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Catalytic Divergent Synthesis of 3*H* or 1*H* Pyrroles by [3 + 2] Cyclization of Allenoates with Activated Isocyanides

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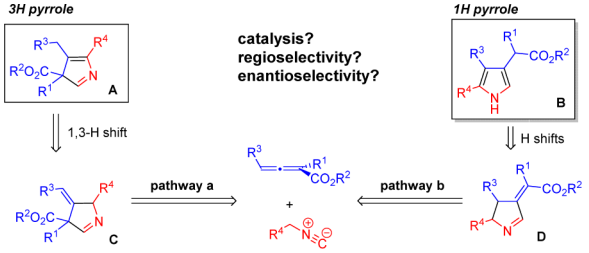
Supporting Information

ABSTRACT: The cyclization of allenoates with activated isocyanides was reported for the first time. While Ag catalysis led to an unprecedented enantioselective synthesis of 3*H* pyrroles, a simple procedure using PPh_3 produced a wide range of polysubstituted 1*H* pyrroles with high efficiency.

The development of efficient and atom economical processes for the preparation of valuable heterocycles remains an important goal in synthetic organic chemistry. In particular, the construction of pyrroles, one of the most abundant and useful classes of *N*-heterocycle,[1] is still under active investigation for which transition metal-catalyzed cyclization strategies have proven highly fruitful.[2] In contrast, the isomeric nonaromatic 3*H* pyrroles (**A** in Scheme 1) have been poorly studied due to their difficult access, although some of them have been shown to possess antitumor or antimicrobial activities.[3] The few previously reported syntheses of 3*H* pyrrole either were low yielding to produce a mixture of isomers or required harsh reaction conditions and suffered from a narrow substrate scope.[4] To the best of our knowledge, no enantioselective synthesis of this class of heterocycle has been reported.

Scheme 1. 3*H* or 1*H* Pyrrole from Reaction of Allenoates with Activated Isocyanides

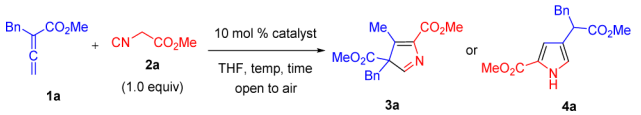


Activated isocyanides such as isocyanoacetates have proven to be a versatile functionality to undergo cyclization with various π-systems for heterocycle synthesis.[5−8] In particular, substituted pyrroles can be obtained from the reaction of isocyanoacetate with nitroalkenes (as in Barton−Zard pyrrole synthesis),[9] alkynoates (catalyzed by copper reported from the groups of Yamamoto[8a] and de Meijere[8b]), and even simple terminal alkynes (catalyzed by silver reported by the groups of Bi[8g] and Lei[8h]). Based on our group's continuous interest in isocyanoacetate chemistry,[7i] we became interested in the reaction between isocyanoacetate and allenoate,[10,11] and we envisioned such a combination of two versatile functionalities may lead to an efficient synthesis of difficult-to-access 3*H* pyrroles.

As illustrated in Scheme 1, the [3 + 2] cyclization of isocyanoacetate and allenoate may proceed with different regioselectivity to generate intermediate **C** or **D** (or other isomers). Once **C** is formed, it should undergo a facile 1,3-H shift to produce 3*H* pyrrole **A**. While 3*H* pyrroles without 3,3-disubstitution is known to readily rearrange to 1*H* pyrroles through a 1,3-H shift driven by aromatization, compound **A** bearing a quaternary carbon can be produced as a stable compound. Alternatively, intermediate **D** will most likely undergo multiple H-shifts to produce 1*H* pyrrole **B**. The focus of this study was whether an efficient catalytic method could be developed that will allow regio- and stereoselective synthesis of 3*H* or 1*H* pyrroles. Herein we report operationally simple procedures using silver or phosphine catalysis to deliver these products as well as related *N*-heterocycles from allenoates and activated isocyanides with high efficiency and stereoselectivity.

The readily available allenoate **1a** and isocyanoacetate **2a** were chosen as the model substrates. Various metal salts with strong basicity that could deprotonate the isocyanoacetate to deliver the enolate reactivity of **2a** were evaluated; selected data are summarized in Table 1. At 0 °C, we were excited to observe that the desired product **3a** could be obtained by using copper or silver salts, albeit with low yield due to the formation of other side products (entries 1−3). When the reaction was carried out at ambient temperature using Ag_2CO_3, however, the reaction was

Table 1. Identification of Divergent Reaction Profile[a]



entry	metal	ligand	temp (°C)	time (h)	yield (%)[b] **3a**:**4a**
1	Cu_2O	–	0	12	10:<2
2	Ag_2O	–	0	24	24:<2
3	Ag_2CO_3	–	0	24	37:<2
4	Ag_2CO_3	–	24	3	19:<2
5	Ag_2CO_3	PPh_3	24	1	**55**:<2
6	–	PPh_3	24	24	<2:**18**

[a]The reactions were carried out open to air. [b]Isolated yields.

