Letter

Highly Regioselective Synthesis of Multisubstituted Pyrroles via Ag-Catalyzed [4+1C]insert Cascade

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Highly Regioselective Synthesis of Multisubstituted Pyrroles *via* Ag-Catalyzed [4+1C]^{insert} Cascade

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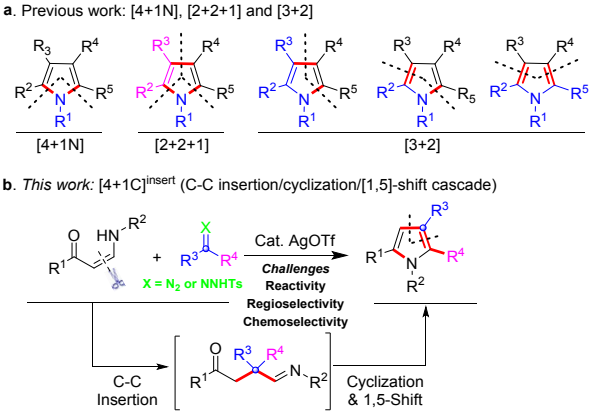
ABSTRACT: An efficient [4+1C]^{insert} approach to the coupling of enaminones with donor/acceptor or donor/donor carbenes by AgOTf catalyzed C–C bond carbenoid formal insertion/cyclization/[1,5]-shift cascade reaction was successfully developed, providing distinct chemo- and regio-selective multisubstituted pyrroles. The plausible reaction mechanism involves two catalytic cycles: in the first one, silver ions regioselectively catalyze the C–C bond formal insertion reaction; in the second one, silver ions chemo- and regio-selectively control the cyclization and [1,5]-shift reactions. This method not only provides convenience and applies atom economy in the synthesis multisubstituted pyrroles but also presents an entry point for further pyrrole diversification via facile modification of resulting 4-H-pyrrole products, as displayed by a short formal synthesis of the natural product lamellarin L.

KEYWORDS: *C–C insertion*, *[4+1C]*, *[1,5]-shift*, *cascade*, *pyrrole*.

Multisubstituted pyrroles, which are valuable five-membered heterocycles, are found in various biologically active natural products, pharmaceuticals, and materials.[1] Various synthetic strategies, including [4+1N], [3+2], and [2+2+1] cycloaddition or coupling (Scheme 1a), have been developed toward pyrrole architecture. [2,3] However, the direct, region-defined synthesis of multisubstituted pyrroles remains a significant challenge.[2a, 2c,4] To develop a complementary approach to diversely substituted pyrroles, we envisage the retrosynthetic possibility of knocking out a carbon atom on the pyrrole ring to design a [4+1C]^{insert} cascade reaction (Scheme 1b).[5]

Remarkable progress in metal-/organo-catalytic cascade reactions has been reported over the past two decades.[6] Exploring new types of cascade transformation attracts considerable research interest. Transition metal-catalyzed carbon insertion into C–C bond is recently emerging as a promising synthetic process;[7,8] however, this type of reaction is rarely used to initiate a cascade transformation.[9] To expand the classes and utilities of cascade transformation, we report on a type of cascade transfromation involving a previously unreported AgOTf catalyzed carbenoid C–C bond insertion into enaminone[10] compounds, which chemoselectively and regioselectively yield multisubstituted pyrroles. The Bi research group recently disclosed a formal insertion of diazo compounds into the C–C bond of 1,3-dicarbonyl species to produce acyclic 1,4-dicarbonyl products.[8a,8j] No previous studies the synthesis of pyrrole by C–C insertion cascade have thus far been reported. Our [4+1C]^{insert} cascade reaction not only represents a new type of cascade transformation but also constitutes a complementary process toward multisubstituted pyrroles with excellent chemo- and regio-selectivities.

