ORGANIC LETTERS

2010
Vol. 12, No. 18
4176−4179

Diamine-Free Lithiation−Trapping of *N*-Boc Heterocycles using *s*-BuLi in THF

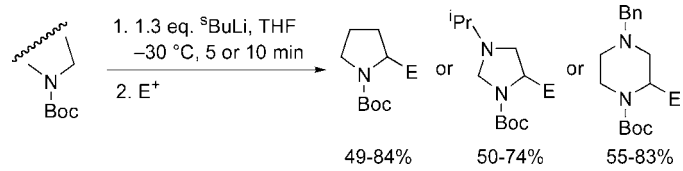
Graeme Barker,[†] Peter O'Brien,*[,†] and Kevin R. Campos[‡]

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K., and Department of Process Research, Merck Research Laboratories, Rahway, New Jersey 07065

paob1@york.ac.uk

Received July 30, 2010

ABSTRACT

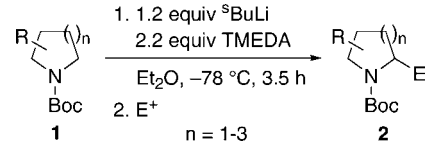


A diamine-free protocol for the *s*-BuLi-mediated lithiation−trapping of *N*-Boc heterocycles has been developed. In the optimized procedure, lithiation is accomplished using *s*-BuLi in THF at −30 °C for only 5 or 10 min. Subsequent electrophilic trapping or transmetalation−Negishi coupling delivered a range of functionalized pyrrolidines, imidazolidines, and piperazines in 43−83% yield.

In 1989, Beak and Lee described a simple and effective method for the α-functionalization of *N*-Boc heterocycles **1** → **2** *via* lithiation−trapping (Scheme 1).[1] The lithiation was accomplished using *s*-BuLi and TMEDA in Et_2O at −78 °C for 3.5 h, conditions that have become widely adopted for carrying out such α-functionalizations.[1,2] Indeed, recent examples in alkaloid natural product syntheses,[3] lithiation of *N*-Boc piperazines,[4] and synthesis of potential pharmaceuticals[5] have all made use of these standard lithiation conditions.

Recently, a key observation from our own work led us to consider whether a simpler protocol for the racemic lithiation of *N*-Boc heterocycles could be developed. In particular, we speculated that the diamine may not be required and that the lithiation could be successfully carried out at higher and more convenient temperatures over much shorter reaction times. In this paper, a simple and effective diamine-free lithiation of *N*-Boc heterocycles at −30 °C is presented.

Scheme 1. Lithiation−Trapping of *N*-Boc Heterocycles **1** Using *s*-BuLi/TMEDA in Et_2O



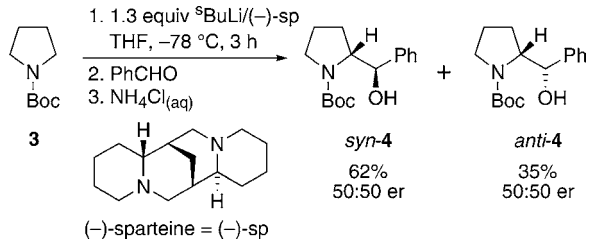
Our starting point in the development of a diamine-free lithiation protocol was an observation from an attempted asymmetric deprotonation using *s*-BuLi and (−)-sparteine in THF. Thus, lithiation of *N*-Boc pyrrolidine **3** using *s*-BuLi/(−)-sparteine in THF at −78 °C for 3 h and subsequent trapping with benzaldehyde delivered two separable diastereomeric hydroxy pyrrolidines *syn*-**4** (62% yield) and *anti*-**4** (35% yield) (Scheme 2). Not unexpectedly,[6] both *syn*-**4** and *anti*-**4** were formed in 50:50 er, a result which is most likely explained either by a lack of complexation of (−)-sparteine

[†] University of York.
[‡] Merck Research Laboratories.

