An Investigation of Imidazole and Oxazole Syntheses Using Aryl-Substituted TosMIC Reagents[1]

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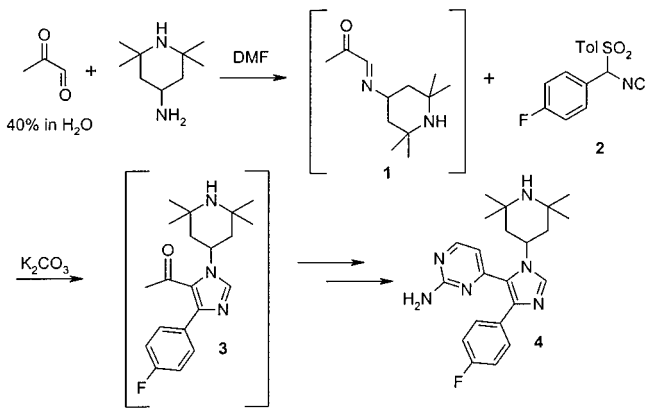
This article describes efficient and mild protocols for preparing polysubstituted imidazoles in a single pot from aryl-substituted tosylmethyl isocyanide (TosMIC) reagents and imines generated in situ. Traditional imine-forming reactions employing virtually any aldehyde and amine followed by addition of the TosMIC reagent delivers 1,4,5-trisubstituted imidazoles with predictable regiochemistry. Employing chiral amines and aldehydes, particularly those derived from α-amino acids, affords imidazoles with asymmetric centers appended to N-1 or C-5 with excellent retention of chiral purity. 1,4-Disubstituted imidazoles are also readily prepared by a simple variant of the above procedure. Selecting glyoxylic acid as the aldehyde component of this procedure leads to intermediates such as **48**, which readily undergo decarboxylation and elimination of the tosyl moiety to deliver 1,4-disubstituted imidazoles in high yields. Alternatively, using NH_4OH as the amine component in conjunction with a variety of aldehydes delivers 4,5-disubstituted imidazoles in moderate to good yields in a single pot while avoiding the need for protecting groups. Finally, the facile preparation of mono- and disubstituted oxazoles from these TosMIC reagents and aldehydes is described.

Introduction

Imidazoles are a common component of a large number of natural products and pharmacologically active molecules.[2] The prevalence and importance of this component makes methods which facilitate their preparation highly valuable. Despite intensive synthetic interest in these heterocycles during the past century, few methods have emerged which are general and capable of delivering highly functionalized imidazoles.[3] In addition, many of the available methods utilize intermediates which are difficult to prepare, such as α-functionalized carbonyl and α-diamino compounds.[3] One promising and conceptually different approach to imidazole synthesis was reported by van Leusen in 1977 involving cycloaddition of tosylmethyl isocyanides (TosMICs) to carbon−nitrogen double bonds.[4] However, since the advent of TosMIC chemistry little work has been done to establish the scope and limitations of this chemistry when directed toward imidazole synthesis. In particular, most of the examples published to date use imines which have been devoid of any additional functionality.

Scheme 1



We recently described a one-pot synthesis of imidazole **4,** a potent inhibitor of p38 MAP kinase, employing the route shown in Scheme 1.[5] Conversion of pyruvaldehyde to imidazole **3** by the reaction of tosylisonitrile **2**[6] with imine **1** in DMF containing significant amounts of water is the cornerstone of this sequence**.** The facility with which **1** and **2** react, even in the presence of water,

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§ Analytical Sciences Department.

(1) This paper is dedicated to the memory of our colleagues Ken Tubman and Lendon Pridgen, deceased August 1, 1999.

(2) For examples, see: Greenlee, W. J.; Siegl, P. K. S. *Annu. Rep. Med. Chem.* **1992**, *27*, 59. Hodges, J. C.; Hamby, J. M.; Blankley, C. J. *Drugs Future* **1992**, *17*, 575. Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449. Meanwell, N. A.; Romine, J. L.; Seiler, S. M. *Drugs Future* **1994**, *19*, 361. Rizzi, J. P.; Nagel, A. A.; Rosen, T.; McLEan, S.; Seeger, T. *J. Med. Chem.* **1990**, *33*, 2721. Shapiro, G.; Gomez-Lor, B. *J. Org. Chem.* **1994**, *59*, 5524. Adams, J. L.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Webb, E. F.; Hall, R.; Sorenson, M.; Lee, J. C.; Ayrton, A.; Griswold, D. E.; Gallagher, T. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3111.

(3) For imidazole syntheses, see: Ebel, K. In *Methoden der Organischen Chemie (Houben-Weyl)*; Band E8c, Hetarene III/Teil 3; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1994; pp 1−215. Grimmett, M. R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1980; Vol. 27, p 241. Grimmett, M. R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1970; Vol. 12, p 103. See also, Reiter, L. A. *J. Org. Chem.* **1987**, *52*, 2714. Lantos, I.; Zhang, W. Y.; Shui, X.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 7092. Nunami, K.; Yamada, M.; Fukui, T.; Matsumoto, K. *J. Org. Chem.* **1994**, *59*, 7635. Hunt, J. T.; Bartlett, P. A. *Synthesis* **1978**, 741.

(4) van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153. van Leusen, A. M. *Lect. Heterocycl. Chem.* **1980**, *5*, S-111.

(5) Sisko, J. *J. Org. Chem.* **1998**, *63*, 4529.

(6) Sisko, J.; Mellinger, M., Sheldrake, P. W.; Baine, N. H. *Tetrahedron Lett.* **1996**, *37*, 8113. Sisko, J.; Mellinger, M., Sheldrake, P. W.; Baine, N. H. *Org. Synth.*, in press.

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presents new opportunities for expanding TosMIC chemistry for the synthesis of imidazoles from small molecule building blocks with multiple functionalities. Although published procedures employing substituted TosMIC reagents imply the need for strictly anhydrous conditions,[4,7] the results shown in Scheme 1 belie that notion. Described herein are the results of an investigation which has culminated in the development of processes for the efficient synthesis of functionally rich 1,4- and 4,5-disubstituted imidazoles, as well as 1,4,5-trisubstituted imidazoles, under partially aqueous conditions. Notable features of these methods are the mild reaction conditions, experimental simplicity, and extensive functional group compatibility. A brief investigation of the reaction of these TosMIC reagents with aldehydes to form oxazoles is also presented.

Results and Discussion

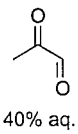
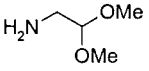
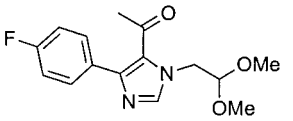
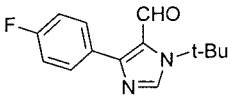
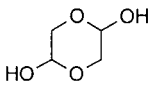
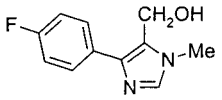
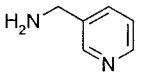
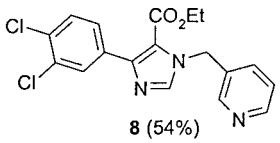
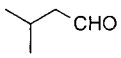
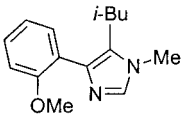
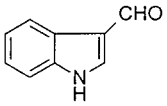
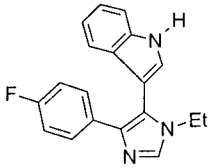
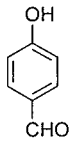
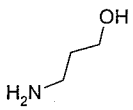
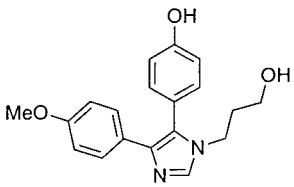
Preparation of 1,4,5-Trisubstituted Imidazoles. Several years ago we described an improved procedure for the preparation of aryl-substituted tosylmethyl isonitriles.[6] Prior to this report, few examples of such reagents existed and little was known about their chemistry.[4,7] The examples shown in Table 1 illustrate the stuctural diversity which can be achieved using these reagents in this one-pot, three-component reaction. In each case, the imines are prepared in situ prior to the addition of the TosMIC reagent. In addition to providing the desired imidazoles in good yields, the reactions are also experimentally simple. The reactions work well in most common organic solvents (EtOAc, THF, MeCN, DMF, CH_2Cl_2, MeOH) and require only very mild bases to promote the cycloaddition (piperazine, morpholine, K_2CO_3). The choice of reaction conditions is typically governed by the solubility of the aldehyde and amine as well as ease of product isolation. For instance, the combination of DMF/K_2CO_3 is typically the best choice for ensuring successful TosMIC/imine cycloadditions. However, other solvent/base combinations can be equally effective and avoid difficulties associated with removing DMF from the product.