Scheme 1. Synthetic Strategies Used to Prepare Pyrroles

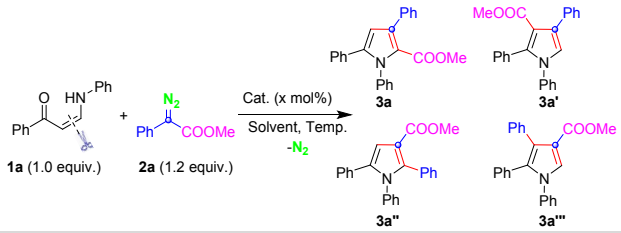


α-Diazocarbonyl compounds are important synthons exhibiting rich and unexpected chemistry.[7a,7c,11] Many research groups,[12] including Wang,[12a] Feng,[9a] Beller,[12g] and our group,[12c] have demonstrated that metal carbene originating from α-diazocarbonyl compounds can engage in cascade reactions where the metal carbene triggers subsequent inter-/intramolecular transformation. Enaminones have also recently attracted particular attention because of the unique push–pull electronic properties of the C–C double bond.[13] On the basis of achievements in carbene chemistry by silver–catalysis,[14] we investigated whether low-cost silver catalysis could be used to mediate C–C bond cascade transformation. This process is highly favorable for the synthesis of multisubstituted pyrroles,

considering its potential to minimize the degree of functionality required for a starting material.

Toward this goal, we developed a [4+1C]^{insert} approach to the coupling of enaminones with donor/acceptor or donor/donor carbenes by AgOTf-catalyzed C–C bond carbenoid insertion/cyclization/[1,5]-shift cascade reaction, providing distinct chemo- and regio-selective multisubstituted pyrroles.

Table 1. Optimization of Reaction Conditions for [4+1C]^{insert} Cascade[a]

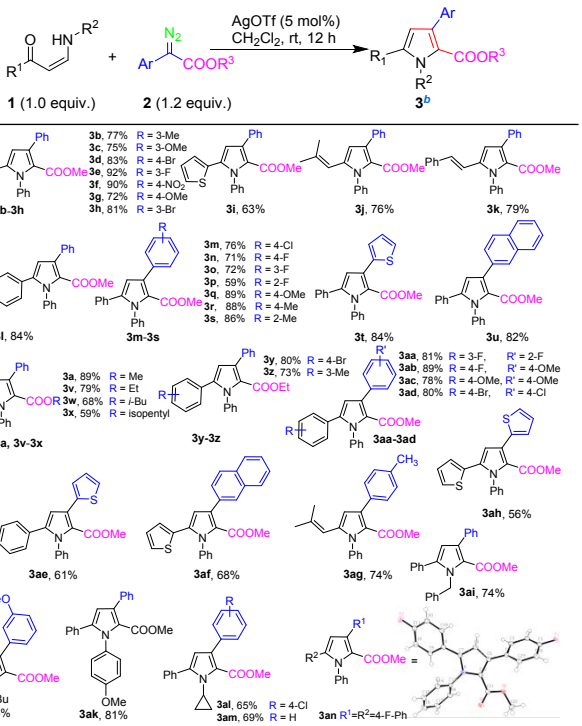


Entry	Cat. (x mol %)	Solvent	*T* (°C)	Yield (%)[b] 3a	3a', 3a'', and 3a'''
1	$Pd(OAc)_2$ (5)	CH_2Cl_2	25	2	nd[c]
2	$Rh_2(OAc)_4$ (5)	CH_2Cl_2	25	4	nd
3	AgOAc (5)	CH_2Cl_2	25	34	nd
4	PPh_3AuNTf_2 (5)	CH_2Cl_2	25	5	nd
5	CF_3CO_2Ag (5)	CH_2Cl_2	25	52	nd
6	Ag_2CO_3 (5)	CH_2Cl_2	25	0	nd
7	$AgNO_3$ (5)	CH_2Cl_2	25	3	nd
8	AgOTf (5)	CH_2Cl_2	25	89	nd
9	AgF (5)	CH_2Cl_2	25	21	nd
10	$PhCO_2Ag$ (5)	CH_2Cl_2	25	0	nd
11	$C_3F_7CO_2Ag$ (5)	CH_2Cl_2	25	26	nd
12	$Yb(OTf)_3$ (10)	CH_2Cl_2	25	0	nd
13	$La(OTf)_3$ (10)	CH_2Cl_2	25	0	nd
14	$Sc(OTf)_3$ (10)	CH_2Cl_2	25	0	nd
15	$Ca(OTf)_3$ (10)	CH_2Cl_2	25	0	nd
16	AgOTf (5)	THF	25	68	nd
17	AgOTf (5)	CH_3CN	25	59	nd
18	AgOTf (5)	CH_2Cl_2	40	80	nd
19[d]	AgOTf (1)	CH_2Cl_2	25	79	nd
20[d]	AgOTf (10)	CH_2Cl_2	25	86	nd

