

Heteroaromatic Synthesis *via* Olefin Cross-Metathesis: Entry to Polysubstituted Pyridines

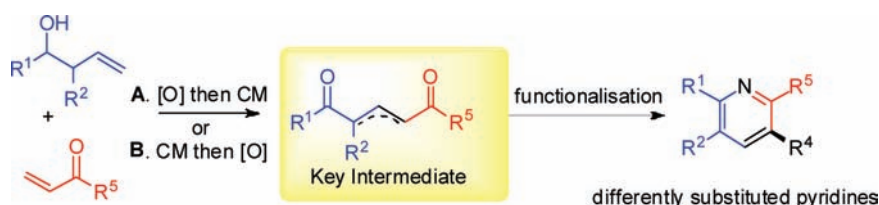
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ABSTRACT



The olefin cross-metathesis reaction provides a rapid and efficient method for the synthesis of α,β -unsaturated 1,5-dicarbonyl derivatives which then serve as effective precursors to mono–tetrasubstituted pyridines. Manipulation of the key 1,5-dicarbonyl intermediate allows access to pyridines with a wide range of substitution patterns. An extension of this methodology facilitates the preparation of pyridines embedded within macrocycles, as exemplified by an efficient synthesis of (*R*)-(+)-muscopyridine. High levels of regiocontrol, short reaction sequences, and facile substituent variation are all notable aspects of this methodology.

Of all heteroaromatic compounds, pyridines are unrivalled in terms of their pharmacological significance.^{1,2} Consequently, the development of methods for the preparation of highly substituted pyridine derivatives is of importance to medicinal chemistry and represents a worthwhile goal of organic synthesis. Substantial and exciting progress has been made in the derivatization of pre-existing pyridine frameworks using metal-catalyzed cross-coupling protocols.³ However, another flexible and also complementary approach involves the development of *de novo*

pyridine methodologies.⁴ Ideally, any new method should enable the concise combination of readily available materials in a convergent, predictable, and regiocontrolled manner.

Recent studies from our laboratory,^{5,6} and others,⁷ have focused upon incorporating the olefin metathesis reaction into methodologies for the synthesis of heteroarenes. In

† Author for correspondence regarding the X-ray structures.

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(2) See ref 1 within: Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Quéguiner, G. *Synlett* **2002**, 1008.

(3) For representative examples, see: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, 61, 2245. Cho, S. H.; Hwang, S. J.; Chang, S. J. *Am. Chem. Soc.* **2008**, 130, 9254. Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, 75, 8180. Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2010**, 49, 1115. For a review, see: Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, 36, 1036.

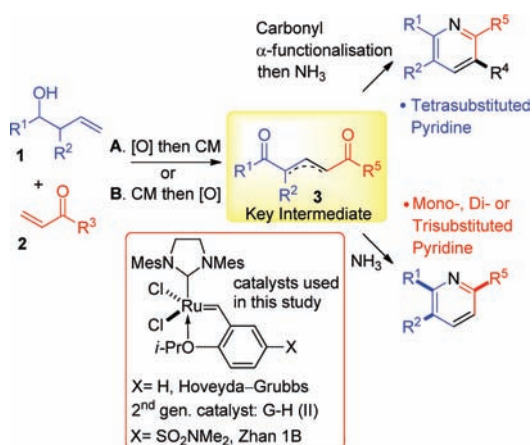
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(7) For a comprehensive review, see: van Otterlo, W. A. L.; de Koning, C. B. *Chem. Rev.* **2009**, 109, 3743. See also: Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, 59, 4029. Yoshida, K.; Kawagoe, F.; Hayashi, K.; Horiuchi, S.; Imamoto, T.; Yanagisawa, A. *Org. Lett.* **2009**, 11, 515.

