JOC Note
pubs.acs.org/joc

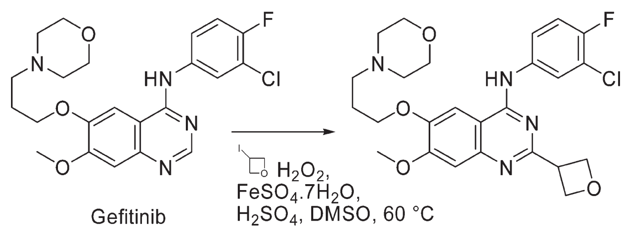
Preparation of Heteroaryloxetanes and Heteroarylazetidines by Use of a Minisci Reaction

Matthew A. J. Duncton,* M. Angels Estiarte, Russell J. Johnson, Matthew Cox, Donogh J. R. O'Mahony, William T. Edwards, and Michael G. Kelly

Evotec (USA), Two Corporate Drive, South San Francisco, California 94080

matthew.duncton@evotec.com; mattduncton@yahoo.com

Received May 20, 2009



Introduction of oxetan-3-yl and azetidin-3-yl groups into heteroaromatic bases was achieved by using a radical addition method (Minisci reaction). To demonstrate utility, the process was used to introduce an oxetane or azetidine into heteroaromatic systems that have found important uses in the drug discovery industry, such as the marketed EGFR inhibitor gefitinib, a quinolinecarbonitrile Src tyrosine kinase inhibitor, and the antimalarial hydroquinine.

The addition of carbon-centered radicals to heteroaromatic systems has a rich history dating from the late nineteenth century.[1a] However, the utility of these reactions in preparative organic chemistry has been a relatively recent development, after studies by Dou and Minisci demonstrated that yields may be improved by use of protonated heteroaromatic bases as reacting substrates (Figure 1).[1−3] As such, addition of a radical to a heteroaromatic base is now commonly referred to as a "Minisci reaction". Although the academic community has provided many impressive examples of both intermolecular[1,4] and intramolecular[1a,5] variants of Minisci reactions, its adoption by those working in industry has been somewhat less developed.[6] In part, this may be due to moderate conversion and regiochemical issues when examining intermolecular examples of the reaction (Figure 1).[1]

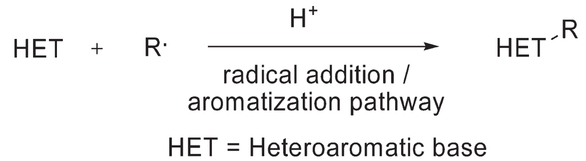


FIGURE 1. Minisci reaction with heteroaromatic bases.

Recently, we had reason to investigate the introduction of an oxetan-3-yl group into aryl and heteroaryl starting materials.[7] Our work was inspired by Rogers-Evans, Carreira, and co-workers, who showed that oxetanes are "promising modules in drug discovery", yielding impressive improvements in drug-like qualities when incorporated into a model substrate.[8] More recently, the same researchers have postulated that an oxetane can be a surrogate for a carbonyl group.[9] Unfortunately, there are few synthetic methods for

(1) For an excellent review on the addition of radicals to pyridines, quinolines, and isoquinolines, including an enlightening discussion on the historical development of these reactions, see: (a) Harrowven, D. C.; Sutton, B. J. *Prog. Heterocycl. Chem.* **2004**, *16*, 27–53. For other excellent reviews see also: (b) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489–519. (c) Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocycl. Chem.* **1990**, *27*, 79–96.

(2) (a) Dou, H. J. M.; Lynch, B. M. *Tetrahedron Lett.* **1965**, *6*, 897–901. (b) Dou, H. J. M. *Bull. Soc. Chim. Fr.* **1966**, 1678–1679. (c) Dou, H. J. M.; Lynch, B. M. *Bull. Soc. Chim. Fr.* **1966**, 3815–3820. (d) Dou, H. J. M.; Lynch, B. M. *Bull. Soc. Chim. Fr.* **1966**, 3820–3823. See also: (e) Lynch, B. M.; Chang, H. S. *Tetrahedron Lett.* **1964**, *5*, 2965–2968, for arylation of a postulated pyridinium or imidazolium intermediate with phenyl radicals.

