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C2-Alkenylation of N-heteroaromatic compounds *via* Brønsted acid catalysis†

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Substituted heteroaromatic compounds, especially those based on pyridine, hold a privileged position within drug discovery and medicinal chemistry. However, functionalisation of the C2 position of 6-membered heteroarenes is challenging because of (a) the difficulties of installing a halogen at this site and (b) the instability of C2 heteroaryl-metal reagents. Here we show that C2-alkenylated heteroaromatics can be accessed by simple Brønsted acid catalysed union of diverse heteroarene *N*-oxides with alkenes. The approach is notable because (a) it is operationally simple, (b) the Brønsted acid catalyst is cheap, non-toxic and sustainable, (c) the *N*-oxide activator disappears during the reaction, and (d) water is the sole stoichiometric byproduct of the process. The new protocol offers orthogonal functional group tolerance to metal-catalysed methods and can be integrated easily into synthetic sequences to provide polyfunctionalised targets. In broader terms, this study demonstrates how classical organic reactivity can still be used to provide solutions to contemporary synthetic challenges that might otherwise be approached using transition metal catalysis.

Introduction

Nitrogen heterocycles are core motifs in the majority of small molecule pharmaceuticals and drug candidates. Within this context, substituted pyridine based systems, including quinolines and isoquinolines, are by far the most common.[1] Consequently, modular C–C bond forming strategies for the functionalisation of 6-membered heteroarenes are highly prized. The low nucleophilicity of these ring systems means that electrophilic aromatic substitution approaches are not suitable, and so predominant methodologies rely on metal-catalysed cross coupling (Suzuki, Stille, Heck *etc.*). Within the context of C2-alkenylated derivatives, two complementary strategies therefore emerge (Scheme 1A). The first involves the coupling of a C2-halogenated derivative with either a vinyl metal reagent[2] or an alkene.[3] The former approach provides greater control, whereas the latter option is more direct and atom economical, however, both options often suffer from modest yields.[2,3] The second strategy relies on an inverse arrangement wherein a C2-metalated heteroarene, itself often prepared from a C2-halogenated precursor, is cross-coupled with an appropriated vinyl halide partner.[4] This approach is hampered by the well-established propensity of the heteroaryl metal reagent to undergo competitive proto-demetalation during cross-coupling.[4] For both approaches, the C2-halogenated precursor usually cannot be prepared directly from the parent heteroarene, with the most general approaches involving a two-step sequence of oxidation to the *N*-oxide and halogenation.[5,6]

To circumvent the inefficiencies and atom/step economy issues outlined above, efforts have focussed on the use of *N*-oxides as heteroaryl metal surrogates.[7,8] This functionality renders the heteroarene π-system electron-rich, such that selective C2 metalation (especially palladation) can be exploited.[7] However, the requirement to remove the *N*-oxide activator in a subsequent reduction step detracts from the utility of this approach.[7,9] In an ideal scenario, the *N*-oxide would serve as both an activator and internal oxidant in the C–C bond forming process, such that the target heteroarene is generated directly. There are limited examples where this has been achieved.[10] In the context of this study, the most relevant work is that of Wu, who showed that C2-alkenylation of sparsely functionalised quinoline and isoquinoline *N*-oxides with electron deficient olefins can be achieved under Pd(II)-catalysed conditions (Scheme 1B, eqn (1)); the protocol was not applicable to pyridines.[10a] Additionally, Antonchick and Bering have developed a Petasis-like approach to the C2-alkenylation of quinolines (Scheme 1B, eqn (2)).[11] The protocol was not applied to other classes of heteroarene and requires prefunctionalisation of the alkene partner. Here we demonstrate a complementary approach that uses a simple Brønsted acid catalyst (TsOH) for the coupling of heteroarene *N*-oxides with alkenes to provide C2-alkenylated products, *including pyridines*,