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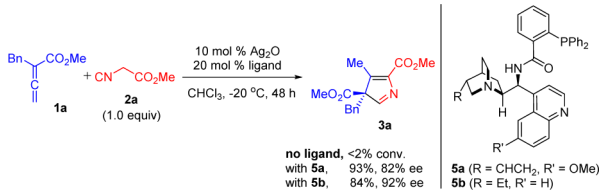
messy affording **3a** in only 19% yield (entry 4). In an effort to modulate the reactivity between **1a** and **2a**, the addition of ligands such as PPh_3 was examined, which to our delight led to a higher yield of **3a** (55%, entry 5). It is noteworthy that under these conditions no product corresponding to pathway b (Scheme 1) was observed. Inspired by the recent advances of phosphine catalysis of allenes with various electrophiles,[12] we also tested the control reaction using only PPh_3 as the catalyst. Intriguingly, 2,4-disubstituted pyrrole **4a** was formed as the exclusive product, albeit in low yield (entry 6).[8a] This observation represents an interesting example of a catalyst-controlled divergent reaction.[13]

The observation of dramatic ligand effect prompted us to examine a wide range of ligands and in particular chiral ones aiming toward an efficient as well as enantioselective synthesis of 3*H* pyrroles bearing all-carbon quaternary center.[14] In particular, the Dixon group has introduced cinchona alkaloid-based phosphine ligands for highly enantioselective Ag-catalyzed aldol and Mannich reactions of isocyanoacetates.[15a,b] In our hands, this family of catalysts proved remarkably effective for highly enantioselective double [3 + 2] cyclization of isocyanoacetate with α-iminoesters[7h] as well as for 3*H* pyrrole synthesis after extensive screening of different catalysts. It is noteworthy that a dramatic ligand acceleration effect was observed with this catalytic system so that a lower temperature of −20 °C could be employed to produce **3a** in high yield and ee (Scheme 2).

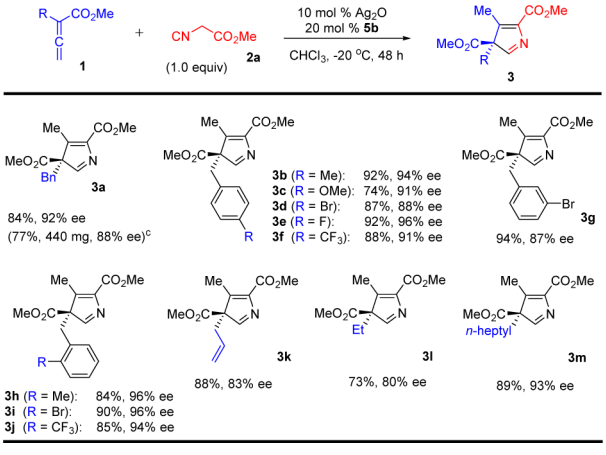
Scheme 2. Optimization of Enantioselective Cyclization



The scope of this simple catalytic procedure proved to be broad (Scheme 3). Various allenoates **1** underwent smooth reaction with **2a** in a 1:1 ratio at −20 °C. 3*H* Pyrrole **3** with different 3-substituents including benzyl derivatives (**3a**−**3j**) as well as allyl (**3k**) and alkyl (**3l**, **3m**) groups were all obtained in high yield (73−94%) with good to excellent ee (80−96%). 3*H* Pyrroles have been utilized as aza-diene for Diels−Alder reaction before;[4e] in our studies we have also identified new reactivity involving addition to the imine moiety. Details along these lines will be reported in due course.

