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Preparation of Tri- and Tetrasubstituted Allenes via Regioselective Lateral Metalation of Benzylic (Trimethylsilyl)alkynes Using TMPZnCl·LiCl

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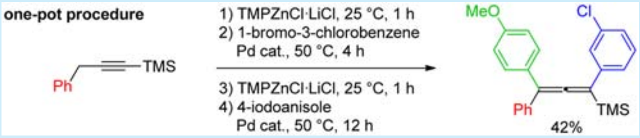
Ⓢ *Supporting Information*

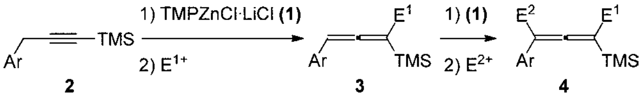
ABSTRACT: The zincation of various 1-(trimethylsilyl)-3-aryl-1-propynes with TMPZnCl·LiCl followed by a Pd-catalyzed coupling with aryl halides provides arylated allenes in 52−92% yield. Subsequent metalation with TMPZnCl·LiCl and cross-coupling with a second different aryl halide provides regioselectively tetrasubstituted allenes in 42−70% yield. This sequence can be performed in a one-pot procedure. DFT calculations and NMR studies support the formation of allenylzinc and propargyllithium intermediates starting from 1-(trimethylsilyl)-3-phenyl-1-propyne.



Allenic structures are found in a number of useful organic molecules such as natural products[1] or materials.[2] They are also important intermediates[3] for carbo- and heterocycle synthesis,[4] making the preparation of substituted allenes a valuable synthetic target.[5] Various transition-metal-catalyzed functionalizations of the allenic moiety have been reported.[6] For example, Ma reported the preparation of trisubstituted allenes using a Pd-catalyzed arylation of zincated allenes obtained by LDA deprotonation of the corresponding allenes.[7]

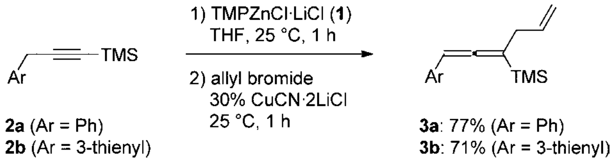
Recently, we have reported that TMPZnCl·LiCl (**1**, TMP = 2,2,6,6-tetramethylpiperidyl) is an excellent base for the selective metalation of various substrates.[8] The high kinetic basicity of **1** allows the efficient metalation of a range of organic molecules including nitriles, esters, and various functionalized unsaturated molecules.[9] We have envisioned that lateral metalations[10] of benzylic alkynes of type **2** with TMPZnCl·LiCl (**1**) will produce intermediate allenylzinc reagents, which after quenching with an electrophile E^{1+} will produce trisubstituted allenes of type **3** (Scheme 1).[7]

Scheme 1. Successive Lateral Metalation of Benzylic Alkynes of Type 2 with TMPZnCl·LiCl (1)



A subsequent metalation with TMPZnCl·LiCl (**1**) will give a new zincated intermediate, which after trapping with a second electrophile E^{2+} will furnish tetrasubstituted allenes of type **4**. Herein, we report the successful realization of this reaction sequence using a palladium-[11] or a copper-catalyzed[12] reaction of 1-(trimethylsilyl)-3-aryl-1-propynes with electrophiles.

Scheme 2. In Situ Trapping of Zinc Reagents with CuCN·2LiCl and Subsequent Allylation Reaction



In preliminary experiments, we have treated the TMS-protected alkyne (**2a**) with TMPZnCl·LiCl (**1**; 1.2 equiv) in THF at 25 °C for 1 h. Addition of CuCN·2LiCl (30 mol %) and allyl bromide led to the allylated allene **3a** in 77% yield, indicating that TMPZnCl·LiCl (**1**) achieved a smooth deprotonation of the benzylic hydrogen.[13] This result was confirmed by extending the metalation to the heterobenzylic derivative (**2b**), which after allylation, similarly produced the corresponding allene (**3b**) in 71% yield (Scheme 2). With these results in hand, we examined the direct Pd-catalyzed arylation of the TMS-protected alkynes of type **2**. Thus, the reaction of the alkynes **2a**−**c** with TMPZnCl·LiCl (**1**; 1.2 equiv) in THF at 25 °C for 1 h, followed by the addition of an aryl or heteroaryl bromide or iodide (**5a**−**j**), provides the arylated allenes **3a**−**p** in 52−92% yield (Table 1). As Pd catalyst, we have found after an extensive screening that three catalytic systems gave the best results: (a) 2% Pd(OAc)$_2$/2% DPE-Phos;[14] (b) 2% Pd(OAc)$_2$/4% S-Phos;[15] (c) 2% PEPPSI-*i*-Pr.[16] Both donor- and acceptor-substituted aryl halides afforded the trisubstituted allenes **3c**−**k** in 60−92% yield (entries 1−9). The thienyl-substituted alkyne (**2b**) behaves similarly and produced the allenes (**3l**−**m**) in 65−78% yield (entries 10−11). Remarkably, an ester substituent is perfectly tolerated, and the alkyne (**2c**) leads to the corresponding trisubstituted allenes

