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Indium(III) Chloride-Catalyzed Propargylation/Amination/Cycloisomerization Tandem Reaction: One-Pot Synthesis of Highly Substituted Pyrroles from Propargylic Alcohols, 1,3-Dicarbonyl Compounds and Primary Amines

Xiao-tao Liu,[a] Lei Huang,[a] Fei-jian Zheng,[a] and Zhuang-ping Zhan[a,*]

[a] Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, Fujian, People's Republic of China
Fax: (+86)-592-218-0318; phone: (+86)-592-218-0318; e-mail: zpzhan@xmu.edu.cn

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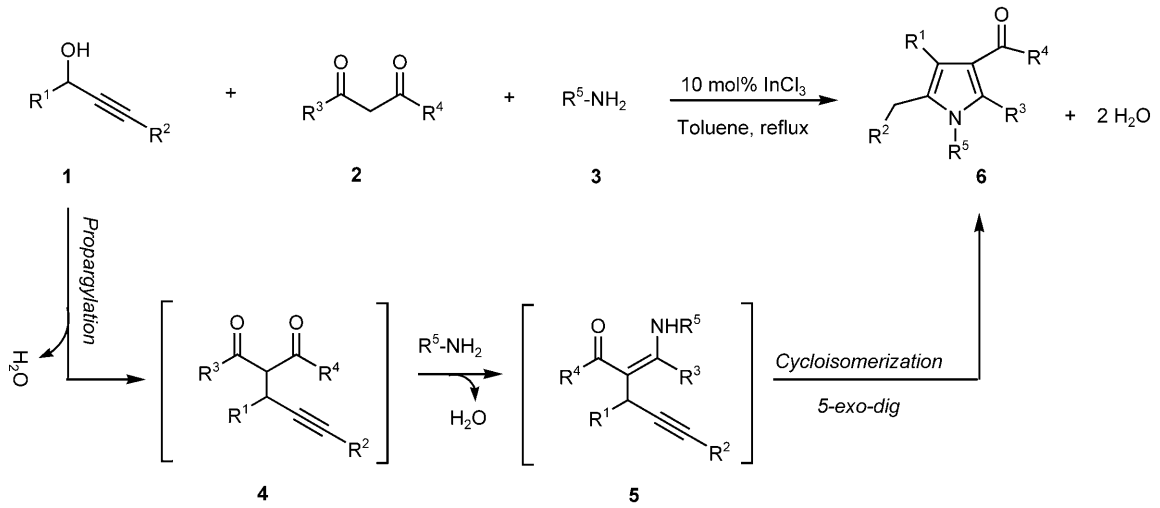
Abstract: A convenient one-pot propargylation/amination/cycloisomerization tandem process has been developed for the synthesis of highly substituted pyrroles derivatives from propargylic alcohols, 1,3-dicarbonyl compounds and primary amines using indium(III) chloride as a multifunctional catalyst. This method provides a flexible and rapid route to substituted pyrroles.

Keywords: 1,3-dicarbonyl compounds; indium(III) chloride; primary amines; propargylic alcohols; pyrroles; tandem reactions

Introduction

The ever-increasing complexity of organic target molecules necessitates the introduction of new methods for the efficient assembly of functionalized intermediates from simple precursors. An appealing strategy toward this end is the development of novel tandem reactions whereby sequential transformations can be performed without isolation or purification of intermediates in a single-pot with minimal work-up.[1] Especially, the finding and utilization of a single catalyst to promote several transformations in a selective manner is a promising area of research.[2] Such direct synthesis routes help to avoid side-product formation and loss of starting material as well as to reduce capital investment and operation costs.

Transition metal-catalyzed cyclization reactions of unsaturated systems provide access to structural motifs not accessible through their thermal counterparts. This is exemplified by the applications of transition metal-catalyzed cycloaddition or cycloisomerization of acyclic precursors for the synthesis of substituted pyrroles.[3–7] The corresponding multicomponent coupling reactions proceeding directly from simple and readily available substrates are much less studied. Recently, efficient sequential reactions of propargylic alcohols, carbonyl compounds and primary amines in the presence of $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*Cl]/PtCl_2$[8] or $CF_3CO_2H/Ru(II)$,[9] which lead to the synthesis of substituted pyrroles, have been reported. However, two or more catalysts are needed in these reactions. To the best of our knowledge, there is no propargylation/amination/cycloisomerization tandem reaction for the synthesis of substituted pyrroles in the presence of a single catalyst reported in the literature. As the results of development on the transition metal-catalyzed propargylic substitution reaction in our group,[10] herein, we wish to report a highly efficient propargylation/amination/cycloisomerization tandem reaction for the synthesis of substituted pyrroles directly from propargylic alcohols, 1,3-dicarbonyl compounds and primary amines using indium(III) chloride as catalyst. The process is outlined in Scheme 1. Indium(III) chloride acts as a multifunctional catalyst and effectively catalyzes the three reaction processes in a single reaction vessel. A wide range of secondary propargylic alcohols bearing not only terminal alkyne groups but also internal alkyne groups can effectively be employed and a number of functionalities, such as chloro, cyano, bromo, ester, and methoxy, are tolerated under the reaction conditions.



