A Novel Indium-Catalyzed Three-Component Reaction: General and Efficient One-Pot Synthesis of Substituted Pyrroles

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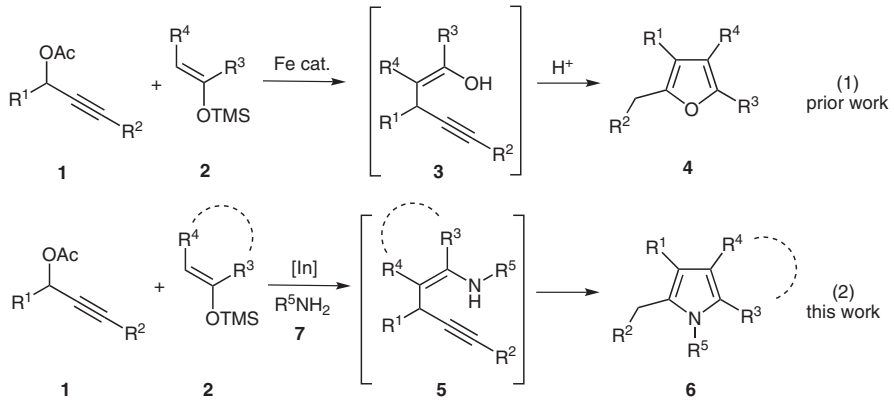
Abstract: A convenient and general approach towards the synthesis of substituted pyrroles from propargylic acetates, silyl enol ethers, and primary amines was described. This novel transformation was catalyzed by indium trichloride in a one-pot synthesis, and high yields of various pyrrole derivatives were obtained.

Key words: pyrrole, indium, one-pot reaction, propargylic acetate, enoxysilane

Pyrrole is an extremely important heterocyclic unit broadly found in naturally occurring and biologically active molecules and frequently used as building block in material science, pharmaceutical chemistry, and organic synthesis.[1] Accordingly, substantial attention has been paid to develop efficient, general, and economic approaches for their synthesis. Two principal strategies are commonly used for the preparation of substituted pyrroles: one is the functionalization of preexisting pyrrole-containing precursors through the introduction of new functional groups, and the other is assembly of a new pyrrole ring by cycloisomerization of acyclic precursors. The former method is not generally applicable due to the exceedingly high reactive activity of pyrrole rings which usually polymerized in the presence of Brønsted or Lewis acids.[2] In contrast, the latter route has greater potential for rapidly obtaining diversity in functionalized pyrroles. Among the many new cycloisomerization reactions, metal-catalyzed one-pot transformations are the most attractive, since those reactions can directly construct complicated pyrrole-containing molecules from readily accessible starting materials under mild conditions.[3] Although many advances have emerged in the past decade, no examples of preparation for substituted pyrroles directly from propargylic acetates, silyl enol ethers, and amines have existed. Consequently, it is highly desirable to explore this interesting field. Herein, as a result of the exploitation of metal-catalyzed propargylic substitution reaction in our group,[4] we wish to report a highly efficient one-pot reaction for the synthesis of substituted pyrroles from propargylic acetates, silyl enol ethers, and primary amines using indium trichloride as the catalyst.[5]

Recently, we described a general and effective approach toward the expeditious assembly of substituted furans from propargylic acetates and silyl enol ethers.[6] It was proposed that propargylic acetates **1** and silyl entol ethers **2** underwent an $FeCl_3$-assisted nucleophilic substitution in MeCN, leading to a γ-alkynyl ketone intermediates **3** which, upon a subsequent PTSA-catalyzed cycloisomerization, transformed into the final furan compounds **4** (Scheme 1, equation 1). Aiming at expanding the scope of this novel one-pot reaction, we became interested in developing synthetic protocols for substituted pyrrole rings (Scheme 1, equation 2).

