Syntheses of Highly Substituted Furan and Pyrrole Derivatives via Lithiated 3-Aryl-1-methoxyallenes: Application to the Synthesis of Codonopsinine

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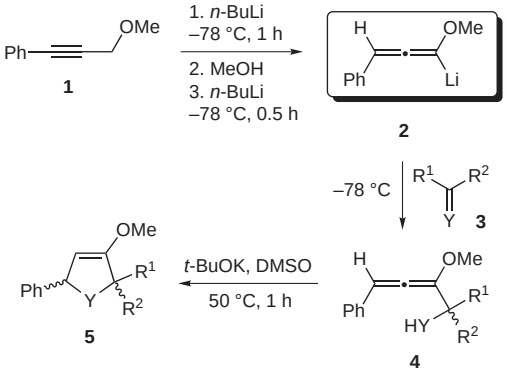
Abstract: Lithiated 1-methoxy-3-phenylallenes were generated in situ from a phenyl-substituted propargylic ether. They smoothly combined with aldehydes, ketones, or imines to give allenyl adducts, which cyclized to highly substituted heterocycles either under basic conditions or with silver nitrate assistance. Analogously, a dihydropyrrole derivative was obtained by the addition of anisyl-substituted lithiated methoxyallene derivative to an *N*-tosyl imine and subsequent cyclization of the intermediate. The two diastereomers obtained were subsequently transformed into the alkaloid (±)-codonopsinine and one of its epimers. The key steps of these sequences are highly diastereoselective hydroborations of silyl enol ethers quantitatively leading to hydroxylated intermediates.

Key words: methoxyallene, organo lithium compounds, pyrroles, hydroboration, alkaloids

Lithiated alkoxyallenes are versatile C-3 building blocks in organic syntheses.[1] Arens et al.[2] generated the simplest compound in this series for the first time by treating methoxyallene with *n*-butyllithium in diethyl ether at –40 °C. Its addition to aldehydes or ketones provided allenyl alcohols which were transformed into a variety of interesting compounds.[3] Trisubstituted pyrroles and trisubstituted 5,6-dihydropyridines were also synthesized by the reaction of lithiated alkoxyallenes with 2-vinyloxyethyl isothiocyanate.[4] Recently, our group used lithiated alkoxyallenes for the stereoselective preparation of synthetically useful five- and six-membered heterocycles.[5] As part of our continued interest in this field we generated 3-aryl-substituted lithiated 1-alkoxyallenes[6] for an intended synthesis of higher substituted heterocycles. To the best of our knowledge there are no reports on the reaction of these allene derivatives with aldehydes, ketones, or imines. This effort allowed us to introduce not only alkyl groups but also aryl groups into the 5-position of pyrrole[7] and furan derivatives.[8] These heterocyclic compounds are of particular interest because many biologically active compounds contain these skeletons.[9]

Treatment of methyl(3-phenylpropargyl) ether (**1**)[10] with one equivalent of *n*-butyllithium at –78 °C and addition of one equivalent of methanol after one hour afforded 3-phenyl methoxyallene. Addition of a second equivalent of *n*-butyllithium, to this in situ prepared intermediate, subsequently afforded 1-lithiated 1-methoxy-3-phenylallene (**2**) (Scheme 1). This intermediate smoothly added to various electrophiles **3** such as aldehydes, ketones, and imines.[11] Reaction of **2** with aldehydes **3a** or **3b** or acetone **3c** followed by quenching with methanol furnished allenyl alcohols **4a**–**c**. All these steps from alkyne **1** to alcohols **4a**–**c** were carried out in a one-pot fashion. Due to their moderate stability, crude primary adducts **4** were not purified, however, they were sufficiently stable to carry out the subsequent cyclizations. Reaction of **4a** and **4b** with potassium *tert*-butoxide in dimethyl sulfoxide[3b] (Method 1) furnished *cis*/*trans* mixtures of **5a** or **5b** in 45% and 42% yields, respectively (Scheme 1). Similarly, **4c** cyclized to give 3-methoxy-2,2-dimethyl-5-phenyl-2,5-dihydrofuran (**5c**) in 26% overall yield. The cyclization of **4a**–**c** with silver nitrate in acetonitrile[12] (Method 2) was also attempted, but only complex product mixtures were obtained in the case of allenyl alcohols **4a** and **4c**. Compound **4b** gave **5b** in 32% yield (dr 15:85) under these conditions.



3–5	Y	R^1	R^2	yield of **5** (%)	dr
a	O	H	Me	45	50 : 50
b	O	H	Ph	42	55 : 45
c	O	Me	Me	26	–
d	NPh	H	Ph	55 (*Method 2*)	45 : 55

Scheme 1 Synthesis of dihydrofurans **5a**–**c** and dihydropyrrole derivative **5d** starting from alkyne **1**.