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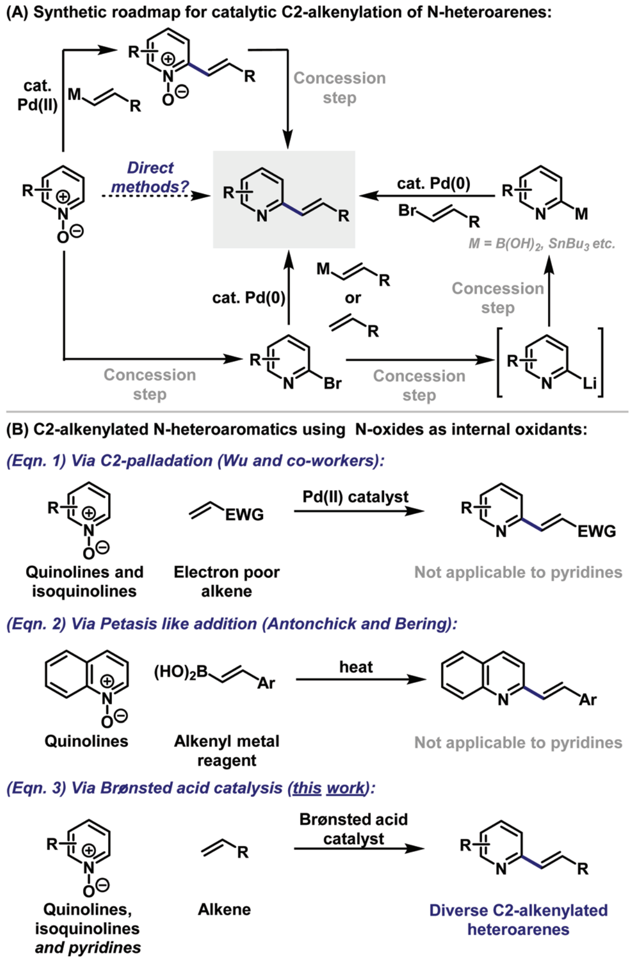


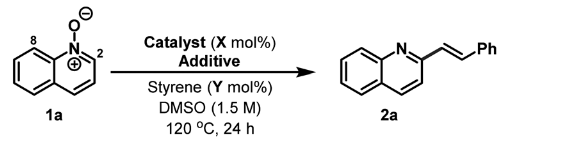
Scheme 1

directly.[12] Water is the sole stoichiometric byproduct, the protocol is operationally simple, avoiding the use of toxic and scarce precious metal catalysts, and the method offers orthogonal functional group compatibility *versus* existing approaches.

Results and discussion

Our studies were initiated by observations made during attempts to promote iridium-catalysed ($[IrCp^*Cl_2]_2/AgPF_6$) C8-alkenylation of quinoline *N*-oxide **1a** with styrene in DMSO.[13] Instead of the target transformation, C2-alkenylated derivative **2a** was formed in quantitative yield (Table 1, entry 1). Mindful of the studies of Wu and co-workers,[10a] we conducted a series of deuterium exchange experiments, which indicated that metalation occurred at both C8 and C2. However, further control experiments revealed that the iridium complex was not necessary for C–C bond formation and adduct **2a** could be isolated in 71% yield using solely $AgPF_6$ as catalyst (entry 2). Based on this, a range of Lewis and Brønsted acids were evaluated in place of $AgPF_6$ (entries 3–9), leading to the observation that 5 mol% TsOH could promote the transformation in 81%

Table 1 Selected optimisation results



Entry	Catalyst	*X*	Additive	*Y*	Yield of **2a**
1	$[IrCp{\cdot}Cl_2]_2/AgPF_6$	5	None	450	Quantitative
2	$AgPF_6$	5	None	450	71%
3	BzOH	5	None	450	28% (+63% **1a**)
4	CuI	5	None	450	67% (+ 9% **1a**)
5	$Cu(OTf)_2$	5	None	450	70%
6	$PdCl_2$	5	None	450	67%
7	$Zn(TFA)_2$	5	None	450	27% (+18% **1a**)
8	$Sc(OTf)_3$	5	None	450	46%
9	$TsOH{\cdot}H_20$	5	None	450	81%
10	$TsOH{\cdot}H_20$	50	None	450	60%
11	$TsOH{\cdot}H_20$	5	Water[a]	450	96%
12	$TsOH{\cdot}H_20$	5	Water[a]	300	82%
13[b]	$TsOH{\cdot}H_20$	5	None	300	84%
14	None	n/a	Water[a]	300	25%
15	None	n/a	None	450	<5% (+>90% **1a**)