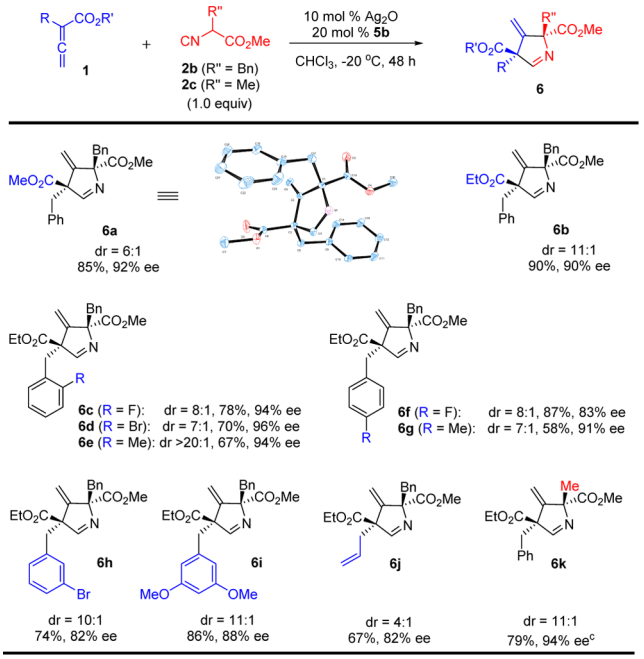
To further extend the scope of this catalytic system, the reaction of **1a** with substituted isocyanoacetate **2b** was examined under the same conditions (Scheme 4). Gratifyingly, the direct

Scheme 3. Enantioselective Synthesis of 3*H* Pyrrole[a−b]



[a]The reactions were carried out at −20 °C under ambient atmosphere for 48 h. [b]Isolated yields. [c]2 mmol-scale reaction.

Scheme 4. Cyclization of Substituted Isocyanoacetates[a−b]



[a]See Scheme 3. [b]Isolated yields of the major diastereomer. [c]The reaction time was 7 days.

[3 + 2] cyclization product **6a** possessing an exocyclic olefin (corresponding to **C** in Scheme 1) was obtained in high yield and 92% ee, with a good dr of 6:1 (85% isolated major diastereomer). The formation of **6a** not only provided strong support for the mechanism of formation of 3*H* pyrrole **3** through [3 + 2] cyclization followed by a 1,3-H shift (that is not possible in the case of **6a**) but also highlighted the versatility of our method to prepare *N*-heterocycles bearing multiple quaternary stereocenters.[14]

The same set of conditions could be used to produce a wide range of heterocycles **6**. The use of an ethyl ester analog of **1a** led to **6b** in higher dr and similar ee. Various substituted benzyl groups (**6c**−**6i**) as well as an allyl substituent (**6j**) on the allenoate structure could be tolerated to yield the products in high yield and selectivity (82−96% ee; dr up to >20:1). Finally, use of methyl-substituted isocyanoacetate **2c** yielded **6k** in excellent stereoselectivity as well. In all cases, the yields refer to that of the isolated major diastereomer. The relative and absolute configuration of **6a** was unambiguously assigned by single crystal X-ray analysis, and those of other products were assigned by analog. It is also worth noting that all the reactions were carried out under an ambient atmosphere; exclusion of air or moisture was not required.

Recognizing the synthetic utility of conversion of readily available allenoates to polysubstituted pyrroles, we decided to optimize the PPh_3-catalyzed reaction (entry 6, Table 1). Various

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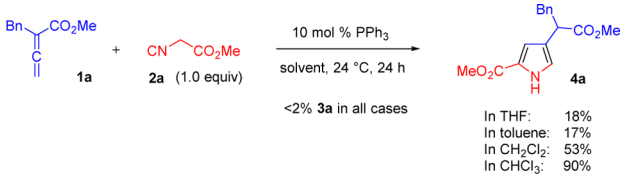
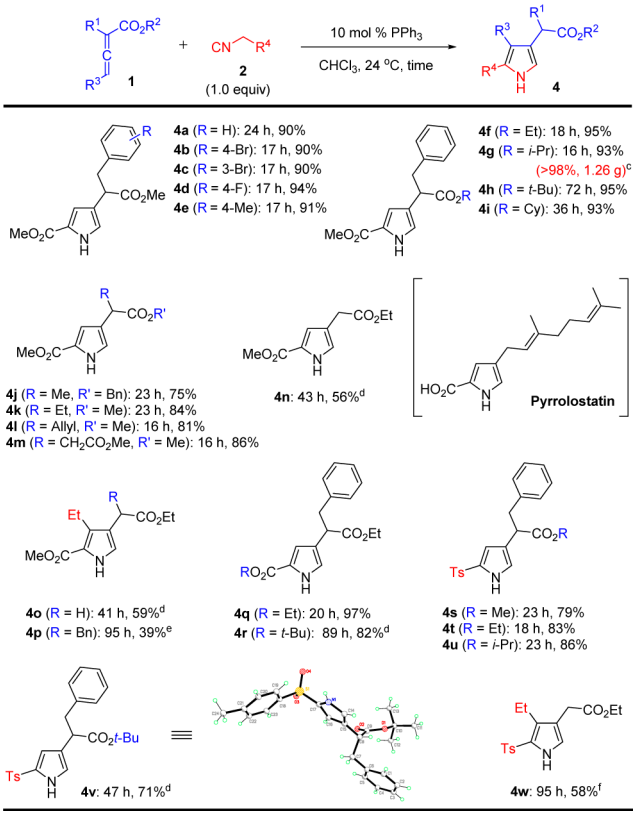
trialkylphosphines (e.g., PCy_3), diarylmonoalkyl-phosphines (e.g., $Ph_2PCH_2PPh_2$), and triarylphosphines were examined, and the simple and inexpensive PPh_3 was determined to be the optimal choice. After the screening of reaction conditions, a dramatic solvent effect was discovered (Scheme 5). Chloroform proved superior to all others leading to a highly efficient synthesis of **4a**.