[a]Reaction conditions: In a 10 mL reaction tube, enaminone **1a** (1 mmol), diazoester **2a** (1.2 mmol), metal catalyst (0.05 mmol), solvent 5 mL, under air (1 atm), stirred for 12 h at room temperature. [b]Isolated yield of **3a** based on **1a**. [c]nd means not detected. [d]Detailed survey of catalyst dosage was listed in SI file.

Our initial attempt involved the cascade reaction of *N*-phenyl-enaminone **1a** and phenyl diazoester **2a** by using various metal catalysts (5 mol%) in dichloromethane. When the reaction was performed using AgOAc as catalyst at room temperature for 12 h (Table 1), the envisioned pyrrole **3a** was obtained in 34% isolated yield. The C–C bond insertion/cyclization/[1,5]-shift cascade reaction showed exclusive chemoselectivity and regioselectivity, considering that 1,3,5-triphenyl pyrrole-2-carboxylate **3a** was the only product formed in the reaction; the products **3a′**, **3a″**, or **3a‴** were not detected. With these results, we continued to optimize the reaction conditions. Catalyst screening displayed that AgOTf produced a higher yield (89%) of corresponding 1*H*-pyrrole than that of Ag_2CO_3, and $PhCO_2Ag$ and other trifluoro-methane-sulfonates failed to realize such transformation (Table 1, entries 5-15). Solvent screening revealed that CH_2Cl_2 was the best solvent; by contrast, THF or CH_3CN as the reaction solvent reduced the yield of the reaction to varying degrees. Room temperature was also determined as the best temperature for the reaction. The optimal catalyst dosage was determined as 5 mol% (Table S2, SI). The increase (entry 20) or decrease (entry 19) in catalyst dosage reduced the reaction efficiency. The yield of the desired product **3a** was not increased by extending the reaction time to 24 h.

Table 2. Reaction Scope of Enaminones 1 with Aryl Diazoesters 2[a]