(3) Minisci, F.; Galli, R.; Cecere, M.; Malatesta, V.; Caronna, T. *Tetrahedron Lett.* **1968**, *8*, 5609–5612.

(4) For applications of Minisci reactions to the field of medicinal chemistry from academic laboratories see: (a) Tadashi, M.; Sawada, S.; Nokata, K. *Heterocycles* **1981**, *16*, 1713–1717. (b) Martin, I.; Anvelt, J.; Vares, L.; Kuehn, I.; Claesson, A. *Acta Chem. Scand.* **1995**, *49*, 230–232. (c) Jain, R.; Cohen L. A.; El-Kadi, N. A.; King, M. M. *Tetrahedron* **1997**, *53*, 2365–2370. (d) Murthy, K. S. K.; Knaus, E. E. *Drug Dev. Res.* **1999**, *46*, 155–162. (e) Narayanan, S.; Vangapandu, S.; Jain, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1133–1136. (f) Naider, N. *J. Heterocycl. Chem.* **2002**, *39*, 511–521. (g) Du, W.; Kaskar, B.; Blumbergs, P.; Subramanian, P.-K.; Curran, D. P. *Bioorg. Med. Chem.* **2003**, *11*, 451–458. (h) Jain, R.; Vaitilingam, B.; Nayyar, A.; Palde, P. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1051–1054. (i) Kaur, N.; Lu, X.; Gershengorn, M. C.; Jain, R. *J. Med. Chem.* **2005**, *48*, 6162–6165. (j) Kaur, N.; Monga, V.; Lu, X.; Gershongorn, M. C.; Jain, R. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 433–443. (k) Nayyar, A.; Monga, P.; Malde, A.; Coutinho, E.; Jain, R. *Bioorg. Med. Chem.* **2007**, *15*, 626–640. (l) Palde, P. B.; McNaughton, B. R.; Ross, N. T.; Gareiss, P. C.; Mace, C. R.; Spitale, R. C.; Miller, B. L. *Synthesis* **2007**, 2287–2290. (m) Monga, V.; Meena, C. L.; Kaur, N.; Kumar, S.; Pawar, C.; Sharma, S. S.; Jain, R. *J. Heterocycl. Chem.* **2008**, *45*, 1603–1608.

(5) Bowman, R. W.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803–1822.

(6) For applications of Minisci reactions to the field of medicinal chemistry from industrial laboratories see: (a) Sawada, S.; Okijima, S.; Aiyama, R.; Nokata, K.; Furuta, T.; Yokokura, T.; Sugino, E.; Yamaguchi, K.; Miyasaka, T. *Chem. Pharm. Bull.* **1991**, *39*, 1446–1454. (b) Sawada, S.; Nokata, K.; Nagata, H.; Furuta, T.; Yokokura, T.; Miyasaka, T. *Chem. Pharm. Bull.* **1991**, *39*, 2574–2580. (c) Sawada, S.; Matsuoka, S.; Nokata, K.; Nagata, H.; Furuta, T.; Yokokura, T.; Miyasaka, T. *Chem. Pharm. Bull.* **1991**, *39*, 3183–3188. (d) Giannousis, P.; Carlson, J.; Leimer, M. *Process Chemistry in the Pharmaceutical Industry*; Gadamesetti, K. G., Ed.; Dekker: New York, 1999; pp 173−188. (e) Phillips, O. A.; Murthy, K. S. K.; Fiakpui, C. Y.; Knaus, E. E. *Can. J. Chem.* **1999**, *77*, 216–222. (f) Cowden, C. J. *Org. Lett.* **2003**, *5*, 4497–4499. (g) Uraguchi, A.; Yamamoto, K.; Ohtsuka, Y.; Tokuhisa, K.; Yamakawa, T. *Appl. Catal.* **2008**, *342*, 137–143.