(1) Beak, P.; Lee, W. K. *Tetrahedron Lett.* **1989**, *30*, 1197.
(2) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.
(3) (a) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3464. (b) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745.
(4) Berkheij, M.; van der Sluis, L.; Sewing, C.; den Boer, D. J.; Terpstra, J. W.; Hiemstra, H.; Iwema Bakker, W. I.; van den Hoogenband, A.; van Maarseveen, J. H. *Tetrahedron Lett.* **2005**, *46*, 2369.
(5) (a) Le Bourdonnec, B.; Goodman, A. J.; Graczyk, T. M.; Belanger, S.; Seida, P. R.; DeHaven, R. N.; Dolle, R. E. *J. Med. Chem.* **2006**, *49*, 7290. (b) Guillame, M.; Cuypers, J.; Dingenen, J. *Org. Process Res. Dev.* **2007**, *11*, 1079.

10.1021/ol1017799
Published on Web 08/18/2010

Scheme 2. Attempted Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine **3** Using *s*-BuLi/(−)-Sparteine in THF

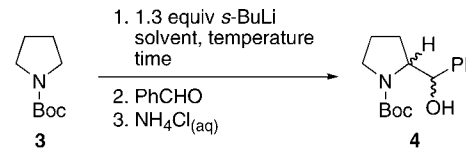


to *s*-BuLi in THF[7] or by a faster rate of lithiation of *N*-Boc pyrrolidine **3** by *s*-BuLi/THF compared to *s*-BuLi/(−)-sparteine. Either way, racemic adducts *syn*-**4** and *anti*-**4** (formed in a total yield of 97%) will presumably have been generated *via s*-BuLi/THF-mediated lithiation of **3**, suggesting that the diamine is not required. This result led us to investigate a diamine-free racemic lithiation protocol using *s*-BuLi in THF.

To start with, we used the lithiation−benzaldehyde trapping of *N*-Boc pyrrolidine **3** (using 1.3 equiv of *s*-BuLi) to optimize the solvent, temperature, and lithiation time (Table 1). The diastereomeric adducts *syn*-**4** and *anti*-**4** were isolated separately, but for ease of comparison of results, the combined % yield is presented in Table 1.[8] At −78 °C in Et_2O, lithiation of **3** using *s*-BuLi is slow, and adducts **4** were obtained in only 8% yield after a lithiation time of 60 min (entry 1). This result is consistent with the need for a ligand (such as TMEDA) to promote the *s*-BuLi-mediated lithiation in Et_2O.[1,2] In contrast, use of the more coordinating solvents THF and methyl-THF[9] under identical conditions (−78 °C, 60 min lithiation time) was far more successful: adducts **4** were obtained in 89% and 92% yields, respectively (entries 2 and 3). Our initial objective was to determine whether high yielding lithiation could be maintained at higher temperatures and shorter reaction times.

At −40 °C with a lithiation time of 60 min, a set of results similar to those at −78 °C were obtained (entries 4−6). However, after lithiating for 60 min at −30 °C, adducts **4** were isolated (37% yield) only in THF (entries 7−9). As a result, our subsequent efforts focused on THF as the solvent, and much higher yields were obtained after lithiation times

Table 1. Optimization of the Diamine-Free Lithiation of *N*-Boc Pyrrolidine **3**

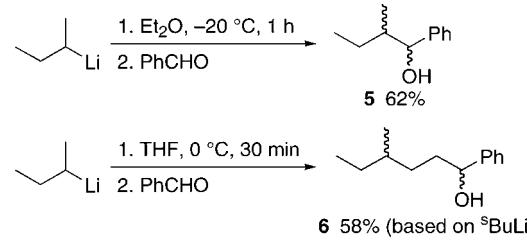


entry	solvent	temp (°C)	time (min)	yield (%)[a]
1	Et_2O	−78	60	8
2	THF	−78	60	89
3	methyl-THF	−78	60	92
4	Et_2O	−40	60	26
5	THF	−40	60	64
6	methyl-THF	−40	60	94
7	Et_2O	−30	60	0
8	THF	−30	60	37
9	methyl-THF	−30	60	0
10	THF	−30	10	89
11	THF	−30	5	84
12	methyl-THF	−30	5	73
13	THF	−20	30	10
14	THF	−20	5	66
15	THF	−20	2	57
16	THF	−10	5	29
17	THF	−10	1	0
18	THF	0	30	0

