Tetrahedron Letters 50 (2009) 1105–1109

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient synthetic route to substituted tetrahydropyrimidines by $Cu(OTf)_2$-mediated nucleophilic ring-opening followed by the [4+2] cycloaddition of *N*-tosylazetidines with nitriles

Manas K. Ghorai *, Kalpataru Das, Amit Kumar

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

ARTICLE INFO

Article history:
Received 8 November 2008
Revised 2 December 2008
Accepted 4 December 2008
Available online 13 December 2008

Keywords:
Azetidine
[4+2] cycloaddition
$Cu(OTf)_2$
S_N2
Tetrahydropyrimidine
1,3-Diamine

ABSTRACT

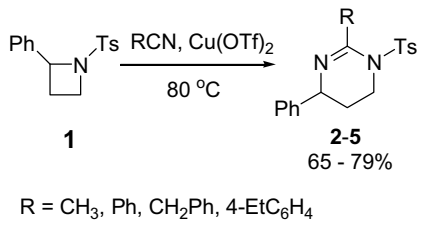
A highly efficient strategy for $Cu(OTf)_2$-mediated S_N2 type nucleophilic ring-opening followed by the [4+2] cycloaddition reactions of a number of 2-aryl-*N*-tosylazetidines with nitriles to afford a variety of substituted tetrahydropyrimidines in excellent yields is reported. The resulting tetrahydropyrimidines could easily be transformed into synthetically important 1,3-diamines by acid-catalyzed hydrolysis. The strategy has been extended to the synthesis of enantiomerically pure tetrahydropyrimidines from enantiopure disubstituted azetidines. The reaction proceeds through an S_N2 type mechanism as proposed by us earlier.

Small-ring aza-heterocycles are valuable building blocks in organic synthesis.[1] Cycloaddition reactions of four-membered aza-heterocycles with various dipolarophiles are of contemporary interest due to the potential biological activities of the resulting heterocycles.[2] There are only a few successful reports for the cycloaddition of azetidines with different dipolarophiles employing $BF_3{\cdot}OEt_2$ and a Pd(II)complex as the catalysts.[3] We recently reported $Zn(OTf)_2$-mediated cycloaddition of 2-aryl-*N*-tosylazetidines with a variety of nitriles to synthesize substituted tetrahydropyrimidines.[4] However, the $Zn(OTf)_2$-mediated reaction was found to be sluggish especially with 2-aryl-*N*-tosylazetidines having electron-withdrawing substituents in the aryl ring compared to that of 2-phenyl-*N*-tosylazetidine. We have recently found $Cu(OTf)_2$ an efficient Lewis acid (LA) to effect the [4+2] cycloaddition of carbonyls with enantiopure 2-phenyl-*N*-tosylazetidine to give non-racemic oxazinanes in moderate to high enantiomeric excess.[5] Based on the experimental results, we proposed an alternative S_N2 type of mechanism for this transformation in contrast to the earlier proposed mechanism involving a 1,4-dipole.[3a–c] Similar results were obtained for the [3+2] cycloaddition of *N*-sulfonylaziridines with nitriles[6a] and carbonyls.[6b] $Cu(OTf)_2$ is an efficient catalyst in the organic synthesis for effecting several transformations, for example, oxidations of alkyl radicals,[7] aziridinations,[8] asymmetric conjugate additions,[9] asymmetric Mannich-type reactions,[10] oxidative couplings,[11] asymmetric Friedel–Craft reactions,[12] and cycloaddition reactions.[13] Moreover, $Cu(OTf)_2$ can easily be prepared by following a known method,[7] and can be handled in air for quick transfer. In continuation of our research activities in Lewis acid-mediated S_N2 type ring-opening of small-ring aza-heterocycles, we found $Cu(OTf)_2$ an efficient LA for the [4+2] cycloaddition reaction of *N*-tosylazetidine with nitriles.[14] We report, herein, $Cu(OTf)_2$-mediated S_N2 type nucleophilic ring-opening followed by [4+2] cycloaddition reactions of a number of 2-aryl-*N*-tosylazetidines with nitriles to afford a variety of substituted tetrahydropyrimidines in excellent yields.