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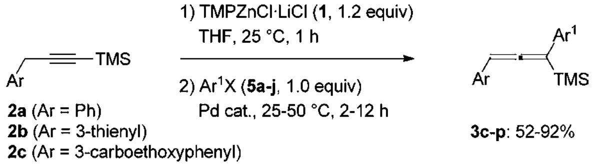
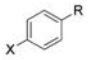
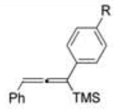
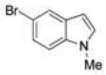
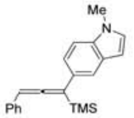
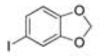
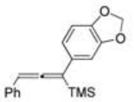
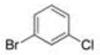
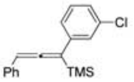
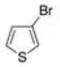
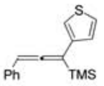
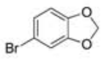
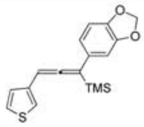
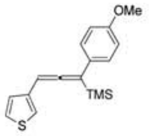
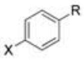
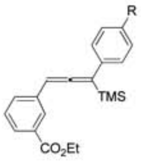
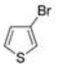
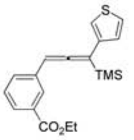
Table 1. Zincation with TMPZnCl·LiCl (1) Followed by a Negishi Cross-Coupling Reaction with Various Electrophiles



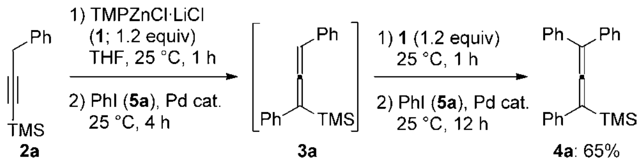
entry	electrophile^{a} (°C, h)^{b}	product yield (%)^{c}
		
1	**5a** R = H, X = I (25, 4)	**3c**: 68^{d}
2	**5b** R = OMe, X = I (25, 5)	**3d**: 76^{d}
3	**5c** R = NMe$_2$, X = Br (50, 4)	**3e**: 66^{e}
4	**5d** R = OPiv, X = Br (50, 6)	**3f**: 71^{f}
5	**5e** R = SMe, X = Br (50, 6)	**3g**: 75^{f}
6	 **5f** (50, 3)	 **3h**: 64^{f}
7	 **5g** (25, 4)	 **3i**: 92^{f}
8	 **5h** (50, 4)	 **3j**: 60^{f}
9	 **5i** (25, 2)	 **3k**: 73^{g}
10	 **5j** (50, 12)	 **3l**: 65^{f}
11	**5a** (50, 2)	 **3m**: 78^{f}
		
12	**5a** R = H, X = I (25, 2)	**3n**: 52^{d}
13	**5b** R = OMe, X = I (25, 2)	**3o**: 59^{d}
14	 **5i** (25, 3)	 **3p**: 74^{g}

[a] 1.0 equiv of electrophile was used. [b] Reaction time at 25 or 50 °C for full conversion. [c] Isolated yield of analytically pure product. [d] Pd catalyst: 2% Pd(OAc)$_2$/4% S-Phos. [e] Pd catalyst: 4% Pd(OAc)$_2$/4% DPE-Phos. [f] Pd catalyst: 2% Pd(OAc)$_2$/2% DPE-Phos. [g] Pd catalyst: 2% PEPPSI-*i*Pr.

(**3n−p**) in 52−74% yield (entries 12−14). In all cases, the arylation is regiospecific (only allenic derivatives are obtained and no arylated propargylic compounds could be detected).