Table 1 shows a number of examples of this chemistry. Entries 1−4 show imidazoles with C-5 substituents at various oxidation states which are poised for further manipulations. Aldehyde **6** (entry 2) ensues from the reaction of the di-*tert*-butylimine of glyoxal[8] with 1 equiv of isonitrile **2**. The initially formed imidazole imine is hydrolyzed with aqueous HCl to deliver the aldehyde **6**. Alkyl, aryl, and heteroaryl aldehydes work equally well, as shown in entries 5−7, and highlight the ease with which unprotected functionalities can be accommodated in this mildly basic process.

A variety of TosMIC reagents containing electron-poor and electron-rich aryl rings have been prepared by our standard method[6] and show comparable reactivity. One exception is the *o*-bromophenyl derivative of **2** which failed to react with several imines under all conditions tried. This lack of reactivity can be attributed to the increased congestion surrounding the benzylic carbon since TosMIC reagents similar to **2** with electron-deficient aryl rings are, in general, very reactive. The only other ortho aromatic-substituted TosMIC reagent which was investigated, *o*-methoxyphenyl derivative **2c**, undergoes clean cycloaddition to form imidazole **9** (Table 1). Unfortunately, *alkyl*-substituted TosMIC reagents and TosMIC itself have so far been unreactive partners under all conditions tried.[9]

Dialdehydes and diamines have also been used successfully in this multicomponent reaction to generate dimeric bis-imidazoles. Glutaric dialdehyde, available as a 50% aqueous solution, readily reacts with 2 equivalents of allylamine to form the corresponding diimine **14** in situ

Table 1. Synthesis of 1,4,5-Trisubstituted Imidazoles from Tosylisonitriles and Imines Generated in Situ

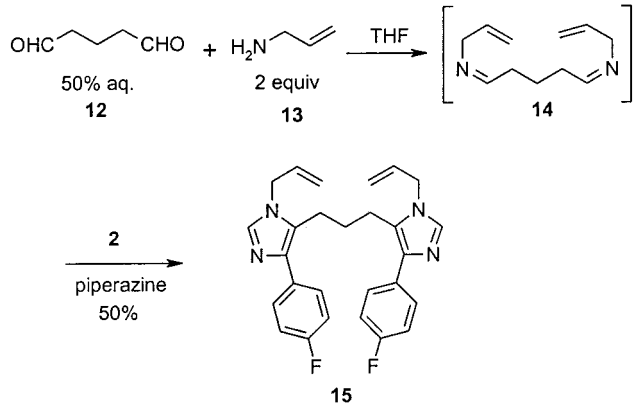
Entry	Aldehyde	Amine	Product (Yield)
1[a]	 40% aq.		 **5** (71%)
2[a]	OHC-CHO 40% aq.	t-BuNH$_2$	 **6** (63%)
3[a]		MeNH$_2$ 40% aq.	 **7** (83%)
4[b]			 **8** (54%)
5[c]		MeNH$_2$ 40% aq.	 **9** (62%)
6[a]		EtNH$_2$ 70% aq.	 **10** (49%)
7[d]			 **11** (67%)

[a] (4-Fluorophenyl) tosylmethyl isonitrile (**2**) was used. [b] (3,4-Dichlorophenyl) tosylmethyl isonitrile (**2b**) was used. [c] (2-Methoxyphenyl) tosylmethyl isonitrile (**2c**) was used. [d] (4-Methoxyphenyl) tosylmethyl isonitrile (**2c**) was used.

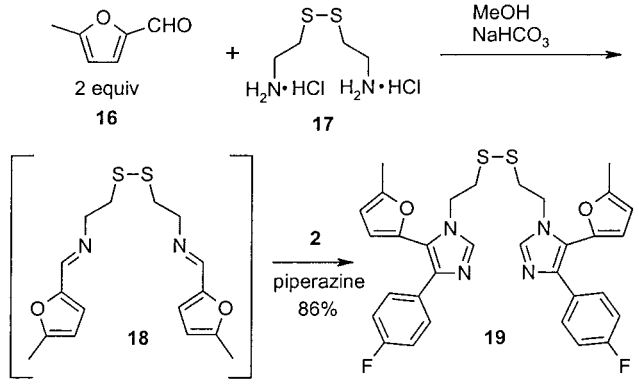
(7) (a) DiSanto, R.; Costi, R.; Massa, S.; Artico, M. *Synth. Commun.* **1995**, *25*, 795. (b) Sasaki, H.; Nakagawa, H.; Khuhara, M.; Kitagawa, T. *Chem. Lett.* **1988**, 1531.

(8) Haaf, M.; Schmiedl, A.; Schmedake, T. A.; Powell, D. R.; Millevolte, A. J.; Denk, M.; West, R. *J. Am. Chem. Soc.* **1998**, *120*, 12714.

Scheme 2



Scheme 3



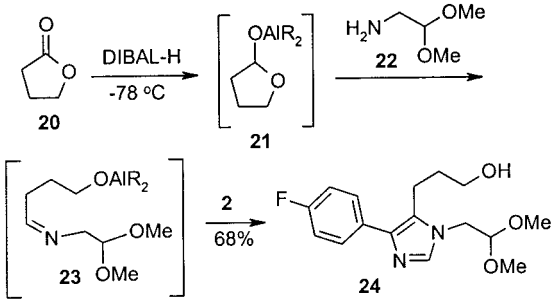
(Scheme 2). Cycloaddition of **14** with isonitrile **2** proceeds smoothly to deliver the bis-imidazole **15** in 50% isolated yield.

Likewise, bis-imidazoles connected via N-1, such as **19**, are accessible using a similar process from the corresponding diamines (Scheme 3). Diimine **18** is easily prepared from the di-HCl salt of cysteamine (**17**) and 5-methylfurfural (**16**) in aqueous methanol containing $NaHCO_3$. Subsequent [3 + 2] cycloaddition of **18** with **2** proceeds smoothly to deliver bis-imidazole **19** in 86% isolated yield.