We initially examined the cycloaddition of 2-phenyl-*N*-tosylazetidine **1** with acetonitrile as the solvent in the presence of $Cu(OTf)_2$. When **1** was treated with acetonitrile in the presence of 1.0 equiv of $Cu(OTf)_2$ at 80 °C, the corresponding tetrahydropyrimidine **2** was obtained in excellent yield within 10 mins.[15] The progress of the reaction was comparatively slow when the reaction was performed at lower temperatures, or by taking smaller amounts of LA. Under optimal conditions,[16] **1** was reacted with various nitriles (Scheme 1) to give the corresponding tetrahydropyrimidines **2–5** in good to excellent yields (Table 1). The reaction was studied with an equivalent amount of acetonitrile in DCM, THF, $CHCl_3$, and benzene as the solvent. In all these cases, azetidine **1** underwent a competitive ring-opening rearrangement to produce allylamine **6** as a byproduct with a poor yield of cycloaddition

* Corresponding author. Tel.: +91 512 2597518; fax: +91 512 2597436.
E-mail address: mkghorai@iitk.ac.in (M.K. Ghorai).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.035



Scheme 1. $Cu(OTf)_2$-mediated [4+2] cycloaddition of 2-aryl-*N*-tosylazetidine with nitriles.

product **2** as shown in Scheme 2. The $Cu(OTf)_2$-mediated rearrangement of 2-aryl-*N*-tosylazetidine leading to allylamine has been described in our earlier work.[17]

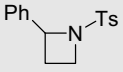
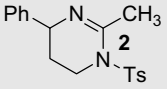
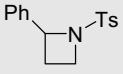
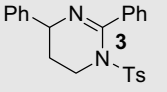
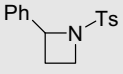
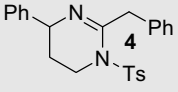
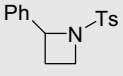
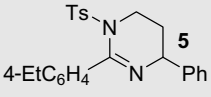
Further, to study the effect of the 2-aryl group on the $Cu(OTf)_2$-mediated [4+2] cycloaddition with nitriles, a number of azetidines **7**–**10** with different aryl groups were prepared following our reported procedure[4] and studied for a cycloaddition reaction with nitriles. Under optimal conditions, all azetidines underwent a smooth cycloaddition reaction with nitriles to give tetrahydropyrimidine derivatives **11**–**17**. The results are shown in Table 2. When 2-(4-methoxyphenyl)-1-(phenylsulfonyl)azetidine **10** (Table 2, entry 7) was reacted with benzonitrile under the same conditions, tetrahydropyrimidine derivative **17** was produced within 1 min or even at rt within 10 min. In contrast, 2-(3-bromophenyl)-1-tosylazetidine **9** (Table 2, entry 5) reacted with acetonitrile slowly under the same conditions to provide tetrahydropyrimidine **15** in 63% yield along with the corresponding allylamine (15%).

Although we have demonstrated earlier that the LA-mediated nucleophilic ring-opening of 2-phenyl-*N*-tosylazetidine follows an S_N2 pathway,[5] the mechanism of the cycloaddition reaction with nitriles was further investigated. Enantiomerically pure (*S*)-**1** was reacted with acetonitrile as the solvent in the presence of $Cu(OTf)_2$ at rt for 1 h to produce non-racemic tetrahydropyrimidine **2** in 38–40% ee with 10% isolated yield (95% brsm). When the reaction was continued for 4 h, **2** was obtained in 23% ee with 60% isolated yield indicating the decrease in ee of **2** with increasing time. These observations are in support of our earlier proposed mechanism for the cycloaddition reaction as shown in Scheme 3. $Cu(OTf)_2$ is coordinated to the nitrogen atom of heterocycle **18** and generates a highly reactive species **19**. Subsequently, it undergoes a [4+2] cycloaddition reaction with the nitrile to provide non-racemic tetrahydropyrimidine **22**. We rationalized the reduced enantioselectivity of **2** due to the partial racemization of (*S*)-**1** (through the interconversion of **19** and **21**) before the nucleophilic ring-opening step, as shown in Scheme 3. Convincing evidence to support this mechanistic proposal has been provided in our earlier work.[18]