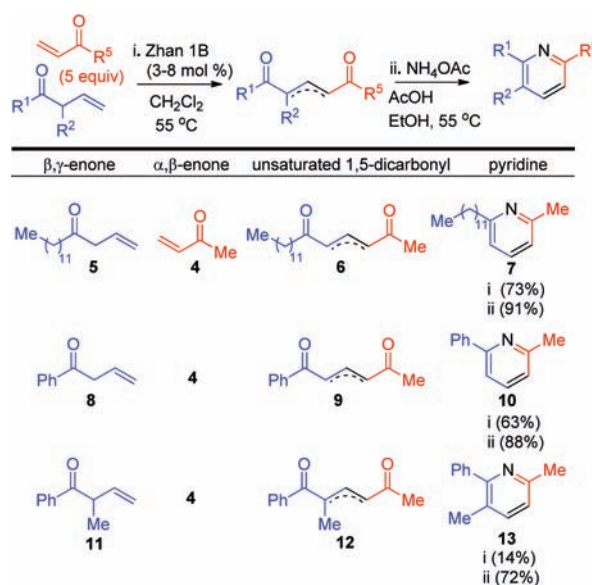
Scheme 1. Olefin CM for the Synthesis of Pyridines



particular, protocols based upon ring-closing olefin metathesis (RCM) provide efficient access to a range of heteroaromatic classes.⁸ Most recently, we have applied the powerful olefin cross-metathesis process (CM)⁹ to the synthesis of di- and trisubstituted furans and pyrroles.¹⁰ An attractive aspect of CM-based strategies resides in the utilization of metathesis for both convergent fragment coupling and provision of unsaturation for the aromatic target. Herein, we report an extension of this concept to the synthesis of pyridines.

Our approach to pyridines involves an olefin CM-based protocol for the synthesis of substituted α,β -unsaturated 1,5-dicarbonyl derivatives **3** (Scheme 1). These are assembled from homoallylic alcohol precursors **1** by oxidation and then olefin CM with an α,β -enone component **2**. Alternatively, inversion of the alcohol oxidation and CM events provides equally concise access to **3**. Treatment with ammonia then converts the 1,5-dicarbonyl intermediate **3** directly to the pyridine target.¹¹ Modification of **3** through enolate chemistries enables access to higher substitution patterns. In all cases, the CM sequence allows the *combination* of simple precursors and reactions to

Scheme 2. Substituted Pyridines via Enone–Enone CM



provide complex pyridines with high levels of substitution and regiocontrol.

Our initial investigations centered upon the CM of β,γ -enones with α,β -enones to afford the required 1,5-dicarbonyl derivatives directly (Scheme 2). Under optimized conditions, the CM of β,γ -enone **5** with methyl vinyl ketone proceeded in 73% yield using the Zhan 1B catalyst.¹² The dicarbonyl intermediate **6**, formed as an inconsequential mixture of alkene regioisomers, was then converted to the pyridine **7** upon exposure to NH_4OAc under mildly acidic conditions. This chemistry provides a general method for the introduction of substituents at the 2- and 6-positions of the pyridine ring, although extension to more highly substituted variants was problematic. For example, CM of sterically encumbered β,γ -enone **11** with methyl vinyl ketone afforded dicarbonyl **12** in 14% yield; these inefficiencies prompted the investigation of alternative reaction sequences.

Olefins bearing proximal alcohol groups have emerged as a special substrate class for CM. Enhanced levels of reaction efficiency may be due to hydrogen bonding between the hydroxyl group and the chloride ligands on the metathesis catalyst.¹³ Accordingly, CM of homoallylic alcohol **14** with methyl vinyl ketone was efficient, and upon completion,¹¹ Dess–Martin periodinane (DMP) was added to the reaction to afford the dicarbonyl **9** in one pot (Scheme 3: compare the CM of **4** and **11** to that of **4** and **18**). As before, conversion to pyridine **10** occurred with NH_4OAc .¹¹ Extension to more highly substituted derivatives, based upon more complex homoallylic alcohols,

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(9) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733. Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441. For a recent review, see: Nolan, S. P.; Clavier, H. *Chem. Soc. Rev.* **2010**, *39*, 3305.