[a] Combined total yield of *syn*-**4** and *anti*-**4** after purification by column chromatography.

of only 10 min (89% yield, entry 10) or 5 min (84% yield, entry 11). These lithiation conditions (−30 °C, THF or methyl-THF, 5 or 10 min) proved optimal. At temperatures above −30 °C, yields of adducts **4** ranged from 0 to 66% (entries 13−18), and lower yields were generally obtained for longer lithiation times at a particular temperature. From this, we conclude that, at temperatures above −30 °C, some of the *s*-BuLi is consumed by reaction with THF.[10] To probe the *s*-BuLi-mediated decomposition of THF and Et_2O, we carried out the experiments summarized in Scheme 3. Thus,

Scheme 3. Investigation of the *s*-BuLi-Mediated Decomposition of Et_2O and THF



combining *s*-BuLi in Et_2O at −78 °C for 60 min and then adding benzaldehyde led to a 62% yield of a 50:50 mixture

(6) For examples of low enantioselectivity of organolithium/(−)-sparteine-mediated reactions in THF, see: (a) Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158. (b) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715. (c) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (d) Bertini Gross, K. M.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679. (e) Pakulski, Z.; Koprowski, M.; Pietrusiewicz, K. M. *Tetrahedron* **2003**, *59*, 8219. (f) Kessar, S. V.; Singh, P.; Nain Singh, K.; Venugopalan, P.; Kaur, A.; Bharatam, P. V.; Sharma, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 4506. (g) Huang, J.; O'Brien, P. *Chem. Commun.* **2005**, 5696.

(7) Sott, R.; Håkansson, M.; Hilmersson, G. *Organometallics* **2006**, *25*, 6047.

(8) In all cases, the diastereoselectivity was ∼75:25 *syn*-**4**:*anti*-**4** (as determined by ^{1}H NMR spectroscopy of the crude product). The isolated yield of *syn*-**4** and *anti*-**4** obtained after chromatography is provided in the Supporting Information.

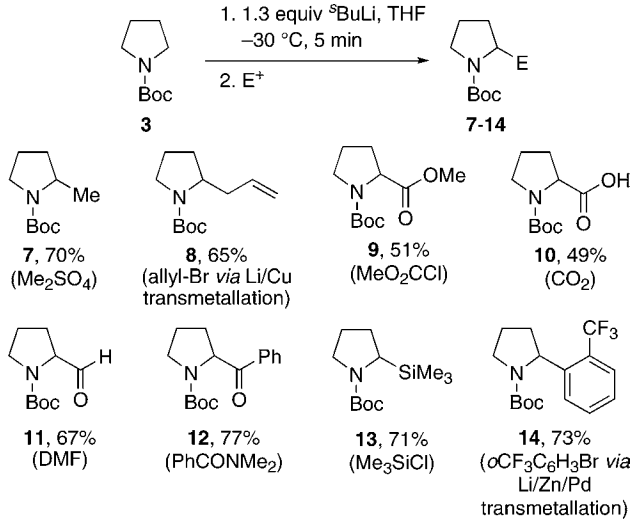
(9) Methyl-THF is an attractive alternative solvent to THF since it is produced from renewable resources. Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11*, 156.