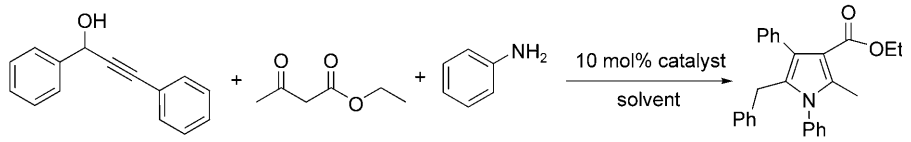
Scheme 1. Synthesis of highly substituted pyrroles from propargylic alcohols, 1,3-dicarbonyl compounds and primary amines.

Results and Discussion

To extend the scope of the $FeCl_3$- or $Cu(OTf)_2$-catalyzed propargylic substitution reaction,[10c,d] we sought to explore the coupling of propargylic alcohols with 1,3-dicarbonyl compounds and the followed amination/cycloisomerization tandem reaction for the synthesis of highly substituted pyrroles using $FeCl_3$ or $Cu(OTf)_2$ as a single catalyst. Initially, propargylic alcohol **1a** (0.5 mmol) was treated with 1,3-dicarbonyl compounds **2a** (0.6 mmol) in the presence of 10 mol% $FeCl_3$ in toluene, aniline **3a** (0.6 mmol) was added directly to the reaction after consumption of **1a** and then **t**he reaction mixture was heated to reflux for an additional 24 h. The tandem reaction led not to the expected pyrrole **6aa**, but to the intermediate γ-alkynyl ketone **4a** (Scheme 1). Gratifyingly, switching the catalyst to $Cu(OTf)_2$ furnished the highly substituted pyrrole **6aa** in 45% yield (Table 1, entry 4). To identify suitable conditions for the tandem process,[11] the series of Lewis acids from Table 1 was screened. Fortunately, indium(III) chloride provided the best results in comparison to other Lewis acids investigated and was effective in catalytic quantities (10 mol%) (Table 1, entry 1). The combination of AgOTf and $Cu(OTf)_2$ also produced the highly substituted pyrrole **6aa** in 85% isolated yield (Table 1, entry 5), whereas two catalysts were needed. Other catalysts such as $FeCl_3$, $BiCl_3$, or $Hg(OAc)_2$ did not promote the reaction. Furthermore, the propargylation/amination/cycloisomerization proceeded smoothly without exclusion of moisture or air from the reaction mixture. The choice of the solvent also played a crucial role. Further optimization led to the discovery that toluene and 1,2-dichloroethane as solvent were able to facilitate the transformation. However, the use of toluene instead of 1,2-dichloroethane obviously reduced the reaction time from 24 h to 3.5 h (Table 1, entry 1 *vs.* entry 10).

With the identification of the optimal conditions in hand, the scope of the substrates was investigated. Typical results are shown in Table 2. To our delight, all the secondary propargylic alcohols **1** bearing not only a terminal alkyne group but also an internal alkyne group participated well in the reaction, providing the propargylation/amination/cycloisomerization products in good yields with complete regionselectivity. Among the propargylic alcohols that were examined, internal propargylic alcohol **1a** (R^2 = Ph) gave the most desirable result, providing the highly substituted pyrroles in high to excellent yields (Table 2, entries 1–7). Internal propargylic alcohols **1b** and **1d** (R^2 = TMS, *n*-Bu) gave desirable results (Table 2, entries 9 and 10, 13-15), although slightly longer reaction times were required. Terminal propargylic alcohol **1c** (R^2 = H) also participated in the reaction in moderate yields (Table 2, entries 11 and 12).[9,12] Unfortunately, the primary aliphatic progargylic alcohol **1k** (R^1 = H; R^2 = Ph) and secondary aliphatic progargylic alcohol **1l** (R^1 = CH_3; R^2 = Ph) failed to give highly substituted pyrroles (Table 2, entries 22 and 23). The experimental results suggested a mechanism through the formation of a propargylic cation intermediate. The instability of the propargylic cation intermediate made the sequential reaction less favorable. Propargylic alcohol **1f** possessing an electron-donating group at the aryl ring (R^1 = 4-MeO-C_6H_4) reacted smoothly with 1,3-dicarbonyl compound **2a** and aniline **3a** affording the pyrrole **6fa** in high yield (Table 2, entry 17). Moreover, substrates **1e** and **1i** possessing strong electron-withdrawing groups at the aryl ring (R^1 = 4-MeOOC-C_6H_4, 4-CN-C_6H_4) were also successfully employed in the reaction to give the pyrroles **6ea** and **6ia** in 79% and 66% isolated yields, respectively (Table 2, en-

