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Synthesis of 2,4,6-trisubstituted pyridines *via* an olefin cross-metathesis/Heck–cyclisation–elimination sequence†

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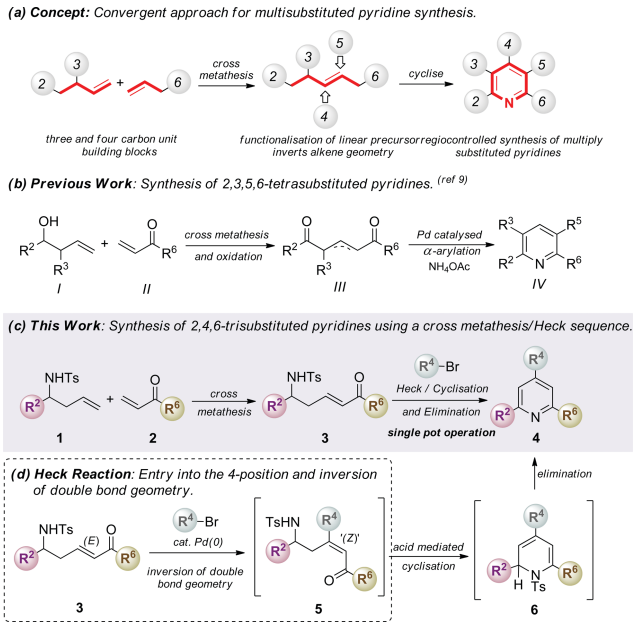
Heck reactions were performed on α,β-unsaturated-δ-sulfonamido intermediates, derived from cross metathesis, to allow the instalment of substituents at the β position. Subsequent one-pot cyclisation/elimination provides an operationally simple, catalytic and convergent synthesis of 2,4,6-trisubstituted 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.[1] In addition, many ligands used in transition metal catalysis also contain substituted pyridines.[2] Consequently, a range of *de novo* methods for pyridine synthesis have emerged.[3,4] As a counter-point to this approach, methods for the functionalisation of existing pyridines are also well documented.[5] 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,[6] although an isolated example has been reported for the direct functionalisation of pyridines at the C-4 position.[7]

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.[8] 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 α-arylation reaction led to a short route into 2,3,5,6-tetrasubstituted pyridines *IV*.[9] However, the introduction of a substituent at C-4 was not possible *via* this chemistry. 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.



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

With this goal in mind, we envisaged that the CM between homoallylic sulfonamides **1** with vinyl ketones **2** would provide α,β-unsaturated-δ-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).[10] Cyclisation promoted by acidic conditions should take place to form **6** and subsequent elimination of sulfinate would allow the formation of the desired trisubstituted pyridines.[11]

We were pleased to find that cross metathesis using the air stable Hoveyda–Grubbs 2nd 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*).[12] It was

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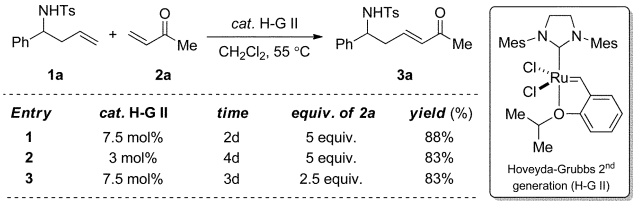


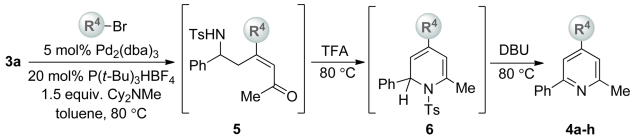
Entry	cat. H-G II	time	equiv. of 2a	yield (%)
1	7.5 mol%	2d	5 equiv.	88%
2	3 mol%	4d	5 equiv.	83%
3	7.5 mol%	3d	2.5 equiv.	83%

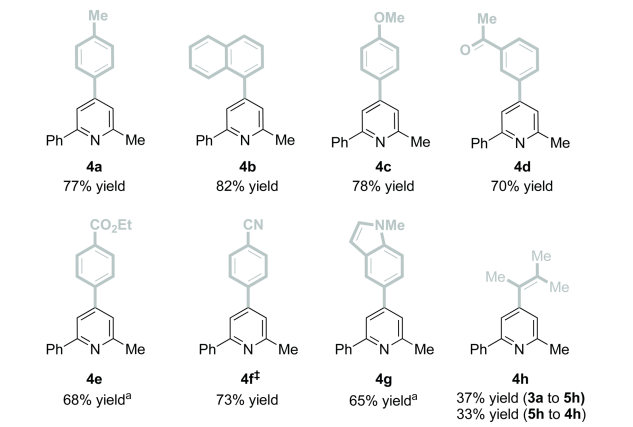
Scheme 2 Cross metathesis of **1a** and **2a**.

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 and 3*).

