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2021

Wang, B., Li, Y., Pang, J. H., Watanabe, K., Takita, R. & Chiba, S. (2021). Hydromagnesiation of 1,3-enynes by magnesium hydride for synthesis of tri- and tetra-substituted allenes. *Angewandte Chemie International Edition*, 60(1), 217-221. <https://dx.doi.org/10.1002/anie.202012027>

<https://hdl.handle.net/10356/154832>

<https://doi.org/10.1002/anie.202012027>

This is the peer reviewed version of the following article: Wang, B., Li, Y., Pang, J. H., Watanabe, K., Takita, R. & Chiba, S. (2021). Hydromagnesiation of 1,3-enynes by magnesium hydride for synthesis of tri- and tetra-substituted allenes. *Angewandte Chemie International Edition*, 60(1), 217-221, which has been published in final form at <https://doi.org/10.1002/anie.202012027>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Hydromagnesiation of 1,3-enynes by magnesium hydride for synthesis of tri- and tetra-substituted allenes

Bin Wang,^[a,†] Yihang Li,^[a,†] Jia Hao Pang,^[a] Kohei Watanabe,^[b] Ryo Takita,^{*,[b]} and Shunsuke Chiba^{*,[a]}

[a] Dr. B. Wang, Y. Li, Prof. Dr. S. Chiba
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences
Nanyang Technological University
Singapore 637371 (Singapore)
E-mail: shunsuke@ntu.edu.sg

[b] Dr. Kohei Watanabe, Prof. Dr. R. Takita
Graduate School of Pharmaceutical Sciences, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
E-mail: takita@mol.f.u-tokyo.ac.jp

[†] These authors contributed equally.

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Abstract: A protocol for regio-controlled hydromagnesiation of 1,3-enynes was developed using magnesium hydride that is generated *in situ* by solvothermal treatment of sodium hydride (NaH) and magnesium iodide (MgI₂) in THF. The resulting allenylmagnesium species could be converted into tri- and tetra-substituted allenes by subsequent treatment with various carbon- and silicon-based electrophiles with the aid of CuCN as a catalyst.

Hydrometallation of carbon-carbon unsaturated bonds such as alkenes and alkynes is a promising protocol for generation of the corresponding organometallic species, that can often function as a nucleophile to undergo downstream formation of a new covalent linkage with various electrophiles.^[1] For this purpose, regioselectivity of the hydrometallation would be of crucial importance to efficiently enhance molecular complexity. If conjugation of two carbon-carbon unsaturated bonds is present in the substrates, multiple possibilities should be taken into account for the regioselectivity of their hydrometallation and ensuing downstream functionalization of the resulting organometallic nucleophiles. In this regard, readily accessible 1,3-enynes have been employed as a substrate of choice for the studies of their hydrometallation (Scheme 1), where transition-metal catalysis has advanced the state-of-the-art (Scheme 1A).^[2] In this regard, transition-metal hydrides based on palladium,^[3,4] copper,^[5–7] and ruthenium/iridium complexes^[8] have commonly been engaged in 1,2/1,4-hydrometallation of 1,3-enynes as a typical reaction mode with several exceptions.^[9,10] The resulting propargyl/allenyl metal intermediates could be functionalized with various sets of electrophiles (E⁺) and the reaction course (i.e. α -functionalization for allene synthesis or γ -functionalization for alkyne synthesis) could vary depending on the types of the electrophiles.

On the other hand, the reductive molecular transformations of 1,3-enynes promoted by main group metal hydrides have been underdeveloped and the reported examples have been strictly limited to hydroalumination by aluminum hydrides (Scheme 1B). As for the regioselectivity trend, aluminum hydrides commonly target the alkyne moiety to form 1,3-dienes with subsequent functionalization such as protonation (Scheme 1B-i),^[11] whereas

A. Hydrometallation by transition metal hydrides

B. Hydroalumination by aluminum hydrides

(i) non-guided approaches: alkyne selective

(ii) hydroxy-guided approach for allene construction

C. anti-Hydromagnesiation of aryl alkynes by MgH₂

D. Hydromagnesiation of 1,3-enynes by MgH₂ (this work)

Scheme 1. Hydrometallation of 1,3-enynes and alkynes by metal hydrides.

