One-pot highly efficient synthesis of substituted pyrroles and *N*-bridgehead pyrroles by zinc-catalyzed multicomponent reaction†

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A convenient zinc(II) chloride-catalyzed regioselective propargylation/amination/cycloisomerization process has been developed for the synthesis of substituted pyrrole derivatives from propargylic acetates, enoxysilanes and primary amines. Various aromatic and aliphatic propargylic acetates participate well in the reaction, providing the propargylation/amination/cycloisomerization products in good yields with complete regioselectivity. The one-pot multicomponent coupling reaction furnishes substituted pyrroles in high yields by circumventing the intermediates' isolation. Zinc(II) chloride acts as a multifunctional catalyst and catalyzes three mechanistically distinct processes in a single-pot. The protocol developed has been extended to the synthesis of *N*-bridgehead pyrroles containing polycyclic fragments.

Introduction

Substituted pyrroles represent indispensable structural motifs, broadly found in biologically active natural products, as well as molecular sensors.[1] Moreover, *N*-bridgehead pyrroles containing polycyclic fragments and their partially or completely reduced analogues constitute the basic skeleton of many alkaloids with well recognized pharmacological properties.[2] Accordingly, substantial attention has been paid to developing efficient methods for the synthesis of substituted pyrroles. The traditional routes to their preparation are multistep reactions, as illustrated by the Paal–Knorr cyclization of amines with pre-formed 1,4-diketones. As an alternative, recent strategies for the synthesis of pyrroles are mainly based on transition metal-catalyzed cycloaddition or cycloisomerization of acyclic precursors, many of which provide structures not easily generated by classical routes.[3–5] Despite numerous advances, the corresponding multicomponent coupling reactions direct from several readily available and easily diversified building blocks are much less studied.[6] Hence, the development of new, mild, and versatile synthetic methods to access functionalized pyrroles has remained an ongoing challenge.

Substituted pyrroles are highly biologically active, and have proven to display antimycobacterial activity[7] and to inhibit cytokine-mediated diseases.[8] The intriguing molecular architectures prompt us to study the feasibility of synthesizing substituted pyrroles. To the best of our knowledge, no examples of the synthesis of substituted pyrroles directly from propargylic acetates, enoxysilanes and amines have ever been reported. Herein, as the results of development on the transition metal-catalyzed propargylic substitution reaction in our group,[9] we wish to report a highly efficient propargylation/amination/cycloisomerization reaction for the synthesis of substituted pyrroles directly from propargylic acetates, enoxysilanes and primary amines using zinc(II) chloride as a multifunctional catalyst (Scheme 1).

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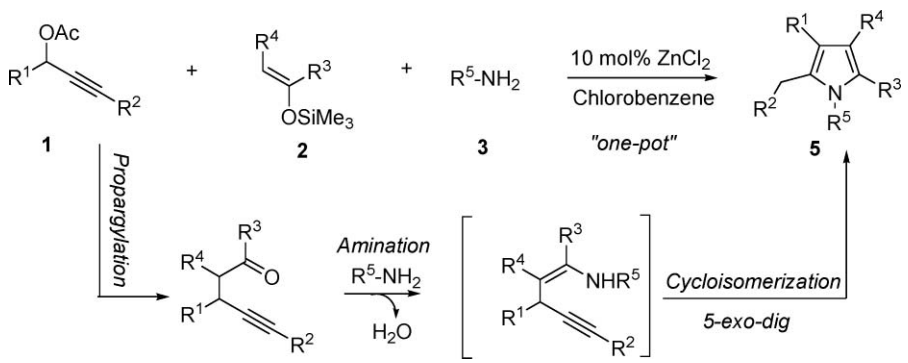
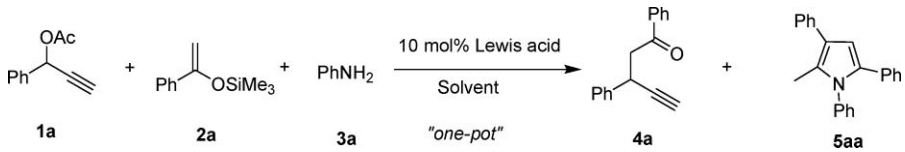
Results and discussion

We recently described a straightforward approach to the synthesis of substituted furans from propargylic acetates and enoxysilanes.[9c] The process, which proceeds in a one-pot manner, involves initial



Scheme 1 Synthesis of pyrroles from propargylic acetates, enoxysilanes and primary amines.