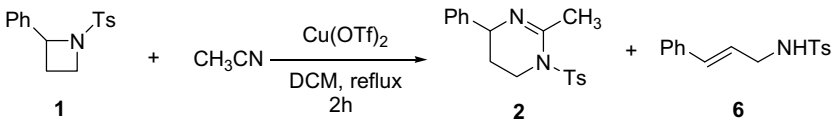
The cycloaddition products were found to be very labile, and gave hydrolyzed products 1,3-diamines under acidic conditions. Various tetrahydropyrimidines on treatment with 1(N) HCl produced corresponding 1,3-diamines **23**–**26** in good yields (Table 3).[19] 1,3-diamines are useful intermediates in organic synthesis.[20] Moreover, 1,3-diamines are important structural units present in a number of peptidomimetic inhibitors of the HIV-1 protease, used for the treatment of AIDS.[21]

The scope of the methodology was further extended for the cycloaddition of enantiomerically pure cis-disubstituted azetidines[22] **27a–b** with acetonitrile to give highly substituted enantiopure tetrahydropyrimidines **28a–b** and **29a–b** in 80% combined yield with 4,6-trans geometry (**28a–b**) as the major diastereomer in both the cases (Scheme 4). The diastereomers **28** and **29** were obtained in pure forms by simple column chromatography. The

Table 1
$Cu(OTf)_2$-mediated [4+2] cycloaddition of 2-phenyl-*N*-tosylazetidine with different nitriles[a]

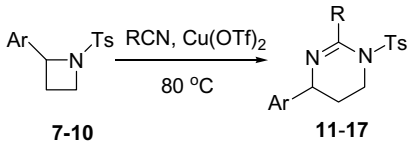
Entry	Azetidine	Nitrile	Product (**2**–**5**)	Time (min)	Yield[b] (%)
1		CH_3CN	 **2**	10	79 (95%)[c]
2		PhCN	 **3**	10	72
3		Ph CH_2CN	 **4**	10	68
4		4-EtC_6H_4CN	 **5**	10	65

[a] In all the cases nitrile was served as solvent.
[b] Isolated yield after column chromatographic purification.
[c] Yield was determined by ^1H NMR analysis of the crude reaction mixture.

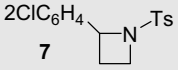
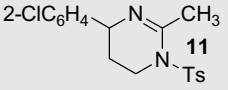
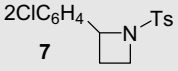
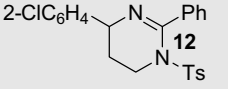
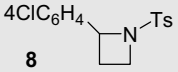
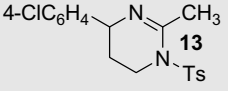
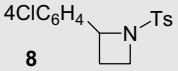
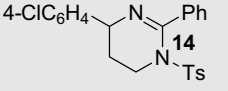
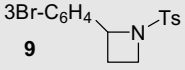
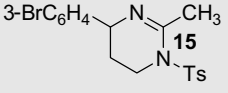
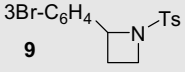
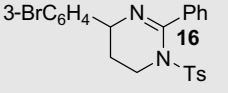
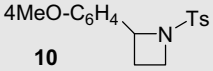
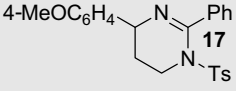


Scheme 2. Competitive ring-opening reaction of 2-phenyl-*N*-tosylazetidine with acetonitrile in DCM as a solvent.