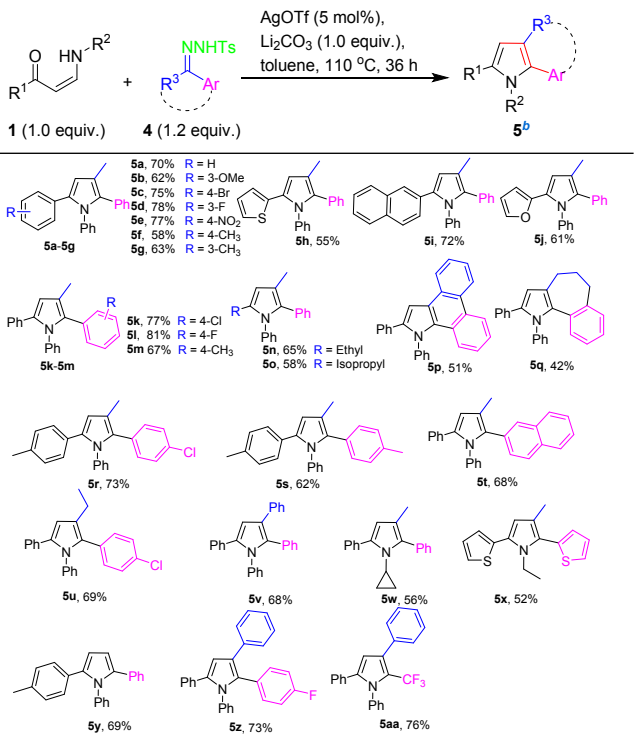


[a]Reaction conditions: In a 10 mL reaction tube, enaminone **1** (1 mmol), diazoester **2** (1.2 mmol), AgOTf (0.05 mmol), and CH_2Cl_2 (5 mL), under air, stirred for 12 h at room temperature. [b]Isolated yield of **3** based on **1**.

Under optimized reaction conditions, the scope of enaminone starting materials (**1**) was investigated with a variety of aryl diazoesters (**2**) (Table 2). A range of enaminones was first examined. The cascade reaction generally tolerated a broad range of substituted enaminones (**3b**–**3h**: R^1= *m*-Me, *m*-OMe, *m*-F, *m*-Br, *p*-OMe, *p*-NO_2, or *p*-Br phenyl) to afford high to excellent yields of the corresponding multisubstituted 1*H*-pyrroles. A study on the electronic influence of the phenyl group (R^1) indicated that although both electron-donating (e.g., **3g**) and electron-withdrawing (e.g., **3e** and **3f**) groups worked well and resulted in good yields, electron-deficient enaminones achieved a higher yield (92% yield). Moreover, the cascade reaction produced equally satisfactory results by using thiophenyl **3i** and naphthalenyl **3l**. Notably, both aliphatic styrene **3k** and isobutene **3j** can be introduced as substrates in this cascade reaction. Similarly, a range of donor/acceptor diazoesters, including substituted aryl, 2-thienyl, and 2-naphthyl, obtained high to excellent yields of desired products under the standard conditions (**3m**–**3u**), whereas the acceptor-only (e.g., ethyl

diazoacetate) diazo compounds failed to accomplish this cascade reaction with the same reaction sequence. Different R^3 groups of aryl diazoesters exerted evident steric effects, with Methyl, Ethyl, and *i*-Bu (in this particular order) exhibiting the highest efficiency, followed by isopentyl (**3a**, **3v**–**3x**). Finally, functional *N*-substituents (R^2), such as benzyl, *p*-OMe phenyl, n-Bu, and cyclopropyl were compatible under the standard reaction conditions, thus leading to products **3ai**, **3aj**, **3ak,** and **3al** in 74%, 66%, 81%, and 65% yield, respectively (Table 2). To verify the structure of the multisubstituted pyrrole, **3an**[15] was selected as the representative compound and was characterized by X-ray crystallography (Table 2, **3an**).

Table 3. Reaction Scope of Enaminones 1 with *N*-tosylhydrazones 4[a]

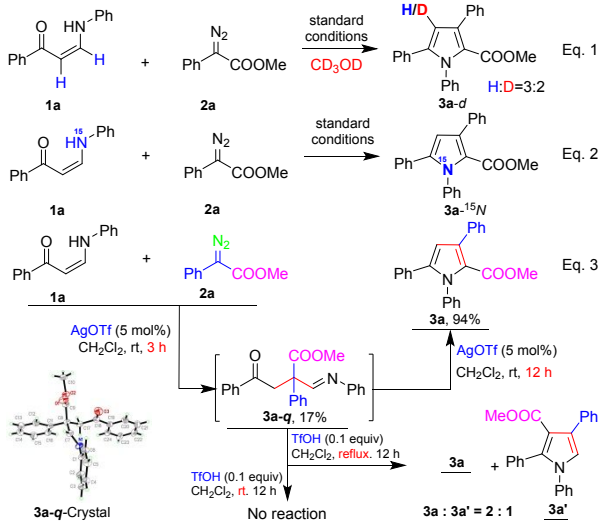


[a]Reaction conditions: In a 10 mL reaction tube, enaminone **1** (1 mmol), *N*-tosylhydrazones **4** (1.2 mmol), Li_2CO_3 (1.0 mmol), AgOTf (0.05 mmol), and toluene (5 mL), under air, stirred for 36 h at 110 °C. [b]Isolated yield of **5** based on **1**.

