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Divergent, Enantioselective Synthesis of Pyrroles, 3*H* Pyrroles and Bicyclic Imidazolines by Ag- or P-Catalyzed [3 + 2] Cycloaddition of Allenoates with Activated Isocyanides

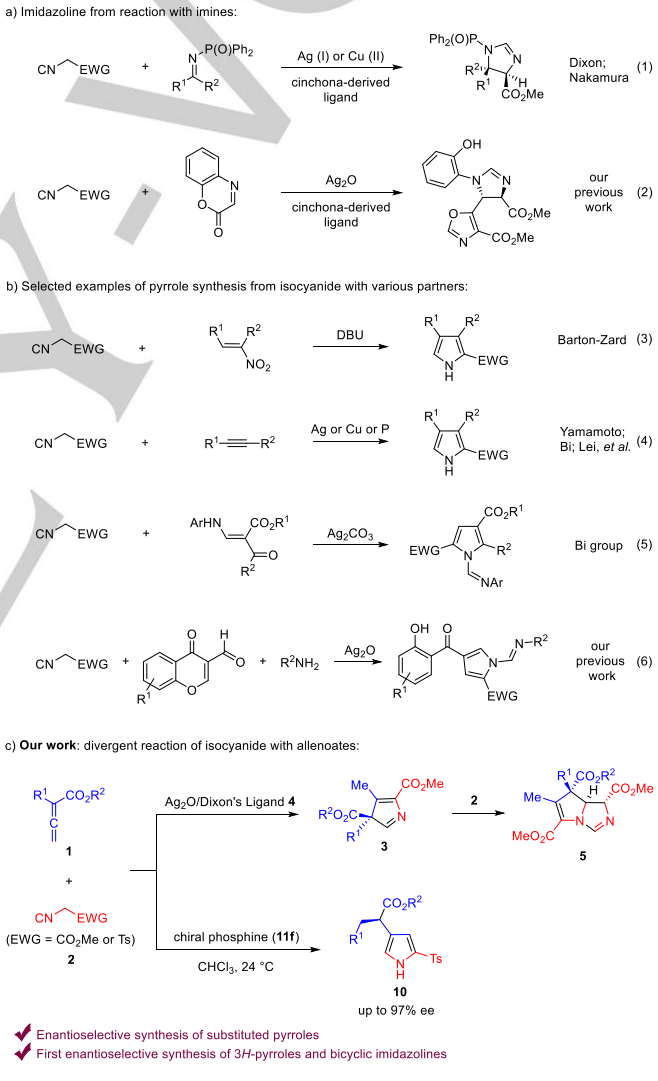
Germaine Pui Yann Kok,[+] Pan-Lin Shao,[+,§,*] Jia-Yu Liao, Siti Nur Fairuz Bte Sheikh Ismail, Weijun Yao, Yixin Lu[*] and Yu Zhao[*]

Abstract: We report herein our detailed investigation of divergent, stereoselective formal [3 + 2] cycloadditions of allenoates with activated isocyanides catalyzed by silver or phosphine-based catalysts. Silver catalysis is capable of delivering a range of 3*H*-pyrroles in high stereoselectivities. These enantioenriched heterocycles can either undergo sequential cyclisation with isocyanoacetates to deliver unprecedented bicyclic imidazolines with excellent yields and stereoselectivity or undergo unusual aromatization pathways leading to poly-substituted pyrroles. On the other hand, a simple mix-and-go procedure using an amino acid-derived phosphine as the catalyst produces pyrroles bearing a benzylic stereocenter with good enantioselectivity.

Introduction

The efficient and stereoselective synthesis of important heterocycles is a focal objective in synthetic organic chemistry. For such processes, activated isocyanides such as isocyanoacetate hold great potential by nature of its versatile functionality.[1] It has been reported that they can readily undergo cycloaddition with various π-systems including carbonyls,[2] imines,[3] α,β-unsaturated carbonyls[4] and activated alkenes or alkynes[5] to furnish a wide range of heterocycles (Scheme 1).

