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An enantioselective synthesis of α-alkylated pyrroles *via* cooperative isothiourea/palladium catalysis†

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Herein we describe the direct enantioselective Lewis base/Pd catalysed α-allylation of pyrrole acetic acid esters. This provides high isolated yields of highly enantioenriched products and exhibits broad reaction scope with respect to both reaction partners. The products can be readily elaborated in a manner which points towards potential applications in target directed synthesis.

A large number of natural and designed molecules possess an alkyl-bearing stereogenic centre next to the 2-position of the pyrrole ring. This is exemplified by the pyrrolidizine alkaloid dehydroretronecine **1**[1] and the commercial analgesic α-ketorolac **3** (Fig. 1),[2] but also extends to the indolizidine alkaloid tashiromine **2**[3] and the complex naturally-occurring chemotherapeutic mitomycin C **4**,[4] where the corresponding pyrrolidine framework might reasonably be accessed *via* directed reduction of an appropriate α-chiral pyrrole precursor scaffold.[5]

Our laboratory has continued interest in the potential of cooperative Lewis base/transition metal-catalysed reactions as a means to prepare important yet synthetically challenging molecular scaffolds in enantioenriched form. Our prior efforts in this area have established C1-ammonium enolates as effective nucleophiles for transition metal electrophiles such as cationic π(ally)Pd intermediates.[6,7] Critical to the demonstrated efficiency and generality of this cooperative two-catalyst construct is the separation of the source of enantiocontrol (administered by the Lewis base) from the Pd centre. This permits the reactivity of the Pd-catalyst to modified and modulated without compromising the levels of enantioselectivity and is therefore complementary to existing asymmetric transition metal catalysis, which relies on ligand-centred stereocontrol.[6]

Driven by the clear value of synthetic access to α-chiral 2-pyrrole acetic acids we expected that C1-ammonium enolates derived from pyrrole-acetic acid esters would engage a wide range of π(allyl)Pd electrophiles to provide a general method by which to prepare these valuable scaffolds (Fig. 1, **5**). While C1-ammonium enolates have a prodigious history as ester enolate equivalents in asymmetric Lewis base catalysis,[8] only recently have these species been directed toward the preparation of important α-chiral pyrrole scaffolds. In seminal advances, Smith and colleagues have described enantioselective isothiourea Lewis base catalysed Michael addition reactions of C1-ammonium enolates derived from pyrrole-containing carboxylic acids **6** and **9** (Scheme 1, a and b).[9] Firstly, a one pot *intramolecular* Michael addition/lactonization/ring opening sequence provides ready access to useful 5/5 bicyclic pyrrole scaffolds reminiscent of pyrrolizidine alkaloids in high yield and with high levels of diastereo- and enantioselectivity (Scheme 1a).[9a] Secondly, enantioselective *intermolecular* Michael addition to acceptor **10** proceeded *via* a similar mechanism to provide products **11** bearing *trans*-configured vicinal stereocentres.[9b] The significance of this latest study is

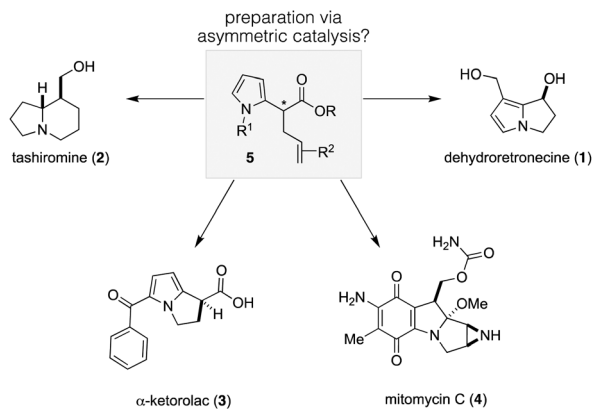

Fig. 1 Representative natural products and pharmaceuticals possessing the α-alkyl 2-pyrrole substructure.