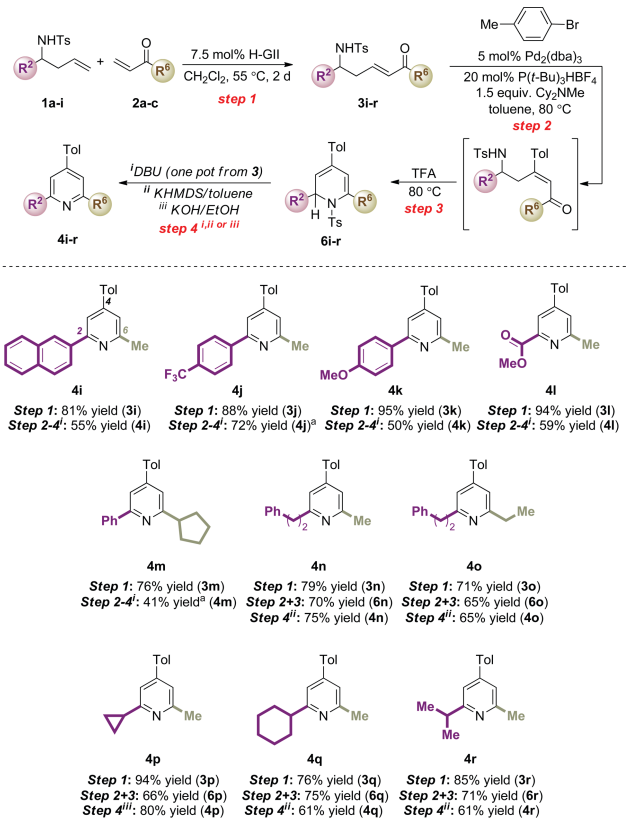
Upon examining the scope of the Heck reaction, it was found that electron neutral (**4a,b**), electron rich (**4c**) and electron deficient (**4d–f**) aryl bromides worked well in the Heck reaction (Scheme 3).‡ Typical conditions for the Heck reaction require 5 mol% of $Pd_2(dba)_3$ and 20 mol% $P(t\text{-}Bu)_3HBF_4$, as a monodentate bulky electron rich ligand.[13] 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**.[14] 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.

Despite the extensive use of vinyl halides in Pd(0) catalysed cross coupling reactions, we were surprised to find that only limited examples of intermolecular Heck reactions have been reported using vinyl halides.[15] 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





Scheme 3 Scope of the one-pot Heck-reaction/cyclisation/elimination on **3a**. [a]10 mol% $Pd_2(dba)_3$, 40 mol% $P(t\text{-}Bu)_3HBF_4$ were used.



Scheme 4 Scope of the R^2 and R^6 components in the pyridine formation. [a]10 mol% $Pd_2(dba)_3$, 40 mol% $P(t\text{-}Bu)_3HBF_4$ were used.

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**.[16] 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^2 component worked well in the Heck reaction/cyclisation/elimination reaction to furnish **4i–l** in moderate to good yields over three steps.[17]

Surprisingly, when the R^6 substituents on **3m** were bulky aliphatic or aryl components, it was found that the Heck/cyclisation sequence became very stubborn.[18] 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^2 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.

We have successfully extended our investigation into using a cross metathesis approach for the synthesis of heteraromatics

and a representative library of unsymmetrical 2,4,6-trisubstituted pyridines has been 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.

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Notes and references

‡ Single crystal diffraction data for **4f** were collected at 150 K[19] using a Nonius Kappa CCD Diffractometer (λ = 0.71073 Å). Data were reduced using DENZO/SCALEPACK.[20] The structure was solved with SuperFlip[21] and refined by full-matrix least squares on F^2 using CRYSTALS.[22] All non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were treated in the usual manner.[23] See ESI† for full refinement details; CCDC 834833.

Single crystal data: $C_{19}H_{14}N_2O_6$, M_r = 270.33, triclinic, $P\bar{1}$. a = 8.0582(2) Å, b = 9.9181(3) Å, c = 9.9557(3) Å, α = 62.2103(15)°, β = 85.9715(14)°, γ = 87.9363(12)°, V = 702.17(4) Å, data/restraints/parameters—3194/0/190, R_{int} = 0.019, final R_1 = 0.0431, wR_2 = 0.1084 ($I > 2\sigma(I)$), $\Delta\rho_{min,max}$ = −0.22, +0.29 e Å^3.

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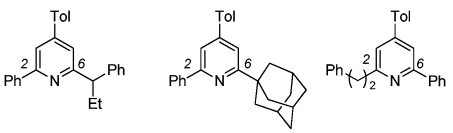
17 The structure of pyridine **4l** was confirmed by characteristic NOE enhancements. See ESI† for full details.

18 Despite an efficient cross metathesis (step 1), our efforts to persuade other substrates to undergo a one pot Heck (step 2) and cyclisation (step 3) resulted either in low conversion or decomposition. Ongoing work to widen the scope will be reported in due course



step 1: 68%
step 2: 73%
step 3: unreactive

step 1: 73%
step 2+3: decomposition

step 1: 65%
step 2: 23%

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