Imidazolines are an important class of *N*-heterocycles as they are ubiquitous in natural products and also in biologically active molecules.[6] For instance, imidazoline receptor I-1 binds to clonidine and other imidazolines to lower blood pressure through the inhibition of the sympathetic nervous system.[7] Besides that, imidazolines are also prevalent scaffolds in *N*-heterocyclic carbene (NHC) organocatalysts.[8] Scheme 1a highlights some examples of imidazoline synthesis. Following Orru's classical report on imidazoline synthesis via a three-component condensation using an amine, an aldehyde and a substituted isocyanoacetate,[3c] stereoselective reactions between imines and isocyanoacetates have been successfully developed in recent years. In 2014, Dixon *et al*.[3h] and Nakamura *et al*.[3i] showed that with the use of silver or copper salts in combination with chiral cinchona-derived ligand, a highly diastereo- and enantioselective imidazoline synthesis could be obtained (Eq. 1). Our group also reported a highly stereoselective, double cyclisation of isocyanoacetates with cyclic α-imino esters using the Dixon-type catalyst, in which both functionalities in the substrate underwent cyclization (Eq. 2).[3j]



Scheme 1. Heterocycle synthesis from activated isocyanides. a) Formation of imidazoline from reaction with imines. b) Pyrrole synthesis from isocyanide with various partners. c) This work: divergent reaction of isocyanoacetate with allenoates using Ag- or P-catalysis.

Pyrroles represent another important class of *N*-heterocycles and likewise, they are found abundantly in naturally occurring compounds such as porphyrins, chlorophylls,

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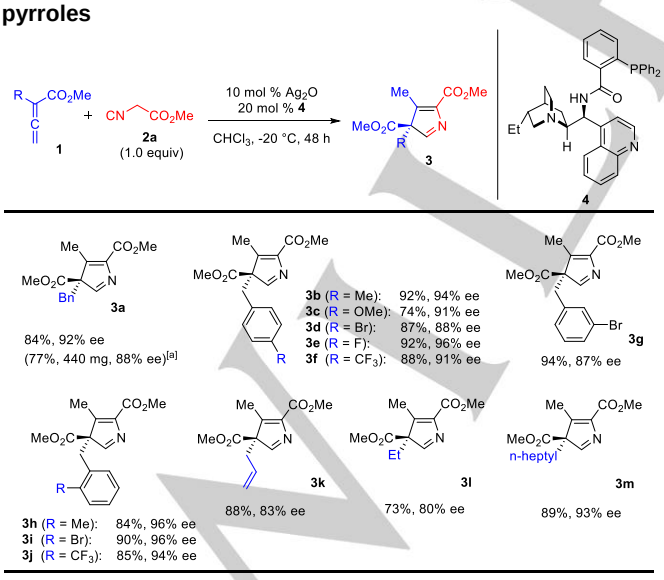
vitamin B12 and lamellarins from marine organisms, which has promising biological activities.[9] Out of various synthetic strategies for pyrrole synthesis, the cycloaddition of isocyanoacetates with activated alkenes, alkynes and β-enaminones has been achieved (Scheme 1b). In 1990, Barton and Zard discovered that isocyanoacetates can undergo cyclisation with nitro-olefins to give substituted pyrroles (Eq. 3).[5a] Cycloaddition of alkynes with isocyanoacetates also readily occur (Eq. 4) and can be catalyzed by phosphine or copper (Yamamoto *et al.*)[5b] or via silver catalysis (Bi *et al.* and Lei *et al.*)[5g-h] More recently, the group of Bi and our group have independently shown that isocyanoacetates can react with *in situ* formed imines from β-enaminones[4d] (Eq. 5) or 3-formylchromones with amines (Eq. 6).[4e] All these examples of pyrrole synthesis, to the best of our knowledge, have not been adopted for asymmetric synthesis.

Our group has been interested in the application of activated isocyanides to new modes of heterocycle synthesis. Very recently, we discovered highly intriguing divergent reactivities between allenoates with isocyanoacetates to access 3*H* pyrroles or aromatic pyrroles by the use of either silver or phosphine catalysts (synthesis of **3** or **10** in Scheme 1c).[10] We were intrigued by the possibility of using chiral phosphine to realize an unprecedented enantioselective pyrrole synthesis. In addition, we were also interested in exploring the reactivity of the novel 3*H* pyrroles that were never prepared in an enantioenriched form before. Herein we report our full studies along these lines. Not only have we identified intriguing reactivities of the 3*H* pyrroles that allowed the preparation of unprecedented bicyclic imidazolines, we have also come up with a simple mix-and-go procedure using an amino acid-derived phosphine as the catalyst that produces pyrroles bearing a benzylic stereocenter with good enantioselectivity (Scheme 1c).