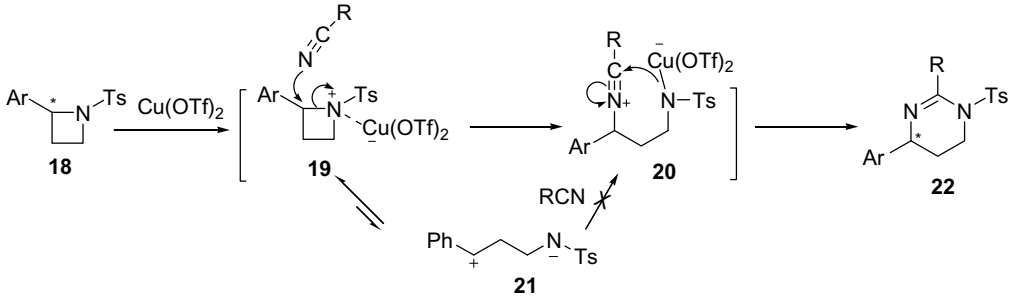
Table 2
$Cu(OTf)_2$-mediated [4+2] cycloaddition of 2-aryl-*N*-tosylazetidine with acetonitrile and benzonitrile[a]



7-10 **11-17**

Entry	Azetidine (**7–10**)	Nitrile	Product (**11–17**)	Time (min)	Yield[b] (%)
1	 **7**	CH_3CN	 **11**	30	68
2	 **7**	PhCN	 **12**	20	62
3	 **8**	CH_3CN	 **13**	10	72
4	 **8**	PhCN	 **14**	10	70
5	 **9**	CH_3CN	 **15**	180	63
6	 **9**	PhCN	 **16**	20	70
7	 **10**	PhCN	 **17**	10[c]	55

[a] In all the cases nitrile was served as solvent.
[b] Isolated yield after column chromatographic purification.
[c] Reaction was performed at rt.

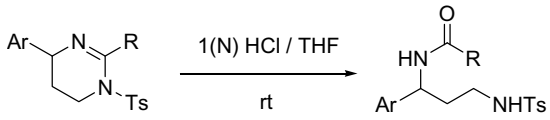


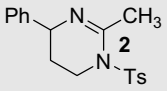
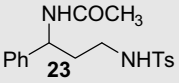
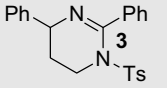
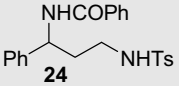
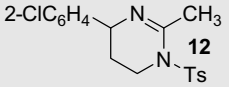
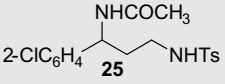
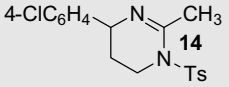
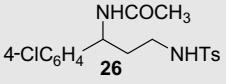
Scheme 3. Proposed mechanism for the [4+2] cycloaddition of 2-aryl-*N*-tosylazetidine with nitriles.

diastereomeric ratio was determined by the isolated yields of both the diastereomers (**28** and **29**) from column chromatography and ^1H NMR of the crude reaction mixture. The relative stereochemistry of the chiral substituted tetrahydropyrimidines (**28a** and **29a**) was determined by NOE measurements. The relative stereochemistry of the starting azetidines **27a–b** at C4 had been inverted in the major cycloaddition products (**28a–b**), which clearly supports the involvement of an S_N2 type pathway during a cycloaddition reaction.