Table 1. Optimization of the formation of highly substituted pyrroles.[a]



1a 2a 3a 6aa

Entry	Catalyst	Solvent	Time [h][b]	Isolated yield [%][c]
1	$InCl_3$	toluene	3.5	85
2	$InCl_3$	toluene	24	76[d]
3	AgOTf	toluene	24	0
4	$Cu(OTf)_2$	toluene	8	45
5	$Cu(OTf)_2$/AgOTf	toluene	4	85[e]
6	$FeCl_3$	toluene	24	0
7	$BiCl_3$	toluene	24	0
8	$Hg(OAc)_2$	toluene	24	0
9	$InCl_3$	CH_3CN	36	26
10	$InCl_3$	DCE	24	84
11	$InCl_3$	CH_3NO_2	12	5
12	$InCl_3$	C_2H_5OH	24	0

[a] *Reaction conditions:* 10 mol% of catalyst, 1.0 equiv. of **1a** (0.5 mmol), and 1.2 equiv. of **2a** (0.6 mmol), solvent (2 mL), at 60 °C for 2 h, 1.2 equiv. of **3a** (0.6 mmol) then added for the period of time indicated at reflux.
[b] Reaction time for propargylation/amination/cycloisomerization.
[c] Isolated yield of pure product based on propargylic alcohol **1a**.
[d] 5 mol% $InCl_3$.
[e] *Reaction conditions:* 5 mol% of $Cu(OTf)_2$, 1.0 equiv. of **1a** (0.5 mmol), and 1.2 equiv. of **2a** (0.6 mmol), toluene (2 mL), at 60 °C for 2 h. 1.2 equiv. of **3a** (0.6 mmol) and 10 mol% of AgOTf then added for an additional 2 h at reflux.

tries 16 and 20). Obviously, electron-rich propargylic alcohols provided the desired products in higher yields than electron-poor propargylic alcohols. Additionally, propargylic alcohol **1j** (R^1 = 2-thienyl; R^2 = Ph) also participated to give the product in 86% isolated yield (Table 2, entry 21). It should be noted that functional groups such as chloro, cyano, bromo, ester, and methoxy in the propargylic alcohols were readily carried through the tandem reaction, allowing for the subsequent elaboration of the products. The reaction proceeded smoothly under mild conditions and air was tolerated.

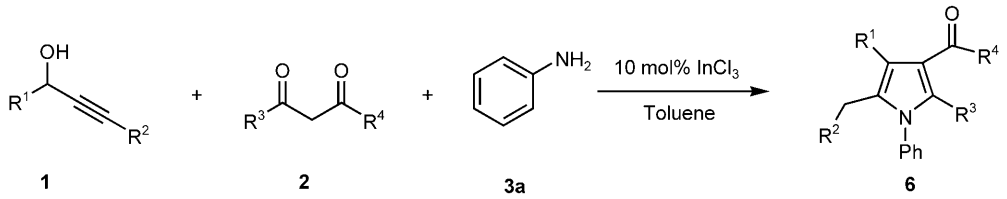
A variety of 1,3-dicarbonyl compounds **2** was also employed to examine the generality of the method. For example, β-keto esters (Table 2, entries 1–3, 9, 11, 13, 16–21) and β-diketones (Table 2, entries 4–7, 10, 12, 14 and 15) were treated with propargylic alcohols **1** and aniline **3a**, and the corresponding highly substituted pyrroles were obtained in moderate to good yields. While increasing the steric nature of the β-keto esters and β-diketones also influenced the efficiency of the reaction, **2c** and **2g** required prolonged reaction times for better conversation (Table 2, entries 3 and 7). However, on using diethyl malonate **2h**, no pyrrole was observed (Table 2, entry 8). Remarkably, non-symmetrical diketones also reacted rapidly with propargylic alcohols and aniline affording the highly substituted pyrroles (Table 2, entries 5, 6, 10 and 15) in good yields with complete chemoselectivity.