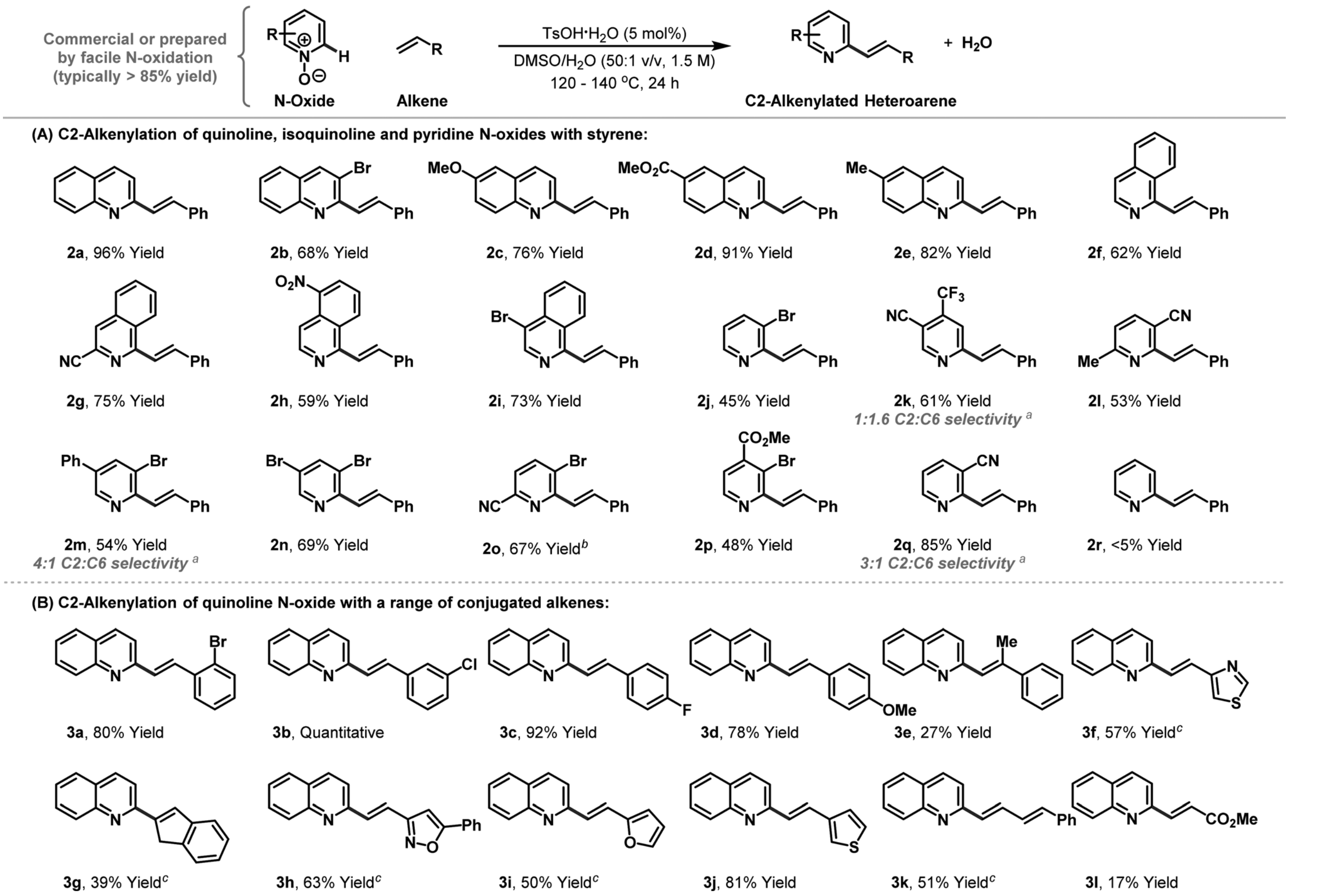
[a] 50 : 1 (v/v) mixture with DMSO. [b] Run under air in reagent grade DMSO.

yield (entry 9). Higher loadings of TsOH were detrimental, presumably due to competitive acid catalysed polymerisation of styrene (entry 10). However, further refinement was achieved by using a 50 : 1 ratio of DMSO : water as solvent (entry 11). Under these conditions, the loading of styrene could be decreased to 300 mol% and **2a** was generated in 82% yield (entry 12). In the absence of acid catalyst, **2a** was formed in only 25% yield (entry 14), and, additionally, no product was observed when both water and the acid catalyst were omitted, with **1a** being recovered intact (entry 15). The reaction can be run under air, using reagent grade DMSO, and efficiency is maintained (entry 13), however, lower reaction temperatures are not effective.