(7) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. *Org. Lett.* **2008**, *10*, 3259–3262.

(8) Wuitchik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736–7739.

(9) Wuitchik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Marki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4512–4515.

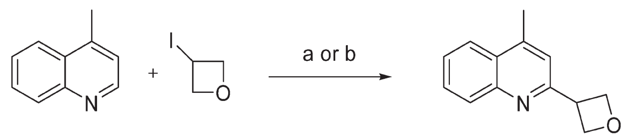
Published on Web 07/17/2009 DOI: 10.1021/jo9010624

the preparation of aryl- and heteroaryloxetanes. For example, methods of oxetan-3-yl formation have relied on the cyclization of 1,3-diols,[10] or the addition of an organometallic to oxetan-3-one, followed by reductive deoxygenation.[8] Our own research group recently addressed some of these limitations by showing that the parent oxetan-3-yl group can be introduced into certain benzenoid substructures, using an alkyl−aryl Suzuki coupling.[7] However, this method proved to be less useful when trying to introduce an oxetane into a heteroaromatic ring. We therefore sought an alternative procedure for such compounds, and were drawn to the possibility of using a radical-based approach. In this paper, we show that a Minisci reaction can be used to incorporate an oxetan-3-yl, or azetidin-3-yl group, into heteroaromatic bases in moderate yield. The reaction shows particular promise for functionalization of heterocyclic scaffolds that have found importance for the development of kinase inhibitors and antimalarials within the drug discovery industry. For example, an oxetane group was introduced into a lead quinolinecarbonitrile inhibitor of Src tyrosine kinase, the marketed EGFR inhibitor gefitinib (Iressa; AstraZeneca), and the antimalarial hydroquinine.

Our initial interest focused on the addition of an oxetane group into the heteroaromatic base lepidine. Since 3-iodooxetane was readily available, from both synthesis and commercial sources,[11] it was decided to use this building block as a starting material. An examination of the literature indicated that Minisci's conditions of H_2O_2 and catalytic $FeSO_4$ in DMSO could generate a secondary radical for addition into the protonated base.[12,13] Thus, these conditions were first investigated. As can be seen from Scheme 1, the use of H_2SO_4 as the acid component gave the best results (condition a). The use of trifluoroacetic acid, which has been utilized in many other Minisci-type transformations,[14] gave a low yield of the desired product (condition b). As expected, unreacted starting material was also isolated from the mixture.

Having settled on H_2SO_4 as the acid of choice, we began to examine the reaction using other heteroaromatic bases. As can be seen from Table 1, heteroaromatic bases such as quinoline, isoquinoline, pyridine, pyridazine, benzothiazole, benzimidazole, quinoxaline, quinazoline, and phthalazine could all be reacted smoothly to provide the oxetane product in low-to-moderate yield after purification. In some instances, hydrolysis products were observed when certain chloro- or ether-substituted substrates were employed (entries 10−12).

SCHEME 1. Introduction of the Oxetan-3-yl Group into Lepidine



[a]Reagents and conditions: (a) $FeSO_4 \cdot 7H_2O$, H_2O_2, H_2SO_4, DMSO, rt (40% desired product and ca. 15% mixture of desired product and recovered starting material). (b) $FeSO_4 \cdot 7H_2O$, H_2O_2, TFA, DMSO, rt (5% desired product and 65% recovered starting material).

Next, we examined the ability of the reaction to incorporate an azetidine group into select heteroaromatic bases (Table 2). Gratifyingly, the use of the standard conditions of H_2SO_4, H_2O_2, and $FeSO_4$ in DMSO gave rise to the desired product, with no evidence of Boc protecting group removal, even when the reactions were assisted with mild heating (entries 1−6).