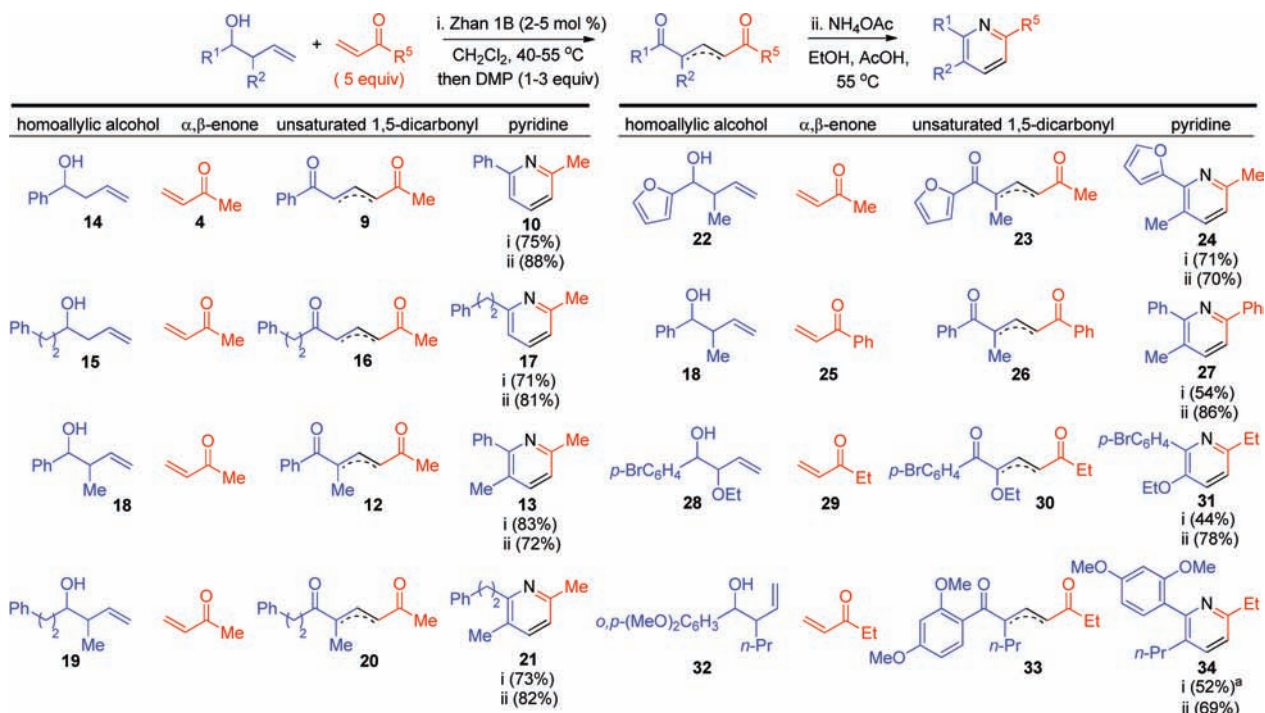
(10) Donohoe, T. J.; Bower, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3373. Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 4094. See also: Shafi, S.; Kędziołek, M.; Grela, K. *Synlett* **2011**, 124.

(11) This transformation is well established. For a recent example, see: Tokujii, S.; Takahashi, Y.; Shinmori, H.; Shinokubo, H.; Osuka, A. *Chem. Commun.* **2009**, 1028.

(12) Zhan, Z.-Y. J. U.S. Patent, 2007, 20070043180; this catalyst is commercially available. It was necessary to use 5 equiv of the enone component to ensure maximum yields from the CM reaction.

(13) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378.

Scheme 3. Substituted Pyridines via Homoallylic Alcohol–Enone CM



^aHoveyda–Grubbs II catalyst was used at 80 °C in PhMe.

meant that mono-, di-, and trisubstituted pyridines could be prepared. This methodology is efficient for the introduction of alkyl and aryl groups onto the pyridine and also allows the introduction of heteroatom groups such as alkoxy substituents (**31**).