Results and Discussion

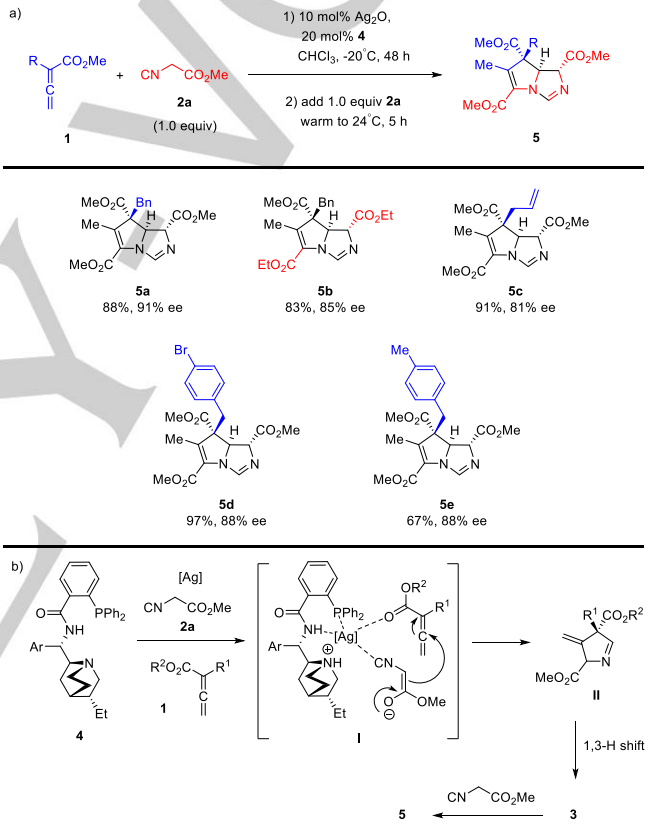
Formation of bicyclic imidazoline and derivatization of 3*H* pyrroles



Unless otherwise noted, the reactions were carried out at -20 °C under ambient atmosphere for 48 h.
[a]2 mmol scale reaction.

Scheme 2. Ag-catalysed enantioselective synthesis of 3*H* pyrrole.

In 2015, our group reported the first enantioselective synthesis of 3*H* pyrroles using Ag_2O and Dixon's ligand **4** (Scheme 2). As shown, the reaction between allenoates **1** and isocyanoacetates **2a** tolerated various substitutions on the allenoates to deliver a wide range of 3*H* pyrroles **3** bearing a quaternary center in good to excellent enantioselectivity. This represents the first highly enantioselective catalytic synthesis of 3*H* pyrroles. As originally proposed by the Dixon group,[2g] the silver Lewis acid presumably binds to this class of ligand in a bidentate fashion using the phosphine and amide moieties, which coordinates both isocyanide and the electrophile. The basic quinuclidine nitrogen is likely involved in the deprotonation of isocyanoacetate to generate the enolate nucleophile.

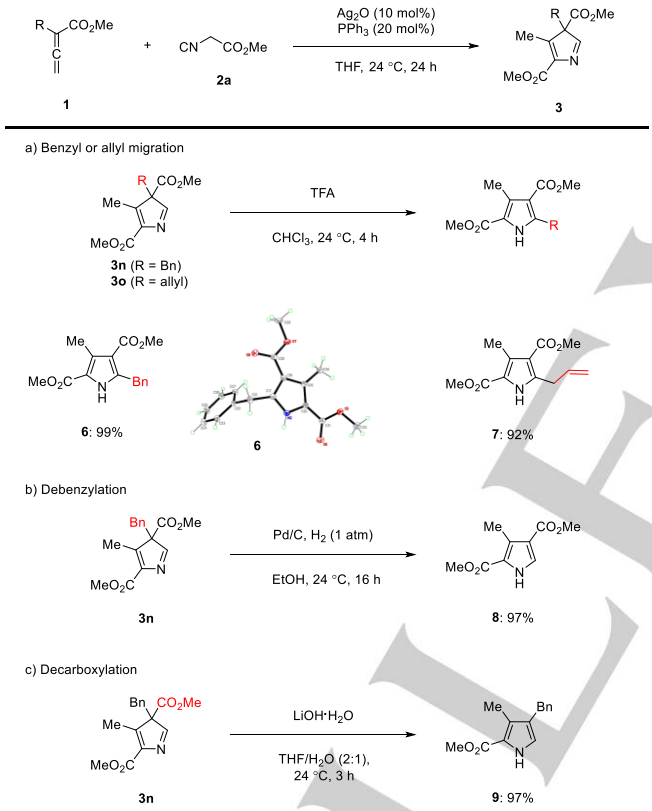


Scheme 3. a) Ag-catalysed one-pot sequential cyclisation of bicyclic imidazolines. b) Proposed mechanism for the formation of **5**.