The scope of the new process with respect to the *N*-oxide component is outlined in Table 2A. Electronically and sterically diverse quinoline *N*-oxides all participated smoothly to provide the targets **2b–e** in high yield. The protocol can be extended to isoquinoline *N*-oxides and this enables highly selective alkenylation of the C1 position, again providing targets **2f–i** in good to excellent yield. Pyridine based *N*-oxides can also be accommodated as long as the arene possesses electron-withdrawing groups. Indeed, alkenylation of parent pyridine *N*-oxide to provide **2r** was not successful, but 3-cyanopyridine *N*-oxide did undergo smooth conversion to afford target **2q** with 3 : 1 C2 *vs.* C6 selectivity, favouring the indicated isomer. Other electron-withdrawing groups such as halides, trifluoromethyl groups and esters also render pyridine *N*-oxides sufficiently reactive for the process, thereby providing access to range of valuable derivatives, which in many cases have suitable handles for further functionalisation.

The scope of the alkene component has been assessed using quinoline *N*-oxide **1a** as the heteroarene partner

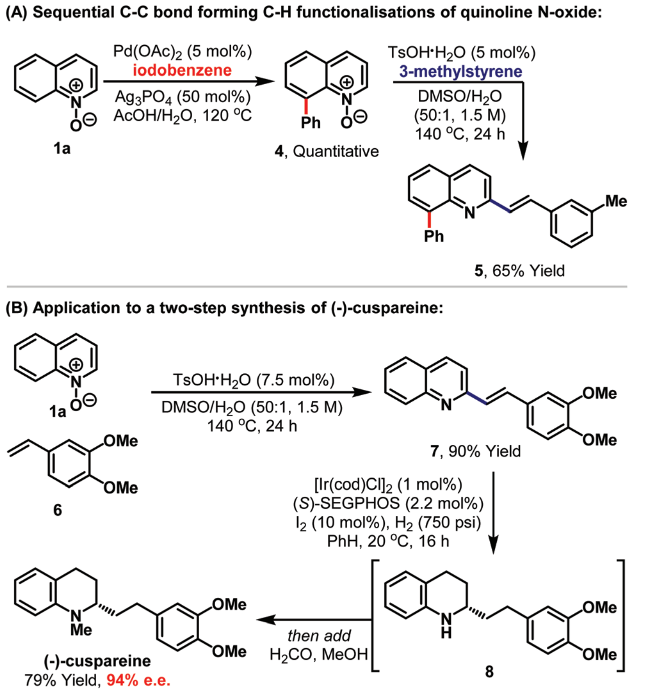
Table 2 Scope and limitations of the Brønsted acid catalysed C2-alkenylation protocol



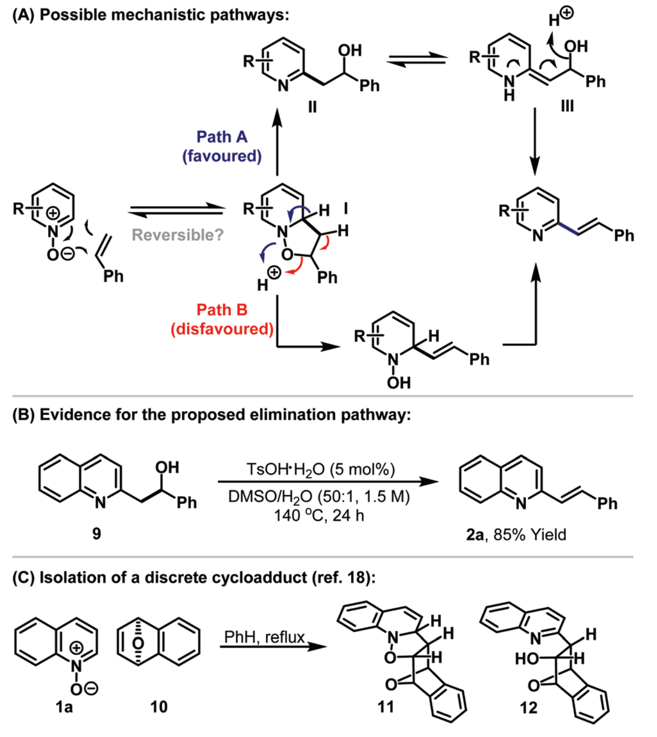
[a] Selectivities were determined by ^1H NMR analysis of crude material. [b] Ac_2O (100 mol%) employed as additive. [c] TFA (5 mol%) used as catalyst in 50 : 1 NMP : H_2O (v/v).