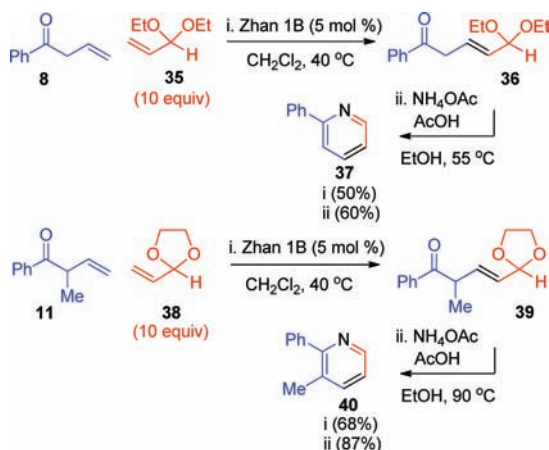
The formation of pyridines without a substituent at R⁵ is more challenging as the requisite aldehydic unsaturated 1,5-dicarbonyl intermediates were found to be sensitive to purification. However, cross-metathesis of, for example, **8** with acrolein diethylacetal **35**¹⁴ was reasonably efficient and afforded intermediate **36** which, upon exposure to NH₄OAc, delivered monosubstituted pyridine **37** in good yield (Scheme 4).

Similarly, CM of β,γ -enone **11** with vinylidioxolane **38** (this CM partner was less sensitive to steric hindrance) afforded 2,3-disubstituted pyridine **40**. Here, oxidation to the β,γ -enone *prior* to CM was more efficient than oxidation after CM of the analogous homoallylic alcohol.

Tetrasubstituted pyridines are not directly attainable *via* this methodology due to inefficiencies associated with the demanding CM of 1,1-disubstituted olefins. Trisubstituted α,β -unsaturated 1,5-dicarbonyl intermediates (formed *via* the CM–oxidation sequence) are, however, readily manipulated to allow the eventual installation of an extra substituent onto the pyridine core (Scheme 5). For example, Pd-catalyzed α -arylation of **12**, **20**, and **23** with a range

(14) O’Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1091. An excess of the acetal component was required to maximize the yield of cross-metathesis.

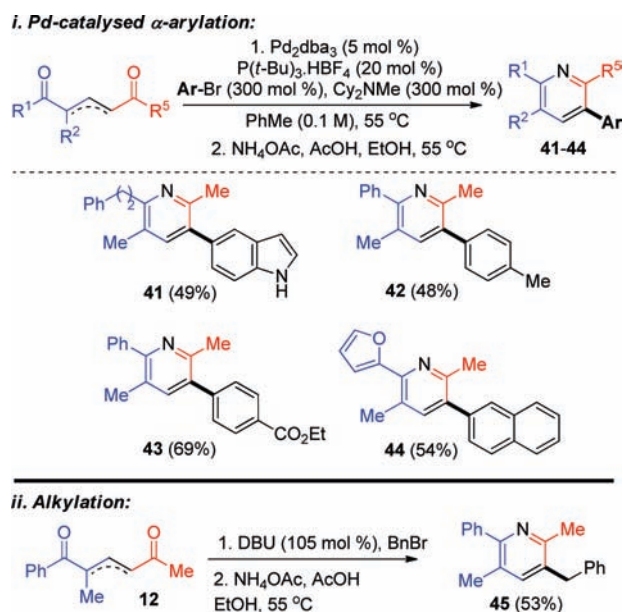
Scheme 4. Substituted Pyridines *via* Acetal CM



of aryl bromides afforded, after exposure of the products to NH₄OAc, diverse tetrasubstituted pyridines **41**–**44** bearing aryl moieties at C(5).¹⁵ Single regioisomers were obtained from the α -arylation event, and Heck arylation of the olefinic moiety was not observed; the structures of both **42** and **43** were confirmed by X-ray crystallographic analysis. Similarly, base-promoted alkylation of the dicarbonyl derivative

(15) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1545.

Scheme 5. α -Functionalization of α,β -Unsaturated 1,5-Dicarbonyl Intermediates



12 ultimately provided pyridine **45** bearing an alkyl group at C(5). It is important to note that the transformations outlined in Scheme 5 are representative of a much broader range of potential manipulations for the introduction of extra substituents onto the pyridine target.