Table 1 Reaction optimization[a]



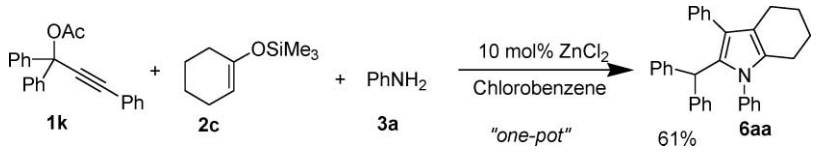
Entry	Catalyst	Solvent	Time/h[b]	Isolated yield (%)[c]	
				4a	**5aa**
1	$ZnCl_2$	Chlorobenzene	1.5	0	83
2	AgOTf	Chlorobenzene	24	0	0
3	$Cu(OTf)_2$	Chlorobenzene	5	0	61
4	$Cu(OAc)_2$	Chlorobenzene	24	0	0
5	CuI	Chlorobenzene	24	0	0
6	$CuSO_4$	Chlorobenzene	24	0	0
7	$FeCl_3$	Chlorobenzene	12	36	25
8	$InCl_3$	Chlorobenzene	1.5	0	67
9	$BiCl_3$	Chlorobenzene	12	27	16
10	$AlCl_3$	Chlorobenzene	12	27	40
11	$SnCl_4$	Chlorobenzene	24	0	0
12	$Zn(OTf)_2$	Chlorobenzene	24	0	0
13	$BF_3{\cdot}Et_2O$	Chlorobenzene	12	36	20
14	$Bi(OTf)_3$	Chlorobenzene	12	29	38
15	$RuCl_3{\cdot}3H_2O$	Chlorobenzene	24	0	0
16	$HAuCl_4{\cdot}3H_2O$	Chlorobenzene	24	0	0
17	$Mg(ClO_4)_2$	Chlorobenzene	24	0	0
18	5% $ZnCl_2$	Chlorobenzene	12	34	46
19	$ZnCl_2$	CH_3CN	10	39	34
20	$ZnCl_2$	DCE	10	42	38
21	$ZnCl_2$	CH_3NO_2	12	0	0
22	$ZnCl_2$	1,4-Dioxane	12	0	0
23	$ZnCl_2$	Toluene	10	5	17
24	$ZnCl_2$	*p*-Xylene	12	0	0

[a] Reaction conditions: 10 mol% of catalyst, 1.0 equiv. of **1a** (0.5 mmol), and 2.0 equiv. of **2a** (1.0 mmol), solvent (2 mL) at 75 °C for 0.3 h, followed by the addition of 2.0 equiv. of **3a** (1.0 mmol). Amination/cycloisomerization proceeded at reflux. [b] Reaction time for amination/cycloisomerization at reflux. [c] Isolated yield of pure product based on propargylic acetate **1a**.

$FeCl_3$-promoted nucleophilic substitution of propargylic acetates with enoxysilanes in acetonitrile and subsequent cycloisomerization of the resulting intermediate γ-alkynyl ketone catalyzed by PTSA in toluene. Encouraged by the successful synthesis of substituted furans, we became interested in developing approaches toward substituted pyrroles when a primary amine is introduced into the reaction medium, and tested the multicomponent reaction of propargylic acetate **1a**, enoxysilane **2a** and primary amine **3a**.

Initially, treatment of a chlorobenzene solution of propargyl acetate **1a** and 2.0 equiv. of enoxysilane **2a** with 10 mol% $FeCl_3$ at 75 °C for 0.3 h, followed by the addition of 2.0 equiv. of aniline **3a** and then heating to reflux for an additional 12 h, afforded the desired substituted pyrrole **5aa** in 25% yield along with uncyclized γ-alkynyl ketone **4a** in 36% yield (Table 1, entry 7). To optimize the reaction conditions, we first investigated a variety of Lewis acids for their effectiveness at catalyzing this reaction. Fortunately, zinc(II) chloride provided the best results in comparison to other Lewis acids investigated and led to the formation of the desired product with complete regioselectivity in high yield at reflux after 1.5 h (Table 1, entry 1). Other Lewis acids, such as $BiCl_3$, $AlCl_3$, $BF_3{\cdot}Et_2O$ or $Bi(OTf)_3$, also produced some of the desired substituted pyrrole **5aa**, but the amination/cycloisomerization of the intermediate γ-alkynyl ketone **4a** did not proceed to completion even after 12 h at reflux (Table 1, entries 9, 10, 13 and 14). On the other hand, $Cu(OTf)_2$ and $InCl_3$ rapidly consumed the starting propargylic acetate **1a** and the intermediate **4a**, but produced the desired product only in moderate yield (Table 1, entries 3 and 8). Other catalysts such as AgOTf, $Cu(OAc)_2$, CuI, $CuSO_4$, $SnCl_4$, $Zn(OTf)_2$, $RuCl_3{\cdot}3H_2O$, $HAuCl_4{\cdot}3H_2O$ or $Mg(ClO_4)_2$ were unreactive (Table 1, entries 2, 4–6, 11, 12 and 15–17). Decreasing the catalyst loading to 5 mol% led to a longer reaction time and gave a lower yield of **5aa** (Table 1, entry 18). Furthermore, the reaction proceeded smoothly under "open-flask" conditions without exclusion of moisture or air from the reaction mixture. The choice of the solvent also played a crucial role. Acetonitrile, 1,2-dichloroethane and toluene as solvents only produced the desired product **5aa** in low yields (Table 1, entries 19, 20 and 23). In other solvents, such as CH_3NO_2, 1,4-dioxane and *p*-xylene, no cyclization products were observed (Table 1, entries 21, 22 and 24). However, employing chlorobenzene (PhCl) as the solvent produced a further improvement and provided **5aa** in 83% yield (Table 1, entry 1).