(Table 2B). Diverse mono-substituted aryl- and heteroaryl-alkenes are tolerated, with acceptable to high yields achieved in each case. More heavily substituted alkenes also participate, but generate the targets with lower efficiency. For example, alkenylation of quinoline *N*-oxide with indene provide adduct **3g** in 39% yield. Likewise, α-methyl styrene did participate, but target **3e** was generated in only 27% yield, albeit as a single geometric isomer. The directness of the approach may make it suitable for combinatorial synthesis were the operational simplicity of the protocol can offset any inherent inefficiencies. Preliminary results suggest that other classes of alkene may also be effective; for example, 1-phenyl butadiene provided adduct **3k** in 51% yield. Using the current conditions, electron deficient alkenes are not suitable and methyl acrylate generated β-heteroarylated system **3l** in only 17% yield.[14]

The protocol seems well suited to multistep synthetic sequences and we have demonstrated this in contexts where the method is used in tandem with transition metal catalysis (Scheme 2A). Pd-catalysed C8-selective arylation of quinoline *N*-oxide **1a**, using iodobenzene, proceeded smoothly under conditions reported by Larionov and co-workers.[13f] Adduct **4**, in which the *N*-oxide is still intact, then underwent Brønsted acid catalysed C2-alkenylation to provide disubstituted quinoline **5** in 65% yield. In this approach, serial metal-Brønsted acid catalysis is used to achieve sequential C–C bond forming C–H functionalisations, where the *N*-oxide first acts as a directing group and then as an internal oxidant. The method also has the potential to streamline syntheses of natural product targets. For example, Brønsted acid catalysed union of commercially available styrene **6** and *N*-oxide **1a** afforded alkenylation product **7** in 90% yield (Scheme 2B). Hydrogenation of the alkene and pyridine units was then achieved under asymmetric Ir-catalysed conditions reported by Zhou and co-workers to provide tetrahydroquinoline **8**.[15] To maximise use of the valuable Ir-catalyst, this intermediate was not isolated, and instead the vessel was depressurised and a solution of aqueous formaldehyde in methanol was added. Re-pressurisation with hydrogen then facilitated iridium-catalysed reductive amination to install the *N*-methyl group of (−)-cuspareine, which was formed in 79% yield and 94% ee, thereby constituting the most efficient synthesis of this antimalarial alkaloid



Scheme 2 Integration of the Brønsted acid catalysed C2-alkenylation protocol into synthetic sequences.



Scheme 3 Mechanistic considerations for the C2-alkenylation process.

reported to date.[16,17] Note that the only stoichiometric by-product of the entire sequence is water.

The C2-alkenylation process likely proceeds *via* initial dearomatising 1,3-dipolar cycloaddition between the *N*-oxide and the alkene (Scheme 3A).[18,19] This provides intermediate **I**, which can undergo acid catalysed elimination *via* either the N–O (Path A) or C–O bond (Path B). The former seems more likely, given that N–O bonds are generally weaker and because elimination *via* this pathway directly re-establishes aromaticity. Acid catalysed elimination of the hydroxyl group may be facilitated by tautomerisation to enamine **III** rather than occurring directly from **II**.[20] In most cases we have not observed the intermediate alcohol during the course of the reaction, which indicates that this process occurs reasonably fast. The proposed elimination mechanism is based on the observations that (a) only mild acidic conditions are required, (b) elimination still occurs for processes involving acrylates (see 3l) (which should disfavour E1 elimination from **II**) and (c) the efficiency of elimination is dependent on the heteroarene moiety. This latter assertion is based on the observation that for **2o** significant quantities of intermediate alcohol (approximately 65%) remained and this necessitated addition of acetic anhydride to effect complete elimination. To demonstrate the feasibility of the proposed elimination, we prepared alcohol **9** (see the ESI†). Subjection of this to optimised alkenylation conditions (in the absence of styrene) resulted in smooth dehydration to quinoline **1a** (Scheme 3B).