Further extension of this chemistry affords macrocyclic pyridines, such as (*R*)-(+)-muscopyridine,¹⁶ *via* utilization of the key metathesis event for macrocyclization (Scheme 6). Accordingly, Wadsworth–Emmons olefination of commercially available undecenal provided acrylate **47** which was subjected to asymmetric copper catalyzed addition of a methyl Grignard to provide ester **48** in high yield and with excellent levels of enantiopurity ($\geq 95\%$ ee).¹⁷ This intermediate was then advanced to the key metathesis precursor **50** over four steps involving (i) Weinreb amide formation,¹⁸ (ii) olefin epoxidation, (iii) double addition of a vinyl Grignard, and (iv) Dess–Martin oxidation. Exposure of **50** to the metathesis-based pyridine formation sequence, but employing high dilution for the metathesis step, afforded (*R*)-(+)-muscopyridine $\{[\alpha]_{\text{D}}^{25} +10.8$ (*c* 0.5, CHCl_3); lit. $[\alpha]_{\text{D}}^{23} +12.5$ (*c* 1.8, CHCl_3)¹⁹ in 42% yield. An alternative end game, involving macrocyclization of the corresponding homoallylic alcohol, was less successful: while RCM was efficient, the ensuing oxidation was problematic. The route

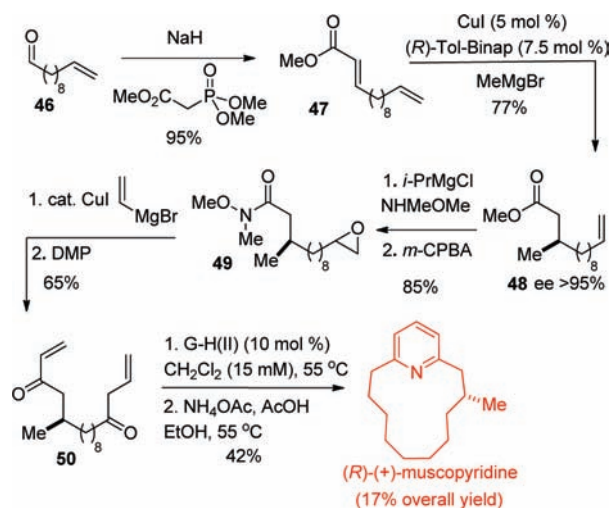
(16) Schinz, H.; Ruzicka, L.; Geyer, U.; Prelog, V. *Helv. Chim. Acta* **1946**, *29*, 1524.

(17) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 276. Wang, S.-Y.; Lum, T.-K.; Ji, S.-J.; Loh, T.-P. *Adv. Synth. Catal.* **2008**, *350*, 673.

(18) Weinreb, S. M.; Nahm, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(19) Hagiwara, H.; Katsumi, T.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Org. Chem.* **2000**, *65*, 7231.

Scheme 6. Intramolecular “CM-Based” Approach to Muscopyridine



shown proceeds in 17% yield over eight steps and compares well to the most efficient asymmetric syntheses reported to date.²⁰

The olefin CM reaction provides a straightforward method for the synthesis of α,β -unsaturated 1,5-dicarbonyl derivatives which then serve as effective precursors to mono-, di-, and trisubstituted pyridines. Tetrasubstituted pyridines are available *via* further manipulation of the key 1,5-dicarbonyl intermediate. A related intramolecular strategy facilitates the preparation of pyridines embedded within macrocycles, as exemplified by a highly efficient synthesis of (*R*)-(+)-muscopyridine. High levels of regio-control, short reaction sequences, and facile substituent variation are all notable aspects of this pyridine methodology. Consequently, this chemistry provides an attractive strategy for medicinal chemistry applications.

Acknowledgment. We thank the EPSRC for financial support and the Oxford Chemical Crystallography Service for use of instrumentation.

Supporting Information Available. Copies of ^1H and ^{13}C NMR spectra and experimental procedures are available. The structure of pyridines **7**, **10**, **13**, **17**, **27**, **37**, **40**, and (*R*)-(+)-muscopyridine were determined by comparison of the spectroscopic data reported in the literature. The structure of pyridines **21**, **34**, **41**, and **45** were determined by characteristic NOE enhancements. The structure of pyridines **42** and **43** were determined by X-ray crystallographic analysis. The structure of pyridines **24**, **31**, **34**, and **44** were assigned by analogy to the aforementioned compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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