(10) (a) Gilman, H.; Gaj, B. J. *J. Org. Chem.* **1957**, *22*, 1165. (b) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833.

of diastereomeric alcohols **5**. Clearly, there was no noticeable reaction of the *s*-BuLi with Et_2O and direct nucleophilic addition of *s*-BuLi ensued. In contrast, a similar experiment in THF at 0 °C for 30 min gave a 50:50 diastereomeric mixture of homologated alcohols **6** (58% yield from *s*-BuLi since 2 equiv are used up in generating **6**). Such homologated adducts result from α-lithiation of THF, subsequent decomposition of lithiated THF to give a lithium enolate and ethene,[11] carbolithiation of ethene by *s*-BuLi to give a homologated organolithium reagent,[12] and eventual addition of this primary organolithium to benzaldehyde.

Ultimately, we selected 1.3 equiv of *s*-BuLi in THF at −30 °C for 5 min for the lithiation of *N*-Boc pyrrolidine **3** and trapped with a range of electrophiles, focusing predominantly on C−C bond-forming reactions. The results are presented in Scheme 4. Methylation (using Me_2SO_4) and allylation (using

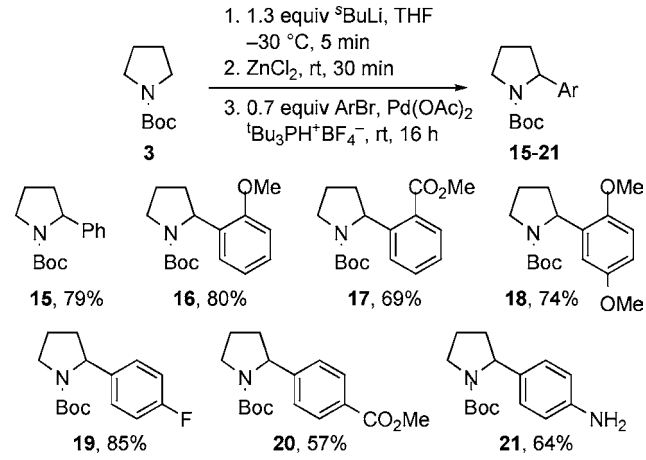
Scheme 4. Lithiation−Trapping of *N*-Boc Pyrrolidine **3** Using *s*-BuLi/THF at −30 °C for 5 min



allyl bromide with transmetalation to the cuprate[13]) proceeded smoothly to give **7** (70% yield) and **8** (65% yield), respectively. Reaction with MeO_2CCl gave **9** in only 51% yield as the product reacted further to give the α,α-disubstituted pyrrolidine (18% yield).[14] Reaction with carbon dioxide gave a 49% yield of adduct **10**. We successfully introduced aldehyde and ketone functionality (→ **11** and **12**) *via* reaction with DMF and $PhCONMe_2$, respectively. Silylation using Me_3SiCl was similarly high-yielding. Finally, arylated pyrrolidine **14** was synthesized in 73% yield *via* a transmetalation−Negishi coupling protocol.[15]

The lithiation−transmetalation−Negishi coupling process was further extended to synthesize the seven arylated pyrrolidines **15**−**21** (Scheme 5). For this, the racemic

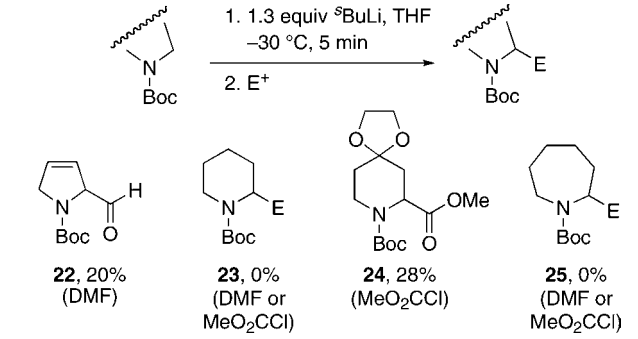
Scheme 5. Lithiation−Transmetallation−Negishi Coupling of *N*-Boc Pyrrolidine **3**



lithiated pyrrolidine was prepared using the standard lithiation protocol (**3**, 1.3 equiv of *s*-BuLi, THF, −30 °C, 5 min). Then, transmetalation to an organozinc reagent was accomplished using $ZnCl_2$ to give a stock solution. Aliquots (equivalent to 1.0 mmol) of the stock solution were used in seven parallel Negishi coupling reactions.[15a] After workup and purification, arylated pyrrolidines **15**−**21** were obtained in 57−85% yields (Scheme 5).