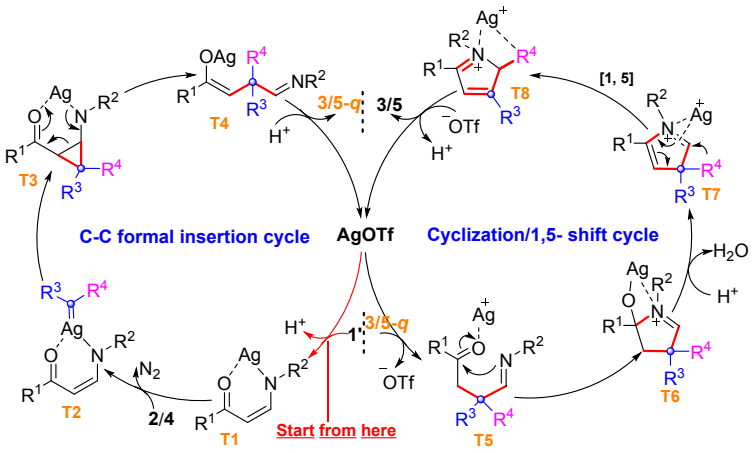
Aryl diazoesters act as donor/acceptor carbene precursors that can efficiently perform cascade reaction; thus we subsequently studied the reactivity of *N*-tosylhydrazones[16] (**4**) as donor/donor-carbene sources with different substituents in the cascade reaction (Table 3). The release of carbene from *N*-tosylhydrazones **4** requires base catalysis. Thus, we first screened for the effects of varying bases and temperatures under the standard conditions (Table S1, SI). By adding 1 equivalent of Li_2CO_3 to the standard reaction conditions and increasing the temperature to 110 °C for 36 h, the cascade reaction was performed efficiently. The regioselectivity and chemoselectivity of the reaction were as-expected, with the electron-deficient aryl group migrating to the C2-position of the pyrrole ring; meanwhile, the alkyl insertion site remains in the C3-position of the pyrrole ring. Under the newly optimized reaction conditions, various substituted enaminones (R^1 = aryl, heteroaryl, and alkyl; R^2 = phenyl, ethyl, and cyclopropyl) reacted well with different tosylhydrazones (Ar = substituted phenyl, and thiophenyl; R^3 = methyl, and ethyl) affording the desired products in good yield (**5a**–**5aa**). The substituents of the enaminone continued to exert electronic effects: electron-deficient enaminones performed more efficiently than electron-rich enaminones (78% yield). Notably, donor-only diazo compounds (e.g., *N*-tosylhydrazone derived from benzaldehyde) obtained the desired product (**5y**) in high yield under the standard conditions. Meanwhile, by using cyclic tosylhydrazones as a reaction substrate, indole, and cyclohepta[*b*]pyrrole derivatives were finally produced (**5p** and **5q**). In addition, donor–donor diazo compounds derived from unsymmetrical aryl ketones or other EWGs apart from the esters group (e.g., **5z** and **5aa)** can be used in this cascade reaction. The results showed that the products remain highly chemo- and regio-selective. Lastly, the NOE spectra of **5a** confirmed that the Ar group was shifted to the C2-position of the pyrrole ring (Figure S1, SI).