To demonstrate further utility to the field of medicinal chemistry, we decided to incorporate an oxetane, or azetidine, into some pharmacologically active starting materials (Table 3). Thus, 6-methoxy-4-methylquinoline and hydroquinine were chosen as model substrates of antimalarials (entries 1−3). The reaction with hydroquinine is of special note, due to its complex molecular architecture. Also of significance was the use of quinolinecarbonitrile and quinazoline starting materials, as these heterocyclic bases have been critically important for the development of kinase inhibitors within medicinal chemistry (entries 3−5). For example, reactions with a quinolinecarbonitrile Src tyrosine kinase inhibitor[15] (entries 4 and 5) provided the desired oxetane and azetidine products in reasonably good yield (38% and 43%, respectively). A successful reaction with the marketed EGFR kinase inhibitor gefitinib[16] was also accomplished (entry 6).

The results in Tables 1−3 are significant as they demonstrate that an oxetane, or azetidine, can be incorporated into a wide variety of substrates, whose heterocyclic backbone is frequently encountered during medicinal chemistry programs. Although yields for the above transformations are modest, the method is powerful, affording unique products in a single step that could be difficult to obtain by alternative procedures. As such, the reaction conditions outlined in this paper should provide a useful starting point for those wishing to introduce an oxetane or azetidine into a heteroaromatic nucleus. Additionally, specific examples have not been optimized, so an improvement in yield may be possible with a thorough investigation of individual conditions. It should also be noted that many functional groups are compatible with the reaction conditions. Thus, protection and deprotection strategies are not usually required, and compounds with complex structures, or sensitive functionality,

(10) (a) Searles, S.; Hummel, D. G.; Nukina, S.; Throckmorten, P. E. *J. Am. Chem. Soc.* **1960**, *82*, 2928–2931. (b) Castro, B.; Selve, C. *Tetrahedron Lett.* **1973**, *14*, 4459–4460. (c) Picard, P.; Leclercq, D.; Bats, J. P.; Moulines, J. *Synthesis* **1981**, 550–551. (d) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 5210–5219. (e) Katritzky, A. R.; Fan, W.; Li, Q. *Youji Huaxue* **1988**, *8*, 53–57.

(11) For the studies detailed in this paper, 3-iodooxetane from commercial sources and material synthesized according to Clark et al. (Clark, S. L.; Polak, R. J.; Wojtowicz, J. A. US Patent 1966-557376, 1966; *Chem. Abstr.* **1970**, *73*, 35211) was used (see also ref 7 and the Supporting Information). For studies with 1-Boc-3-(iodo)azetidine, material from commercial sources was used.

(12) Minisci, F.; Vismara, E.; Fontana, F. *J. Org. Chem.* **1989**, *54*, 5224–5227.

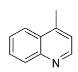
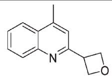
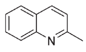
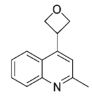
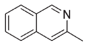
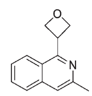
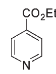
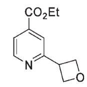
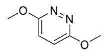
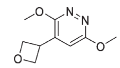
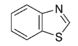
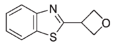
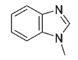
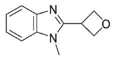
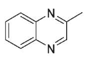
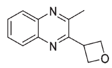
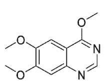
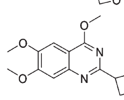
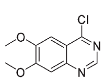
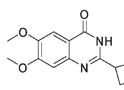
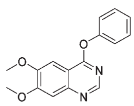
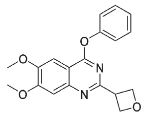
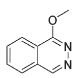
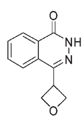
(13) A reviewer enquired whether oxetane itself could be used as a reactant, since other cyclic ethers have been used in Minisci reactions. However, such a reaction would most likely yield the oxetan-2-yl product. For a comparable reaction with THF see: Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* **1986**, *51*, 4411–4416. Nonetheless, the reviewer's suggestion is interesting, and should be explored further.

(14) (a) Fontana, F.; Minisci, F.; Vismara, E. *Tetrahedron Lett.* **1987**, *28*, 6373–6376. (b) Minisci, F.; Vismara, E.; Fontana, F.; Barbosa, M. C. N. *Tetrahedron Lett.* **1989**, *30*, 4569–4572. (c) Coppa, F.; Fontana, F.; Minisci, F.; Pianese, G.; Torotreto, P.; Zhao, L. *Tetrahedron Lett.* **1992**, *33*, 687–690.