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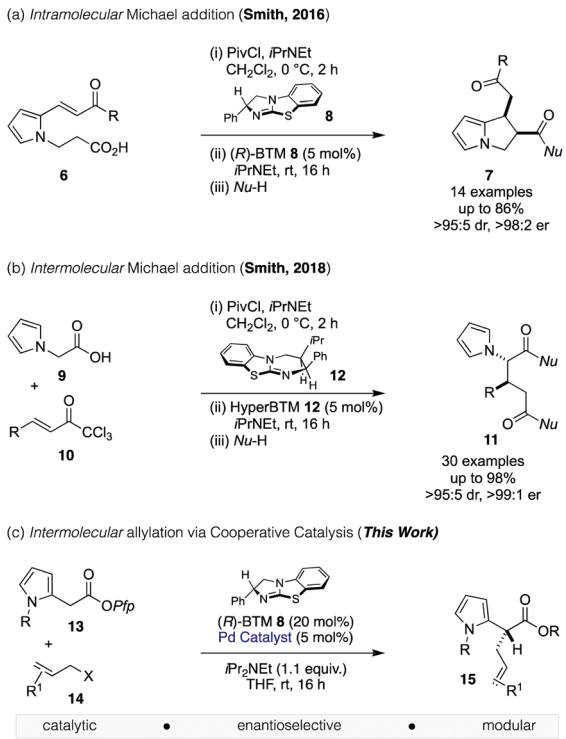
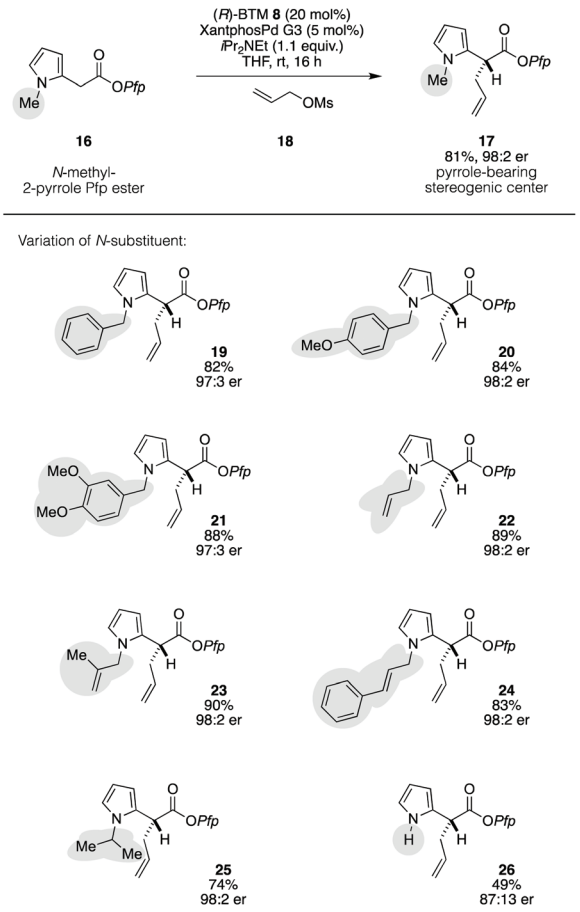


Scheme 1 Current and proposed methods using pyrrole-substituted C1-ammonium enolates.