We next investigated the scope of the primary amines **3**. The typical results are depicted in Table 3. Aromatic (Table 3, entries 1, 2, 8, 9 and 13) and aliphatic primary amines (Table 3, entries 3–5, 10, 11 and 14) could be efficiently incorporated into the pyrrole framework. The reaction proceeded smoothly when the aryl groups of the primary amines were substituted with electron-donating (Table 3, entries 1 and 2) and electron-withdrawing groups (Table 3, entries 8 and 9). Aliphatic primary amines required slightly longer reaction times, but maintained high yields. Unfortunately, the optically active primary amine **3g** could not afford the desired product under the same reaction conditions, possibly due to the steric bulkiness of **3g**. Further screening of various catalysts led to the discovery that the use of the combination of $Cu(OTf)_2$ and AgOTf was ideal, providing the desired pyrrole **6kg** in 86% isolated yield (Table 3, entry 7), with the stereogenic centre in the initial amine not being affected during the transformation. However, the trimethylsilyl group could not be tolerated under this condition and had fallen off during work-up. Notably, an amide also participated in the reaction, albeit in somewhat lower yield (Table 3, entry 12). Propargylic alcohol **1m** (R^1 = 1-naphthyl) readily underwent the propargylation/amination/cycloisomeriza-

tion to afford the highly substituted pyrroles **6ma** and **6mb** in good yields with complete regioselectivity (Table 3, entries 13 and 14).

Accordingly, we hoped to extend the application of this method to the synthesis of N-H pyrroles. The β-enamino esters or ketones that might be the key intermediates for the transformation, were produced through amination of the γ-alkynyl ketones. Firstly, we employed NH_4OAc or NH_4Cl as sources of the N-H unit of the pyrrole. Unfortunately, none of the de-

Table 2. Synthesis of highly substituted pyrroles **6** from propargylic alcohols **1**, 1,3-dicarbonyl compounds **2** and primary amine **3a**.[a]



1 **2** **3a** **6**

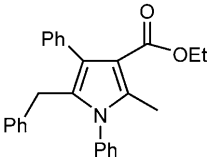
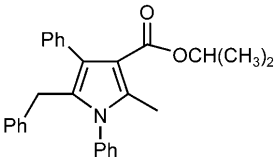
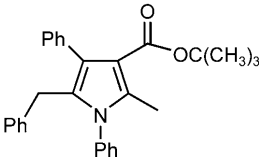
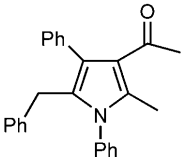
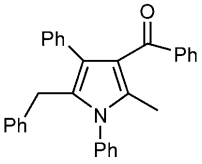
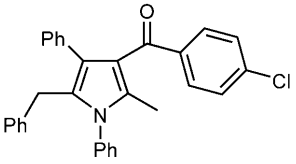
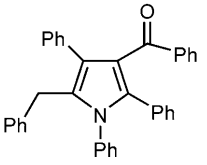
Entry	Propargylic alcohol	1,3-Dicarbonyl compound	Product	Time [h][b]	Isolated yield [%][c]
1		**2a:** $R^3=CH_3$; $R^4=OEt$	**6aa** 	3.5	85
2		**2b:** $R^3=CH_3$; $R^4=OCH(CH_3)_2$	**6ab** 	3.5	84
3		**2c:** $R^3=CH_3$; $R^4=OC(CH_3)_3$	**6ac** 	5	65
4	**1a:** $R^1=Ph$; $R^2=Ph$	**2d:** $R^3=R^4=CH_3$	**6ad** 	3.5	78
5		**2e:** $R^3=CH_3$; $R^4=Ph$	**6ae** 	3	93
6		**2f:** $R^3=CH_3$; $R^4=4\text{-Cl-}C_6H_4$	**6af** 	3	89
7		**2g:** $R^3=R^4=Ph$	**6ag** 	24	70
8		**2h:** $R^3=OEt$; $R^4=OEt$	–	24	0

Table 2. (Continued)