(15) Boschelli, D. H.; Wang, Y. D.; Ye, F.; Wu, B.; Zhang, N.; Dutia, M.; Powell, D. W.; Wissner, A.; Arndt, K.; Weber, J. M.; Boschelli, F. *J. Med. Chem.* **2001**, *44*, 822–833.

(16) Barker, A. J.; Gibson, K. H.; Grundy, W.; Godfrey, A. A.; Barlow, J. J.; Healy, M. P.; Woodburn, J. R.; Ashton, S. E.; Curry, B. J.; Scarlett, L.; Henthorn, L.; Richards, L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1911–1914.

TABLE 1. Introduction of an Oxetane Group into Heterocyclic Bases

Entry	Starting material		Product		Yield[a]
1	**1a**		**2a**		40
2	**1b**		**2b**		32
3	**1c**		**2c**		46[b]
4	**1d**		**2d**		24[b]
5	**1e**		**2e**		22[c]
6	**1f**		**2f**		30
7	**1g**		**2g**		5[b,d]
8	**1h**		**2h**		22[c]
9	**1i**		**2i**		38[c]
10	**1j**		**2j**		36[c]
11	**1k**		**2k**		28[c,e]
12	**1l**		**2l**		34[c]

[a]Percentage yield of isolated product from reaction of heteroaromatic base (1 equiv) with 3-iodooxetane (2 equiv), $FeSO_4 \cdot 7H_2O$ (3 × 0.3 equiv), H_2O_2 (2 × 3 equiv), H_2SO_4 (2 equiv) in DMSO at room temperature. [b]Reaction performed at 40 °C. [c]Reaction performed at 60 °C. [d]Difficulties with product isolation encountered. [e]Compound **2k** (14% yield) and compound **2j** (14% yield).

can participate in the reaction. For example, starting materials containing an alkyl group, alcohol, ether, amine, aniline, nitrile, ester, carbamate, and arylhalide were all successfully employed in our studies.

The introduction of oxetane or azetidine groups into heterocyclic bases with pharmacological activity may be useful for a variety of reasons. For example, inclusion of a strategically placed oxetane may give rise to molecules with improved drug-like characteristics and, or, a reduced side-effect profile.[8] In the case of kinase inhibitors, the influence of an oxetane group can be assessed by kinome-wide screening.[17] As an extension, it is possible that other decorated heterocyclic bases possessing pharmacological activity could be functionalized, in an intermolecular fashion, using the reaction outlined in this paper, or related Minisci transformations. For example, previous studies have shown that many groups such as aryl,[1,2] alkyl[1] (including trifluoromethyl[6g] and perfluoroalkyl[18]), cycloakyl,[1] acyl,[19] aldehyde (including masked aldehyde),[20] carbamoyl,[21] α-alkoxymethyl,[22] and hydroxymethyl[23] may be incorporated into a multitude of heterocyclic bases. Related processes employing ketyl radicals (Emmert reaction)[24] and silyl radicals[4g] have also shown promising results. Understanding the scope and limitation of these reactions with functionalized substrates, such as those encountered in the "drug universe", would serve to increase the attractiveness of this important transformation.

In summary, this paper describes the incorporation of an oxetane and azetidine group into heteroaromatic bases using a radical-based (Minisci) approach. The reaction proceeds in low-to-moderate yield with a broad range of substrate. Of particular significance were successful transformations with chemotypes from antimalarial and kinase research. Future studies will focus on the introduction of an oxetane, azetidine, or other small saturated heterocycle into alternative bioactive molecules. Additionally, the use of different carbon-centered radicals should also be explored.

(17) Goldstein, D. M.; Gray, N. S.; Zarrinkar, P. P. *Nat. Rev. Drug Disc.* **2008**, *7*, 391–397.

(18) Antonietti, F.; Mele, A.; Minisci, F.; Punta, C.; Recupero, F.; Fontana, F. *J. Flourine Chem.* **2004**, *125*, 205–211.