We suggest that the success of the alkenylation process relies upon the ability to trap efficiently isoxazolidine **I**. 1,3-Dipolar cycloadditions between aromatic *N*-oxides and alkenes to form discrete initial cycloadducts are rare, with the only documented cases involving strained alkenes.[18,19] Building on earlier work by Wittig and Steinhoff,[18a] Hisano and co-workers succeeded in isolating and characterising cycloaddition product **11**, derived from quinoline **1a** and alkene **10** (Scheme 3B).[18b] In the Wittig study ring cleavage product **12** was also observed (*cf.* **I** to **II**) although its stereochemistry was not confirmed.[18a] In other cases examined by Hisano, subsequent rearrangement processes were fast, which indicates that successful exploitation of **I** requires productive methods to divert it to target products.[19] For the processes outlined here this is achieved by acid catalysed capture of **I** to afford **II**. Significantly, in the absence of acid/water, no cycloaddition is observed and starting material is recovered intact (see Table 1, entry 15). This suggests that the cycloaddition step may be reversible. If reversibility is a factor then a key issue is the energetic penalty involved in the dearomatising cycloaddition step. The heterocyclic ring systems of quinolines and isoquinolines possess less aromatic stabilisation than pyridines,[21] and for this latter class, more electron deficient variants are more susceptible to dearomatisation.[22] These trends in stabilisation provide an appealing rationalisation for the relative ease of the alkenylation reactions outlined in Table 2. A more sophisticated interpretation, which might also explain the regioselectivities observed for pyridine and isoquinoline *N*-oxides, must take into account the orbital energy match during the cycloaddition step (*i.e.* the kinetic feasibility of the process).[23]

Conclusions

In summary, we report a simple Brønsted acid catalysed approach to the synthesis of diverse C2-alkenylated N-heteroaromatic compounds. The protocol relies on thermally promoted (3 + 2) dearomatising cycloaddition between an *N*-oxide and an alkene to generate an isoxazolidine. The Brønsted acid catalyst then promotes N–O cleavage and dehydration to the target. We believe the method has high utility because (a) it is operationally simple, (b) the Brønsted acid catalyst is cheap, non-toxic and sustainable, (c) the *N*-oxide activator disappears during the reaction, (d) water is the sole stoichiometric by-product of the process and (e) the functional group tolerance is orthogonal to metal-catalysed methods. Furthermore, we have demonstrated that the protocol can be integrated easily into synthetic sequences to provide polyfunctionalised targets, as exemplified by a highly concise synthesis of (−)-cuspareine and sequential *N*-oxide directed C–C bond forming C–H functionalisations of quinoline. Although inherently valuable, C2-alkenylated heteroarenes also function as precursors to C2-alkylated derivatives and as substrates for an emerging range of metal catalysed C–C/C–H bond forming processes.[24] Given these considerations and the simplicity of our approach, which takes advantage of an intermediate routinely used in other contexts,[1a] it is likely that the protocol described here will find wide utility in synthesis and pharmaceutical chemistry. In broader terms, this study demonstrates how classical organic reactivity can still be used to provide solutions to contemporary synthetic challenges that might otherwise be approached using transition metal catalysis.

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Notes and references

1 (*a*) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337; (*b*) V. Bonnet, F. Mongin, F. Trécourt, G. Breton, F. Marsais, P. Knochel and G. Quéguiner, *Synlett*, 2002, 1008.

2 For example, see: Y. Zou, G. Yue, J. Xu and J. Zhou, *Eur. J. Org. Chem.*, 2014, 5901.

3 For example, see: M. L. Kantam, P. V. Reddy, P. Srinivas and S. Bhargava, *Tetrahedron Lett.*, 2011, **52**, 4490.

4 Contemporary approaches rely on modified 2-pyridyl boron-based reagents. Selected examples: (*a*) K. L. Billingsley and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 4695; (*b*) G. R. Dick, D. M. Knapp, E. P. Gillis and M. D. Burke, *Org. Lett.*, 2010, **12**, 2314; (*c*) G. R. Dick, E. M. Woerly and M. D. Burke, *Angew. Chem., Int. Ed.*, 2012, **51**, 2667; (*d*) S. Sakashita, M. Takizawa, J. Sugai, H. Ito and Y. Yamamoto, *Org. Lett.*, 2013, **15**, 4308.