Next, the scope of the racemic lithiation protocol was explored with other *N*-Boc heterocycles (Scheme 6). Using

Scheme 6. Lithiation-Trapping of *N*-Boc Heterocycles Using *s*-BuLi/THF at −30 °C for 5 min



N-Boc 3-pyrroline, our best result was using lithiation−DMF trapping: aldehyde **22** was obtained in a disappointing 20% yield. Unfortunately, we have been unable to apply the *s*-BuLi/THF-mediated lithiation−trapping to *N*-Boc piperidine and *N*-Boc azepine. In both cases, trapped adducts were not detected using a wide range of conditions (e.g., −78 °C for 3 or 6 h; −40 °C for 1 or 3 h; −30 °C for 5 min) and

(11) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560.

(12) Bartlett, P. D.; Friedman, S.; Stiles, M. *J. Am. Chem. Soc.* **1953**, *75*, 1771.

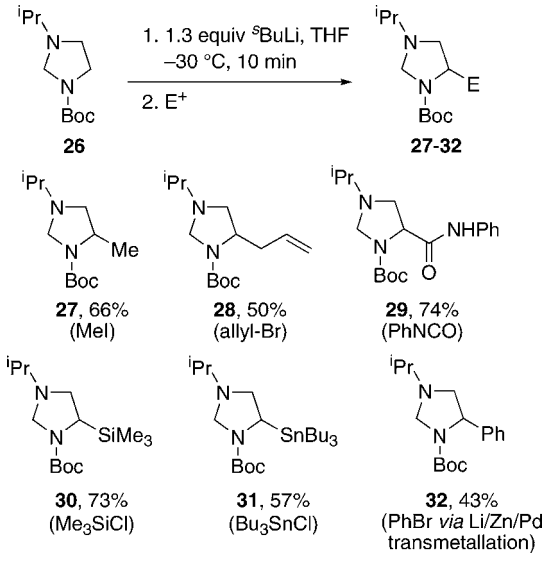
(13) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076.

(14) The formation of the α,α-disubstituted pyrrolidine indicates that enolization of **9** by *s*-BuLi is faster than reaction of *s*-BuLi with MeO_2CCl. Use of 2.6 equiv of *s*-BuLi/3.0 equiv of MeO_2CCl gave a 76% yield of the α,α-disubstituted pyrrolidine (see Supporting Information).

different electrophiles (DMF or MeO_2CCl). In one piperidine example, we obtained a 28% yield of ester **24** from the corresponding acetal-protected *N*-Boc piperidine. The lower reactivity of *N*-Boc piperidine and *N*-Boc azepine toward lithiation has been noted previously.[16,17]

We had better success with *N*-Boc imidazolidine **26** and *N*-Boc piperazine **33** both of which are more active substrates toward α-lithiation. The lithiation−trapping of *N*-Boc imidazolidine **26** using *s*-BuLi in THF at −78 °C for 1 h was reported by Coldham and co-workers.[18] However, yields were limited to 32−50%, and the authors proposed that, in this unsymmetrical *N*-Boc heterocycle, rotamer interconversion *via* rotation about the N−CO bond is very slow at −78 °C and only one rotamer underwent lithiation. We considered that better yields of substituted imidazolidines might be possible at higher temperatures where rotamer interconversion could be facilitated. In the end, it was found that lithiation using 1.3 equiv of *s*-BuLi in THF at −30 °C for 10 min worked well and, after trapping, delivered substituted *N*-Boc imidazolidines **27**−**32** in 43−75% yields (Scheme 7). Notably, yields in excess of 50% were obtained using