With optimal conditions in hand, the substrate scope of the zinc-catalyzed propargylation/amination/cycloisomerization reaction was examined. Typical results are shown in Table 2. To our delight, propargylation/amination/cycloisomerization occurred with a range of secondary aromatic propargylic acetates (R^1 = aryl), including phenyl (Table 2, entries 1–22) and phenyl rings substituted with electron-withdrawing (Table 2, entries 23 and 24) or electron-donating (Table 2, entries 25 and 26) groups,



Scheme 2 Synthesis of the pyrrole **6aa**

affording the substituted pyrroles in good yields with complete regioselectivity. Electron-rich propargylic acetates provided the desired products in higher yields than electron-poor propargylic acetates. Sterically encumbered *ortho*-substituted phenyl groups (Table 2, entry 26) did not affect the course of the reaction. Moreover, fused aromatic and heteroaromatic substrates were also successfully employed in the reaction to give the pyrroles **5ia** and **5ja** in 79 and 83% isolated yields, respectively (Table 2, entries 27 and 28). Among the propargylic acetates that were examined, substrates containing a terminal alkynyl unit ($R^2 = H$) gave desirable results, providing the substituted pyrroles in high yields (Table 2, entries 1–6). Substrates containing an internal alkynyl unit (R^2 = TMS, *n*-Bu, phenyl) also underwent smooth reaction to give the substituted pyrroles, and required slightly longer reaction times, but maintain high yields (Table 2, entries 7–28). The trimethylsilyl group was removed either in the course of the reaction or during workup (Table 2, entries 7–9 and 27). It should be noted that in all cases the reactions proceeded with complete regioselectivity and functional groups such as bromo, ester, and methoxy in the propargylic acetates were readily carried through the reaction, allowing for the subsequent elaboration of the products.

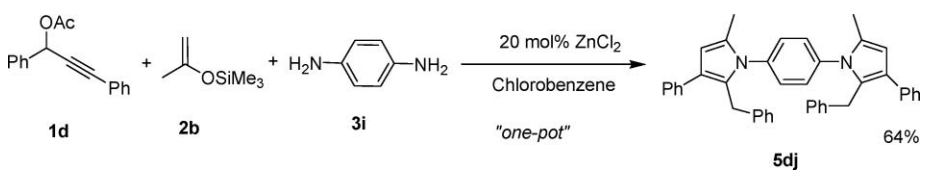
The reaction was not limited to secondary propargylic acetates. For example, tertiary propargylic acetate **1k** readily underwent propargylation/amination/cycloisomerization to afford the substituted pyrrole **6aa** in 61% yield through the formation of allenyl isomer[10] (Scheme 2).

We next turned to examine the scope of the enoxysilane component of the reaction (Table 2), and the corresponding pyrroles were obtained in good yields. Enoxysilanes **2a** and **2b** participate as nucleophiles in the reaction without a noticeable difference. On the other hand, increasing the steric nature of enoxysilane influenced the efficiency of the reaction, cyclic enoxysilane **2c** required slightly prolonged reaction times.

With respect to the amines, the $ZnCl_2$-catalyzed multicomponent reaction is quite general. Aromatic (Table 2, entries 1–4, 6–8, 10, 13–18, and 21–28) and aliphatic primary amines (Table 2, entries 5, 9, 11, 12, and 19–20) could be efficiently incorporated into the pyrrole framework. The reaction proceeded smoothly when the aryl group of the primary amines were substituted with electron-donating (Table 2, entries 3, 10, 17 and 21) and electron-withdrawing groups (Table 2, entries 4, 13, 18 and 22). Aliphatic primary amines required slightly longer reaction times, but maintain high yields. Additionally, symmetrical amine **3i** also participated in zinc-catalyzed propargylation/amination/cycloisomerization, smoothly affording oligomer **5dj** with complete regioselectivity (Scheme 3). This process has the potential to access oligoaryls of well-defined conjugation lengths, a class of compounds that show promise as new optoelectronic materials.[11]