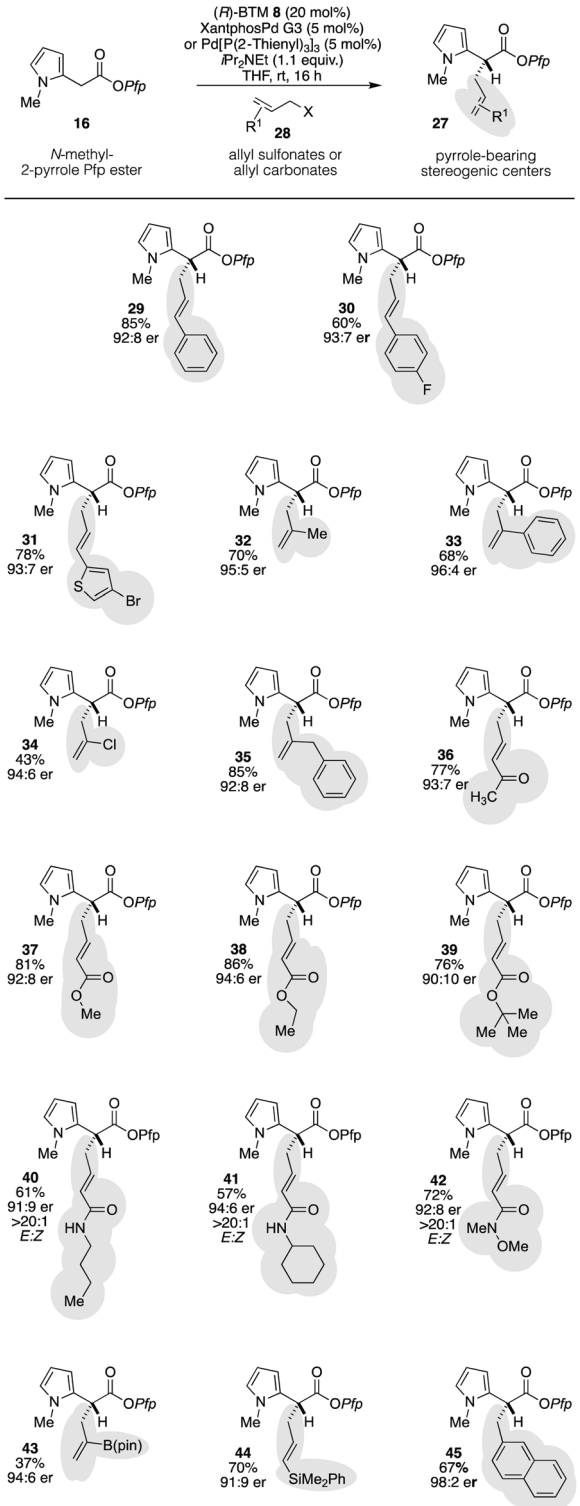
Scheme 2 Evaluation of *N*-substituent.

further enhanced as it is the first report of α-nitrogenous C1-ammonium enolates being successfully prepared and utilized *via* isothiourea Lewis base catalysis. Inspired by these reports and recognizing the modularity of our cooperative catalysis framework we sought to prepare useful scaffolds **5** (Fig. 1) *via* direct enantioselective α-functionalization of pyrrole-2-acetic acid esters.

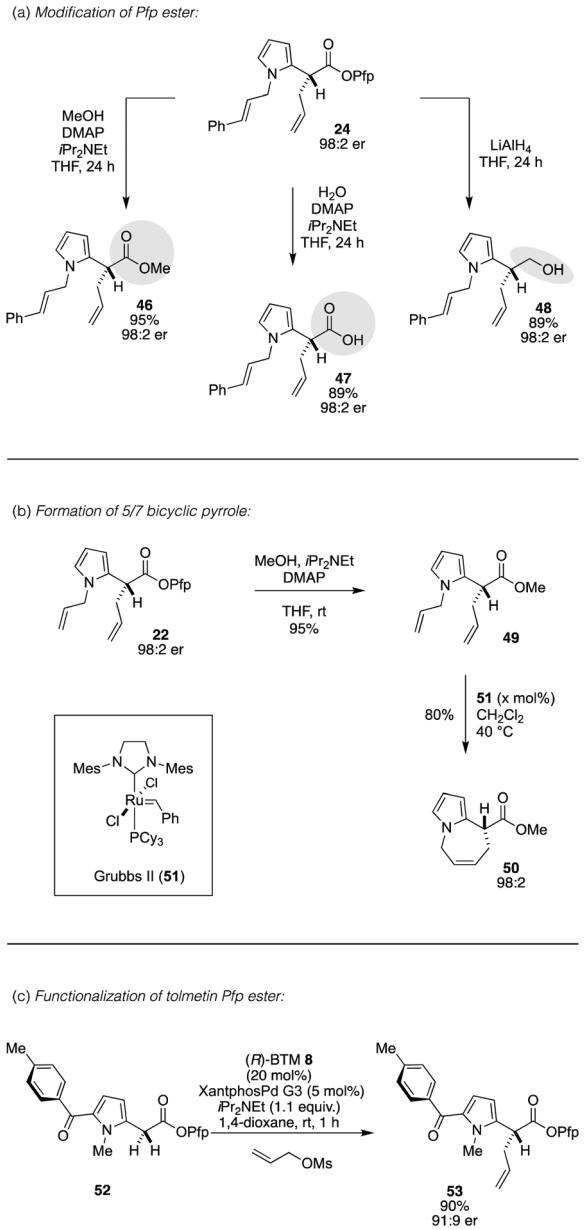
We began by evaluating the direct allylation of *N*-methyl-2-pyrrole Pfp ester **16** with allyl mesylate **18** (Scheme 2). Our original conditions[6a] employing Birman's benzotetramisole **8**[10] in combination with Buchwald's 3rd generation Xantphos-ligated Pd precatalyst[11] have proven very effective for a range of nucleophile/electrophile combinations and, as expected, these provided desired product **17** in high isolated yield and with excellent levels of enantioselectivity (81%, 98 : 2 er). Noteworthy is the lack of allylated pyrrole products that would arise from the electron-rich *N*-methylpyrrole serving as a competitive nucleophile.[12] Encouraged by this we surveyed the effect of *N*-substitution; *N*-benzyl **19**, *p*-methoxybenzyl **20** and 3,4-dimethoxybenzyl **21** substituents functioned with comparable efficiency as did *N*-allyl substituted nucleophiles **22–24**, and the more sterically demanding *N*-iPr substituted pyrrole **25**. Finally, the unsubstituted pyrrole **26** also gave the expected product albeit with lower efficiency and more modest enantioselectivity.