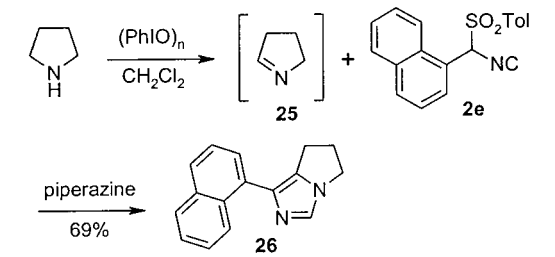
In addition to those prepared in the classical method, imines generated by less direct routes can also undergo cycloaddition with these TosMIC reagents with equal success to form interesting products. For example, reduction of γ-valerolactone (**20**) with DIBAL at −78 °C leads to lactol **21** (Scheme 4). Without isolation, this intermediate was condensed with aminoacetaldehyde dimethyl acetal (**22**) to generate imine **23** which undergoes the desired cycloaddition with TosMIC **2**. From this one-pot sequence, adduct **24** can be isolated in 68% yield.

Several groups have reported an interest in using fused, bicyclic imidazoles as the nucleus for new classes

Scheme 4



Scheme 5



of antiviral and antibiotic agents. The syntheses developed for these substrates, however, are lengthy and low-yielding.[10] We considered the reaction of a cyclic imine with an aryl-substituted TosMIC reagent as a viable alternative to this potentially useful class of molecules. Moriarty has shown that secondary, cyclic amines are readily oxidized by the action of $(PhIO)_n$ to the corresponding imine.[11] Although these imines can be difficult to isolate due to their propensity to trimerize, they are well-suited for our one-pot approach. In the event, treatment of pyrrolidine with $(PhIO)_n$ in CH_2Cl_2 for 15 min at room temperature produces 1-pyrroline (**25**) (Scheme 5). Addition of TosMIC reagent **2e** and piperazine yields the fused, bicyclic imidazole **26** in a single operation in 69% isolated yield.

We have also investigated a process wherein the *aldehyde and imine* are generated in situ prior to cycloaddition with a TosMIC reagent. Floyd and coworkers have reported the conversion of phenacyl halides to the corresponding α-keto aldehydes under mild conditions.[12] Thus, stirring bromide **27** in a $DMSO/H_2O$ mixture for 24 h at room temperature produces aldehyde **28** (Scheme 6). Addition of the primary amine **29** leads to formation of the imine **30** which reacts with **2f** to form the ketoimidazole **31** in 50% overall yield. This efficient, one-pot method allows rapid entry to a class of molecules that have been difficult to attain by literature methods.[13]

Preparation of Chiral 1,4,5-Trisubstituted Imidazoles. Another family of attractive target molecules for this methodology are 2-imidazol-1-yl alkanoic acids. Despite their promise as pharmaceutical agents, few methods exist for the preparation of such compounds in optically pure form.[14] The extensive functional group

(9) This observation is rather surprising in light of the original results reported by van Leusen et al.[4] In that seminal paper, the reaction of TosMIC with simple, isolated imines is reported to work well under mild conditions in protic solvents (e.g., t-$BuNH_2$ or K_2CO_3 in MeOH). However, fairly subtle stereoelectronic effects seem to govern the outcome of these reactions. For example, *C,N*-diaryl- and *C,N*-dialykylimines react with TosMIC to give the corresponding imidazoles in good to excellent yields while *C*-aryl,*N*-alkylimines react poorly with TosMIC to give low yields of imidazole product (0−37%). In the only example of its kind reported, the methyl-substituted TosMIC reagent combines with a *C,N*-diarylimine to give the imidazole in 75% yield, but required the action of NaH in an aprotic solvent (DME).

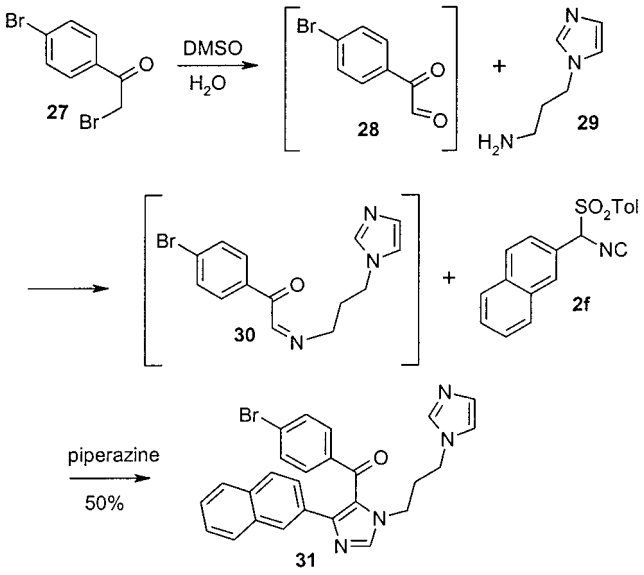
(10) Frannowski, A.; Seliga, C.; Bur, D.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 934. Nishi, T.; Higashi, K.; Soga, T.; Takemura, M.; Sato, M. *J. Antibiot.* **1994**, *47*, 357. Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E. *J. Med. Chem.* **1991**, *34*, 725. See also: Aldabbagh, F.; Bowman, W. R.; Mann, E. *Tetrahedron Lett.* **1997**, *38*, 7937.

(11) Ochiai, M.; Inenaga, M.; Nagao, Y.; Moriarty, R. M.; Vaid, R. K.; Duncan, M. P. *Tetrahedron Lett.* **1988**, *29*, 6917.

(12) Floyd, M. B.; Du, M. T.; Fabio, D. F.; Jacob, L. A.; Johnson, B. D. *J. Org. Chem.* **1985**, *50*, 5022.

(13) See ref 5 and references therein.

Scheme 6



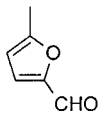
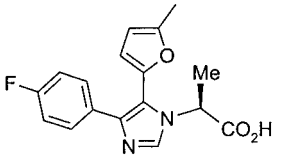
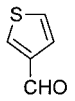
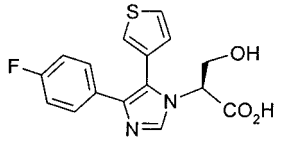
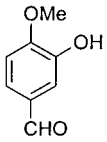
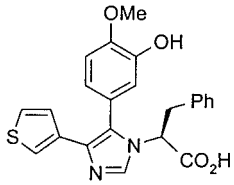
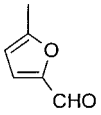
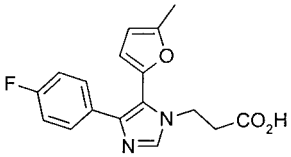
compatibility that has been demonstrated in these cycloadditions led us to pursue this class of compounds using imines derived from optically pure amino acids. The results are shown in Table 2. Following the procedure of Narita,[15] the desired imines are readily prepared in situ by allowing an aldehyde and an amino acid in MeOH: H_2O (10:1) to react in the presence of 1 equiv of NaOH. Upon addition of the TosMIC reagent and piperazine, the desired compounds are obtained in high yield with >99% ee. In addition to α-amino acids, we have also demonstrated the utility of β-alanine (entry 4) in this sequence for the preparation the homologated carboxylic acids.

We also recognized the potential for incorporating a chiral center at C-5 of the imidazole ring by using, among other things, a chiral α-amino aldehyde. These aldehydes are readily available by several methods,[16] and in certain instances are commercially available. Aldehyde **36** and the primary amine **22** produce the desired imine which undergoes cycloaddition with **2** to deliver imidazole **37** in high yields with 96.4% ee (Scheme 7).

Preparation of 1,4-Disubstituted Imidazoles. During the course of these investigations, we had cause to examine the reaction shown in Scheme 8. Cycloaddition of imine **39**, prepared in situ from a 40% aqueous solution of pyruvaldehyde and amine **38**, with isonitrile **2** and K_2CO_3 in DMF leads to ketone **40** in 75% isolated yield. Surprisingly, when the reaction is run at 0 °C the product **40** is contaminated with 15−20% of the 1,4-disubstituted imidazole **41**.