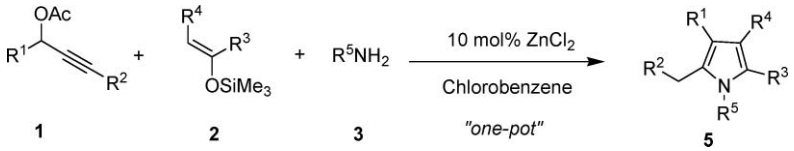
Under the above standard conditions, attempts to extend the $ZnCl_2$ system to the secondary aliphatic propargylic acetate (R^1 = alkyl) were not successful. We reasoned that the process proceeded through a propargylic cation intermediate. Instability of the propargylic cation intermediate made sequential reaction less favorable. The polarity of the solvent could have a significant effect on the outcome of the reaction. By further screening of solvents, we were pleased to find that nitromethane was ideal, leading to the rapid formation of the intermediate γ-alkynyl ketone **4** which could be directly used for the next amination/cycloisomerization, without purification, to afford the substituted pyrroles in good yields with complete regioselectivity (Table 3). Other solvents, such as chlorobenzene, 1,2-dichloroethane, acetonitrile, and THF, were less efficient or did not promote the reaction. For example, propargylic acetate **1l** (0.5 mmol) was treated with enoxysilane **2b** (1.0 mmol) in the presence of 10 mol% $ZnCl_2$ in nitromethane. Upon reaction completion, nitromethane was removed *in vacuo*, followed by the addition of chlorobenzene (2 mL) and amine **3a** (1.0 mmol). The reaction was heated to reflux for 3 h. The desired product **5la** was gained in 72% yield. The other results are depicted in Table 3. Similar yields and diversity can be attained in this process as observed with the secondary aromatic propargylic acetates. Methyl and pentyl substituents at the propargylic position (Table 3, entries 1–3) are well tolerated and can be incorporated into the pyrroles. Unfortunately, the primary aliphatic propargylic acetate **1n** ($R^1 = H$; R^2 = Ph) failed to give substituted pyrrole (Table 3, entry 4).

In the hope of extending the application of this method to the synthesis of the N–H pyrrole, we examined the effect of variation of ammonia source, which we thought would readily allow for the reaction. Firstly, we employed NH_4OAc, NH_4Cl and ammonium carbamate as sources of the N–H unit of the pyrrole. Unfortunately, these variations did not deliver the desired N–H pyrrole. We were pleased to find that the 2-chloroethyl moiety is a versatile protecting group for the pyrrole nitrogen atom.[12] Deprotection of the *N*-(2-chloroethyl)pyrrole is accomplished by



Scheme 3 Synthesis of the oligomer **5dj**.

Table 2 Synthesis of substituted pyrroles **5** from secondary aromatic propargylic acetates **1**, enoxysilanes **2** and primary amines **3**[a]