In our initial study, we hypothesized that the pyrrole core **6** could be assembled by metal-catalyzed substitution–cycloisomerization of propargylic acetates **1**, silyl enol



Scheme 1 Synthesis of substituted furans and pyrroles by metal-catalyzed one-pot approach

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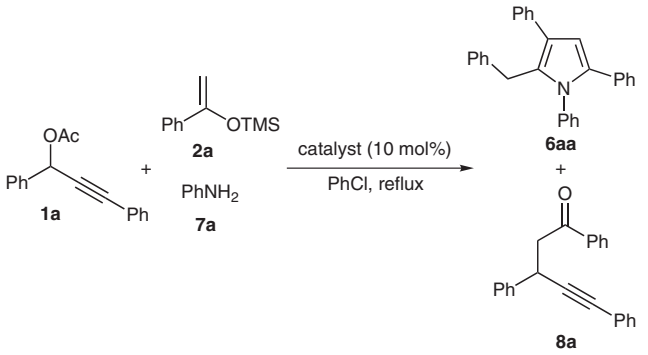
ethers **2**, and primary amines **7** (Scheme 1, equation 2). To this end, propargyl acetate **1a** and 2.0 equivalents of silyl enol ether **2a** were treated in the presence of 10 mol% $FeCl_3$ in chlorobenzene at 75 °C for 30 minutes, followed by adding 2.0 equivalents of aniline (**7a**). Then, the reaction was heated to refluxing temperature for an additional 12 hours. It was found that **1a**, **2a**, and **7a** underwent the desired cycloisomerization, affording the targeted pyrrole **6aa** in 36% yield along with an acyclic γ-alkynyl ketone **8a** in 57% yield (Table 1, entry 1). On the basis of our previous observation, we reasoned that the poor yield of pyrrole **6aa** was probably due to the weak ability of $FeCl_3$ to activate the alkyne bond. Therefore, AgOTf and $Cu(OTf)_2$, generally considered possessing stronger Lewis acidity and alkynophilicity, were adopted as the catalysts under the same reaction conditions as $FeCl_3$. Gratifyingly, it was found that the reactions were drastically improved and the desired product **6aa** was obtained in 71% yield when the transformation was performed in the presence of 10 mol% $Cu(OTf)_2$ (Table 1, entry 3). In contrast, the reaction catalyzed by AgOTf resulted in neither pyrrole nor γ-alkynyl ketone (Table 1, entry 2). While using a combination of AgOTf and $Cu(OTf)_2$ as co-catalyst, we were pleased to find a good yield of pyrrole that was obtained without any detectable γ-alkynyl ketone intermediate (Table 1, entry 4). Further screening of metallic Lewis acids brought very different results (Table 1, entries 5–13), among which $InCl_3$ proved to be the most effective catalyst and demonstrated higher catalytic efficacy than that of the combination of $Cu(OTf)_2$ and AgOTf (Table 1, entry 10).

Notably, reducing the loading of $InCl_3$ from 10 mol% to 5 mol% made a remarkable adverse influence on the reaction, in which the pyrrole **6aa**[7,8] and the γ-alkynyl ketone **8a** were obtained in 61% and 19% yields, respectively (Table 1, entry 17). It was indicative of that utilization of 10 mol% of $InCl_3$ was indispensable to effect the complete conversion of γ-alkynyl ketones into the final pyrroles. Screening with reaction solvents showed that PhCl was still the optimal solvent for this one-pot reaction (Table 1, entries 10, 18–22).

Exhaustive optimization indicated that employment of 10 mol% of $InCl_3$ in chlorobenzene was reasonably efficient for the construction of pyrrole ring in the same vessel. Importantly, the isolation of γ-alkynyl ketone intermediate is not necessary. Next, with the optimized combination of catalyst and solvent in hand, the generality of this cycloisomerization reaction was examined. To our delight, we found this transformation to be very general for a wide range of propargylic acetates, silyl enol ethers, and primary amines. Typical results are shown in Table 2, and the reaction proceeded smoothly without exclusion of moisture or air. The primary aromatic amines reacted very well, providing the cycloisomerization products in 79–88% yields (Table 2, entries 1–4), among which electron-withdrawing as well as electron-donating groups on aromatic rings were well tolerated. In contrast, the reactions of aliphatic primary amines comprising benzylamines proceeded much more sluggishly (with prolonged reaction time), but still afforded the desired products in good

Table 1 Optimization of Catalysts and Solvents for the One-Pot Synthesis of Substituted Pyrroles[a]