Scheme 5. Optimization of Phosphine Catalysis



Using this catalytic protocol, a wide range of di- and trisubstituted pyrroles could be accessed (Scheme 6). Different

Scheme 6. Pyrrole Synthesis by PPh_3 Catalysis[a–b]

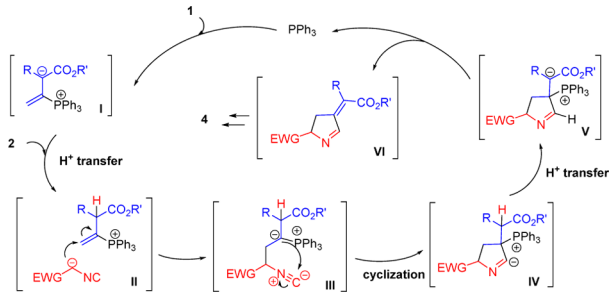


[a]See Table 1 footnote a. [b]See Table 1 footnote b. [c]4 mmol-scale reaction for 24 h. [d]20 mol % PPh_3. [e]50 mol % PPh_3. [f]30 mol % PPh_3.

substituents on allenoates were well tolerated (**4a**–**4p**). Different isocyanoacetates as well as tosylmethylisocyanide could also be used to produce **4q**, **4r**, and **4s**–**4w** in good to high yields. The high efficiency of this process, coupled with the operational simplicity (use of cheap PPh_3 as the catalyst and running reactions open to air), makes it an attractive method for pyrrole synthesis. The related 2,4-disubstituted pyrroles such as Pyrrolostatin[16] are important targets in medicinal chemistry, and the current method provides a rapid access to the core structure of those compounds.

This method represents a new entry to phosphine-catalyzed umpolung reactions.[17] As illustrated by the proposed mechanism in Scheme 7, intermediate **I** formed by addition of PPh_3 to **1** is

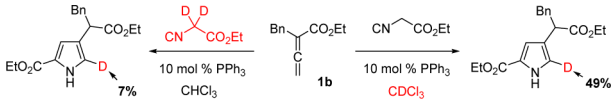
Scheme 7. Proposed Mechanism for the Formation of 4



reported to be capable of deprotonating Brønsted acidic substrates such as malonate to generate analogs of ion pair **II** and then ylide **III**.[17a,b] With an isocyanide functionality in this case, the ylide is believed to undergo cyclization to generate **IV**. Proton transfer followed by elimination of phosphine then yields **VI** that is eventually transformed to the final product **4**.

In an effort to better understand the reaction profile, deuterium labeling studies were carried out. As shown in Scheme 8, while the use of D_2-isocyanoacetate led to surprisingly low

Scheme 8. Deuterium Labeling Studies



deuterium labeling on the pyrrole ring, the use of $CDCl_3$ resulted in significant deuterium labeling (49% vs 7%). This interesting observation suggests that proton transfer (**IV** to **V** in Scheme 7) is facilitated by chloroform bearing a slightly acidic proton by proton shuffling, which is consistent with the dramatic solvent effect (Scheme 5).[18]

In conclusion, we have developed divergent cyclization of allenoates with activated isocyanides under Ag or phosphine catalysis to produce 3*H* and 1*H* pyrroles and other related *N*-heterocycles. Current efforts are focused on the application of the current catalytic systems to the preparation of other types of *N*-heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[§]J.-Y.L. and P.-L.S. contributed equally.

Notes

The authors declare no competing financial interest.

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