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## COMMUNICATION

Synthesis of 2,4,6-Trisubstituted Pyridines *via* an Olefin Cross-Metathesis/Heck-Cyclisation-Elimination Sequence.Timothy J. Donohoe,<sup>\*a</sup> John F. Bower,<sup>a</sup> David B. Baker,<sup>a</sup> José A. Basutto,<sup>a</sup> Louis K. M. Chan<sup>a</sup> and Peter Gallagher<sup>b</sup><sup>5</sup> Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

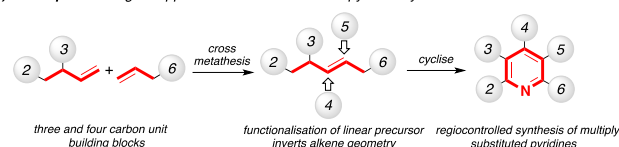
DOI: 10.1039/b000000x

The olefin cross metathesis reaction provides an efficient<sup>0</sup> method for the synthesis of  $\alpha,\beta$ -unsaturated- $\delta$ -sulfonamido ketones as (*E*)-linear precursors for pyridine synthesis. A Heck reaction was performed on this linear intermediate to install substitution at the C-4 position and simultaneously inverts the geometry of the double bond. Subsequent one-pot cyclisation/elimination provides an operationally simple, catalytic and convergent synthesis of 2,4,6-trisubstituted pyridines.

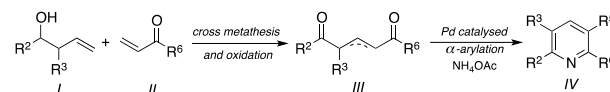
Substituted pyridines are a unique class of compounds that feature heavily in several pharmaceutical targets, as well as being a common motif in many natural products.<sup>1</sup> In addition, many ligands used in transition metal catalysis also contain substituted pyridines.<sup>2</sup> Consequently, a range of *de novo* methods for pyridine synthesis have emerged.<sup>3,4</sup> As a counterpoint to this approach, methods for the functionalisation of existing pyridines are also well documented.<sup>5</sup> Recently described methods for the catalytic direct functionalisation of pyridine and its derivatives have also proved attractive but are mainly limited to the C-2 and C-3 positions,<sup>6</sup> although an isolated example has been reported for the direct functionalisation of pyridines at the C-4 position.<sup>7</sup>

We have previously demonstrated that a disconnection using a tandem cross metathesis (CM)/Heck coupling could provide a facile entry into highly substituted furans and pyrroles.<sup>8</sup> Extension of this strategy should also provide a regio-controlled, catalytic route to multi-substituted pyridines, in a convergent manner (Scheme 1a). Recent work in our laboratory has demonstrated that using the CM between *I* and *II* could provide 1,5-dicarbonyl intermediates *III* (Scheme 1b). Further functionalisation using a Pd catalysed  $\alpha$ -arylation reaction led to a short route into 2,3,5,6-tetrasubstituted pyridines *IV*.<sup>9</sup> However, the introduction of a substituent at C-4 was not possible *via* this chemistry.

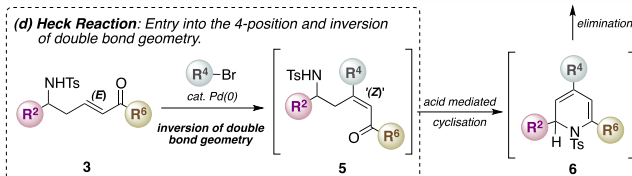
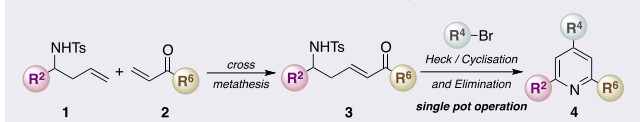
(a) Concept: Convergent approach for multisubstituted pyridine synthesis.



(b) Previous Work: Synthesis of 2,3,5,6-tetrasubstituted pyridines. (ref 9)



(c) This Work: Synthesis of 2,4,6-trisubstituted pyridines using a cross metathesis/Heck sequence.

**Scheme 1.** Cross metathesis approach for the synthesis of unsymmetrical 2,4,6-trisubstituted pyridines.

We were interested in further investigating the utility of the CM based approach for synthesising pyridines with different substitution patterns, especially those allowing access to the C-4 position. With this goal in mind, we envisaged that the CM between homoallylic sulfonamides **1** with vinyl ketones **2** would provide  $\alpha,\beta$ -unsaturated- $\delta$ -sulfonamido ketones **3**, as key synthetic intermediates for elaboration (Scheme 1c). Further functionalisation using the Heck reaction should allow the introduction of substitution at the 4-position. Therefore, the proposed route provides a complementary substitution pattern around the pyridine ring when compared to our previous work. Note that the success of this method relies on the well-established inversion of the double bond geometry during the Heck reaction to provide a '(Z)'-trisubstituted alkene **5** (Scheme 1d).<sup>10</sup> Cyclisation promoted by acidic conditions should take place to form **6** and subsequent elimination of sulfinate would allow the formation of the desired