An intriguing discovery was made during our investigation. When the amount of **2a** (relative to **1**) was increased, an unexpected side product was obtained, which was identified to be a sequential [3 + 2] cycloaddition product **5** (Scheme 3). Clearly, the cyclic imine moiety in 3*H* pyrrole **3** served effectively as an electrophile to undergo reaction with isocyanoacetate to deliver an unprecedented bicyclic imidazoline. This sequential cycloaddition also proceeded with superb level of diastereoselectivity, although the reaction required slightly higher temperature to proceed to full conversion. Under the optimal conditions, when the crude reaction for 3*H* pyrrole

synthesis was warmed up to room temperature and 1 equivalence of **2a** was added, a few representative bicyclic imidazolines **5a-e** could be obtained in excellent yields as a single diastereomer and with retention of stereochemistry from the first step. The relative configuration of compounds **5a** was assigned by NOESY (see Supporting Information for more details) and the other compounds were assigned by analogy.

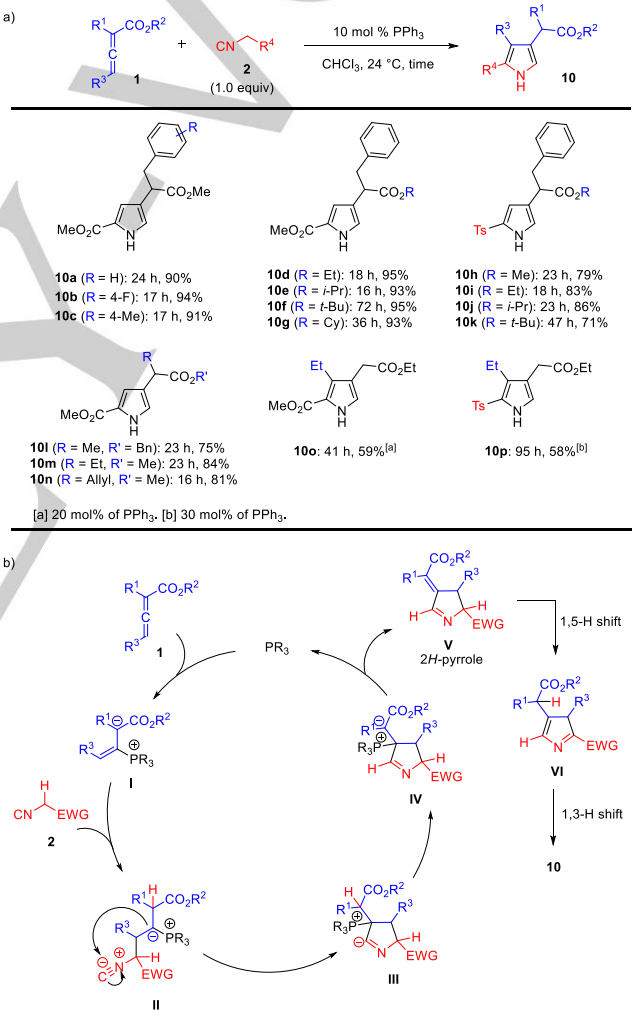
Based on the proposed mechanism by Dixon *et al*.,[3i] it is postulated that Dixon ligand **4** creates a chiral pocket by binding with silver, which in turn coordinates with allenoate **1** and the enolate form of isocyanoacetate **2a** to form intermediate **II** via [3 + 2] cyclisation. This exocyclic olefin subsequently undergoes a 1,3-H shift to form 3*H* pyrrole **3**. Then, another equivalent of isocyanoacetate **2a** undergoes another [3 + 2] cyclisation with **3** to form bicyclic imidazoline **5**. The configuration of the second cyclisation is believed to be dictated by the chirality created in the first step.



Scheme 4. Derivatization of 3*H* pyrroles **3** to give various polysubstituted 1*H* pyrroles.