To gain insights into the reaction mechanism, we first conducted isotopic labeling experiments under the standard conditions (Scheme 2). Deuterium hydrogen-labeling experiments were conducted, and the pyrrole product of deuterium hydrogenation at the C4-position was detected (Scheme 2, Eq. 1). ^{15}N was also retained in the 1*H*-pyrrole product when ^{15}N-labeled enaminones were used as starting materials in the cascade reaction (Scheme 2, Eq. 2). These results showed that an exchange of active hydrogen atoms occurred in the catalytic cycle, and that nitrogen atoms in the pyrrole ring were introduced by the enaminones. To obtain evidence for C–C bond insertion and Ag-catalyzed selective control, we separated the intermediate 1,4-iminone (**3a**-*q*) containing a quaternary carbon center under standard conditions (Scheme 2, Eq. 3). A single crystal structure (Scheme 2, **3a**-*q*-Crystal)[14] confirmed that this compound was the product of the C–C bond formal insertion reaction of the enaminone and diazoester. In addition, 1,4-iminone (**3a**-*q*) could be converted into 1*H*-pyrrole products **3a** under standard conditions; however under TfOH catalysis, no reaction occurred at room temperature, and two selective products (**3a** and **3a′**) appeared in the reflux, indicating that the silver ion controlled several reaction steps, including the C–C bond insertion reaction, as well as the condensation and migration reactions.

Scheme 2. Control Experiments

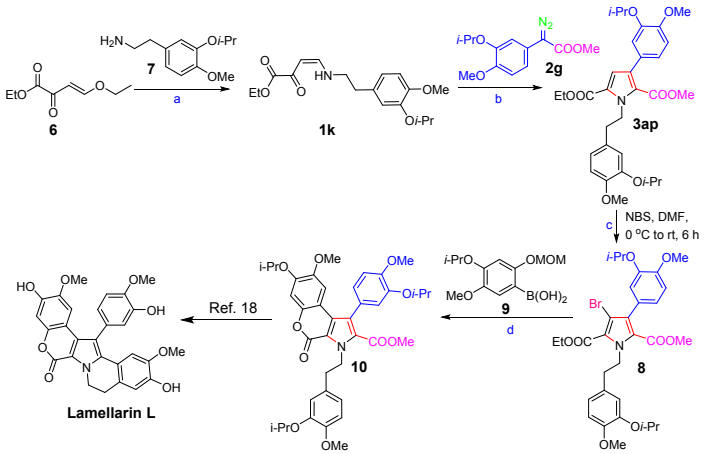


Scheme 3. Plausible Reaction Mechanism for AgOTf Catalyzed [4+1C]^{insert} Synthesis of Multisubstituted Pyrroles



On the basis of these results and control experiments, we propose a plausible catalytic cycle for AgOTf-catalyzed [4+1C]^{insert} cascade synthesis of multisubstituted pyrroles with enaminone **1** and diazoester **2/4** (Scheme 3). In the silver catalyzed C-C bond insertion cycle, cis/trans-enaminone were in thermodynamic equilibrium, in which cis-enaminone **1′** was first converted by AgOTf into silver enaminone **T1**, which reacted with diazoester **2/4** to give electrophilic silver carbenoid **T2** following the loss of N_2. Cyclopropanation of **T2** resulted in the intermediate **T3**. Owing to the assistance of the nitrogen lone pairs and ring strain, the C–C bond is regioselectively cleaved at the α,β-position of the carbonyl group to yield silver enolate **T4**. Upon protonation by HOTf, **T4** released 1,4-iminone **3/5**-*q* with an all-carbon quaternary center following regeneration of the silver catalyst (Scheme 3, left cycle). In contrast to the existing catalytic methods used for the insertion of diazoesters into 1,3-dicarbonyl compounds,[8a,8c-e] the cyclopropanation in the current study selectively occurred at the double bond of the predominant enamine form rather than the enol imine form or the previously reported pathway that relied on the ability of the migrating groups, in which migration of the C2 carbon atom would likely be disfavored. The regioselective cyclopropanation represents a novel mode of carbenoid reactivity. Subsequently, in the Ag-catalyzed cyclization/[1,5]-shift steps, 3*H*-pyrrole **T7** was formed via the dehydration of the hydroxyl-pyrroline **T6**, formed by the intramolecular condensation of 1,4-iminone **T5** driven by the coordination of silver with N and O atoms. Then, Ag^+ induced chemo- and regio-selective thermal [1,5]-shift of the 3*H*-pyrrole **T7** yielded the 2*H*-pyrrole **T8**, which was dehydroaromatized to produce multisubstituted 1*H*-pyrroles **3/5** (Scheme 3, right cycle). Numerous studies have been conducted on the thermal [1,5]-sigmatropic rearrangements of 2*H*-pyrroles to ultimately give 1*H*-pyrroles,[17] but similar rearrangements with 3*H*-pyrroles as the starting materials are rarely reported.[8a,18] In contrast to the reported thermolysis of 3*H*-pyrroles used to prepare 1*H*-pyrroles as the dominant product,[18] the AgOTf-catalyzed cascade synthesis of multisubstituted pyrroles regioselectively and chemoselectively produced 1*H*-pyrroles, representing a novel thermal rearrangement of 3*H*-pyrroles.