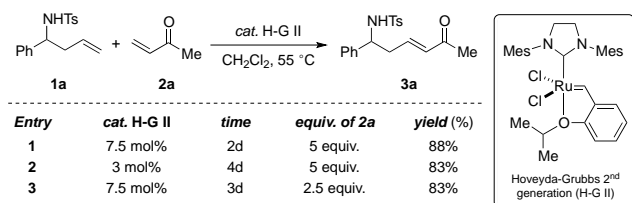
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<sup>†</sup> Electronic Supplementary Information (ESI) available: Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra and experimental procedures are available. See DOI: 10.1039/b000000x/

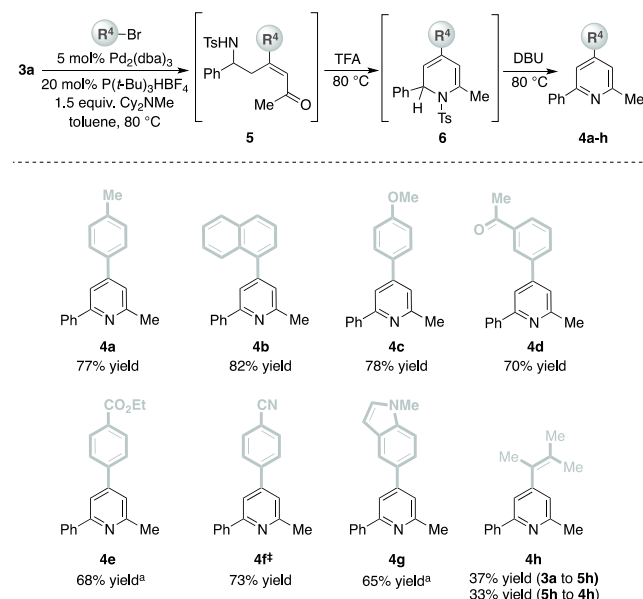
trisubstituted pyridines.<sup>11</sup>

We were pleased to find that cross metathesis using the air stable Hoveyda-Grubbs 2<sup>nd</sup> generation (H-G II) catalyst with homoallylic sulfonamide **1a** and methyl vinyl ketone **2a** afforded **3a**. It was found that 7.5 mol% of H-G II catalyst with 5 equivalents of the vinyl ketone **2a** were optimal to drive the formation of the CM product (Scheme 2, entry 1).<sup>12</sup> It was possible to obtain as good yields of the CM product by either lowering the catalyst loading to 3 mol% or reducing the stoichiometry of **2a**, but longer reaction times were required (Entries 2-3).



Scheme 2. Cross metathesis of **1a** and **2a**.

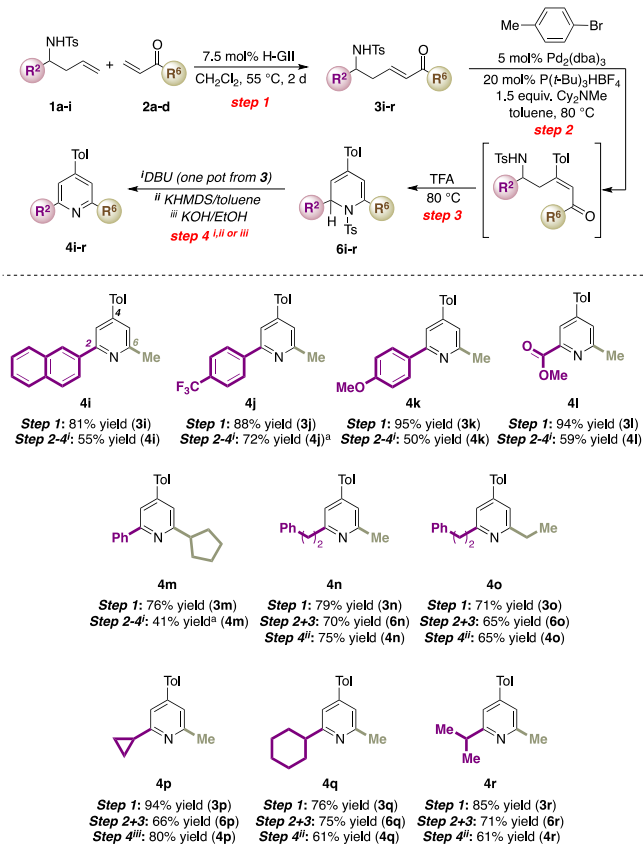
Upon examining the scope of the Heck reaction, it was found that electron neutral (**4a,b**), electron rich (**4c**) and electron deficient (**4d-f**) aryl bromides worked well in the Heck reaction (Scheme 3). Typical conditions for the Heck reaction require 5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub> and 20 mol% P(*t*-Bu)<sub>3</sub>HBF<sub>4</sub>, as a monodentate bulky electron rich ligand.<sup>13</sup> The cyclisation/elimination procedure was also optimised such that upon completion of the Heck reaction by TLC analysis, sequential addition of trifluoroacetic acid (TFA) and then 1,8-diazabicycloundec-7-ene (DBU) would furnish directly the desired pyridines conveniently in a one-pot process, without the need to isolate the intermediates **5** or **6**.<sup>14</sup> We were delighted to find that heteroaromatics such as *N*-methylindole also underwent the one-pot Heck/cyclisation/elimination to give **4g** in a respectable 65% yield.