It is noteworthy that the presence of the quaternary stereocenter in 3*H* pyrroles **3** is essential for the stabilities of these non-aromatic heterocycles. Without the fully substituted carbon center, the related 3*H* pyrroles are known to undergo highly facile tautomerization through H-transfer to yield the corresponding aromatic 1*H* pyrroles. In attempts to further explore the utility of our 3*H* pyrrole products, a series of derivatization was carried out on **3** (Scheme 4). Intriguingly, treatment of **3n** or **3o** with TFA in $CHCl_3$ under ambient temperature enabled an effective migration of the benzyl or allyl group to produce tetra-substituted pyrroles **6** and **7** in excellent yields respectively (Scheme 4a). When compound **3n** was placed under 1 atm of H_2 with Pd/C in ethanol at room temperature, the benzyl group was removed and rearrangement occurred to yield the more stable tri-substituted pyrrole **8** again in nearly quantitative yield (Scheme 4b). Finally, treatment of **3n** with $LiOH.H_2O$ in a 1:1 mixture of THF:H_2O cleaved the ester group to give tri-substituted pyrrole **9**. It is worth noting that racemic 3*H* pyrroles **3** can be accessed by the use of simple Ag_2O and PPh_3; this combined with these simple procedures, resulted in an efficient preparation of poly-substituted pyrroles.

Formation of enantioenriched 1*H* pyrroles



Scheme 5. a) Selected examples of 1*H* pyrrole synthesis by PPh_3 catalysis. b) Proposed mechanism for the formation of **10**.

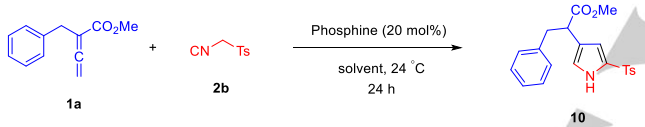
In contrast to the reaction of **1** and **2** under silver catalysis, simple PPh_3 works as an effective catalyst for the formation of polysubstitutted 1*H* pyrroles from the reaction of **1** and **2** using a simple mix-and-go procedure (Scheme 5a). Di- or tri-substituted

pyrroles bearing a benzylic stereogenic center can be accessed in good efficiency. Both isocyanoacetate and the analogous *p*-toluenesulfonylmethyl isocyanide could be used for the 1*H* pyrrole synthesis.

With this method in hand, we were particularly attracted to the development of an asymmetric variant of this process to deliver, for the first time, enantioenriched pyrroles. A close examination of the mechanistic pathway for the pyrrole synthesis, however, points out a few key challenges to overcome.

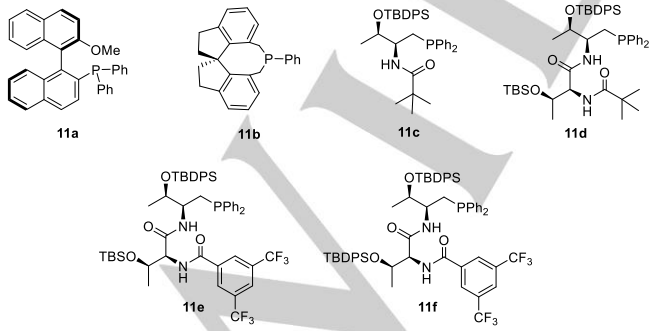
As illustrated in Scheme 5b, a key intermediate **I** is formed upon nucleophilic addition of the phosphine catalyst to **1**, which then deprotonates **2** to generate the nucleophile *in situ*. The formation of ylide **II** would actually serve as the key enantio-determining step when a chiral phosphine catalyst is used. Cyclisation to form intermediate **III** is then followed by solvent-assisted proton transfer and release of catalyst to yield 2*H* pyrrole **V**. At this stage, we propose two sequential 1,5- and 1,3-H shift will take place to convert **V** to **VI** and then the desired product **10**.[11] Based on the proposed mechanism, it is important to note that not only the chiral catalyst has to be capable of inducing high enantioselectivity for the formation of intermediates **II** to **V**, the formation of final product **10** from **V** also has to proceed with high degree of retention of stereoselectivity.