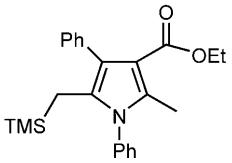
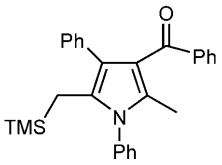
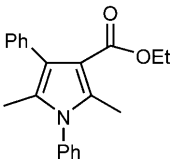
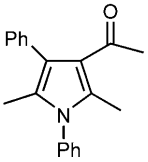
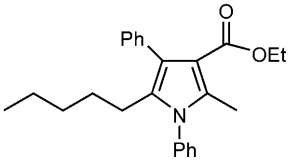
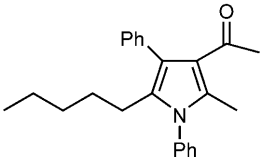
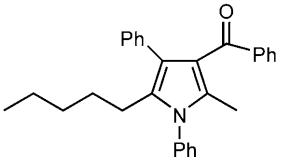
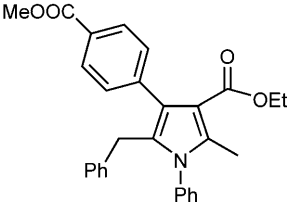
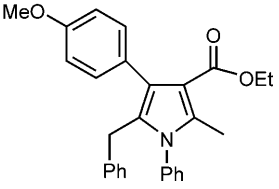
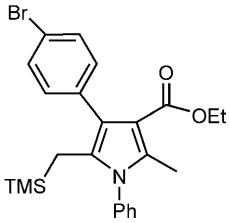
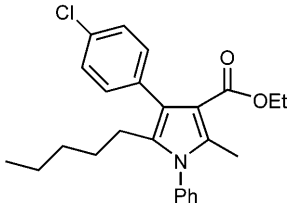
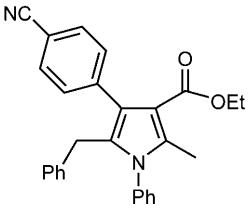
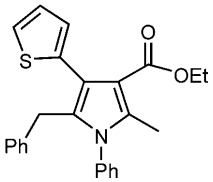
Entry	Propargylic alcohol	1,3-Dicarbonyl compound	Product	Time [h][b]	Isolated yield [%][c]
9	**1b:** $R^1=Ph$; $R^2=TMS$	**2b:** $R^3=CH_3$; $R^4=OEt$	**6ba** 	5	83
10		**2e:** $R^3=CH_3$; $R^4=Ph$	**6bb** 	4	89
11	**1c:** $R^1=Ph$; $R^2=H$	**2a:** $R^3=CH_3$; $R^4=OEt$	**6ca** 	6	46
12		**2d:** $R^3=R^4=CH_3$	**6cb** 	6	42
13	**1d:** $R^1=Ph$; $R^2=n$-Bu	**2a:** $R^3=CH_3$; $R^4=OEt$	**6da** 	6	72
14		**2d:** $R^3=R^4=CH_3$	**6db** 	6	69
15		**2e:** $R^3=CH_3$; $R^4=Ph$	**6dc** 	6	81
16	**1e:** $R^1=$4-MeOOC-C_6H_4; $R^2=Ph$	**2a:** $R^3=CH_3$; $R^4=OEt$	**6ea** 	4	79
17	**1f:** $R^1=$4-MeO-C_6H_4; $R^2=Ph$	**2a:** $R^3=CH_3$; $R^4=OEt$	**6fa** 	3	89

Table 2. (Continued)

Entry	Propargylic alcohol	1,3-Dicarbonyl compound	Product	Time [h][b]	Isolated yield [%][c]
18	**1g:** R^1 = 4-Br-C_6H_4; R^2 = TMS	**2a:** R^3 = CH_3; R^4 = OEt	**6ga** 	5.5	80
19	**1h:** R^1 = 4-Cl-C_6H_4; R^2 = *n*-Bu	**2a:** R^3 = CH_3; R^4 = OEt	**6ha** 	6	70
20	**1i:** R^1 = 4-CN-C_6H_4; R^2 = Ph	**2a:** R^3 = CH_3; R^4 = OEt	**6ia** 	6	66
21	**1j:** R^1 = 2-thienyl; R^2 = Ph	**2a:** R^3 = CH_3; R^4 = OEt	**6ja** 	3.5	86
22	**1k:** R^1 = H; R^2 = Ph	**2a:** R^3 = CH_3; R^4 = OEt	–	24	0
23	**1l:** R^1 = CH_3; R^2 = Ph	**2a:** R^3 = CH_3; R^4 = OEt	–	24	0

[a] *Reaction conditions:* 10 mol% of $InCl_3$, 1.0 equiv. of **1** (0.5 mmol), and 1.2 equiv. of **2** (0.6 mmol), toluene (2 mL), at 60 °C for 2 h or for 3 h (for substrates **1b**, **1d**, **1g** and **1h**), or at 70 °C for 5 h (for substrate **1c**), followed by the addition of 1.2 equiv. of **3a** (0.6 mmol). The amination/cycloisomerization proceeded under reflux for 1-22 h. See Supporting Information for details.

[b] Reaction time for propargylation/amination/cycloisomerization.

[c] Isolated yield of pure product based on propargylic alcohols **1**.

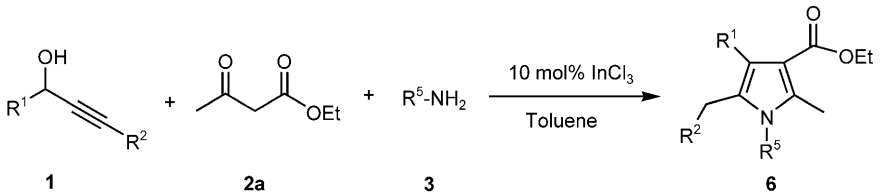
sired product was observed even in the presence of 20 mol% of $InCl_3$ at reflux for 12 h (Table 3, entry 6). We then began searching for an appropriate ammonia source, which we thought would readily allow for the propargylation/amination/cycloisomerization tandem reaction. We were pleased to find that ammonium carbamate[13] gave the desirable result in the tandem reaction. For example, treatment of propargylic alcohols **1** with 1,3-dicarbonyl compounds **2** in toluene followed by amination with ammonium carbamate proceeded uneventfully to give the β-enamino esters **5** (Scheme 1). The next step, a sequential cycloisomerization of β-enamino esters **5**, gave the N-H pyrroles **6** (Scheme 2).[14]