Having established the efficacy of various *N*-substituted 2-pyrrole acetic acid Pfp ester nucleophiles, we moved to assess the scope of electrophiles. We have previously established the versatility of the asymmetric cooperative catalysis protocol *via* alteration of the supporting ligand on Pd to accommodate disparate electronic and steric changes to the allyl electrophile. Accordingly, we assessed the enantioselective allylation of **16** with various allyl electrophiles **28** in combination with the appropriate phosphine ligand (Scheme 3). In each case a comprehensive optimisation of stoichiometry was conducted (see ESI† for details) Cinnamyl electrophiles **29** and **30** gave the linear products in high yields and with high levels of enantioselectivity. Brominated thiophene-containing product **31** indicated the tolerance of S-heterocycles and aryl bromides to these conditions. A variety of 2-substituted electrophiles **32–35** was also well tolerated, as were ester (**37–39**), secondary amide (**40–41**) and Weinreb amide (**42**) substituted electrophiles. Amides **40–42** were obtained as single *E* isomers. Incorporation of BPin (**43**) and $PhMe_2Si$ (**44**) substituents was also possible, which provides opportunity for further functionalization *via* Suzuki–Miyaura[6b,13] and Hiyama–Denmark cross-coupling,[6d,14] respectively. Finally, nucleophile **16** could also be directly benzylated using a 2-naphthyl(diphenyl)phosphate partner giving **45**.[6c]

Having demonstrated the efficient formation of enantioenriched pyrrole-bearing stereogenic centres we sought to demonstrate the useful synthetic elaboration of these products without loss of enantioselectivity. Beginning with Pfp ester **24**



Scheme 3 Evaluation of electrophile scope.



Scheme 4 Elaboration of products.

(Scheme 4a), transesterification to methyl ester **46**, hydrolysis to afford carboxylic acid **47**, and reduction to the corresponding alcohol **48** all proceeded without loss of enantioselectivity.[6,7b] Secondly, we considered the ubiquity of bicyclic pyrroles and pyrrolidines in alkaloid natural products and sought to elaborate our products into related motifs. In relation to this goal, bicyclic pyrrole **50** was prepared *via* a straightforward two step transesterification/ring closing metathesis sequence from **22** without loss in enantioselectivity (Scheme 4b).[15] Finally, we sought to evaluate this method on more complex pyrrole nucleophiles and prepared **53** *via* the enantioselective α-allylation of functionalized pyrrole acetic acid ester **52**, prepared from the NSAID tolmetin (Scheme 4c).

Conclusions

In conclusion, we have described the direct enantioselective α-allylation of 2-pyrrole acetic acid esters *via* cooperative Lewis

base/Pd catalysis. The products are obtained in high yield and enantioselectivity using a range of structurally different nucleophiles and electrophiles and could be modified and elaborated without loss in optical purity. The preparation of bicycle **50** is noteworthy as it demonstrates straightforward access to enantioenriched bicyclic pyrroles and validates the potential suitability of this method to the synthesis of relevant alkaloid natural products. Finally, the enantioselective functionalization of tolmetin-Pfp ester **52** extends our method to more complex pyrrole nucleophiles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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