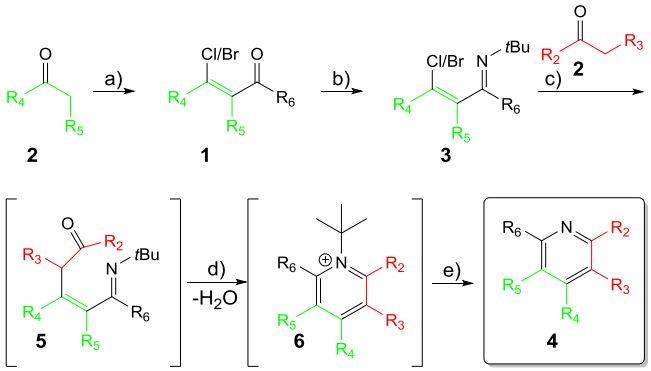
Scientific results

The formation of multiply and selectively substituted pyridines is still a synthetic challenge in the 21st century. In view of the scale of production of various pyridine compounds and the importance of pyridines in the pharmaceutical, agrochemical, and material sciences, a facile and short synthetic route to highly and selectively substituted pyridines is very desirable.

Vinyl compounds **1** can be obtained in one step from ketones **2** in a Vielsmeier haloformylation reaction (Scheme 1).[1] Upon treatment of aldehyde **1** (R_6 = H) with *tert*-butylamine, the corresponding preformed imines **3** were subsequently subjected to a Pd-catalyzed cross-coupling/cyclization/double elimination reaction cascade with ketones **2** under basic conditions to afford pyridines **4** with four substituents introduced selectively. A screening of conditions (solvents, bases and their loadings, catalysts, and temperatures) found conditions with which 2,3,4,5-tetra-substituted pyridines **4** could be obtained from the corresponding vinyl aldehydes **1** in two synthetic steps and in up to 80% yield (Figure 1).[2] The methodology allows the synthesis of pyridines containing ethers (**4a,e,f**), cyclic substrates (**4k,l**), electron-rich (**4a,e,f**), electron-deficient (**4d,g**) and hetero-aromatic rings (**4h,i**) (Figure 1). Importantly, no conversion of **5a** was observed in the absence of palladium. The reaction was also found to give similar yields (up to 80%) when vinyl chlorides instead of vinyl bromides were employed (Figure 1. **4a**, **4j** and **4k**)



Scheme 1: Reagents and conditions: a) $POCl_3$ or $POBr_3$, DMF, 40 °C; b) *t*$BuNH_2$, molecular sieves, CH_2Cl_2, 45 °C; c) (D*t*BPF)$PdCl_2$ or $(Amphos)_2PdCl_2$, LiHMDS, toluene, 70 °C; d) 90 °C; e) 120 °C.

During the course of the optimization, it was found that the employment of a temperature gradient was crucial for the success of the reaction. Monitoring of the reaction progress by MS showed that the cross-coupling between vinyl bromide **1** and ketone **2** occurred at 70 °C, cyclization to intermediate **5** at 90 °C and elimination from **6** at 120 °C. Starting the reaction at 110 °C, on the other hand, led to mostly dehalogenated vinyl derivatives **1**.

[1] B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan, T. G. Driver, *Org. Lett.* **2010**, *12*, 2884–2887.

[2] L. A. Hardegger, J. Habegger, T. J. Donohoe, *unpublished results*

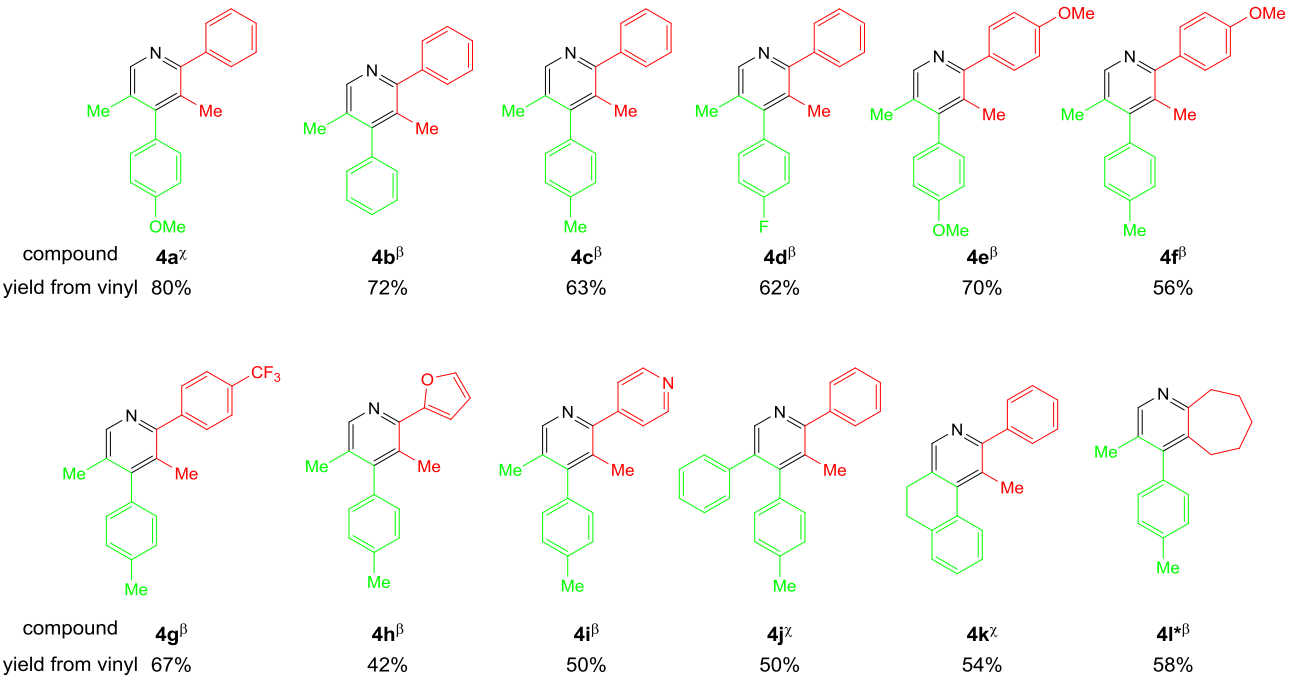


Figure 1. Pyridines **4a–l** synthesized *via* enolate α-vinylation. χ: starting from the corresponding vinyl chloride, β: starting from the corresponding vinyl bromide, *2.5 eq. LDA used.

Conclusion

In summary, a novel methodology based on the palladium-catalyzed enolate α-vinylation of imines was developed to afford a variety of pyridines (**4a–n**) in only three synthetic steps from commercially available compounds. Notably, the reactions described herein represent enolate α-vinylations with more functionality than those reported in literature. To the best of our knowledge, intermolecular enolate α-vinylations have so far only been described for vinyl derivatives with simple, non-functionalized alkyl and aryl substituents.

Socio-economic Impact

Pyridine is the single most important heterocycle in medicinal chemistry. Given its importance in other fields of research such as the agrochemical sector and the materials industry, novel ways for the selective synthesis of pyridines are highly desirable. Our approach relies on catalysis, thereby increasing atom efficiency of any synthesis and reducing waste and production costs. The selective and direct formation of pyridines also facilitates their purification and hence reduces again the time needed for their synthesis and reducing the amount of resources needed.

The future of synthetic chemistry lies in the development of atom-efficient, reliable, and user-friendly procedures for the synthesis of highly valuable and complex chemicals. With our methodology, we have contributed a significant development step for the synthesis of highly and selectively substituted pyridines.