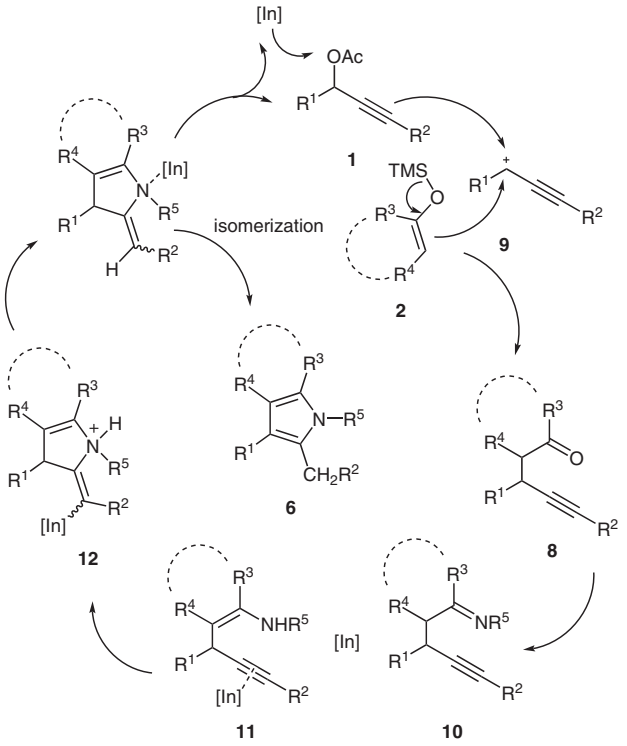


Entry	Catalyst	Solvent	Time (h)[b]	Yield of **6aa** (%)[c]	Yield of **8a** (%)[c]
1	$FeCl_3$	PhCl	12	36	57
2	AgOTf	PhCl	24	0	0
3	$Cu(OTf)_2$	PhCl	5	71	20
4	$Cu(OTf)_2$/AgOTf	PhCl	3	85	0
5	$Cu(OAc)_2$	PhCl	24	0	0
6	CuI	PhCl	24	0	0
7	$CuSO_4$	PhCl	24	0	0
8	$BiCl_3$	PhCl	12	71	21
9	$HAuCl_3{\cdot}3H_2O$	PhCl	10	19	61
10	$InCl_3$	PhCl	1	88	0
11	$RuCl_3{\cdot}3H_2O$	PhCl	24	0	0
12	$Mg(ClO_4)_2$	PhCl	24	0	0
13	$AlCl_3$	PhCl	24	27	46
14	$Zn(OTf)_2$	PhCl	24	0	0
15	$Bi(OTf)_3$	PhCl	12	38	29
16	$SnCl_4$	PhCl	24	0	0
17	$InCl_3$ (5 mol%)	PhCl	10	61	19
18	$InCl_3$	MeCN	10	0	86
19	$InCl_3$	DCE	24	76	19
20	$InCl_3$	$MeNO_2$	10	0	0
21	$InCl_3$	toluene	4	83	5
22	$InCl_3$	*p*-xylene	1	59	0

[a] All reactions were carried out on a 0.5 mmol scale of **1a** using 10 mol% of $InCl_3$, 2.0 equiv of **2a** (1.0 mmol) and 2 mL chlorobenzene at 75 °C for 0.5 h, followed by adding 2.0 equiv of **7a** (1.0 mmol). Imination–cycloisomerization proceeded at reflux for an appropriate time.
[b] Reaction time for imination–cycloisomerization.
[c] Isolated yields based on propargylic acetate **1a**.

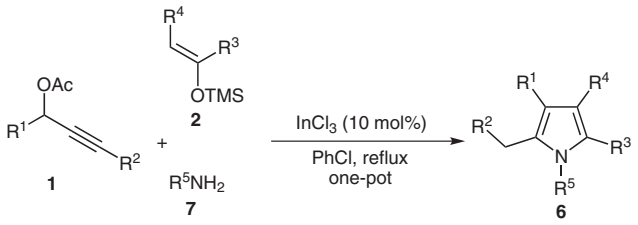
yields. On the other hand, the alkyne part in propaylic substrates bearing either aromatic (R^2 = Ar) or aliphatic substituents (R^2 = Alk) smoothly transformed into the expected products. It was worth mentioning that a TMS group in the substrates was cleaved under the reaction conditions (Table 2, entries 11–16). Thiophenyl-substituted propargylic acetate also gave a good yield (Table 2, entry 20). The transformations of the silyl enol ether of cyclohexanone provided a similar result as good as those of acetone and acetophenone (Table 2, entries 8, 13, and 14), generating the predicted products in moderate to good yields.