Similarly, lithiated allene **2** added to imine **3d** to furnish the corresponding allenyl amine **4d** as a mixture of diastereomers. Cyclization of crude **4d** using Method 2 gave pyrrole derivative **5d** in 55% yield as a mixture of diastereomers (*trans*/*cis* 45:55). The two isomers were separated by fractional crystallization and (2,5-*trans*)-**5d** and (2,5-*cis*)-**5d** were obtained in 25% and 28% yields, respectively. The relative configurations of products **5** were

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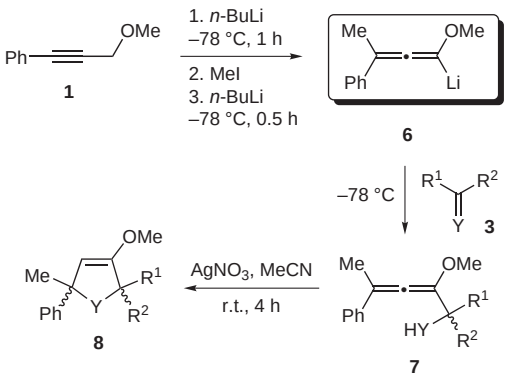
confirmed by comparing their NMR data with those of related compounds (for **5d** see ref. 7c).

We subsequently tried the analogous reactions of electrophiles **3** with lithiated methoxyallene derivative **6**, which bears an additional 3-methyl group. Addition of propargylic ether **1** to one equivalent of *n*-butyllithium at –78 °C followed by reaction with one equivalent of methyl iodide afforded 1-methoxy-3-methyl-3-phenylallene which was directly treated with another equivalent of *n*-butyllithium. This one-pot protocol generated trisubstituted lithiated allene **6**, which smoothly added to benzaldehyde **3b** or acetone **3c** to provide allenyl alcohols **7b** (as a mixture of diastereomers) or **7c** (Scheme 2); these intermediates were again cyclized without purification. Compound **7b** was transformed in 51% overall yield into **8b** (diastereomeric mixture) by employing silver nitrate (Method 2). Cyclization of **7c** using either potassium *tert*-butoxide (Method 1) or silver nitrate (Method 2) afforded pentasubstituted dihydrofuran derivative **8c** in 74% or 84% overall yields, respectively.

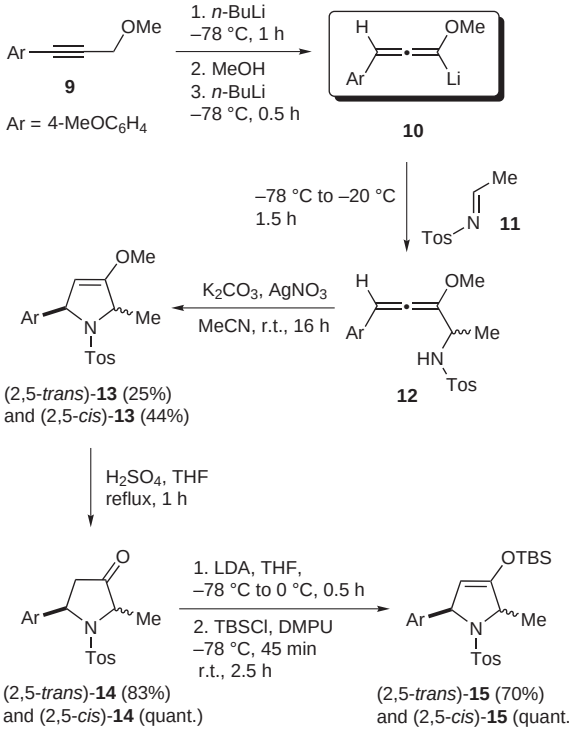


3,7,8	Y	R^1	R^2	yield of **8** (%)	dr
b	O	H	Ph	51	60 : 40
c	O	Me	Me	84	–
d	NPh	H	Ph	78	45 : 55

Scheme 2 Synthesis of dihydrofurans **8b** and **8c** and dihydropyrrole derivative **8d** starting from alkyne **1**.

Similarly, imine **3d** smoothly combined with in situ generated **6** to form allenyl amine **7d**, which on cyclization with silver nitrate afforded **8d** (diastereomeric mixture) in 78% overall yield (*trans*/*cis* 45:55). The mixture was subjected to column chromatography which gave pure *trans*-**8d** and *cis*-**8d** in 35% and 36% yields, respectively.