1 2 3 5

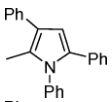
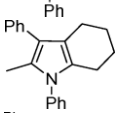
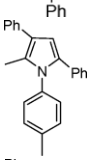
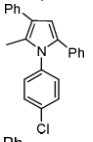
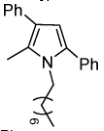
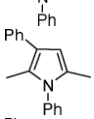
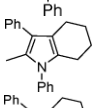
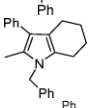
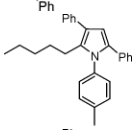
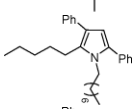
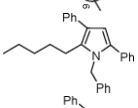
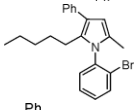
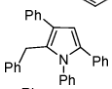
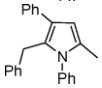
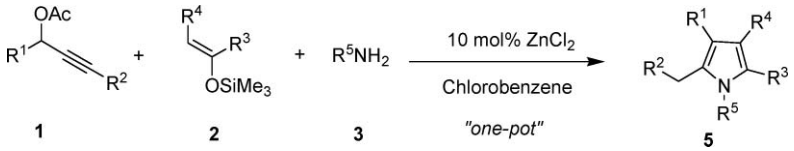
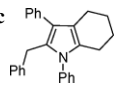
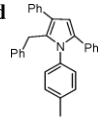
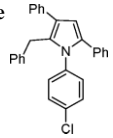
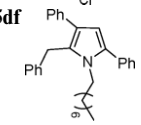
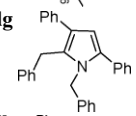
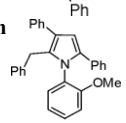
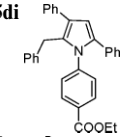
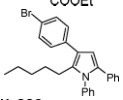
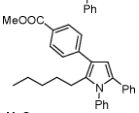
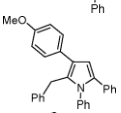
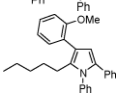
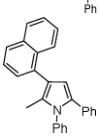
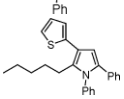
	Propargylic acetate **1**	Enoxysilane **2**	Amine **3**			
Entry	R^1; R^2	R^3; R^4	R^5	Product **5**	Time/h[b]	Yield (%)[c]
1	**1a:** Ph; H	**2a:** Ph; H	**3a:** Ph-	**5aa** 	1.5	83
2	**1a:** Ph; H	**2c:** -$(CH_2)_4$-	**3a:**Ph-	**5ab** 	2	78
3	**1a:** Ph; H	**2a:** Ph; H	**3b:** 4-MePh-	**5ac** 	1.5	84
4	**1a:** Ph; H	**2a:** Ph; H	**3c:** 4-ClPh-	**5ad** 	1.5	81
5	**1a:** Ph; H	**2a:**Ph; H	**3d:** *n*-C_8H_{17}-	**5ae** 	2.5	80
6	**1a:** Ph; H	**2b:** Me; H	**3a:**Ph-	**5af** 	1.5	86
7	**1b:** Ph; TMS	**2b:** Me; H	**3a:**Ph-	**5ba** 	3	77
8	**1b:** Ph; TMS	**2c:** -$(CH_2)_4$-	**3a:**Ph-	**5bb** 	3.5	73
9	**1b:** Ph; TMS	**2c:** -$(CH_2)_4$-	**3e:** $PhCH_2$-	**5bc** 	3.5	72
10	**1c:** Ph; *n*-Bu	**2a:** Ph; H	**3b:** 4-MePh-	**5ca** 	3	86
11	**1c:** Ph; *n*-Bu	**2a:** Ph; H	**3d:** *n*-C_8H_{17}-	**5cb** 	12	80
12	**1c:** Ph; *n*-Bu	**2a:** Ph; H	**3e:** $PhCH_2$-	**5cc** 	10	83
13	**1h:** Ph; *n*- Bu	**2b:** Me; H	**3f:** 2-BrPh-	**5cd** 	5	82
14	**1d:** Ph; Ph	**2a:** Ph; H	**3a:** Ph-	**5da** 	3	87
15	**1d:** Ph; Ph	**2b:** Me; H	**3a:** Ph-	**5db** 	3	91

Table 2 *(Contd.)*

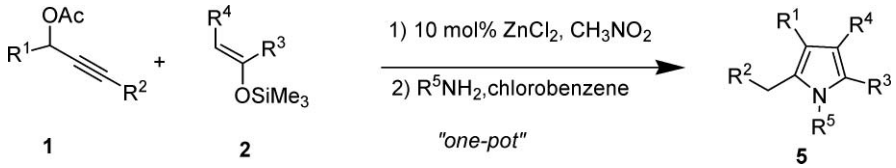


1 2 3 5

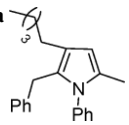
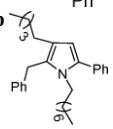
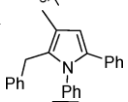
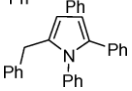
	Propargylic acetate **1**	Enoxysilane **2**	Amine **3**			
Entry	R^1; R^2	R^3; R^4	R^5	Product **5**	Time/h[b]	Yield (%)[c]
16	**1d:** Ph; Ph	**2c:** -$(CH_2)_4$-	**3a:** Ph-	**5dc** 	5	86
17	**1d:** Ph; Ph	**2a:** Ph; H	**3b:** 4-MePh-	**5dd** 	3	90
18	**1d:** Ph; Ph	**2a:** Ph; H	**3c:** 4-ClPh-	**5de** 	3.5	85
19	**1d:** Ph; Ph	**2a:** Ph; H	**3d:** *n*-C_8H_{17}-	**5df** 	12	80
20	**1d:** Ph; Ph	**2a:** Ph; H	**3e:** $PhCH_2$	**5dg** 	10	83
21	**1d:** Ph; Ph	**2a:** Ph; H	**3g:** 2-MeOPh-	**5dh** 	3	86
22	**1d:** Ph; Ph	**2a:** Ph; H	**3h:** 4-COOEtPh-	**5di** 	4	76
23	**1e:** 4-BrPh; *n*-Bu	**2a:** Ph; H	**3a:** Ph-	**5ea** 	3.5	81
24	**1f:** 4-COOMePh; *n*-Bu	**2a:** Ph; H	**3a:** Ph-	**5fa** 	4	77
25	**1g:** 4-MeOPh; Ph	**2a:** Ph; H	**3a:** Ph-	**5ga** 	2.5	91
26	**1h:** 2-MeOPh; *n*-Bu	**2a:** Ph; H	**3a:** Ph-	**5ha** 	3	89
27	**1i:** 1-Naphthyl; TMS	**2a:** Ph; H	**3a:** Ph-	**5ia** 	4	79
28	**1j:** 2-Thienyl; *n*-Bu	**2a:** Ph; H	**3a:** Ph-	**5ja** 	3.5	83

[a] Reaction conditions: 10 mol% of $ZnCl_2$, 1.0 equiv. of **1** (0.5 mmol), and 2.0 equiv. of **2** (1.0 mmol), chlorobenzene (2 mL) at 75 °C for 0.3 h, followed by the addition of 2.0 equiv. of **3** (1.0 mmol). Amination/cycloisomerization proceeded at reflux for 1.5–12 h. [b] Reaction time for amination/cycloisomerization at reflux. [c] Isolated yield of pure products based on propargylic acetates **1**.