As a working hypothesis, we proposed the following plausible mechanism to account for the propargylation, imination, and cycloisomerization cascade of propargylic acetates **1**, silyl enol ethers **2**, and primary amines **7** into the pyrrole units **6** (Scheme 2). First, S_N1 substitution of propargylic cation **9** and silyl enol ethers **2**, the former is generated by assistance of the metal catalyst, leads to γ-alkynyl ketone intermediate **8**, which, upon imination by the primary amine, produces the imine **10**. The imine is in equilibrium with its enamine isomer **11**, which after an intramolecular nucleophilic attack of enamine nitrogen at the In-activated triple bond produces cyclic intermediate **12**. The latter can transform into product **6** via the proton–metal exchange and demetallation sequence. Thus, the catalyst enters into the next catalytic cycle.



Scheme 2 Proposed mechanism for the one-pot synthesis of pyrroles

Table 2 One-Pot Synthesis of Diversely Substituted Pyrroles Catalyzed by $InCl_3$[a]



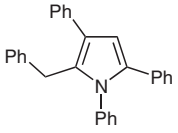
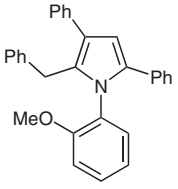
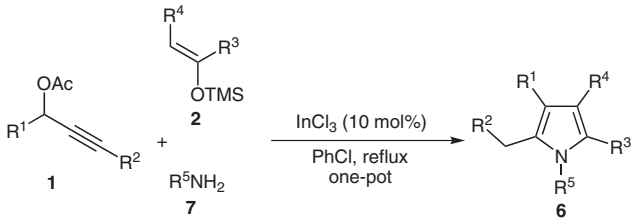
Entry	**1** R^1; R^2	**2** R^3; R^4	**7** R^5	Product **6**	Time (h)[b]	Yield (%)[c]
1	**1a** Ph; Ph	**2a** Ph; H	**7a** Ph	 **6aa**	1	88
2	**1a** Ph; Ph	**2a** Ph; H	**7b** 2-$MeOC_6H_4$	 **6ab**	2	86

Table 2 One-Pot Synthesis of Diversely Substituted Pyrroles Catalyzed by $InCl_3$[a] (continued)



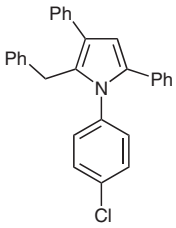
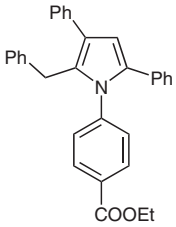
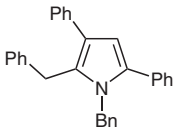
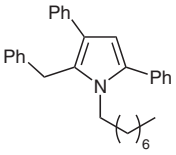
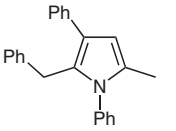
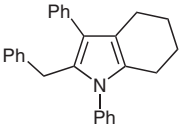
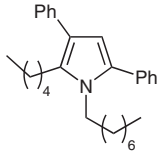
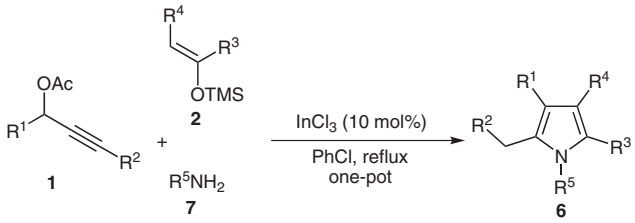
Entry	**1** R^1; R^2	**2** R^3; R^4	**7** R^5	Product **6**	Time (h)[b]	Yield (%)[c]
3	**1a** Ph; Ph	**2a** Ph; H	**7c** 4-ClC_6H_4	 **6ac**	3.5	84
4	**1a** Ph; Ph	**2a** Ph; H	**7d** 4-$EtOOCC_6H_4$	 **6ad**	4.5	79
5	**1a** Ph; Ph	**2a** Ph; H	**7e** Bn	 **6ae**	9	85
6	**1a** Ph; Ph	**2a** Ph; H	**7f** *n*-C_8H_{17}	 **6af**	10	82
7	**1a** Ph; Ph	**2b** Me; H	**7a** Ph	 **6ag**	3	90
8	**1a** Ph; Ph	**2c** $(CH_2)_4$	**7a** Ph	 **6ah**	2.5	87
9	**1b** Ph; *n*-Bu	**2a** Ph; H	**7f** *n*-C_8H_{17}	 **6ba**	10	81