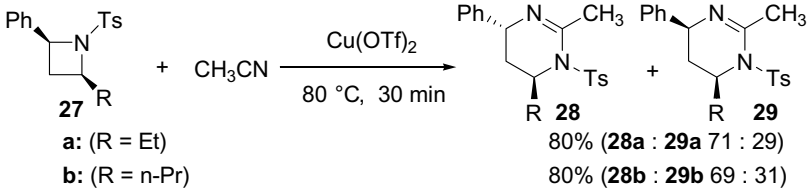
In conclusion, we have demonstrated a novel $Cu(OTf)_2$-mediated [4+2] cycloaddition of 2-aryl-*N*-tosyl azetidines with nitriles for a direct one-step synthesis of substituted tetrahydropyrimidines. The cycloaddition reaction proceeds through an S_N2 type pathway as we proposed earlier. The strategy has been extended for the synthesis of enantiomerically pure tetrahydropyrimidines. Acid-catalyzed hydrolysis of tetrahydropyrimidines leads to the formation of 1,3-diamines. Further synthetic and mechanistic investigations are currently underway in our laboratory.

Table 3
Hydrolysis of tetrahydropyrimidines with 1 (N) HCl



Entry	Tetrahydropyrimidine	Time (h)	Product	Yield[a] (%)
1		12		75
2		12		73
3		8		66
4		15		63

[a] Isolated yield after column chromatographic purification.



Scheme 4. Cycloaddition of 2,4-disubstituted-*N*-tosylazetidines with acetonitrile.

Acknowledgments

M.K.G. is grateful to IIT-Kanpur and DST, India for financial support. K.D. and A.K. thank IIT-Kanpur and CSIR, India, respectively, for research fellowships.

References and notes

1. (a) Davies, D. E.; Storr, R. C.. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon: Oxford, 1984; Vol. 7, Part 5, pp 237–284; (b) Moore, J. A.; Ayers, R. S. In *Chemistry of Heterocyclic Compounds—Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1983; pp 1–217. Part 2; (c) De Kimpe, N.. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Elsevier: Oxford, 1996; Vol. 1, Chapter 1.21, (d) Gribble, G. W.; Joule, J. A.. In *Progress in Heterocyclic Chemistry*; Elsevier: Oxford, 2004; Vol. 16. p 475.
2. (a) De Lucca, G. V.; Liang, J.; Aldrich, P. E.; Calabrese, J.; Cordova, B.; Klabe, R. M.; Rayner, M. M.; Chang, C. H. *J. Med. Chem.* **1997**, *40*, 1707–1719; (b) Messer, W. S., Jr.; Abuh, Y. F.; Liu, Y.; Periyasamy, S.; Ngur, D. O.; Edgar, M. A. N.; El-Assadi, A. A.; Sbeih, S.; Dunbar, P. G.; Roknich, S.; Rho, T.; Fang, Z.; Ojo, B.; Zhang, H.; Huzl, J. J., III; Nagy, P. I. *J. Med. Chem.* **1997**, *40*, 1230–1246; (c) Malin, G.; Iakobashvili, R.; Lapidot, A. *J. Biol. Chem.* **1999**, *274*, 6920–6929; (d) Jones, R. C. F.; Crockett, A. K. *Tetrahedron Lett.* **1993**, *34*, 7459–7462.
3. (a) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun.* **2001**, 958–959; (b) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Tetrahedron Lett.* **2001**, *42*, 6087–6091; (c) Prasad, B. A. B.; Bisai, A.; Singh, V. K. *Org. Lett.* **2004**, *6*, 4829–4831; (d) Yadav, V. K.; Sriramurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 16366–16367; (e) Baeg, J.-O.; Bensimon, C.; Alper, H. *J. Org. Chem.* **1995**, *60*, 253–256; (f) Baeg, J.-O.; Alper, H. *J. Org. Chem.* **1995**, *60*, 3092–3095.
4. Ghorai, M. K.; Das, K.; Kumar, A.; Das, A. *Tetrahedron Lett.* **2006**, *47*, 5393–5397.
5. Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 4373–4377.
6. (a) Ghorai, M. K.; Ghosh, K.; Das, K. *Tetrahedron Lett.* **2006**, *47*, 5399–5403; (b) Ghorai, M. K.; Ghosh, K. *Tetrahedron Lett.* **2007**, *48*, 3191–3195.
7. Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843–855.
8. Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742–2753.
9. Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362–13363.
10. Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507–2515.
11. Kobayashi, Y.; Taguchi, T.; Tokuno, E. *Tetrahedron Lett.* **1977**, *18*, 3741–3742.
12. Zhou, J.; Tang, Y. *Chem. Commun.* **2004**, 432–433.
13. Asao, A.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504–3506.
14. (a) Presented in 2nd J-NOST conference held in Jaipur, India during October 11–14, 2006.; (b) Part of the work is included in the Ph.D. thesis of Kalpataru Das (2007, IIT Kanpur, India).
15. After screening of several Lewis acids under optimized reaction conditions, $Cu(OTf)_2$ was found to be a better and more efficient catalyst to effect the reaction.
16. Representative experimental procedure: A mixture of 2-phenyl-*N*-tosylazetidine **1** (0.35 mmol) and acetonitrile (1 mL) was added to anhyd $Cu(OTf)_2$ (0.35 mmol) under argon and heated at 80 °C for 10 mins. TLC indicated complete consumption of the starting azetidine **1**. Then the reaction mixture was quenched with a saturated aq $NaHCO_3$ solution (1 mL) and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, filtered, and the solvent was removed under vacuum. The crude product was purified by flash column chromatography on deactivated silica gel (deactivated with 1% NEt_3) using ethyl acetate/petroleum ether to provide the corresponding tetrahydropyrimidine **2**. In cases where higher boiling nitriles were used, a modified purification method was followed. The reaction mixture was directly charged on a deactivated basic alumina column followed by washing with petroleum ether to remove and recover excess nitriles. Pure compounds were obtained using ethyl acetate/petroleum ether as eluent.
17. Ghorai, M. K.; Kumar, A.; Das, K. *Org. Lett.* **2007**, *9*, 5441–5444.
18. Ghorai, M. K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, *72*, 5859–5862.