Table 1. Optimization of the Reaction Conditions.[a]



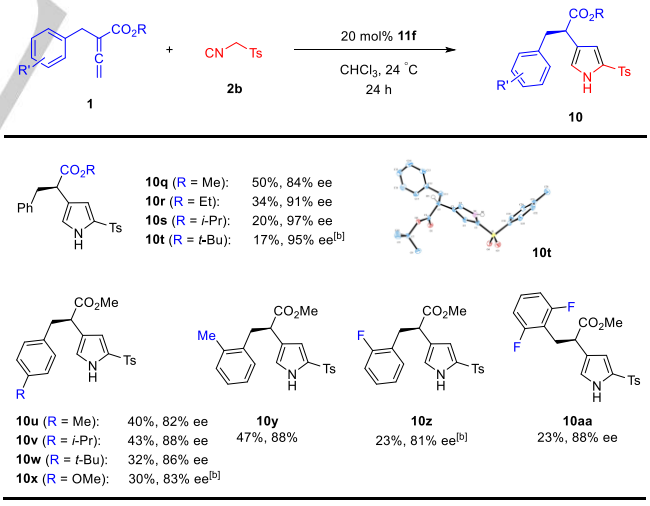
entry	catalyst	solvent	**10** yield (%)[b]	ee (%)[c]
1	**11a**	p-xylene	25	<5
2	**11b**	p-xylene	26	40
3	**11c**	p-xylene	65	37
4	**11d**	p-xylene	30	26
5	**11e**	p-xylene	17	45
6	**11f**	p-xylene	5	64
7	**11f**	$CHCl_3$	60	83
8[d]	**11f**	$CHCl_3$	55	86

[a] Reaction conditions: **1a** (0.1 mmol), **2b** (0.1 mmol), 20 mol% of **11** in $CHCl_3$ (1.0 mL) at 24 °C for 24 h. [b] Isolated yield. [c] Determined by HPLC Chiralpak IC. [d] 0.15 mmol of **2b** was used.



We then turned our attention to the realization of enantioselective pyrrole synthesis under chiral phosphine catalysis. We initiated our optimization of reaction conditions to promote the model reaction between **1a** and **2b** (Table 1).[12] The use of commercially available chiral phosphine catalysts were attempted first (e.g., entries 1-2). However, to our disappointment, the yields were low and only moderate enantioselectivity was obtained. In hopes of improving the enantioselectivity, we then turned our attention to amino acid-derived bifunctional phosphines that were developed by us before.[13] To our delight, by using threonine-derived phosphine **11c** (entry 3), higher yield of **10** was obtained, albeit with low enantioselectivity. We continued to screen a range of amino-acid derived phosphines (entries 4-6) and found that catalyst **11f** gave the best enantioselectivity, although this was achieved at the cost of lower yields. From our previous work, we found that chloroform acts as a proton source in facilitating the formation of **10**. When the solvent was changed from *p*-xylene to chloroform, indeed, a drastic increase in both the yields and enantioselectivity was obtained (entry 7). We also found that increasing the amount of *p*-toluenesulfonylmethyl isocyanide **2b** in the reaction also led to a slight enhancement in enantioselectivity (entry 8).

With the optimal condition in hand, the scope of this catalytic procedure proved to broad. Different substituents on the benzyl ring of the allenoate as well as different ester groups on the activated isocyanides can be well-tolerated to produce pyrroles **10** in good to high enantioselectivity (Scheme 6). Increasing the bulk of the ester from methyl to a *tert*-butyl group experienced enhanced enantioselectivity, albeit at the cost of diminishing yields (**10q**-**10t**). Electron-donating groups at the *para* position of the benzyl ring of the allenoate (**10u-x**) was also well tolerated, with moderate yields and good enantioselectivity. Electron donating groups at the *ortho* position (**10y**) gave moderate yields and good enantioselectivity, whereas election withdrawing groups at the *ortho* position (**10z**) or 2,6-position (**10aa**) suffered low yields but good enantioselectivity. The absolute configuration of **10t** was established unambiguously by single crystal x-ray analysis. The configuration of the other 1*H* pyrroles was assigned by analogy.

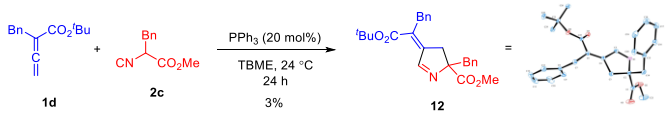


[a] See Table 1. [b] Reaction carried out for 48 h.