Additionally, the indium-catalyzed tandem reaction also proceeded well with symmetrical propargylic alcohols allowing for the synthesis of oligomers containing two pyrrole moieties. For example, symmetrical propargylic alcohol **1n** underwent indium-catalyzed propargylation/amination/cycloisomerization to afford the oligomer **6ra** in 63% isolated yield 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.[15]

On the basis of these data, we propose the process detailed in Scheme 4 as the most likely mechanism for this transformation.[16] Firstly, the ionization of propargylic alcohol **1** would lead to propargylic cation **8** and subsequent nucleophilic attack of the enol **7** gives γ-alkynyl ketone **4**. Reaction of **4** and amine produces the β-enamino ester or ketone **5**. Coordina-

tion of cationic indium(III) to the alkyne forms the π-alkyne indium complex **11** and enhances the electrophilicity of the alkyne. Subsequent *5-exo-dig* nucleophilic attack of the amino group on the β-carbon of the indium(III)-alkyne complex **11** would generate the alkenyl-indium derivative **12**. Protonolysis of **12** completes the catalytic cycle to afford dihydropyrrole **13**, which then undergoes isomerization to pyrrole **6**.

Table 3. Synthesis of highly substituted pyrroles **6** from propargylic alcohols **1**, 1,3-dicarbonyl compound **2a** and primary amines **3**.[a]



1 **2a** **3** **6**

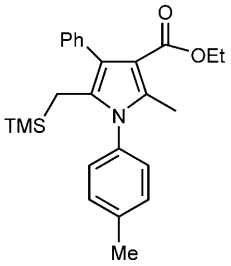
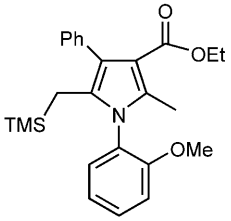
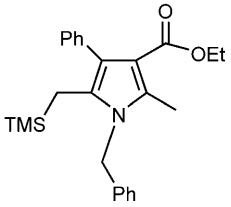
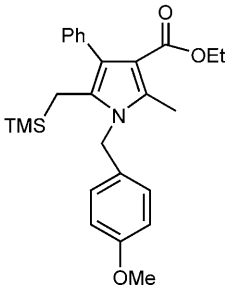
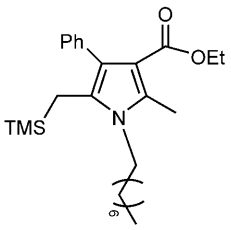
Entry	Propargylic alcohol		Primary amine		Product	Time [h][b]	Isolated yield [%][c]
1		**3a**	4-Me-$C_6H_4NH_2$	**6ka**		5	85
2		**3b**	2-MeO-$C_6H_4NH_2$	**6kb**		5	86
3	**1b:** R^1 = Ph; R^2 = TMS	**3c**	$C_6H_5CH_2NH_2$	**6kc**		6	82
4		**3d**	4-MeO-$C_6H_4CH_2NH_2$	**6kd**		6	85
5		**3e**	$CH_3(CH_2)_6CH_2NH_2$	**6ke**		6	80

Table 3. (Continued)

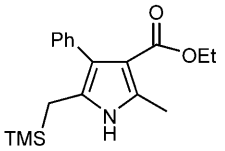
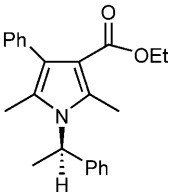
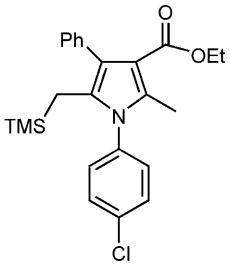
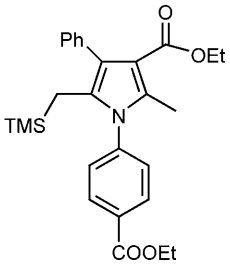
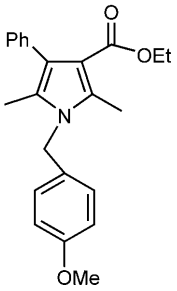
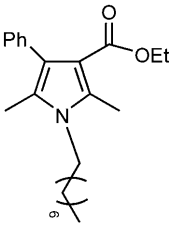
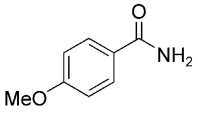
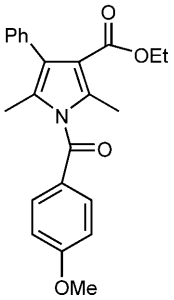
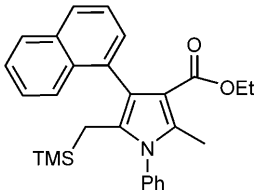
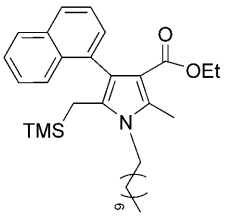
Entry	Propargylic alcohol		Primary amine		Product	Time [h][b]	Isolated yield [%][c]
6		**3f**	NH_4OAc or NH_4Cl	**6kf**		15	0
7		**3g**		**6kg**		5	0 (86)[d]
	1b: R^1 = Ph; R^2 = TMS						
8		**3h**	4-Cl-$C_6H_4NH_2$	**6kh**		5	81
9		**3i**	4-EtOOC-$C_6H_4NH_2$	**6ki**		7	76
10		**3d**	4-MeO-$C_6H_4CH_2NH_2$	**6la**		6	57
	1c: R^1 = Ph; R^2 = H						
11		**3e**	$CH_3(CH_2)_6CH_2NH_2$	**6lb**		6	47