19. *Experimental procedure of the hydrolysis of 2-methyl-4-phenyl-1-tosyl-1,4,5,6-tetrahydropyrimidine* (**2**): 1 (N) solution of HCl (0.34 mmol) was added to a solution of **2** (0.17 mmol) in THF (1 mL), and the mixture was stirred at rt overnight. Later, a saturated aq $NaHCO_3$ solution was added, and the aq layer was extracted with ethyl acetate (3×4.0 mL) and dried over anhyd Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) using 60% ethyl acetate in petroleum ether to provide the pure product **23**. *Characterization data of* **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79–1.97 (m, 2H), 1.89 (s, 3H), 2.33 (s, 3H), 2.71–2.79 (m, 1H), 3.01–3.09 (m, 1H), 4.91–4.97 (m, 1H), 5.81 (br s, 1H, NH), 6.02 (d, J = 7.8 Hz, 1H, NH), 7.11–7.26 (m, 7H), 7.66 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 23.0, 36.0, 40.1, 51.0, 126.5, 127.0, 127.9, 128.9, 129.6, 137.3, 140.7, 143.2, 170.7; HRMS (ES^+) for $C_{18}H_{23}N_2O_3S$ (M+H), calcd 347.1429; found 347.1427.

20. Ashweek, N. J.; Coldham, I.; Haxell, T. F. N.; Howard, S. *Org. Biomol. Chem.* **2003**, *1*, 1532–1544.
21. (a) Getman, D. P.; DeCrescenzo, G. A.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M. L.; Shieh, H.-S.; Stallings, W. C.; Stegeman, R. A. *J. Med. Chem.* **1993**, *36*, 288–291; (b) Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635–3645; (c) Reid, R. C.; March, D. R.; Dooley, M. J.; Bergman, D. A.; Abbenante, G.; Fairlie, D. P. *J. Am. Chem. Soc.* **1996**, *118*, 8511–8517; (d) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656–3664.
22. For the synthesis of *cis*-disubstituted azetidines **27a–b**: Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 2471–2475.