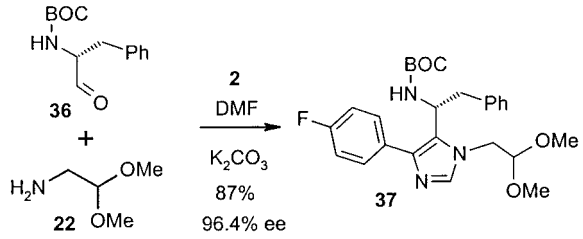
We considered two possible pathways to account for the formation of imidazole **41**. While the first seemed less likely, it was the easier scenario to investigate. Imidazole **41** represents the formal cycloadduct derived from formaldimine **42** reacting with isonitrile **2** (Scheme 9). We speculated that contamination of pyruvaldehyde with formaldehyde[17] could account for the presence of imine **42** in the reaction mixture. This hypothesis was easily tested by mixing 37% aqueous formaldehyde, amine **38**, and **2** under conditions identical to those used in Scheme 8. This reaction, however, yields a new cycloadduct as the major product with only 5−10% of the expected product **41** observed in the reaction mixture. The major product, isolated in 70% yield, was ultimately determined to be the 2-aminooxazoline **44** which results from the

Table 2. Synthesis of 1,4,5-Trisubstituted Imidazoles from Tosylisonitriles and Imines Derived from α- and β-Amino Acids

Entry	Aldehyde	Amino Acid	Product (Yield)
1[a]		L-Alanine	 **32** (67%) >99% ee
2[a]		L-Serine	 **33** (74%) >99% ee
3[b]		L-Phenylalanine	 **34** (79%) >99% ee
4[a]		β-alanine	 **35** (67%)

[a] (4-Fluorophenyl) tosylmethyl isonitrile (**2**) was used. [b] (3,4-Thienyl) tosylmethyl isonitrile (**2g**) was used.

Scheme 7



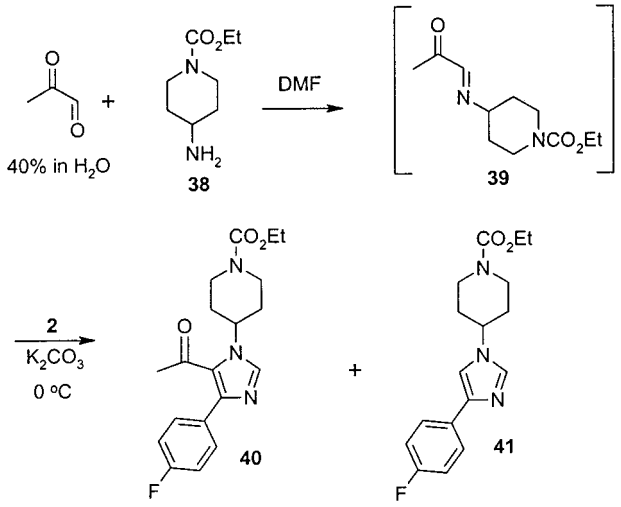
(14) Palkowitz, A. D.; Steinberg, M. I.; Thrasher, K. J.; Reel, J. K.; Hauser, K. L.; Zimmerman, K. M.; Wiest, S. A.; Whitesitt, C. A.; Simon, R. L.; Pfeifer, W.; Lifer, S. L.; Boyd, D. B.; Barnett, C. J.; Wilson, T. M.; Deeter, J. B.; Takeuchi, K.; Riley, R. E.; Miller, W. D.; Marshall, W. S. *J. Med. Chem.* **1994**, *37*, 4508. Zaderenko, P.; Lopez, P.; Ballesteros, P.; Takumi, H.; Toda, F. *Tetrahedron: Asymmetry* **1995**, *6*, 381. Zaderenko, P.; Lopez, M. C.; Ballesteros, P. *J. Org. Chem.* **1996**, *61*, 6825. Birkett, P. R.; King, H.; Chapleo, C. B.; Ewing, D. F.; Mackenzie, G. *Tetrahedron* **1993**, *49*, 11029. Messina, F.; Botta, M.; Corelli, F.; Schneider, M. P.; Fazio, F. *J. Org. Chem.* **1999**, *64*, 3767.

(15) Narita, M.; Akiyama, M.; *Bull. Chem. Soc. Jpn.* **1974**, *47*, 197.

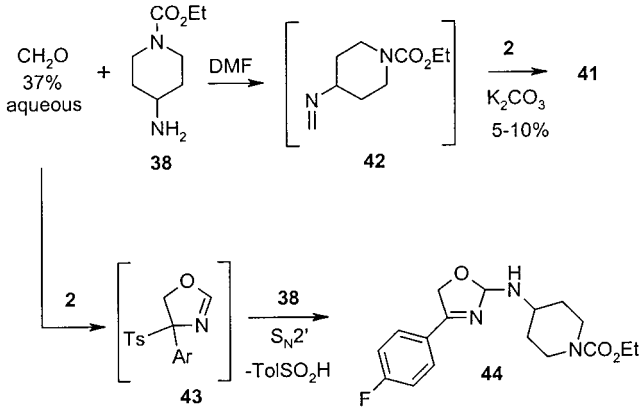
(16) For the preparation of chiral amino aldehydes, see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. McNulty, J.; Still, I. W. *Synth. Commun.* **1992**, *22*, 979. Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676.

(17) Pyruvaldehyde is known to decompose under certain conditions to give formaldehyde, see: Tyndall, G. S.; Staffelbach, T. A.; Orlando, J. J.; Calvert, J. G. *Int. J. Chem. Kinet.* **1995**, *27*, 1009. An alternative explanation would involve deacylation of imine **39** to give formaldimine **42** directly.

Scheme 8



Scheme 9

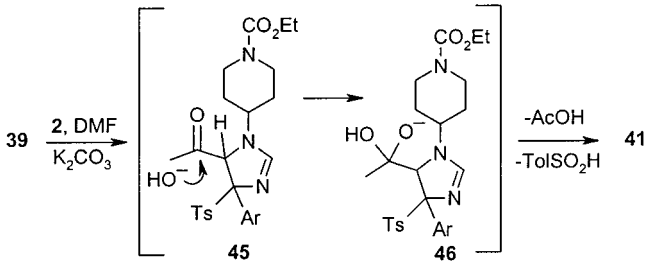


sequence shown in Scheme 9. The slow and incomplete conversion of formaldehyde to imine **42**, made evidence by the low yield of imidazole **41**, allows for the competitive cycloaddition of formaldehyde with reagent **2** to produce the tosyloxazoline **43**. Subsequent addition of the primary amine at C2 and elimination of the toluenesulfinate moiety completes the formation of the observed product **44**.[18] Control experiments confirm this sequence. Cycloaddition of 37% aqueous formaldehdye with **2** proceeds smoothly to give oxazoline **43** in 73% yield. Combining amine **38** with oxazoline **43** in DMF at room temperature leads to clean formation of **44** in high yields.

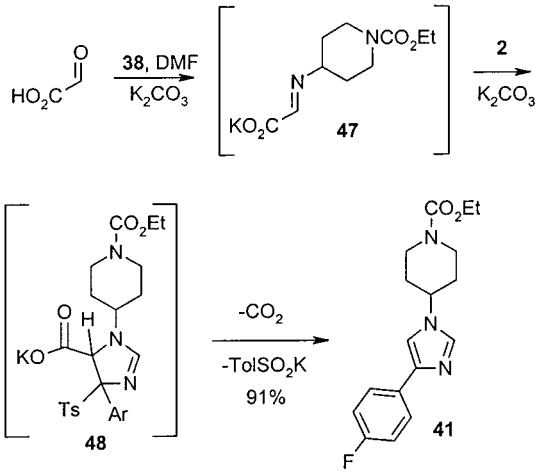
An alternative sequence which could account for **41** is shown in Scheme 10. Addition of a nucleophile (HO^-) to the ketone of putative intermediate **45**[4] gives rise to the tetrahedral intermediate **46**. Ejection of acetic acid followed by elimination of the *p*-toluenesulfinate anion from **46** leads to **41**.