5 S. E. Wengryniuk, A. Weickgenannt, C. Reiher, N. A. Strotman, K. Chen, M. D. Eastgate and P. S. Baran, *Org. Lett.*, 2013, **15**, 792 and references cited therein.

6 An alternative method involves metal catalysed condensation of 2-methyl N-heteroarenes with aldehydes or imines. This approach requires prior installation of a methyl substituent. Selected recent examples: (*a*) B. Qian, P. Xie, Y. Xie and H. Huang, *Org. Lett.*, 2011, **13**, 2580; (*b*) Z. Jamal and Y.-C. Teo, *Synlett*, 2014, 2049.

7 Seminal studies: (*a*) L.-C. Campeau, S. Rousseaux and K. Fagnou, *J. Am. Chem. Soc.*, 2005, **127**, 18020; (*b*) L.-C. Campeau, D. J. Schipper and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 3266; (*c*) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier and K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 3291.

8 Examples of C2 selective C–H alkenylations of pyridine *N*-oxides: (*a*) K. S. Kanyiva, Y. Nakao and T. Hiyama, *Angew. Chem., Int. Ed.*, 2007, **46**, 8872; (*b*) S. H. Cho, S. J. Hwang and S. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 9254; (*c*) L. Ackermann and S. Fenner, *Chem. Commun.*, 2011, **47**, 430.

9 C2 selective C–H alkenylation of pyridines have also been achieved. Selected processes: (*a*) Y. Nakao, K. S. Kanyiva and T. Hiyama, *J. Am. Chem. Soc.*, 2008, **130**, 2448; (*b*) P. Wen, Y. Li, K. Zhou, C. Ma, X. Lan, C. Ma and G. Huang, *Adv. Synth. Catal.*, 2012, **354**, 2135.

10 Examples where *N*-oxides direct metal catalysed C–H activation and serve as the internal oxidant: (*a*) J. Wu, X. Cui, L. Chen, G. Jiang and Y. Wu, *J. Am. Chem. Soc.*, 2009, **131**, 13888; (*b*) X. Huang, J. Huang, C. Du, X. Zhang, F. Song and J. You, *Angew. Chem., Int. Ed.*, 2013, **52**, 12970; (*c*) B. Zhou, Z. Chen, Y. Yang, W. Ai, H. Tang, Y. Wu, W. Zhu and Y. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 12121. See also ref. 13*c* and *g*. For a complementary strategy involving initial nucleophilic addition, see: (*d*) O. V. Larionov, D. Stephens, A. Mfuh and G. Chavez, *Org. Lett.*, 2014, **16**, 864.

11 L. Bering and A. P. Antonchick, *Org. Lett.*, 2015, **17**, 3134.

12 During the preparation of this manuscript Gou, Wang and co-workers reported a conceptually similar approach: H. Xia, Y. Liu, P. Zhao, S. Gou and J. Wang, *Org. Lett.*, 2016, **18**, 1796. This protocol was strictly limited to quinoline-based systems, and required super-stoichiometric acetic acid (300 mol%) in combination with a large excess of the alkene (1000 mol%) (*cf.* this study: C2-alkenylation of quinoline, isoquinoline *and* pyridine *N*-oxides using just 5 mol% TsOH with 300–500 mol% of the alkene partner). See also: R. Kumar, I. Kumar, R. Sharma and U. Sharma, *Org. Biomol. Chem.*, 2016, **14**, 2613.

13 Selected examples of quinoline *N*-oxide directed C8-functionalisation with Rh or Ir catalysts: (*a*) H. Hwang, J. Kim,