Table 3 Synthesis of substituted pyrroles **5** from secondary aliphatic propargylic acetates **1**, enoxysilanes **2** and primary amines **3**[a]



1 **2** **5**

	Propargylic acetate **1**	Enoxysilane **2**	Amine **3**			
Entry	R^1; R^2	R^3; R^4	R^5	Product **5**	Time/h[b]	Yield (%)[c]
1	**1l:** *n*-pent; Ph	**2b:** CH_3; H	**3a:** Ph-	**5la** 	3	72
2	**1l:** *n*-pent; Ph	**2a:** Ph; H	**3d:** *n*-C_8H_{17}-	**5lb** 	10	63
3	**1m:** CH_3; Ph	**2a:** Ph; H	**3a:** Ph-	**5ma** 	3	71
4	**1n:** H; Ph	**2a:** Ph; H	**3a:** Ph-	**5na** 	12	0

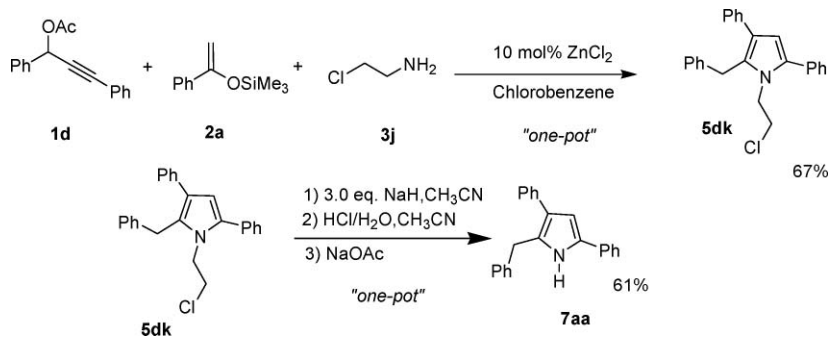
[a] Reaction conditions: 10 mol% of $ZnCl_2$, 1.0 equiv. of **1** (0.5 mmol), and 2.0 equiv. of **2** (1.0 mmol), CH_3NO_2 (2 mL) at r.t. for 1 h. Upon reaction completion, nitromethane was removed *in vacuo*, followed by the addition of chlorobenzene (2 mL) and 2.0 equiv. of **3** (1.0 mmol). Amination/cycloisomerization proceeded at reflux for 3–12 h. [b] Reaction time for amination/cycloisomerization at reflux. [c] Isolated yield of pure products based on propargylic acetates **1**.

means of efficient three-step, one-pot sequences *via* the *N*-vinyl compound and subsequent degradation of the *N*-(1-hydroxyethyl) compound obtained therefrom. The N–H pyrrole **7aa** was afforded in 41% yield over two steps (Scheme 4).

N-Bridgehead pyrroles are found in various alkaloids such as mitomycins, mytomicines and vincetene.[13] The preparation of complex polycyclic heterocycles is an important synthetic goal owing to the use of these molecules as potential pharmaceuticals. Having successfully developed the Zn(II)-catalyzed propargylation/amination/cycloisomerization reaction, we turned to the application of this methodology in the synthesis of *N*-bridgehead pyrroles containing polycyclic fragments. To begin the synthetic sequence, terminal propargylic acetates **1** reacted with enoxysilanes **2** to give the γ-alkynyl ketones **4**. Subsequent Sonogashira coupling of adducts **4** with amines **3** set the stage for zinc-catalyzed intramolecular amination/5-*exo*-*dig*-cycloisomerization to afford *N*-bridgehead pyrroles **8** (Scheme 5). The modular design of this synthetic scheme allows for facile analogue synthesis by appropriate choice of the initial substrates.