Before proceeding with experiments designed to support this mechanism, we opted instead to seek methods to facilitate the expulsion of the C-5 substituent to develop a general method for preparing 1,4-disubstituted imidazoles. Replacing the acetyl moiety of **45** with a carboxylate group was seen as the optimal substitution. In the event, mixing glyoxylic acid, amine **38**, and K_2CO_3 in DMF delivers the expected imine **47** (Scheme 11). Upon addition of reagent **2** and additional base, the putative intermediate **48** thus formed suffers decarboxylation and subsequent elimination of TolSO$_2$K to generate the observed product (**41**) in high yields.

Scheme 10



Scheme 11



This reaction was found to be quite general and accommodates a broad range of functional groups, delivering 1,4-disubstituted imidazoles of varying complexity in good to excellent yields (see Table 3). In addition to the conditions mentioned, aqueous methanol containing NaOH is also an effective combination for forming imine carboxylates similar to **47**. Addition of the TosMIC reagent and a mild base, such as piperazine or morpholine, is sufficient to complete the imidazole synthesis in these cases. Despite the results in Table 2, the use of amino acids in this sequence fail to provide any of the expected 1,4-disubstituted imidazole. NMR studies seem to indicate the formation of the expected imines in DMSO-d_6 with K_2CO_3, but upon addition of **2** they fail to undergo any productive reaction. This shortcoming is circumvented by using an amino acid ester, as shown in entry 6. Combining valine methyl ester hydrochloride with glyoxylic acid in DMF with $NaHCO_3$ and trapping the resultant imine with isonitrile **2b** delivers ester **54** in 83% isolated yield with 98% ee.

Preparation of 4,5-Disubstituted Imidazoles. Having established that aryl-substituted TosMIC cycloadditions with imines are quite general, we considered the possibility of extending this methodology to prepare 4,5-disubstituted imidazoles. Several strategies have been reported for the synthesis of N-unsubstituted imidazoles using TosMIC derivatives. Shih has reported the use of *N*-trimethylsilyl imines as reaction partners with TosMIC derivatives.[19] However, these imines are generally pre-

(18) A similar sequence has been proposed by Buchi et al., to account for the formation of imidazoles from the reaction of amines with tosyloxazolines similar to **43**. However, they apparantly were unable to isolate intermediates similar to **44**. See: Horne, D. A.; Yakushijin, K.; Büchi, G. *Heterocycles* **1994**, *39*, 139.

(19) Shih, N.-Y. *Tetrahedron Lett.* **1993**, *34*, 595.

Table 3. Synthesis of 1,4-Disubstituted Imidazoles from Tosylisonitriles and Imines Generated in Situ

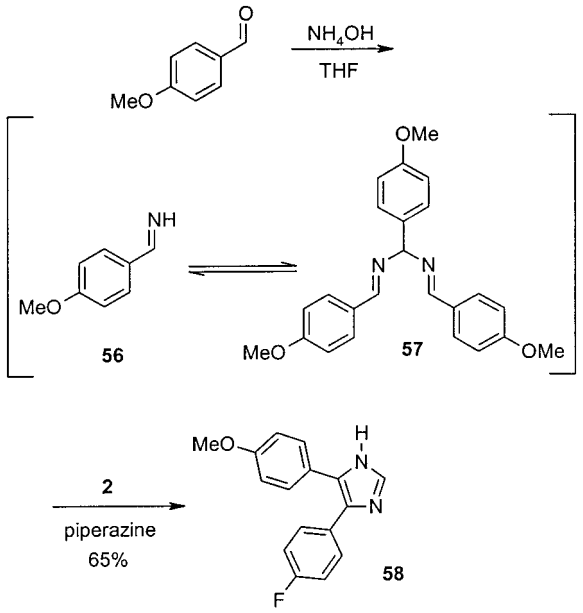
Entry	Amine	Product (Yield)
1[a]	H_2N, OMe, OMe	**49** (81%)
2[a]	t-$BuNH_2$	**50** (86%)
3[a]	$MeNH_2$ 40% aq.	**51** (53%)
4[b]	Me, H_2N, Ph	**52** (87%, 96% ee)
5[c]	H_2N, OH	**53** (79%)
6[d]	H_2N, CO_2Me, HCl	**54** (83%, 98% ee)
7[a]	NH_2, N H	**55** (62%)

[a] (4-Fluorophenyl) tosylmethyl isonitrile (**2**) was used. [b] (3-Thienyl) tosylmethyl isonitrile (**2g**) was used. [c] Phenyl tosylmethyl isonitrile (**2h**) was used. [d] (3,4-Dichlorophenyl tosylmethyl isonitrile (**2b**) was used.

pared under strongly basic conditions which are incompatible with certain substrates. More recently, van Leusen described the cycloaddition of TosMIC with *N*-(dimethylsulfamoyl)aldimines and *N*-tosylimines to obtain 4(5)-monosubstituted imidazoles.[20] While it's likely this method could also prepare 4,5-disubstituted imidazoles, no examples to support this were reported. Regardless, this method requires a separate step (or steps) to prepare the imines and, in the case of the *N*-(dimethylsulfamoyl)aldimines, an additional step to liberate the N-unsubstituted imidazole. Hence, we explored a method to prepare 4,5-disubstituted imidazoles under mild conditions that also avoids a protection/deprotection sequence. For this, the logical choice of reagents was also the cheapest and easiest: NH_4OH.

The reaction of certain aromatic aldehydes with NH_4OH is known to give "hydrobenzamides" **57** in high yields,[21] presumably via the parent arylimines **56** (Scheme

Scheme 12



12). We suspected that either species, **56** or **57**, might be a suitable partner in this cycloaddition reaction for the preparation of 4,5-disubstituted imidazoles (**58**). Accordingly, hydrobenzamide **57** was prepared and isolated by the procedure of Bhawal,[22] and then reacted in a separate step with isonitrile **2** in THF to provide imidazole **58** in 60% isolated yield. Subsequent experiments revealed that the isolation of **57** in a separate step was unnecessary. Simply treating *p*-anisaldehyde with excess NH_4OH (30% aqueous) in THF followed by addition of isonitrile **2** generates imidazole **58** in 65% overall yield in a single operation (Scheme 12). Table 4 shows additional examples of this one-pot transformation. In addition to aryl aldehydes, several alkyl aldehydes have been used with equal success to give the corresponding imidazole products. The low yield reported in entry 2 was in part due to difficulties in isolating the product. From other examples it is apparent that various functional groups are tolerated in the process, including phenols, alcohols, and olefins. Surprisingly, no pyrrole byproducts were obtained from the reaction in entry 7.[23]

Although the results in Table 4 are encouraging, the reaction of NH_4OH with most aldehydes is a poorly understood process which is complicated by a large number of possible intermediates and products.[24] Electronic factors have been found to play a large role in determining the rate and extent to which the hydrobenzamides are formed.[25] These considerations, in addition to the difficulty in monitoring the progress of the aldehyde to hydrobenzamide conversion, have profound effects on the yield of imidazole products obtained from this process. For aldehydes which suffer poor conversion to the hydrobenzamide, the most common side products are 4,5-disubstituted oxazoles which result from cycloaddi-

(20) ten Have, R.; Huisman, M.; Meetsma, A.; van Leusen, A. M. *Tetrahederon* **1997**, *53*, 11355. For another possible alternative method, see: van Leusen, A. M.; Schaart, F. J.; van Leusen, D. *Rec. Trav. Chim. Pays-Bas* **1979**, *98*, 258.