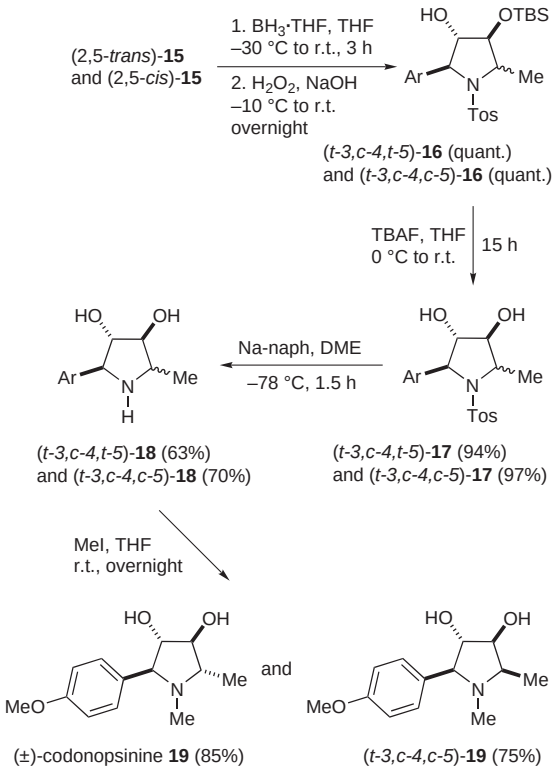
We finally applied the developed straightforward method for the generation of highly substituted dihydropyrrole derivatives to the stereoselective preparation of the alkaloid (±)-codonopsinine.[13] As depicted in Scheme 3, alkyne **9** was successfully transformed into lithiated allene **10** using the sequence of steps described for the generation of **2**. Addition of *N*-tosyl imine **11** to in situ generated **10** furnished allenyl adducts **12**, which on cyclization with silver nitrate in acetonitrile in the presence of potassium carbonate afforded **13** in 78% overall yield, after column chromatography, as a mixture of diastereomers (*trans*/*cis* 45:55).[11] Fractional crystallization allowed isolation of pure (2,5-*trans*)-**13** and (2,5-*cis*)-**13** in 25% and 44% yields, respectively. Subsequent reactions of these two isomers were carried out separately. In general identical reaction conditions were applied and the results were very similar in both series (Schemes 3 and 4). Acid-promoted hydrolysis of the enol ether moiety of **13** gave ketones **14** which were converted into silyl enol ethers **15** under standard conditions.



Scheme 3 Preparation of diastereomeric dihydropyrrole derivatives **15** starting from alkyne **9**.

Hydroboration of the silyl enol ether moiety of isomers **15** with borane in THF installed the second hydroxyl group in **16** with perfect stereoselectivity[5e] for both diastereomeric series (Scheme 4). After desilylation with TBAF to give **17** and detosylation of the nitrogen with sodium naphthalenide[14] the tetrasubstituted pyrrolidine derivatives **18** were obtained in very good yields. Finally, N-methylation was smoothly achieved by stirring **18** with methyl iodide in THF at room temperature to obtain the expected (*t*-3,*c*-4,*t*-5)-**19**, (±)-codonopsinine, and in the second series of experiments the epimer of this alkaloid (*t*-3,*c*-4,*c*-5)-**19**. The spectroscopic data of both isomers are in good agreement with data reported in the literature.[13c]

In summary, we demonstrated that disubstituted and trisubstituted lithiated allenes can easily be generated in situ by an appropriate sequence of reactions with 3-aryl-substituted propargylic ethers such as **1** as precursors. Addition of the generated lithiated species to electrophiles such as carbonyl compounds or imines provided primary adducts which can be cyclized to highly substituted furan



Scheme 4 Synthesis of codonopsinine and one of its epimers.

or pyrrole derivatives. Although the overall yields are only moderate to low in several cases the simplicity of the method should still be attractive. A first application of our method for the generation of highly substituted pyrrolidine derivatives led to a stereoselective synthesis of the alkaloid (±)-codonopsinine and one of its epimers. Further applications and preparation of enantiomerically pure compounds will be reported in due course.