J. Jeong and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 10770; (*b*) J. Jeong, P. Patel, H. Hwang and S. Chang, *Org. Lett.*, 2014, **16**, 4598; (*c*) X. Zhang, Z. Qi and X. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 10794; (*d*) T. Shibata and Y. Matsuo, *Adv. Synth. Catal.*, 2014, **356**, 1516; (*e*) S. Konishi, S. Kawamorita, T. Iwai, P. G. Steel, T. D. Marder and M. Sawamura, *Chem. – Asian J.*, 2014, **9**, 434; (*f*) D. E. Stephens, J. Lakey-Beitia, A. C. Atesin, T. A. Ateşin, G. Chavez, H. D. Arman and O. V. Larionov, *ACS Catal.*, 2015, **5**, 167; (*g*) R. Sharma, R. Kumar, I. Kumar and U. Sharma, *Eur. J. Org. Chem.*, 2015, 7519; (*h*) K. Shin, S.-W. Park and S. Chang, *J. Am. Chem. Soc.*, 2015, **137**, 8584; (*i*) D. E. Stephens, J. Lakey-Beitia, G. Chavez, C. Ilie, H. D. Arman and O. V. Larionov, *Chem. Commun.*, 2015, **51**, 9507, For a review, see: (*j*) T. Iwai and M. Sawamura, *ACS Catal.*, 2015, **5**, 5031.

14 See ref. 10*a* and 12 for protocols that partially address this issue. Aliphatic alkenes are not suitable reaction partners.

15 (*a*) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 10536; (*b*) D.-W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, Y.-G. Zhou and Y.-X. Li, *J. Org. Chem.*, 2009, **74**, 2780.

16 J. H. Rakotoson, N. Fabre, I. Jacquemond-Collet, S. Hannedouche, I. Fourasté and C. Moulis, *Planta Med.*, 1998, **64**, 762.

17 For a review on syntheses of (−)-cuspareine and related alkaloids, see: G. D. Muñoz and G. B. Dudley, *Org. Prep. Proced. Int.*, 2015, **47**, 179.

18 (*a*) G. Wittig and G. Steinhoff, *Justus Liebigs Ann. Chem.*, 1964, **676**, 21; (*b*) T. Hisano, K. Harano, T. Matsuoka, T. Suzuki and Y. Murayama, *Chem. Pharm. Bull.*, 1990, **38**, 605 and references cited therein.

19 For further selected processes where rearrangement (often [1,5]-sigmatropic) occurs after cycloaddition, see: (*a*) R. A. Abramovitch and I. Shinkai, *J. Am. Chem. Soc.*, 1974, **96**, 5265; (*b*) R. E. Banks, R. N. Haszeldine and J. M. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1226; (*c*) T. Matsuoka, T. Hasegawa, K. Harao and T. Hisano, *Heterocycles*, 1992, **33**, 179; (*d*) H. J. Lindner, A. Krebs, J.-H. Förster and V. Sinnwell, *Heterocycles*, 1997, **45**, 811; (*e*) P. Jeschke, A. Harder, W. Etzel, W. Gau, A. Göhrt, J. Benet-Buchholz and G. Thielking, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2375; (*f*) C. Raminelli, Z. Liu and R. C. Larock, *J. Org. Chem.*, 2006, **71**, 4689; (*g*) R. Loska and M. Mąkosza, *Chem. – Eur. J.*, 2008, **14**, 2577.

20 Similar acid-catalysed tautomerisations (**II** to **III**) are known to be facile: M. Rueping and N. Tolstoluzhsky, *Org. Lett.*, 2011, **13**, 1095. The proposed mechanism is akin to that determined for acid-catalysed aldol condensation of acetaldehyde to crotonaldehyde: L. M. Baigrie, R. A. Cox, H. Slebocka-Tilk, M. Tencer and T. T. Tidwell, *J. Am. Chem. Soc.*, 1985, **107**, 3640. The beneficial effects that water provides may be due to it facilitating tautomerisation or acting as a general catalyst for other steps. At the present stage, direct elimination of water from **II** cannot be discounted.

21 M. Mandado, N. Otero and R. A. Mosquera, *Tetrahedron*, 2006, **62**, 12204.

22 For a review, see: Q. Ding, X. Zhou and R. Fan, *Org. Biomol. Chem.*, 2014, **12**, 4807.

23 Computational studies on the processes described here will be a focus of future work.

24 For examples of metal catalysed C–C and C–H bond forming manipulations of 2-vinyl pyridines, see: (*a*) V. Komanduri, C. D. Grant and M. J. Krische, *J. Am. Chem. Soc.*, 2008, **130**, 12592; (*b*) L. Rupnicki, A. Saxena and H. W. Lam, *J. Am. Chem. Soc.*, 2009, **131**, 10386; (*c*) G. Pattison, G. Piraux and H. W. Lam, *J. Am. Chem. Soc.*, 2010, **132**, 14373.