(21) See Corey, E. J.; Kühnle, F. N. M. *Tetrahedron Lett.* **1997**, *38*, 8631 and references therein.

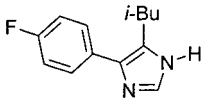
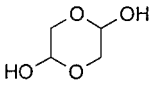
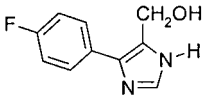
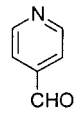
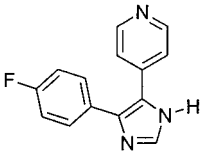
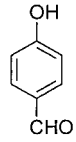
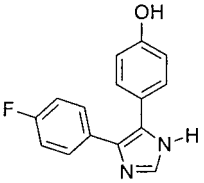
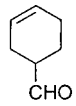
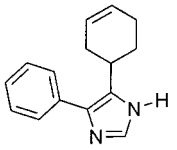
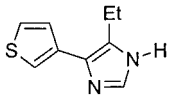
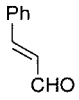
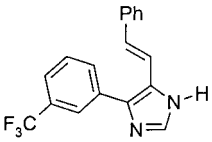
(22) Karupaiyan, K.; Srirajan, V.; Deshmuck, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1998**, *54*, 4375.

(23) van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett.* **1972**, 5337.

(24) Larter, M. L.; Phillips, M.; Ortega, F.; Aguirre, G.; Somanathan, R.; Walsh, P. J. *Tetrahedron Lett.* **1998**, *39*, 4785. Hunter, D. H.; Kim, S. K. *Can. J. Chem.* **1972**, *50*, 669.

(25) Ogata, Y.; Kawasaki, A.; Okumura, N. *J. Org. Chem.* **1964**, *29*, 1985.

Table 4. Synthesis of 4,5-Disubstituted Imidazoles from Tosylisonitriles and Imines Generated in Situ from Aldehydes and NH_4OH

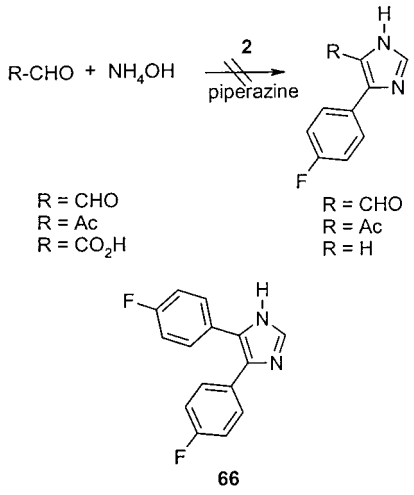
Entry	Aldehyde	Product (Yield)
1[a]	*i*Bu-CHO	 **59** (66%)
2[a]		 **60** (23%)
3[a]		 **61** (60%)
4[a]		 **62** (73%)
5[b]		 **63** (81%)
6[c]	Et-CHO	 **64** (78%)
7[d]		 **65** (41%)

[a] (4-Fluorophenyl) tosylmethyl isonitrile (**2**) was used. [b] Phenyl tosylmethyl isonitrile (**2h**) was used. [c] (3-Thienyl) tosylmethyl isonitrile (**2g**) was used. [d] (3-Trifluoromethyl)phenyl tosylmethyl isonitrile (**2i**) was used.

tion of the TosMIC reagent with the aldehyde.[26] Several low molecular weight aldehydes, such as glyoxal, pyruvaldehyde, and glyoxylic acid, fail to form the expected imidazole products after reaction with NH_4OH (Scheme 13). In these reactions, the only product isolated is imidazole **66**. The structure of this unexpected product was verified by independent synthesis involving the reaction of 4-fluorobenzaldehyde with NH_4OH and reagent **2**. At present, the exact mechanism for the formation of **66** is uncertain. However, it appears that **2** has a limited lifetime under these reaction conditions, and that lacking a suitable cycloaddition partner, it decomposes

(26) van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, 2369.

Scheme 13



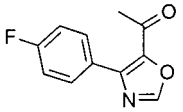
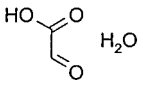
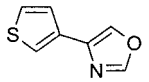
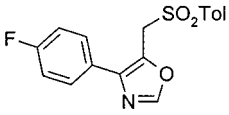
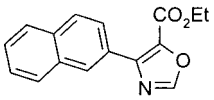
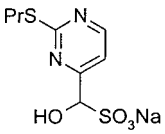
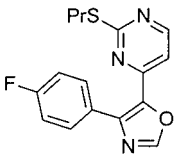
to give an arylimine similar to **56** which undergoes cycloaddition with **2** to give **66**. A reexamination of the crude product mixtures from the reactions in Table 4 showed that **66** is present in most of these reactions, although usually as a minor component (5−10%).

4,5-Disubstituted Oxazoles. Reactions of TosMIC and its alkyl-substituted derivatives with aldehydes are known to give the corresponding oxazoles.[27] Conversely, reactions of aryl-substituted TosMIC reagents with aldehydes have been relatively unexplored.[7b] From the results discussed above, it was clear that these reactions should be particularly facile, require mild reaction conditions, and be tolerant of a broad array of functional groups. Table 5 shows the results of a few reactions that exemplify the ease with which these aldehyde/TosMIC cycloadditions occur. Methyl ketone **67** can be prepared in good yield from pyruvaldehyde and isonitrile **2** (entry 1). To our surprise, small amounts of oxazoline **43** were also found by NMR in the crude reaction mixture (<5%). The presence of this impurity confounds our interpretation of the results in Schemes 8−10 since nucleophilic deacylation of the expected intermediate **73**, as in Scheme 10, should lead to the monosubstituted oxazole **74** (Scheme 14). The presence of **43** instead of **74** implies that decomposition of pyruvaldehyde to formaldehyde under the reaction conditions may occur, at least to a small extent, prior to cycloaddition with **2**.

As expected, glyoxylic acid undergoes cycloaddition with TosMIC reagents to produce the monosubstituted oxazole **68** in good yield (entry 2). Reaction of isonitrile **2** with chloroacetaldehyde gives a somewhat unexpected result (entry 3). Combining the reagents in DMF with K_2CO_3 at room temperature for 18 h leads to oxazoline **75** as the major product (mixture of cis and trans isomers, Scheme 15). Heating the solution to 95 °C to induce elimination of $TolSO_2H$ and form the oxazole ring instead produces the tosylmethyl oxazole **69** exclusively, presumably via chloride **76**. Finally, bisulfite adduct **71** is also capable of smooth cycloaddition with **2** to give oxazole **72** in good yield (entry 5), presumably via the intermediacy of the corresponding aldehyde.

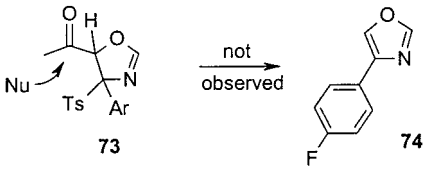
(27) Possel, O.; van Leusen, A. M. *Heterocycles* **1977**, *7*, 77. Saikachi, H.; Kitagawa, T.; Sasaki, H.; van Leusen, A. M. *Chem. Pharm. Bull.* **1979**, *27*, 793. Hiemstra, H.; Houwing, H. A.; Possel, O., van Leusen, A. M. *Can. J. Chem.* **1979**, *57*, 3168.