(19) (a) Caronna, T.; Gardini, G. P.; Minisci, F. *J. Chem. Soc.* **1969**, 201. (b) Gardini, G. P.; Minisci, F. *J. Chem. Soc.* **1970**, 929. (c) Minsci, F.; Caronna, T.; Galli, R.; Malatesta, V. *J. Chem. Soc.* **1971**, 1747–1750. (d) Caronna, T.; Fronza, G.; Minisci, F.; Porta, O.; Gardini, G. P. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1477–1481. (e) Caronna, T.; Fronza, G.; Minisci, F.; Porta, O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2035–2038. (f) Fontana, F.; Minisci, F.; Nogueira, B. M. C.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866–2868. (g) Minisci, F.; Recupero, F.; Cecchetto, A.; Punta, C.; Gambarotti, C.; Fontana, F.; Pedulli, G. F. *J. Heterocycl. Chem.* **2003**, *40*, 325–328.

(20) (a) Gardini, G. P. *Tetrahedron Lett.* **1972**, *13*, 4113–4116. (b) Giordano, C.; Minisci, F.; Vismara, E.; Levi, S. *J. Org. Chem.* **1986**, *51*, 536–537.

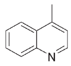
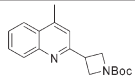
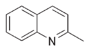
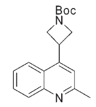
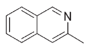
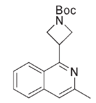
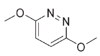
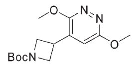
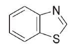
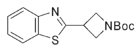
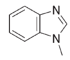
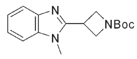
(21) (a) Minisci, F.; Gardini, G. P.; Galli, R.; Bertini, F. *Tetrahedron Lett.* **1970**, *11*, 15–16. (b) Gardini, G. P.; Minisci, F.; Palla, G.; Arnone, A.; Galli, R. *Tetrahedron Lett.* **1971**, *12*, 59–62. (c) Arnone, A.; Cecere, M.; Galli, R.; Minisci, F.; Perchinummo, M.; Porta, O.; Gardini, G. *Gazz. Chim. Ital.* **1973**, *103*, 13–29. (d) Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *J. Org. Chem.* **1984**, *49*, 3364–3367. (e) Coppa, F.; Fontana, F.; Lazzarini, E.; Minisci, F. *Heterocycles* **1993**, *36*, 2687–2696. (f) Minisci, F.; Recupero, F.; Punta, C.; Gambarotti, C.; Antonietti, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.* **2002**, 2496–2497.

(22) (a) Citterio, A.; Gentile, A.; Serravalle, M.; Tinucci, L.; Vismara, E. *J. Chem. Res. Synop.* **1982**, 272–273. (b) Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *J. Chem. Soc., Chem. Commun.* **1983**, 916–917. (c) Citterio, A.; Casucci, D.; Gentile, A.; Serravalle, M.; Venturra, S. *Gazz. Chim. Ital.* **1985**, *115*, 319–324. (d) Minisci, F.; Vasmara, E.; Romano, U. *Tetrahedron Lett.* **1985**, *26*, 4803–4806. (e) Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* **1985**, *41*, 4157–4170. (f) Vismara, E.; Fontana, F.; Minisci, F. *Org. Prep. Proc. Int.* **1988**, *20*, 105–108. (g) Togo, H.; Aoki, M.; Yokoyama, M. *Tetrahedron Lett.* **1991**, *32*, 6559–6562. (h) Togo, H.; Aoki, M.; Yokoyama, M. *Chem. Lett.* **1992**, 1673–1676. (i) Vismara, E.; Torri, G.; Pastori, N.; Marchiandi, M. *Tetrahedron Lett.* **1992**, *33*, 7575–7578. (j) Togo, H.; Aoki, M.; Kuramochi, T.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2417–2427. (k) Togo, H.; Ishigami, S.; Fujii, M.; IkUma, T.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2931–2942. (l) Minisci, F.; Fontana, F.; Bravo, A.; Yan, Y. M. *Gazz. Chim. Ital.* **1996**, *126*, 85–88.