Scheme 4. Formal Synthesis of Lamellarin L



Reaction conditions: [a]Stirred in THF for 12 h at 20–60 °C, 87%. [b]Cat. AgOTf (5 mol%), CH_2Cl_2, stirred for 12 h at rt, 68%. [c]NBS, DMF, 0 °C to rt, 6 h, 99%. [d]1) **9** (2.0 equiv.), $Pd(PPh_3)_4$ (10 mol%), THF, reflux, 18 h, 2) concd HCl, MeOH, reflux 1 h (two-step, 94%).

To show the utility of this method to pyrroles, we applied the C–C bond insertion/cyclization/[1,5]-shift cascade strategy for the synthesis of the pyrrole moiety of lamellarin L. Scheme 4 presents our synthesis of this compound. The desired cascade transformation occurred (**3ap**) under the usual reaction conditions with a yield of 68%. Bromination of the remaining vacant pyrrole position proceeded in quantitative yield to give bromopyrrole **8** (99% yield). Subsequently, chromeno[3,4-*b*]pyrrol-4(3*H*)-one **10** (75% yield) was obtained over two-steps, via Suzuki coupling of bromopyrrole **8** with phenylboronic acid **9** and intramolecular transesterification reaction. Decarboxylation coupling cyclization and deprotection of pyrrole can provide lamellarin L and various related compounds.[1b,19] Compared with that of the industrial (Paal–Knorr) synthesis of pyrrole, the value of the method described in the present study lies not only in its use of readily available starting materials and the number of reaction steps but also its modularity, allowing access to various substituents on the pyrrole ring.

In summary, we demonstrated a distinct chemo- and regioselective cascade catalytic [4+1C]^{insert} cascade reaction for the preparation of pyrroles from enaminones and carbene precursors by using AgOTf. This technique was used to formally synthesize lamellarin L. Control experiments provided a plausible reaction mechanism in which silver ions first catalyzed C–C bond carbene insertion and then controlled cyclization and [1,5]-shift. Further development of this AgOTf-catalyzed pyrrole synthesis is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org. Experimental procedures, characterization data including ^{1}H and ^{13}C NMR spectra, IR spectra and HR-MS, and copies of NMR spectra (PDF)
X-ray data for **3an** (CIF)
X-ray data for **3a-q** (CIF)

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Notes

The authors declare no competing financial interest.

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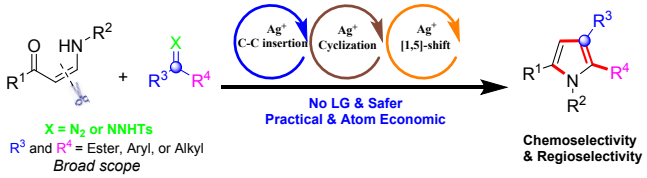

Pyrrole: Ag-catalyzed [4+1C]^{insert} cascade to coupling of enaminones with donor/donor or donor/acceptor carbenes, which provides distinct chemo- and region-selective multisubstituted pyrroles. This atom-economical, environmentally friendly methodology offers easy access to a range of substituted pyrroles in moderate to good yields.