Table 5. Synthesis of 1,4,5-Trisubstituted Imidazoles from Tosylisonitriles and Imines Generated in Situ

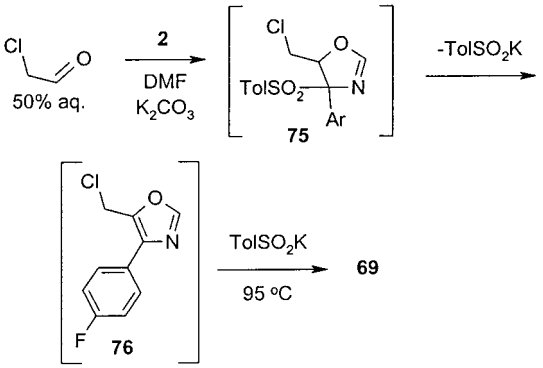
Entry	Aldehyde	Product (Yield)
1[a]	 40% aq.	 **67** (71%)
2[b]		 **68** (79%)
3[a]	 50% aq.	 **69** (63%)
4[c]		 **70** (80%)
5[a]	 **71**	 **72** (62%)

[a] (4-Fluorophenyl) tosylmethyl isonitrile (**2**) was used. [b] (3-Thienyl) tosylmethyl isonitrile (**2g**) was used. [c] 2-Naphthyl tosylmethyl isonitrile (**2f**) was used.

Scheme 14



Scheme 15



Conclusion

The reaction of imines with TosMIC has been known for over 20 years as a trusted method for preparing 1,5-disubstituted imidazoles with predictable regiochemistry. However, in the intervening years, no systematic study has been conducted on the reactivity of substituted TosMIC derviatives, due in large part to the lack of a robust method for their preparation. We have reported here that aryl-substituted TosMIC reagents readily undergo cycloaddition with a variety of simple and polyfunctional imines, under anhydrous or partially aqueous conditions, to give rise to 1,4,5-trisubstituted, as well as 1,4- and 4,5-disubstituted, imidazoles in a single operation. The sequence is conducted under mild conditions and tolerates a host of functional groups. The method can easily accommodate chiral amines and aldehydes, such as those derived from amino acids, to generate products in high enantiomeric excess. Similar cycloadditions with simple and multifunctional aldehydes proceed smoothly to generate a host of interesting oxazoles.

Experimental Section

General Experimental. The ^{13}C spectra of the 4,5-disubstituted imidazoles in Table 4 were collected at 25 °C. Due to annular tautomerism, the width of some signals in the ^{13}C spectrum (10−20 Hz) under these conditions makes them undetectable and accounts for less than the expected number of resonances for these compounds.[28] **WARNING**: Isonitrile **2** is thermally unstable at temperatures above 80 °C. To obtain a margin of safety, care should be taken to avoid heating **2** and similar TosMIC derivatives at temperatures above 35−40 °C.

1-[1-(2,2-Dimethoxyethyl)-4-(4-fluorophenyl)imidazol-5-yl]ethan-1-one (5). A solution of pyruvaldehyde (40% aqueous, 3.97 mL mL, 25.9 mmol) and aminoacetaldehyde dimethyl acetal (3.77 mL, 34.6 mmol) in THF (75 mL) was stirred at ambient temperature for 15 min, at which point the isonitrile **2** (5 g, 17.3 mmol) and piperazine (1.94 g, 22.3 mmol) were added. The solution was stirred an additional 18 h and diluted with EtOAc and water, and the layers were separated. The organic layer was stirred with 3 N HCl for 10 min (to hydrolyze any ketimine product) and then made basic with solid K_2CO_3. The aqueous layer was removed, the organics were concentrated in vacuo to dryness, and the residue was eluted through a short plug of silica gel with EtOAc. The eluent was concentrated to give the product (3.6 g, 71%) as a yellow oil: IR (neat) 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, s), 7.45 (2H, m), 7.11 (2H, t, J = 8.6 Hz), 4.54 (1H, t, J = 5.0 Hz), 4.32 (2H, d, J = 5.0 Hz), 3.41 (6H, s), 2.11 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 162.9 (d, J = 248 Hz), 149.0, 142.3, 131.4 (d, J = 8.3 Hz), 131.2, 127.2, 115.3 (d, J = 21.7 Hz), 103.3, 55.2, 49.2, 29.8. Anal. Calcd for $C_{15}H_{17}N_2O_3F$: C, 61.6; H, 5.9; N, 9.6. Found C, 61.5; H, 5.9; N, 9.4.

3-[1-(2,2-Dimethoxyethyl)-4-(4-fluorophenyl)imidazol-5-yl]propan-1-ol (24). A solution of γ-butyrolactone (1.78 g, 20.7 mmol) in THF (80 mL) was cooled to −78 °C, and DIBAL-H (1.5 M in toluene, 15.2 mL, 22.8 mmol) was added dropwise. After 45 min, aminoacetaldehyde dimethyl acetal (3.27 g, 30.1 mmol) was added, and the solution was allowed to warm to room temperature. After 1 h at this temperature, isonitrile **2** (3.0 g, 10.4 mmol) and piperazine (1.34 g, 15.6 mmol) were added, and the solution was stirred for 18 h. After adding 3 N HCl (6 mL) and EtOAc, the slurry was filtered through a bed of Celite and rinsed with EtOAc. The filtrate was washed with water and concentrated in vacuo. The product which was isolated by silica gel chromatography using EtOAc:MeOH (19:1) crystallized on standing (2.16 g, 68%) as a white solid: IR (neat) 3270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

(28) See Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Thieme: Stuttgart, 1995; p. 167. Papadopoulos, E. P.; Hollstein, U. *Org. Magn. Reson.* **1982**, *19*, 188.

(29) Boehm, J. C.; Smietana, J. M.; Sorenson, M. E.; Garigipati, R. S.; Gallagher, T. F.; Sheldrake, P. L.; Bradbeer, J.; Badger, A. M.; Laydon, J. T.; Lee, J. C.; Hillegass, L. M.; Griswold, D. E.; Breton, J. J.; Chabot-Fletcher, M. C.; Adams, J. L. *J. Med. Chem.* **1996**, *39*, 3929.

δ 7.58 (2H, m), 7.50, (1H, s), 7.02 (2H, t, J = 8.7 Hz), 4.43 (1H, t, J = 5.1 Hz), 3.97 (2H, d, J = 5.1 Hz), 3.57 (2H, t, J = 6.0 Hz), 3.36 (6H, s), 3.06 (1H, br s), 2.84 (2H, t, J = 7.8 Hz), 1.74 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (d, J = 246 Hz), 136.9, 136.7, 131.3, 128.6 (d, J = 7.8 Hz), 127.3, 115.2 (d, J = 21.4 Hz), 103.7, 61.2, 55.1, 47.1, 32.3, 19.8. Anal. Calcd for $C_{16}H_{21}N_2O_3F$: C, 62.3; H, 6.9; N, 9.1. Found C, 62.5; H, 6.9; N, 9.0.