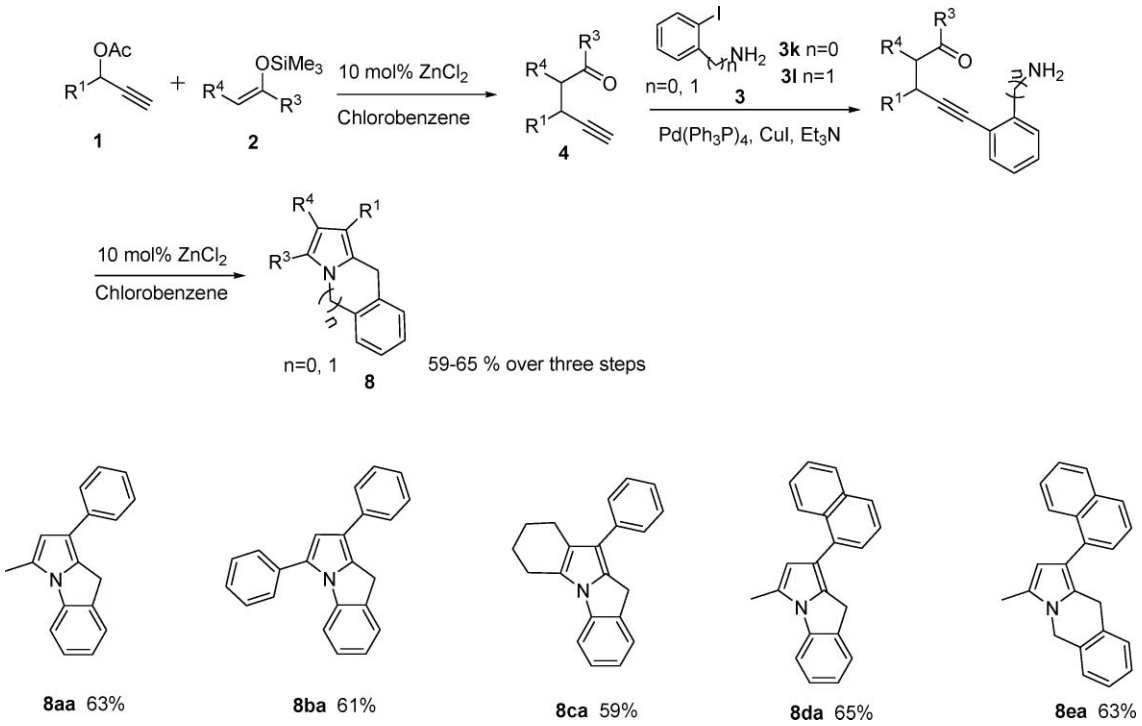
Conclusions

In summary, we have developed an air- and moisture-tolerant zinc-catalyzed regioselective propargylation/amination/cycloisomerization reaction of propargylic acetates, enoxysilanes and primary amines in a single-pot. Zinc(II) chloride, working as a multifunctional catalyst, catalyzes three mechanistically distinct processes in a single-pot under the same conditions. A wide range of aromatic propargylic acetates bearing terminal or internal alkyne groups are readily available and a number of functionalities are tolerated. Additionally, the secondary aliphatic propargylic acetates also could be efficiently incorporated into the pyrrole framework. The broad scope, mild reaction conditions, and experimental ease of this transformation have made it a valuable



1d **2a** **3j** **5dk** **5dk** **7aa**

Scheme 4 Synthesis of the N–H pyrrole **7aa**.



Scheme 5 Synthesis of the *N*-bridgehead pyrroles **8**.

alternative to current available transformations. The protocol developed has been extended to the synthesis of *N*-bridgehead pyrroles containing polycyclic fragments. Further development on this methodology is currently underway in our laboratories.

Experimental

General experimental

Propargylic acetates **1** and enoxysilanes **2** were prepared according to published procedures. All other compounds are commercially available and were used without further purification. Infrared spectra were recorded on a Nicolet AVATER FTIR360 spectrometer. NMR spectra were recorded on a Bruker AVANCE DPX-400 instrument at 400 MHz (^{1}H) or 100 MHz (^{13}C). The chemical shift values (δ) are given in parts per million (ppm) and are referred to the residual peak of the deuterated solvent ($CDCl_3$). MS measurements were performed on Bruker Reflex III mass spectrometer. Elemental analyses were performed with a Perkin–Elmer 2400 microanalyser. Flash chromatography was performed with QingDao silica gel (300–400 mesh).

General procedure for the synthesis of substituted pyrroles (5aa, 5ac–5ae, 5ca–5cd, 5db, 5dc, 5de, 5dg–5fa, 5ha–5ja, 6aa)

To a 10 mL flask, propargylic acetates **1** (0.5 mmol), enoxysilanes **2** (1.0 mmol), chlorobenzene (2.0 mL) and $ZnCl_2$ (0.05 mmol) were successively added. The reaction was allowed to stir at 75 °C for 0.3 h, followed by the addition of primary amines **3** (1.0 mmol). The reaction mixture was heated to reflux temperature for an additional 1.5–12 h until completion by TLC. Upon cooling to room temperature, the reaction mixture was then quenched with 1 M HCl (2 mL), the organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*, and then the residue was purified by silica gel column chromatography (EtOAc–hexane = 1 : 100) to afford the corresponding substituted pyrroles.