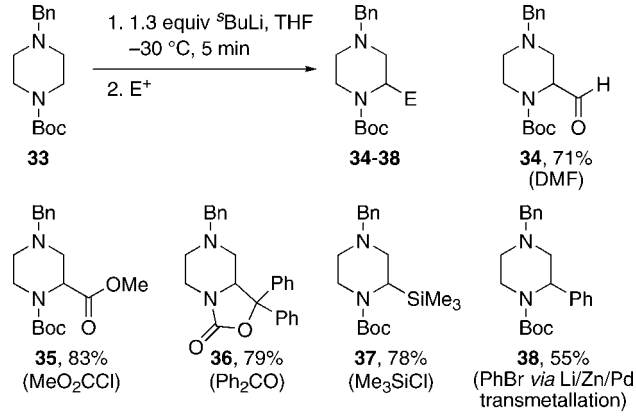
Scheme 7. Lithiation-Trapping of *N*-Boc Imidazolidine **26** Using *s*-BuLi/THF at −30 °C for 10 min



most of the electrophiles. We also carried out the first example of a lithiation−transmetalation−Negishi coupling with *N*-Boc imidazolidine **26**: arylated imidazolidine **32** was obtained in a moderate 43% yield.[19]

Finally, we carried out the *s*-BuLi/THF-mediated lithiation of *N*-Boc piperazine **33**. Lithiation−trapping of *N*-Boc piperazines using *s*-BuLi/TMEDA in Et_2O has been described by van den Hoogenband and van Maarseveen et al.[4] and Coldham et al.[20] Using *s*-BuLi in THF at −30 °C for 5 min, we obtained 71−83% yields of adducts **34**−**37** trapping with DMF, MeO_2CCl, benzophenone, and Me_3SiCl (Scheme 8). A Negishi coupling was also accomplished: arylated piperazine **38** was formed in 55% yield.[19]

Scheme 8. Lithiation-Trapping of *N*-Boc Piperazine **33** Using *s*-BuLi/THF at −30 °C for 5 min



In summary, we report the scope and limitations of a new diamine-free protocol for the racemic lithiation−trapping of *N*-Boc heterocycles. The optimized procedure uses 1.3 equiv of *s*-BuLi in THF at −30 °C for only 5 min (for *N*-Boc pyrrolidine **3** and *N*-Boc piperazine **33**) or 10 min (for *N*-Boc imidazolidine **26**). Examples with a wide range of electrophiles have been included in our study. Although our method is not suitable for less reactive substrates such as *N*-Boc piperidine and *N*-Boc azepine, it is a convenient method for the racemic lithiation−trapping of *N*-Boc pyrrolidine **3**, *N*-Boc imidazolidine **26**, and *N*-Boc piperazine **33**.

Acknowledgment. We thank the EPSRC for a DTA award (to G.B.) and Merck for funding.

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

OL1017799

(15) (a) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (b) Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923.

(16) (a) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889. (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. (c) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260.

(17) Coldham, I.; Raimbault, S.; Whittaker, D. T. E.; Chovatia, P. T.; Leonori, D.; Patel, J. J.; Sheikh, N. S. *Chem.—Eur. J.* **2010**, *16*, 4082.

(18) (a) Ashweek, N. J.; Coldham, I.; Haxell, T. F. N.; Howard, S. *Org. Biomol. Chem.* **2003**, *1*, 1532. (b) Coldham, I.; Copley, R. C. B.; Haxell, T. F. N.; Howard, S. *Org. Lett.* **2001**, *3*, 3799.

(19) With **26** and **33**, the Negishi coupling step required 16 h at reflux.

(20) Robinson, S. P.; Sheikh, N. S.; Baxter, C. A.; Coldham, I. *Tetrahedron Lett.* **2010**, *51*, 3642.