(23) Minisci, F.; Porta, O.; Recupero, F.; Punta, C.; Gambarotti, C.; Pruna, B.; Pierini, M.; Fontana, F. *Synlett* **2004**, 874–876.

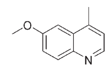
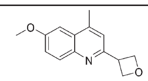
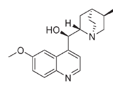
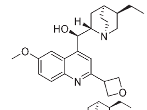
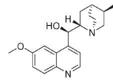
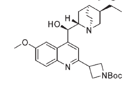
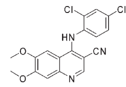
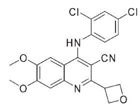
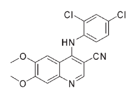
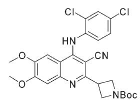
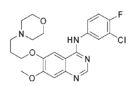
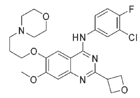
(24) (a) Tilford, C. H.; Shelton, R. S.; Van Campen, M. G. *J. Am. Chem. Soc.* **1948**, *70*, 4001–4009. (b) Lochte, H. L.; Kruse, P. F.; Wheeler, E. N. *J. Am. Chem. Soc.* **1953**, *75*, 4477–4481. (c) Bachman, G. B.; Hammer, M.; Dunning, E.; Schisla, R. M. *J. Org. Chem.* **1957**, *22*, 1296–1302. (d) Russell, C. A.; Crawforth, C. E.; Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1970**, 1406–1407. (e) O'Neill, D. J.; Helquist, P. *Org. Lett.* **1999**, *1*, 1659–1662. (f) Weitgenant, J. A.; Mortison, J. D.; O'Neill, D. J.; Mowery, B.; Puranen, A.; Helquist, P. *J. Org. Chem.* **2004**, *69*, 2809–2815.

TABLE 2. Introduction of an Azetidine Group into Heterocyclic Bases

Entry	Starting material		Product		Yield[a]
1	**1a**		**3a**		30
2	**1b**		**3b**		50
3	**1c**		**3c**		20[b]
4	**1e**		**3d**		41[c]
5	**1f**		**3e**		15
6	**1g**		**3f**		17

[a]Percentage yield of isolated product from reaction of heteroaromatic base (1 equiv) with 1-Boc-3-(iodo)azetidine (2 equiv), $FeSO_4 \cdot 7H_2O$ (3 × 0.3 equiv), H_2O_2 (2 × 3 equiv), H_2SO_4 (2 equiv) in DMSO at room temperature. [b]Reaction performed at 40 °C. [c]Reaction performed at 60 °C.

TABLE 3. Introduction of Oxetane or Azetidine Groups into Pharmacologically-Active Heterocyclic Bases

Entry	Starting material		Product		Yield[a]
1	**4a**		**5a**		31
2	**4b**		**5b**		27[b,c]
3	**4b**		**5c**		17[b,c]
4	**4c**		**5d**		38[d]
5	**4c**		**5e**		43[b]
6	**4d**		**5f**		13[c,d]

[a]Percentage yield of isolated product from reaction of heteroaromatic base (1 equiv) with 3-iodooxetane or 1-Boc-3-(iodo)azetidine (2 equiv), $FeSO_4 \cdot 7H_2O$ (3 × 0.3 equiv), H_2O_2 (2 × 3 equiv), H_2SO_4 (2 or 3 equiv) in DMSO at room temperature. [b]Reaction performed at 50 °C. [c]Difficulties with isolating pure product encountered. [d]Reaction performed at 60 °C.