Table 2 One-Pot Synthesis of Diversely Substituted Pyrroles Catalyzed by $InCl_3$[a] (continued)



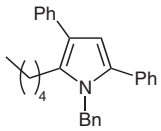
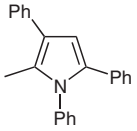
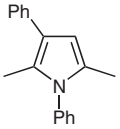
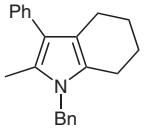
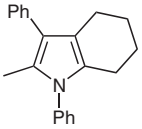
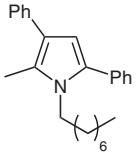
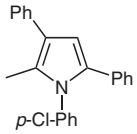
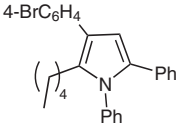
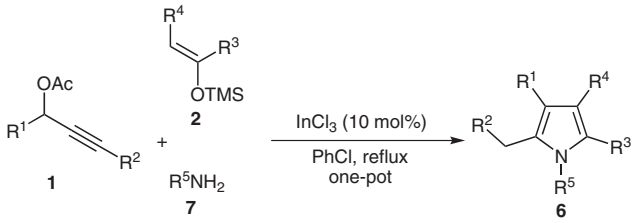
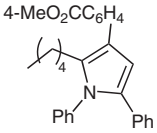
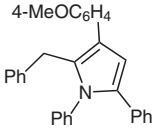
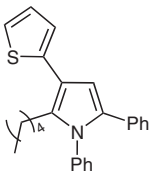
Entry	**1** R^1; R^2	**2** R^3; R^4	**7** R^5	Product **6**	Time (h)[b]	Yield (%)[c]
10	**1b** Ph; *n*-Bu	**2a** Ph; H	**7e** Bn	 **6bb**	10	86
11	**1c** Ph; TMS	**2a** Ph; H	**7a** Ph	 **6ca**	3	67
12	**1c** Ph; TMS	**2b** Me; H	**7a** Ph	 **6cb**	3	72
13	**1c** Ph; TMS	**2c** $(CH_2)_4$	**7e** Bn	 **6cc**	3.5	72
14	**1c** Ph; TMS	**2c** $(CH_2)_4$	**7a** Ph	 **6cd**	6	73
15	**1c** Ph; TMS	**2a** Ph; H	**7f** n-C_8H_{17}	 **6ce**	10	63
16	**1c** Ph; TMS	**2a** Ph; H	**7c** 4-ClC_6H_4	 **6cf**	3.5	74
17	**1d** 4-BrC_6H_4; *n*-Bu	**2a** Ph; H	**7a** Ph	 **6d**	3	83

Table 2 One-Pot Synthesis of Diversely Substituted Pyrroles Catalyzed by $InCl_3$[a] (continued)



Entry	**1** R^1; R^2	**2** R^3; R^4	**7** R^5	Product **6**	Time (h)[b]	Yield (%)[c]
18	**1e** 4-$MeOOCC_6H_4$; *n*-Bu	**2a** Ph; H	**7a** Ph	 **6e**	4	78
19	**1f** 4-$MeOC_6H_4$; Ph	**2a** Ph; H	**7a** Ph	 **6f**	2.5	90
20	**1g** thiophenyl; Ph	**2a** Ph; H	**7a** Ph	 **6g**	3	88

[a] All reactions were carried out on a 0.5 mmol scale of **1** using 10 mol% of $InCl_3$, 2.0 equiv of **2** (1.0 mmol) and 2 mL chlorobenzene at 75 °C for 0.5 h, followed by adding 2.0 equiv of **7** (1.0 mmol). Imination–cycloisomerization proceeded at reflux for 1–10 h.
[b] Reaction time for imination–cycloisomerization at reflux.
[c] Isolated yield based on propargylic acetates **1**.