Table 3. (Continued)

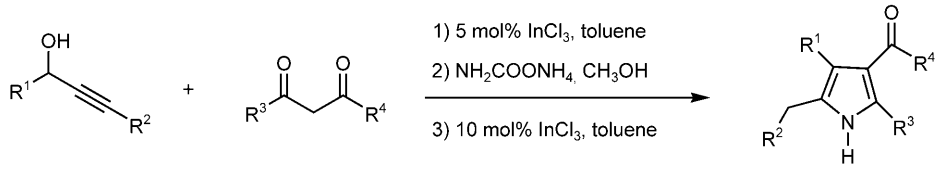
Entry	Propargylic alcohol		Primary amine		Product	Time [h][b]	Isolated yield [%][c]
12	**1c:** R^1 = Ph; R^2 = H	**3h**		**6lc**		17	36
13		**3a**	$PhNH_2$	**6ma**		5	84
	1m: R^1 = 1-naphthyl; R^2 = TMS						
14		**3e**	$CH_3(CH_2)_6CH_2NH_2$	**6mb**		5.5	83

[a] *Reaction conditions:* 10 mol% of $InCl_3$, 1.0 equiv. of **1** (0.5 mmol), and 1.2 equiv. of **2a** (0.6 mmol), toluene (2 mL), at 60 °C for 3 h, or at 70 °C for 5 h (for substrate **1c**), followed by the addition of 1.2 equiv. of **3** (0.6 mmol). The amination/cycloisomerization proceeded under refluxing for 2–12 h at refulx. See Supporting Information for details.

[b] Reaction time for propargylation/amination/cycloisomerization.

[c] Isolated yield of pure product based on propargylic alcohols **1**.

[d] *Reaction conditions:* 5 mol% of $Cu(OTf)_2$, 1.0 equiv. of **1b** (0.5 mmol), and 1.2 equiv. of **2a** (0.6 mmol), toluene (2 mL), at 60 °C for 3 h; 1.2 equiv. of **3g** (0.6 mmol) and 10 mol% of AgOTf then added for an additional 2 h at reflux. See Supporting Information for details.



1a R^1 = Ph; R^2 = Ph; **2b** R^3 = CH_3; R^4 = $OCH(CH_3)_2$ — **6na** 65%

1b R^1 = Ph; R^2 = TMS; **2a** R^3 = CH_3; R^4 = OEt — **6oa** 57%(R^2 = H)

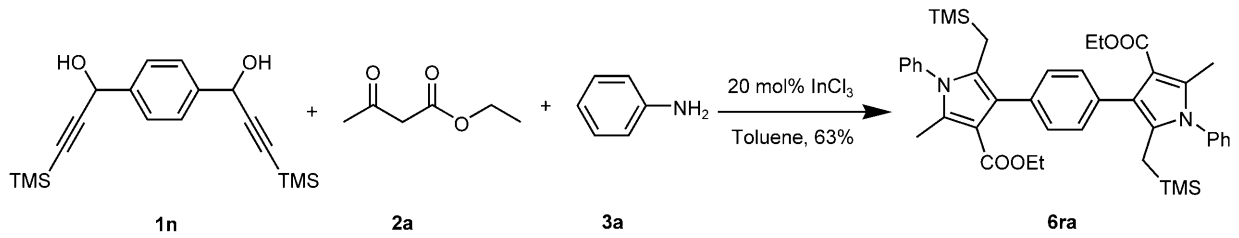
1d R^1 = Ph; R^2 = *n*-Bu; **2a** R^3 = CH_3; R^4 = OEt — **6pa** 56%

1m R^1 = 1-Naphthyl; R^2 = TMS; **2a** R^3 = CH_3; R^4 = OEt — **6qa** 60% (R^2 = H)