Experimental Section

4-Methyl-2-(oxetan-3-yl)quinoline, 2a. H_2O_2 (30% in H_2O; 0.31 mL, 3.0 mmol) was added dropwise over 1−2 min to a stirred solution of lepidine **1a** (132 μL, 1.0 mmol), concentrated H_2SO_4 (107 μL, 2.0 mmol), 3-iodooxetane (368 mg, 2.0 mmol), and iron(II) sulfate heptahydrate (80 mg, 0.3 mmol) in DMSO (10 mL) at room temperature. After 1−2 min a further portion of iron(II) sulfate heptahydrate (80 mg, 0.3 mmol) was added and the mixture was stirred at room temperature for 30 min. Further H_2O_2 (0.31 mL, 3.0 mmol) and iron(II) sulfate heptahydrate (80 mg, 0.3 mmol) was added, and the mixture was stirred for 15 min, then poured into a 0.2 M solution of NaOH (30 mL) and Et_2O (50 mL). The aqueous and organic layers were partitioned and the aqueous layer was extracted with Et_2O (2×25 mL). The combined organic extracts were washed with brine (1×30 mL), dried ($MgSO_4$), and filtered and the solvent was removed under vacuum to leave a crude oil. The oil was purified by preparative thin-layer chromatography with EtOAc/hexanes (3:7) as eluent to give a mixture of lepidine **1a** and desired product **2a** (25 mg), and the desired product **2a** (82 mg, 40%) as a solid. An analytical portion of product **2a** was recrystallized from EtOAc/hexanes for data purposes. ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.07 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.38 (s, 1H), 5.19 (dd, J = 8.3, 6.0 Hz, 2H), 5.05 (t, J = 6.3 Hz, 2H), 4.51 (app. quint., J = 7.5 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 160.6, 147.7, 145.4, 129.8, 129.5, 127.3, 126.2, 123.8, 120.0, 76.9, 42.6, 19.0. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.09; H, 6.53; N, 6.87.

***tert*-Butyl 3-(4-Methylquinolin-2-yl)azetidine-1-carboxylate, 3b.** H_2O_2 (30% in H_2O; 0.86 mL, 9.0 mmol) was added to a stirred solution of quinaldine **1b** (400 mg, 3.0 mmol), concentrated H_2SO_4 (298 μL, 6.0 mmol), 1-Boc-3-(iodo)azetidine (1.58 g, 3.0 mmol), and iron(II) sulfate heptahydrate (200 mg, 0.8 mmol) in DMSO (30 mL) at room temperature. After 30 min a further portion of iron(II) sulfate heptahydrate (200 mg, 0.8 mmol) and H_2O_2 (30% in H_2O; 0.86 mL, 9.0 mmol) was added and the mixture was stirred at room temperature for 30 min. Further H_2O_2 (0.86 mL, 9.0 mmol) and iron(II) sulfate heptahydrate (200 mg, 0.8 mmol) was added, and the mixture was stirred for 120 min, then poured into an ice-cold solution of NaOH and adjusted to pH >10. The aqueous was extracted with Et_2O. The aqueous layer was then saturated with solid NaCl and extracted with $CHCl_3$ until all the product was removed from the aqueous layer. The combined organic extracts were dried ($MgSO_4$), and filtered and the solvent was removed under vacuum to leave a crude residue. The residue was purified by column chromatography on silica gel with EtOAc/hexanes (1:1 to 1:0) as eluent to give the desired product **3b** (450 mg, 50%) as an oil that crystallized on standing. ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.07 (d, J = 8.3 Hz, 1H), 7.70−7.67 (q, J = 7.4 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.28 (s, 1H), 4.49 (t, J = 8.2 Hz, 2H), 4.44−4.38 (m, 1H), 4.17 (br s, 2H), 2.77 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 159.0, 156.4, 148.1, 146.8, 129.8, 129.5, 126.1, 125.0, 122.8, 118.9, 80.0, 54.1, 30.1, 28.5, 25.6; m/z 299.0 $(M + 1)^+$. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.19; H, 7.42; N, 9.21.

Acknowledgment. We thank Andrew Calabrese and Thomas Ryckmans of Pfizer, Sandwich (UK) for insightful discussions about the oxetane motif. We also thank Jonathan Bentley and Rachel Ward of Evotec (UK) for high-resolution mass spectrometry data.

Supporting Information Available: Detailed experimental conditions and copies of analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.