General procedure for the synthesis of substituted pyrrole 5dj

To a 10 mL flask, propargylic acetate **1d** (1.0 mmol), enoxysilane **2b** (2.0 mmol), chlorobenzene (4.0 mL) and $ZnCl_2$ (0.20 mmol) were successively added. The reaction was allowed to stir at 75 °C for 0.3 h, followed by the addition of primary amine **3i** (0.4 mmol). The reaction mixture was heated to reflux temperature for an additional 10 h until completion by TLC. Upon cooling to room temperature, the reaction mixture was then quenched with 1 M HCl (2 mL), the organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*, and then the residue was purified by silica gel column chromatography (EtOAc–hexane = 1 : 100) to afford the substituted pyrrole.

General procedure for the synthesis of substituted pyrroles (5la–5ma)

To a 10 mL flask, propargylic acetates **1** (0.5 mmol), enoxysilanes **2** (1.0 mmol), nitromethane (2.0 mL) and $ZnCl_2$ (0.05 mmol) were successively added. The reaction was allowed to stir at r.t. for 1 h, nitromethane was removed *in vacuo*, followed by the addition of chlorobenzene (2 mL) and amine **3** (1.0 mmol). The reaction mixture was heated to reflux temperature for an additional 3–10 h until completion by TLC. Upon cooling to room temperature, the reaction mixture was then quenched with 1 M HCl (2 mL), the organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The

combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*, and then the residue was purified by silica gel column chromatography (EtOAc–hexane = 1 : 100) to afford the corresponding substituted pyrroles.

General procedure for the synthesis of substituted pyrroles (7aa)

Sodium hydride in mineral oil (60%, 24 mg, 0.6 mmol) was added to a stirred solution of **5dk** (0.186 g, 0.5 mmol) in dry acetonitrile (3.0 mL) maintained in a nitrogen atmosphere. The solution was heated at 50 °C for 2 h and 6 M hydrochloric acid (0.84 mL, 5 mmol) was added dropwise. After an additional 6 h, a solution of sodium acetate (494 mg, 6 mmol) in water (1.0 mL) was added and the solution was heated at reflux temperature for 0.5 h. Upon cooling to room temperature, the solution was extracted with ether (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*, and then the residue was purified by silica gel column chromatography (EtOAc–hexane = 1 : 10) to afford N–H pyrrole **7aa**.

General procedure for the synthesis of *N*-bridgehead pyrroles (8aa–8ea)

A. The synthesis of the γ-alkynyl ketone 4. To a 10 mL flask, propargylic acetates **1** (0.5 mmol), enoxysilanes **2** (1.0 mmol), chlorobenzene (2.0 mL) and $ZnCl_2$ (0.05 mmol) were successively added. The reaction was allowed to stir at 75 °C for 0.3 h. The solvent was removed under reduced pressure by an aspirator, and then the residue was purified by silica gel column chromatography (EtOAc–hexane = 1 : 20) to afford the γ-alkynyl ketone **4**.

B. The synthesis of *N*-bridgehead pyrroles 8. To a stirred solution of $Pd(PPh_3)_4$ (0.025 mmol), CuI (0.025 mmol) in anhydrous Et_3N (3 mL), amines **3** (0.5 mmol) and the γ-alkynyl ketone **4** (0.5 mmol) in Et_3N (2 mL) and THF (1 mL) were added. The reaction mixture was heated at reflux temperature under argon atmosphere for 2 h and then the solvent was removed under reduced pressure, followed by the addition of chlorobenzene (2.0 mL) and $ZnCl_2$ (0.05 mmol). The reaction was stirred at reflux until completion by TLC. Upon cooling to room temperature, the reaction mixture was then quenched with 1 M HCl (2 mL), the organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*, and then the residue was purified by silica gel column chromatography (EtOAc–hexane = 1 : 100) to afford the corresponding *N*-bridgehead pyrroles.

Acknowledgements

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Notes and References

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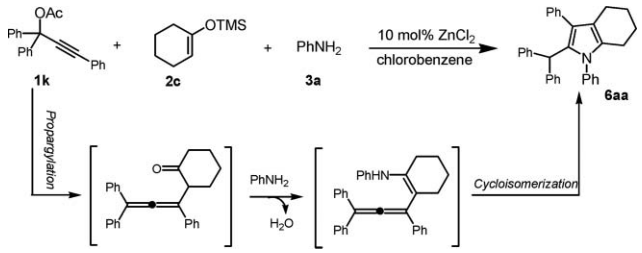
10 An alternative pathway involves trapping of the allenyl cation by enoxysilane, to give allenyl isomer, and subsequent amination/cycloisomerization to pyrrole **6aa**. see: ref. 9c.



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