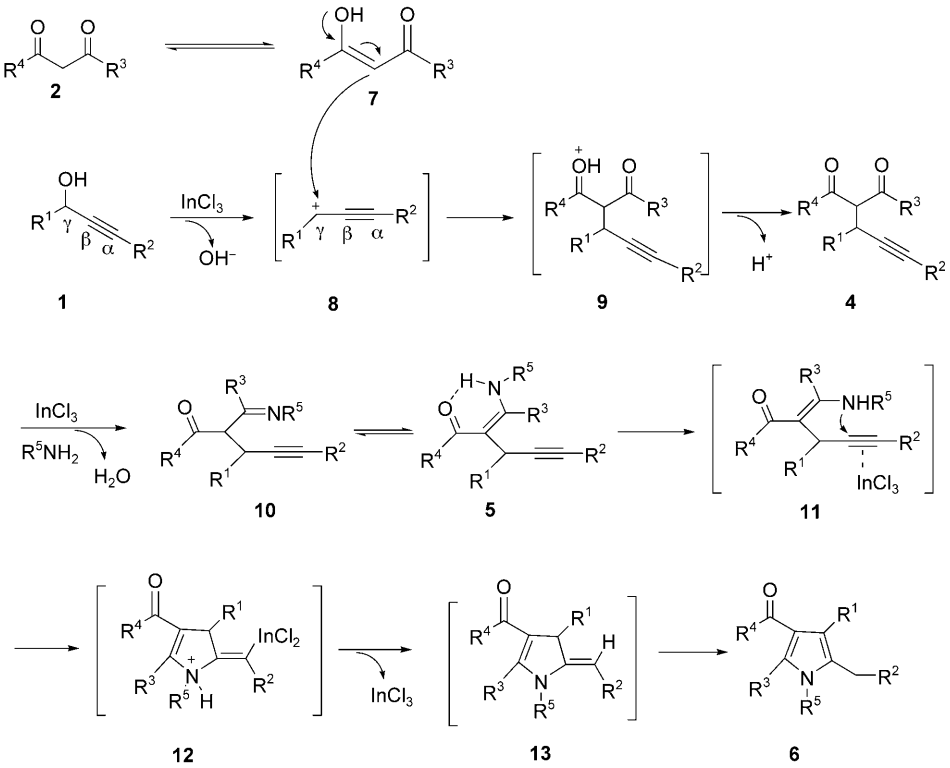
Scheme 2. Synthesis of the N-H pyrroles.

Conclusions

In summary, we have developed a mild, general, and efficient procedure for the synthesis of highly substituted pyrroles directly from propargylic alcohols, 1,3-dicarbonyl compounds and primary amines in a single-pot. A wide range of secondary propargylic alcohols bearing terminal alkyne groups or internal alkyne groups are readily available and a number of functionalities are tolerated. Operational simplicity



Scheme 3. Synthesis of the highly substituted pyrrole **6ra.**



Scheme 4. Proposed mecahnism for the indium-catalyzed propargylation/amination/cycloisomerization reaction.

and minimal waste generation of this process should be beneficial for its large-scale applications. This method provides a flexible and rapid route to the preparation of highly substituted pyrroles and makes it a valuable alternative to currently available transformation. Further applications and studies on the mechanism of the indium(III)-catalyzed tandem reaction are ongoing in our laboratories and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of Highly Substituted Pyrroles

To a 10-mL flask, propargylic alcohols **1** (0.5 mmol), 1,3-dicarbonyl compounds **2** (0.6 mmol), toluene (2.0 mL) and $InCl_3$ (0.05 mmol) were successively added. The reaction mixture was allowed to stir at 60 °C or at 70 °C, and was monitored periodically by TLC, until completion, followed by the addition of primary amines **3** (0.6 mmol). The reaction mixture was heated to reflux temperature for an additional 2–22 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 under vacuum, and then the residue was purified by silica gel column chromatography (EtOAc/hexane) to afford corresponding highly substituted pyrroles **6**.

Supporting Information

General experimental information and characterization data of all compounds are given in the Supporting Infromation.

Acknowledgements

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[12] Compared with the indium-catalyzed tandem reaction, the terminal propargylic alcohol ($R^2 = H$) participated well in the CF_3CO_2H/Ru(II)-catalyzed reaction in high yields, probably due to the coordinated catalyzed results of two catalysts. Moreover, coordination of ruthenium to the terminal alkyne formed a ruthenium-coordinated complex, which was prone to promote the three-component reaction. see: V. Cadierno, J. Gimeno, N. Nebra, *Adv. Synth. Catal.* **2007**, *349*, 382–394.

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[16] An alternative potential pathway, which involves the formation of β-enamino esters and the subsequent propargylation/cycloisomerization to pyrroles, was also studied. Treatment of **3a** and **2a** yielded the β-enamino ester **14a**, which was allowed to react with propargylic alcohol **1a**, affording **6aa** in only 26% yield after 24 h at reflux.