89:11
2	−50	3 min	71	82:18
3	−30	2 min	88	78:22

[a] Yield after purification by chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC (see SI).

asymmetric lithiation trapping of a *N*-Boc piperazine.[5] With the *s*-BuLi/(+)-sparteine surrogate at −78 °C (1 h lithiation time), ester (*S*)-**14** of 89:11 er was formed in 91% yield (entry 1). Higher temperatures (−50 and −30 °C) led to reduced enantioselectivity but good yields (even though lithiation times of only 3 and 2 min were used) (entries 2 and 3). The best enantioselectivity was achieved at −50 °C for 3 min: ester (*S*)-**14** of 82:18 er was generated in 71% yield (entry 2).

In conclusion, we have shown that asymmetric lithiation trapping of *N*-Boc heterocycles can be carried out using *s*-BuLi/chiral diamines at temperatures well above −78 °C. By using short lithiation times (2−30 min) and temperatures in the range −50 to −20 °C, trapped products can be obtained in respectable yields (47−95%) (issues (i) and (ii)) and with 77:23−93:7 er. At temperatures ≤ −30 °C and reaction times of 2−30 min, the reduction in er compared to the −78 °C reaction results appears to be due to a decrease in kinetic selectivity (issue (iii)) rather than due to configurational instability of the lithiated *N*-Boc heterocycle (issue (iv)). This work demonstrates that temperatures above −78 °C should be considered for any asymmetric lithiation reaction using *s*-BuLi and chiral diamines. Indeed, with *N*-Boc pyrrolidine **1**, use of a temperature of −30 °C delivers products in ~90:10 er which represents a considerable energy-saving for any proposed large-scale asymmetric lithiation trapping of this substrate.

Acknowledgment. We thank Pfizer, Merck, EPSRC, and the University of York for funding. We are grateful to James Firth (University of York) for assistance with the piperazine. This paper is dedicated to the memory of Robert (Bob) E. Gawley.

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

The authors declare no competing financial interest.