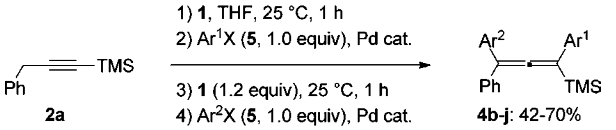
Then, we developed a one-pot procedure allowing a direct conversion of alkyne **2a** to the tetrasubstituted allenes of type **4** (Scheme 3 and Table 2). Thus, alkyne **2a** was treated as before with TMPZnCl·LiCl (**1**, 1.2 equiv) and iodobenzene (**5a**, 1.0 equiv) leading to **3c**, which was not isolated but directly zincated with TMPZnCl·LiCl (**1**, 1.2 equiv) and iodobenzene (**5a**, 1.0 equiv), affording the tetrasubstituted allene **4a** in 65% isolated yield.

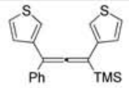
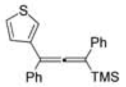
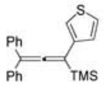
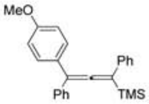
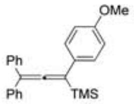
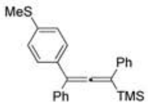
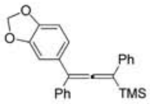
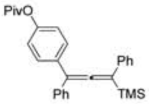
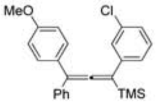
Scheme 3. Successive Zincation with TMPZnCl·LiCl (1) and Subsequent Negishi Cross-Coupling Reactions



Replacing the aryl iodide (**5a**) by 3-bromothiophene (**5i**) similarly produced the tetrasubstituted allene **4b** in 51% yield (Table 2, entry 1). The use of two different aryl or heteroaryl halides was also possible. Thus, treatment of the alkyne (**2a**) with TMPZnCl·LiCl (**1**, 1.2 equiv), a Pd catalyst, and iodobenzene (**5a**, 1.0 equiv) for 4 h at 25 °C led to the intermediate allene **3c**, which was directly metalated with TMPZnCl·LiCl (**1**, 1.2 equiv), Pd catalyst, and 3-bromothiophene (**5i**, 1.0 equiv), affording the tetrasubstituted allene **4c** in 63% overall yield (entry 2). By inverting the addition order of the two electrophiles E^{1+} and E^{2+} using first the heterocyclic bromide (**5i**) and then iodobenzene (**5a**), we have obtained the regioisomeric tetrasubstituted allene **4d** in 47% overall yield (entry 3). This approach was used for the preparation of the tetrasubstituted allenes (**4e−j**) in 42−70% overall yield (entries 4−9). Remarkably, this method allows the synthesis of the tris-3-thienylallene **4k** in 65% yield (Scheme 4). The structure of several allenes (**3c**, **4c**, **4f**, **4k**; Tables 1 and 2) has been confirmed by X-ray diffraction analysis.[17] We have briefly studied the scope of these new metalations of alkynes and allenes and found that the related diyne **6** was similarly zincated

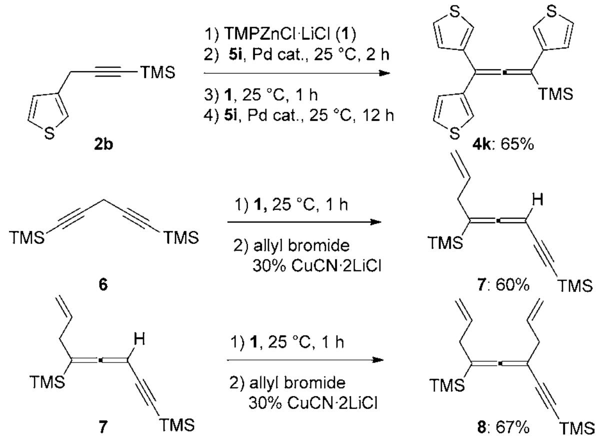
Table 2. One-Pot Tetrafunctionalization of Allenes via Successive Zincation Using TMPZnCl·LiCl (1) and Negishi Cross-Coupling Reactions with Various Electrophiles