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(11) **Conversion of 9 into 13; Typical Procedure**
To a solution of 1-methoxy-4-(3-methoxy-1-propynyl)benzene (**9**; 1.20 g, 6.82 mmol) in Et_2O (15 mL) *n*-BuLi (2.5 M in hexane, 2.73 mL, 6.82 mmol) was added at –78 °C and stirred for 1 h. MeOH (276 μL, 6.82 mmol) was added slowly to the mixture and the resulting solution was warmed with stirring to r.t. (0.5 h). The mixture was cooled again to –78 °C and *n*-BuLi (2.73 mL, 6.82 mmol) was added slowly and the resulting solution was stirred for 0.5 h. Imine **11** (1.34 g, 6.82 mmol) dissolved in Et_2O (15 mL) was slowly transferred to the reaction flask by syringe. After stirring for 1.5 h at –78 °C to –20 °C, the mixture was quenched with H_2O and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine (25 mL) and dried with $MgSO_4$. Filtration and evaporation of solvents in vacuo at r.t. afforded allenyl amine **12** (3.17 g,

dr ca. 50:50), which was used for the subsequent cyclization without purification. The crude product was dissolved in anhyd MeCN (45 mL); K_2CO_3 (2.35 g, 17.0 mmol) followed by $AgNO_3$ (289 mg, 1.70 mmol) were added to the solution. The resulting mixture was stirred for 16 h in the dark under argon, then filtered through a pad of celite, washed with EtOAc, and the filtrate was concentrated in vacuo at r.t. The resulting product was purified by column chromatography on silica gel (hexane–EtOAc, 4:1) to give **13** (1.98 g, 78% from **9**) as a mixture of diastereomers (*trans*/*cis* 45:55). Isomers (2,5-*trans*)-**13** (650 mg, 25%) and (2,5-*cis*)-**13** (1.12 g, 44%) were separated by fractional crystallization.

3-Methoxy-5-(4-methoxyphenyl)-2-methyl-1-tosyl-2,5-dihydro-1*H*-pyrrole (2,5-*trans*)-13. Colorless crystals; mp 138–140 °C. IR (KBr): 3100–3000 (=CH), 3000–2840 (CH), 1670 (C=C), 1610 (CN), 1340, 1160 (RSO_2N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.63 (d, *J* = 6.3 Hz, 3 H, Me), 2.31 (s, 3 H, Ts-Me), 3.62, 3.77 (2 s, 3 H each, OMe), 4.40–4.52 (m, 2 H, 2-H, 5-H), 5.50 (dd, *J* = 1.9, 4.7 Hz, 1 H, 4-H), 6.55–6.65, 6.90–7.00, 7.00–7.10 (3 m, 2 H, 4 H, 2 H, Ar). ^{13}C NMR (126 MHz): δ = 20.9, 21.4 (2 q, Me), 55.4, 57.1 (2 q, OMe), 60.2 (d, C-2), 67.5 (d, C-5), 94.6 (d, C-4), 113.3, 126.7, 128.8, 129.9 (4 d, Ar), 132.1, 138.4, 141.9, 159.4 (4 s, Ar), 157.8 (s, C-3). MS (EI, 80 eV, 30 °C): *m*/*z* (%) = 373 (30) $[M]^+$, 358 (13) $[M – CH_3]^+$, 266 (26) $[M – C_7H_7O]^+$, 218 (100) $[M – C_7H_7SO_2]^+$, 155 (40) $[C_7H_7SO_2]^+$. HRMS (EI, 80 eV, 30 °C): *m*/*z* calcd for $C_{20}H_{23}NO_4S$: 373.13478; found: 373.13450. Anal. Calcd for $C_{20}H_{23}NO_4S$ (373.5): C, 64.32; H, 6.21; N, 3.75. Found: C, 64.29; H, 6.32; N, 3.69.

(**2,5-*cis*)-13**. Brownish liquid. IR (KBr): 3100–3000 (=CH), 3000–2840 (CH), 1665 (C=C), 1610 (CN), 1350, 1160 (RSO_2N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.3 Hz, 3 H, Me), 2.39 (s, 3 H, Ts-Me), 3.54, 3.78 (2 s, 3 H each, OMe), 4.30–4.42 (m, 2 H, 2-H, 5-H), 5.35 (m, 1 H, 4-H), 6.80–6.90, 7.20–7.35, 7.60–7.65 (3 m, 2 H, 4 H, 2 H, Ar). ^{13}C NMR (126 MHz): δ = 21.6, 21.8 (2 q, Me), 55.4, 57.3 (2 q, OMe), 60.3 (d, C-2), 67.2 (d, C-5), 94.0 (d, C-4), 113.8, 127.7, 128.4, 129.6 (4 d, each, Ar), 134.9, 135.5, 143.4, 159.2 (4 s, Ar), 157.3 (s, C-3). MS (EI, 80 eV, 30 °C): *m*/*z* (%) = 373 (8) $[M]^+$, 358 (2) $[M – CH_3]^+$, 266 (11) $[M – C_7H_7O]^+$, 218 (48) $[M – C_7H_7SO_2]^+$, 217 (100), 155 (9) $[C_7H_7SO_2]^+$. HRMS (EI, 80 eV, 30 °C): *m*/*z* calcd for $C_{20}H_{23}NO_4S$: 373.13478; found: 373.13432.

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