Scheme 3. Scope of the one-pot Heck-reaction/cyclisation/elimination on **3a**. <sup>a</sup>10 mol% Pd<sub>2</sub>(dba)<sub>3</sub>, 40 mol% P(*t*-Bu)<sub>3</sub>HBF<sub>4</sub> were used.

Despite the extensive use of vinyl halides in Pd(0) catalysed cross coupling reactions, we were surprised to find only limited examples of intermolecular Heck reactions that have been reported using vinyl halides.<sup>15</sup> Our efforts into effecting a one-pot pyridine formation from **3a** that involves a vinyl substitution at the C-4 position were not successful. However, a low yield of the Heck intermediate **5h** could be isolated. Cyclisation/elimination to give **4h** were also performed but again a poor yield was obtained. Thus, at the current time the introduction of substitution at C-4 is most effective with aromatic groups.

To further expand the utility of this reaction, a range of homoallylic sulfonamides **1a-i** were subjected to CM with different vinyl ketones **2a-c** (Scheme 4). We found that CM reactions under these conditions are highly reliable and gave good to excellent yields of **3i-r**.<sup>16</sup> When the optimised one-pot procedure (steps 2-4) was carried out with bromotoluene as the Heck coupling partner, we found that intermediates with aryl (**3i-k**) and ester (**3l**) moieties as the R<sup>2</sup> component worked well in the Heck reaction/cyclisation/elimination reaction to furnish **4i-l** in moderate to good yields over three steps.<sup>17</sup>



Scheme 4. Scope of the R<sup>2</sup> and R<sup>6</sup> components in the pyridine formation. <sup>a</sup>10 mol% Pd<sub>2</sub>(dba)<sub>3</sub>, 40 mol% P(*t*-Bu)<sub>3</sub>HBF<sub>4</sub> were used.

Surprisingly, when the R<sup>6</sup> substituents on **3m** were bulky aliphatic components, it was found that the Heck reactions became very stubborn. Lower yields of **4m** were obtained despite increased loading of the catalyst (Scheme 4). In order to overcome this problem, bulky aliphatic groups could be installed as the R<sup>2</sup> components instead. We were pleased to find that the Heck

reaction/cyclisation (steps 2 and 3) with  $R^2 = n$ -alkyl (**3n-o**) and  $s$ -alkyl (**3p-r**) all worked well to furnish **6n-r** in good yields. Due to the absence of a neighbouring trigonal centre in these cases,  $R^2$  does not benefit from a lowered  $pK_a$  (in **6n-r**) and so the elimination (step 4) was modified such that upon isolation of **5n-r**, treatment with either KHMDS/toluene or KOH/EtOH gave the desired trisubstituted pyridines in good yields.

## Conclusions

We have successfully extended our investigation into using a cross metathesis approach for the synthesis of heteroaromatics. A representative library of unsymmetrical 2,4,6-trisubstituted pyridines were synthesised. Problems with C-4 functionalisation that we have previously encountered were overcome using a Heck reaction following the cross metathesis. Such key catalytic carbon-carbon bond formation steps (CM and Heck) described herein, provide a simple, convergent and regio-controlled synthesis.

## Notes and references

The authors would like to thank the EPSRC and Eli Lilly Ltd. for financial support.

† Single crystal diffraction data for **4f** were collected at 150 K<sup>18</sup> using a Nonius Kappa CCD Diffractometer ( $\lambda = 0.71073 \text{ \AA}$ ). Data were reduced using DENZO/SCALEPACK.<sup>19</sup> The structure was solved with SuperFlip<sup>20</sup> and refined by full-matrix least squares on  $F^2$  using CRYSTALS.<sup>21</sup> All non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were treated in the usual manner.<sup>22</sup> See the SI/CIF for full refinement details; crystallographic data (excluding structure factors) will be deposited with the Cambridge Crystallographic Data Centre (CCDC XXXXXX-XX) upon acceptance for publication and can be obtained via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

**Single Crystal Data:**  $C_{19}H_{14}N_2O_6$ ,  $M_r = 270.33$ , triclinic,  $P\bar{1}$ ,  $a = 8.0582(2) \text{ \AA}$ ,  $b = 9.9181(3) \text{ \AA}$ ,  $c = 9.9557(3) \text{ \AA}$ ,  $\alpha = 62.2103(15)^\circ$ ,  $\beta = 85.9715(14)^\circ$ ,  $\gamma = 87.9363(12)^\circ$ ,  $V = 702.17(4) \text{ \AA}^3$ , Data/restraints/parameters = 3194/0/190,  $R_{\text{int}} = 0.019$ , Final  $R_1 = 0.0431$ ,  $wR_2 = 0.1084$  ( $I > 2\sigma(I)$ ),  $\Delta\rho_{\text{min,max}} = -0.22, +0.29 \text{ e.\AA}^{-3}$ .

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## Graphical Abstract