In summary, we have developed a general and highly efficient methodology for the synthesis of substituted pyrroles, in which the new rings are assembled by a indium-catalyzed propargylic substitution and subsequent cycloisomerization of propargylic acetates, enoxysilanes, and primary amines. This novel transformation is performed in a one-pot model and a wide range of functionalities are well tolerated, providing a promising and practical route to various pyrrole-containing molecules. Also, this work represents a valuable complement to existing procedures for the synthesis of multisubstituted pyrroles. Further studies to expand the scope of synthetic utility of this reaction are in progress in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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References and Notes

(1) For recent reviews and selected examples, see: (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. F. *Chem. Rev.* **2008**, *108*, 264. (b) Novak, P.; Müller, K.; Santhanam, K. S. V.; Haas, O. *Chem. Rev.* **1997**, *97*, 207. (c) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. (d) Balme, G.; Bouyssi, D.; Monteiro, N. *Heterocycles* **2007**, *73*, 87. (e) Cadierno, V.; Crochet, P. *Curr. Org. Synth.* **2008**, *5*, 343. (f) Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629. (g) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213. (h) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141. (i) Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238. (j) Fürstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582. (k) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *97*, 207.

(2) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, **2000**, 237.

(3) For recent reviews and selected examples, see: (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Eloisa, J.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (c) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-Garcia, I. *Chem. Rev.* **2008**, *108*, 3174. (d) Weibe, J.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149. (e) Kel'in, A. V.; Stromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (f) Chernyak, D.; Gadamsetty, S. B.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 2307.

(4) (a) Ji, W.; Pan, Y.; Zhao, S.; Zhan, Z. *Synlett* **2008**, 3046. (b) Liu, X.; Huang, L.; Zheng, F.; Zhan, Z. *Adv. Synth. Catal.* **2008**, *350*, 2778. (c) Zhan, Z.; Yu, J.; Liu, H.; Cui, Y.; Yang, R.; Yang, W.; Li, J. *J. Org. Chem.* **2006**, *71*, 8298.

(5) For selected examples for In-catalyzed heterocyclic synthesis via cycloisomerization, see: (a) Feng, X.; Tan, Z.; Chen, D.; Shen, Y.; Guo, C.; Xiang, J.; Zhu, C. *Tetrahedron Lett.* **2008**, *49*, 4110. (b) Kim, S. H.; Kim, S. H.; Kim, K. H.; Kim, J. M. *Tetrahedron Lett.* **2010**, *51*, 860.

(6) Zhan, Z.; Cai, X.; Wang, S.; Yu, J.; Liu, H.; Cui, Y. *J. Org. Chem.* **2007**, *72*, 9838.

(7) **General Experimental Methods**
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 PerkinElmer 2400 microanalyser. Flash chromatography was performed with QingDao silica gel (300–400 mesh).

(8) **A Representative Procedure for the Synthesis of Substituted Pyrrole 2-Benzyl-1,3,5-triphenyl-1*H*-pyrrole (6aa)**
To a 10 mL flask, propargylic acetate **1a** (0.5 mmol), enoxysilane **2a** (1.0 mmol), chlorobenzene (2.0 mL), and $InCl_3$ (0.05 mmol) were successively added. The reaction was allowed to stir at 75 °C for 0.5 h, followed by adding primary amines **7a** (1.0 mmol). The reaction mixture was heated to keep refluxing for an additional 1 h until completion (monitored by TLC). Upon cooling to r.t., the reaction mixture was then quenched with 1 M HCl (2 mL). The organic and aqueous layers were separated, and the latter 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. A yellow solid, mp 146–147 °C; yield 87% (0.167 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.52 (m, 2 H), 7.33–7.37 (m, 2 H), 7.07–7.24 (m, 12 H), 6.95–6.97 (m, 2 H), 6.88–6.90 (m, 2 H), 6.66 (s, 1 H), 4.04 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 139.1, 136.9, 134.8, 133.2, 130.2, 129.0, 128.8, 128.7, 128.3, 128.2, 128.1, 128.0, 127.7, 126.1, 125.9 (3), 124.4, 109.6, 31.5 ppm. IR (film): 1493, 1599, 3024 cm^{-1}. ESI-MS: *m/z* (%) = 386 (100) [M + H$^+$]. Anal. Calcd (%) for $C_{29}H_{23}N$: C, 90.35; H, 6.01; N, 3.63. Found: C, 90.38; H, 6.00, N, 3.63.