Scheme 6. Scope of enantioenriched 1*H* pyrroles.[a]

To validate our proposed mechanism shown in Scheme 5a, we reacted α-benzyl substituted isocyanoacetate **2c** with allenote **1a** (Scheme 7), the reaction of which should stop at the 2*H* pyrrole stage (corresponding to intermediate **V** in Scheme 5b)

as the following hydride shift cannot take place. To our delight, we were able to obtain the desired compound **12**, albeit in a small amount. This nonetheless provides significant support for the the reaction pathway shown in Scheme 5b. The configuration of **12** was unambiguously assigned by single crystal x-ray analysis. The low yield of the reaction is attributed to low conversion, possibly due more steric hindrance from substituted isocyanide **2c**. We believe that a number of regioisomers were formed in the reaction. However, our attempts to isolate and assign other isomers of the reaction proved futile. Efforts to further explore this reaction is currently underway.



Scheme 7. Synthesis of 2*H* pyrrole **12**.

Conclusions

In conclusion, we have detailed the enantioselective synthesis of 3*H* pyrroles from the reaction of isocyanoacetates and allenoates under silver catalysis as well as a one-pot, sequential cyclisation to produce unprecedented bicyclic imidazolines in a highly stereoselective fashion. The enantioselective variant of 1*H* pyrrole synthesis with the use of amino acid-derived phosphine is also disclosed. Both methods use simple procedures and are able to tolerate a good range of functional groups. Efforts to further extend the utility of these reactions are underway.

Experimental Section

To a 10 mL vial charged with catalyst **11f** (0.02 mmol) and *p*-toluenesulfonylmethyl isocyanide **2b** (0.15 mmol) was added anhydrous $CHCl_3$ (1.0 mL), followed by allenoate (0.1 mmol). The reaction mixture was then stirred at ambient temperature for 24 h, concentrated and purified by column chromatography (hexanes/ethyl acetate) to afford product **10**.

Acknowledgements

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Keywords: silver catalysis • phosphine catalysis • pyrroles • imidazolines • enantioselectivity

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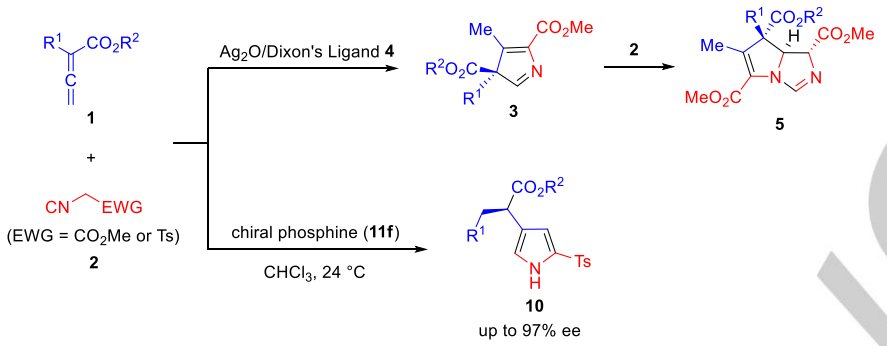

- Enantioselective synthesis of substituted pyrroles
- First enantioselective synthesis of 3*H*-pyrroles and bicyclic imidazolines

We report herein our detailed investigation of divergent, stereoselective formal [3 + 2] cycloadditions of allenoates with activated isocyanides catalyzed by silver or phosphine-based catalysts. Silver catalysis is capable of delivering a range of 3*H*-pyrroles in high stereoselectivities. These enantioenriched heterocycles can either undergo sequential cyclisation with isocyanoacetates to deliver unprecedented bicyclic imidazolines with excellent yields and stereoselectivity or undergo unusual aromatization pathways leading to poly-substituted pyrroles. On the other hand, a simple mix-and-go procedure using an amino acid-derived phosphine as the catalyst produces pyrroles bearing a benzylic stereocenter with good enantioselectivity.

Germaine Kok Pui Yann, Pan-Lin Shao, Jia-Yu Liao, Siti Nur Fairuz Bte Sheikh Ismail, Weijun Yao, Yixin Lu and Yu Zhao

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Divergent, Enantioselective Synthesis of Pyrroles, 3*H* Pyrroles and Bicyclic Imidazolines by Ag- or P-Catalyzed [3 + 2] Cycloaddition of Allenoates with Activated Isocyanides