entry	electrophile[a] (°C, h)[b]	product yield (%)[c]
1	1) **5i** (25, 2) 2) **5i** (25, 12)	 **4b**: 51[d]
2	1) **5a** (25, 4) 2) **5i** (25, 12)	 **4c**: 63[d]
3	1) **5i** (25, 2) 2) **5a** (25, 12)	 **4d**: 47[d]
4	1) **5a** (25, 4) 2) **5b** (25, 12)	 **4e**: 68[d]
5	1) **5b** (25, 5) 2) **5a** (25, 12)	 **4f**: 67[d]
6	1) **5a** (50, 2) 2) **5e** (50, 2)	 **4g**: 64[e]
7	1) **5a** (50, 2) 2) **5g** (50, 3)	 **4h**: 70[e]
8	1) **5a** (50, 2) 2) **5d** (50, 12)	 **4i**: 65[e]
9	1) **5h** (50, 4) 2) **5b** (50, 12)	 **4j**: 42[e]

[a] 1.0 equiv of electrophile was used. [b] Reaction time at 25 or 50 °C for full conversion. [c] Isolated yield of analytically pure product. [d] Pd catalyst: 2% Pd(OAc)$_2$/4% S-Phos. [e] Pd catalyst: 2% Pd(OAc)$_2$/2% DPE-Phos.

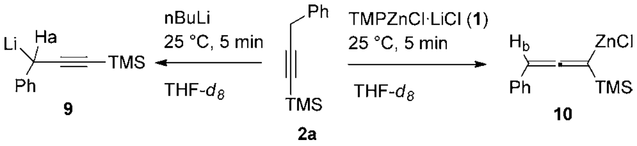
Scheme 4. Preparation of a Tri-3-thienylallene (4k) and Lateral Metalation of Alkynes 6 and 7 with TMPZnCl·LiCl (1)



with TMPZnCl·LiCl (1) within 1 h at 25 °C (Scheme 4).[18] After a copper-catalyzed allylation with allyl bromide, the trisubstituted allene 7 was obtained in 60% yield.[19] The unsaturated alkynylallene 7 was cleanly allylated affording the highly unsaturated product **8** in 67% yield.

In order to establish the nature of the zincated intermediates (allenic or propargylic) occurring during the metalation of **2a**, we performed an NMR study that showed that the lithiation of **2a** produces only the propargylic lithium species **9** as seen by the chemical shift of the propargylic proton H_a at 3.33 ppm in the ^{1}H NMR spectra (Scheme 5).[17]

Scheme 5. NMR Experiments Showed Direct Formation of Allenylzinc Reagent



The zincation of **2a** using TMPZnCl·LiCl (**1**) produces an allenylzinc species **10** (as seen by the allenic ^{13}C signal at 202.8 ppm, no propargyl isomer was observed and the allenic proton (H_b) has a chemical shift of 4.99 ppm in the ^{1}H NMR spectra).[17] From these studies, it becomes clear that the propargyl isomer **9** is the most stable organometallic species in the case of the lithium cation, whereas the allenylzinc structure **10** is the most stable (zinc cation).[20] Theoretical calculations at the MP2 level of theory confirmed a major difference in stability order for the propargyl allenyl isomers of the respective organometallics. An endothermic enthalpy of 1.4 kJ/mol for the two organolithium isomers (**9** and **9a**; Figure 1) is opposed to 7.8 kJ/mol for the zinc species **10** and **10a**.[17]

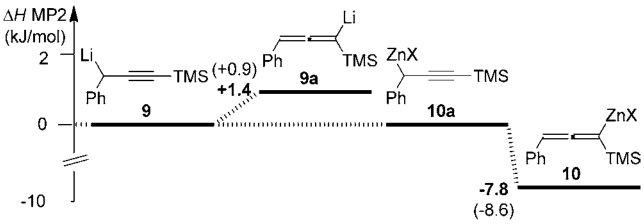


Figure 1. Propargyl allenyl isomerization in THF solution (SMD/B3LYP/6-31G(d)) at the MP2(FC)/6-31+G(d,p) level (Li = Li(THF)$_3$, ZnX = ZnCl(THF)$_2$, gas-phase values in parentheses).

In conclusion, we have reported an efficient Pd-catalyzed arylation of some 1-(trimethylsilyl)-3-aryl-1-propynes using TMPZnCl·LiCl leading to trisubstituted allenes. Interestingly, we have performed a one-pot bis-arylation of 1-(trimethylsilyl)-3-phenyl-1-propyne affording regioselectively tetrasubstituted allenes. Quantum chemical calculations and NMR studies support the formation of allenylzinc and propargyllithium intermediates.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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