3-Naphthylpyrrolidino[1,2-*d*]imidazole (26). To a solution of pyrrolidine (0.42 g, 5.84 mmol) in CH_2Cl_2 (50 mL) was added freshly prepared $(PhIO)_n$ (1.38 g, 5.84 mmol). After 15 min, the isonitrile **2e** (1.25 g, 3.89 mmol) and piperazine (0.5 g, 5.84 mmol) were added, and the solution was stirred an additional 18 h at room temperature. Water and CH_2Cl_2 were added, and the layers were separated. The organics were washed with water and brine and were concentrated in vacuo. After silica gel chromatography using EtOAc, the product was obtained as a viscous yellow oil (0.63 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (1H, d, J = 8.2 Hz), 7.75 (1H, d, J = 7.9 Hz), 7.66 (1H, d, J = 7.9 Hz), 7.49 (1H, d, J = 7.0 Hz), 7.40 (4H, m), 3.65 (2H, t, J = 7.1 Hz), 2.61 (2H, t, J = 7.1 Hz), 2.26 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 134.1, 132.7, 131.3, 130.2, 128.1, 127.0, 126.7, 126.1, 125.7, 125.6, 125.4, 44.2, 29.2, 22.9. Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.0; H, 6.0; N, 12.0. Found C, 81.8; H, 6.2; N, 11.6.

4-Bromophenyl 1-(3-imidazolylpropyl)-4-(2-naphthyl)-imidazol-5-yl ketone (31). A solution of 1,4′-dibromoacetophenone (3.84 g, 13.8 mmol) dissolved in DMSO (23 mL) and water (0.25 mL) was stirred at room temperature for 24 h. Triethylamine (9 mL) was added to adjust the pH of the solution to 8 prior to the addition of 1-(3-aminopropyl)-imidazole (1.65 mL, 13.8 mmol). After 1 h, isonitrile **2f** (2.21 g, 6.91 mmol) and piperazine (0.89 g, 10.4 mmol) were added, and the solution was stirred at room temperature for an additional 24 h. Water was added, and the solution was stirred for 20 min. EtOAc was added, and the layers were separated. The organics were washed with water and brine. The organics were concentrated in vacuo, and the residue was purified by silica gel chromatography using EtOAc:MeOH (9:1). The product (1.68 g, 50%) solidified on standing as a yellow solid: mp = 118−122 °C; IR (KBr) 3072, 1627, 1585, 1506 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (1H, s), 7.70−7.25 (10H, m), 7.15 (2H, d, J = 8.5 Hz), 7.08 (1H, s), 6.91 (1H, s), 4.20 (2H, t, J = 7.2 Hz), 4.01 (2H, t, J = 6.9 Hz), 2.34 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.0, 149.5, 141.1, 137.0, 136.4, 132.8, 132.7, 131.4, 131.0, 130.6, 129.8, 128.9, 127.9, 127.6, 126.6, 126.4, 126.2, 125.76, 118.6, 44.2, 44.1, 32.4; HRMS calcd for $C_{26}H_{21}N_4OBr$ 484.0899, found 484.0901.

(2*S*)-2-[4-(4-Fluorophenyl)-5-(5-methyl(2-furyl))imidazolyl]propanoic Acid (32). A solution of 5-methylfurfural (1.71 g, 15.6 mmol), L-alanine (1.39 g, 15.6 mmol), and NaOH (0.62 g, 15.6 mmol) in MeOH (15 mL) and water (2 mL) was stirred at ambient temperature for 1.5 h prior to the addition of isonitrile **2** (3 g, 10.4 mmol) and piperazine (1.34 g, 15.6 mmol). The solution was stirred an additional 18 h and concentrated under vacuum. The brown syrup was dissolved in water and EtOAc. The solution was adjusted to pH 3.0−3.5 with 3 N HCl and transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted a second time with EtOAc, and the organic layers were combined and concentrated to 25−30 mL. After standing for 1 h, the crystallized product was filtered and rinsed with EtOAc. The product was dried under vacuum to give 2.2 g (67%) of an off-white solid: mp = 171−172 °C; IR (KBr) 3432, 1728 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.1 (1H, br s), 8.02 (1H, s), 7.50 (2H, m), 7.13 (2H, t, J = 8.8 Hz), 6.48 (1H, d, J = 2.8 Hz), 6.25 (1H, d, J = 2.8 Hz), 4.74 (1H, q, J = 7.2 Hz), 2.28 (3H, s), 1.64 (3H, d, J = 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.7, 161.1 (d, J = 244 Hz), 153.2, 140.2, 138.8, 137.2, 130.6, 127.8 (d, J = 7.9 Hz), 118.2, 114.9 (d, J = 21.3 Hz), 113.9, 107.5, 53.3, 17.3, 13.1. Anal. Calcd for $C_{17}H_{15}N_2O_3F$: C, 65.0; H, 4.8; N, 8.9. Found C, 65.0; H, 4.8; N, 8.8. The enantiomeric excess was determined by HPLC using a Chiralcel OD column, with EtOH:hexane:TFA (10:90:0.1) as mobile phase, flow rate of 0.5 mL/min and UV detection at 254 nm. Retention times: *S*-isomer at 12.6 min, *R*-isomer at 15.4 min.

General Procedure for the Preparation of 1,4-Disubstituted Imidazoles. A solution of gyoxylic acid (monohydrate or 50% aqueous solution, 21.6 mmol), K_2CO_3 (43.2 mmol), and amine (25.9 mmol) in DMF (50 mL) was stirred at ambient temperature for 3 h, at which point the isonitrile (17.3 mmol) was added. The solution was stirred an additional 18 h and diluted with TBME and water, and the layers were separated. The aqueous layer was extracted again with TBME, and the organic layers were combined and washed with water. The organic layer was concentrated in vacuo to dryness, and the residue was either recrystallized or purified by flash chromatography.

General Procedure for the Preparation of 4,5-Disubstituted Imidazoles. A solution of the aldehyde (25.9 mmol) and NH_4OH (30% aqueous, 69.2 mmol) in THF (75 mL) was stirred at ambient temperature for 3−8 h, at which point the TosMIC reagent (17.3 mmol) and piperazine (25.9 mmol) were added. The solution was stirred an additional 18 h and diluted with EtOAc and water, and the layers were separated. The organic layer was washed with water and saturated $NaHCO_3$ solution and concentrated in vacuo to dryness. The products were isolated by crystallization or chromatography.

1-[4-(4-Fluorophenyl)-1,3-oxazol-5-yl]ethan-1-one (67). Pyruvaldehyde (40% solution, 3.17 mL, 20.7 mmol), isonitrile **2** (5 g, 17.3 mmol), and K_2CO_3 (2.75 g, 19.9 mmol) were combined in 35 mL of DMF. After 5 h, the solution was diluted with water and extracted with TBME (three times). The combined organic layers were washed with water (three times) and concentrated in vacuo. The residue was crystallized from EtOAc/hexane as a beige crystal (2.48 g, 70%): mp 59−61 °C; IR (KBr) 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (2H, m), 7.95 (1H, s), 7.13 (2H, t, J = 8.8 Hz), 2.58 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.2, 163.8 (d, J = 208 Hz), 150.8, 143.7, 143.5, 131.4 (d, J = 9.3 Hz), 126.1, 115.3 (d, J = 21.4 Hz), 28.3. Anal. Calcd for $C_{11}H_8NO_2F$: C, 64.4; H, 3.9; N, 6.8. Found C, 64.2; H, 3.9; N, 6.5.

Acknowledgment. The authors would like to thank the Analytical Sciences and Physical and Structural Chemistry Departments at SmithKline Beecham, including Ms. Priscilla Offen and Mr. Gary Zuber for obtaining IR spectra, Mr. Lewis Kilmer for obtaining mass spectra, and Dr. Alan Freyer for obtaining and interpreting NMR spectra. In addition, we thank SmithKline Beecham for financial support for A.J.K.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **2b**−**g**,**i**, **8**, **9**, **15**, **31**, **33**, **34**, **37**, **62**, **65**, and **68,** and experimental details and characterization of the isolated products which were not described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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