1,4-hydroalumination towards allenes is enabled when a hydroxy group is installed adjacent to the alkene moiety (Scheme 1B-ii).^[12] We recently disclosed unprecedented reactivity of magnesium hydrides (MgH₂)^[13] generated *in situ* by counter ion metathesis between sodium hydride (NaH) and

A. Hydromagnesiation-protonation of **1a**^[a] B. Hydromagnesiation-allylation of **1a**^[b] C. Hydromagnesiation-downstream functionalization of **1a**^[e]

Scheme 2. Hydromagnesiation of enyne **1a**. [a] The reaction was conducted using 0.5 mmol of enyne **1a** in THF (2.5 mL, 0.2 M) with NaH (1.5 equiv) and MgI₂ (1.5 equiv) at 100 °C for 2 h. [b] The reactions were conducted using 0.5 mmol of enyne **1a** in THF (2.5 mL, 0.2 M) with NaH (1.5 equiv) and MgI₂ (1.5 equiv) at 100 °C for 2 h, followed by CuCN·LiCl (10 mol%) and allyl bromide (**4a**) (1.2 equiv) at 0 °C for 2 h. [c] When sodium deuteride (NaD) was utilized instead of NaH, deuterium was incorporated exclusively at the methyl group of **5aa** (>93% incorporation). [d] The isolated yield of **5aa** obtained from the reaction in a 5 mmol scale. [e] The reactions were conducted using 0.5 mmol of enyne **1a** in THF (2.5 mL, 0.2 M) with NaH (1.5 equiv) and MgI₂ (1.5 equiv) at 100 °C for 2 h, followed by CuCN·LiCl (10 mol%) and electrophiles **4** (1.2 equiv) at 0 °C for 2–4 h. [f] The 2nd step alkylation was conducted using 2 equiv of **4g** at 35 °C for 4 h.

magnesium halides (MgX₂: X = I, Br, or Cl) in THF, that perform *anti*-hydromagnesiation of aryl alkynes and the resulting alkenylmagnesium intermediates could be functionalized with various electrophiles (Scheme 1C).^[14–16] In this context, we wondered how the hydridic reactivity of MgH₂ works toward reductive functionalization of 1,3-enynes. Herein, we report regioselective hydromagnesiation of 1,3-enynes by MgH₂ generated from NaH and MgI₂ in THF for generation of allenyl/propargyl magnesium species and their downstream functionalization with carbon- and silicon-based electrophiles in the presence of CuCN as a catalyst, liberating multifunctionalized tri- and tetra-substituted allenes (Scheme 1D).^[17]

We embarked on our investigation using 4-(4-methoxyphenyl)-1-butene-3-yne (**1a**) as a model substrate. A

survey of various reaction parameters (see the SI for details) revealed that a combination of NaH and MgI₂ is optimal for efficient and regioselective 1,2/1,4-hydromagnesiation of **1a** (Scheme 2). Namely, treatment of **1a** with NaH (1.5 equiv) and MgI₂ (1.5 equiv) in THF at 100 °C allowed for a full conversion of **1a** within 2 h and subsequent aqueous work-up afforded 3-methyl-1-(4-methoxyphenyl)allene (**2a**) in 81% yield along with 8% yield of alkyne **3a**. Formation of **2a** and **3a** suggested the formation of an equilibrium mixture of propargylmagnesium **A** and allenylmagnesium **B** through regioselective 1,2/1,4-hydromagnesiation.^[18] We observed that downstream allylation of the resulting carbanion species **A** and **B** with allyl bromide (**4a**) could be facilitated in the presence of a catalytic amount of CuCN·2LiCl,^[19] affording trisubstituted allenes **5aa** in good yield as a sole product (Scheme 2B). A deuterium labeling experiment using NaD revealed that a deuterium was exclusively installed on the methyl group of **5aa**, unambiguously supporting the 1,2/1,4-hydromagnesiation process. Functionalization with external alkyl electrophiles for the synthesis of substituted allenes through hydrometallation of 1,3-enynes has remained elusive.^[20–23] Encouraged by the preliminary outcome, we next investigated the scope of the alkyl electrophiles (Scheme 2C). This downstream functionalization was found to be compatible with use of *t*-butyl 2-bromomethylacrylate (**4b**), benzyloxymethyl chloride (**4c**), propargyl bromide **4d** and benzyl bromide (**4e**), providing the corresponding tri-substituted allenes **5** in good to moderate yields (Scheme 2C). To install a methyl group, use of methyl tosylate (**4f**) was found to be optimal.^[24] The protocol also allowed for use of non-activated alkyl bromide **4g**. The protocol was also amenable to install a silyl group using chlorosilanes **4h** and **4i** to afford synthetically useful allenylsilanes **5ah** and **5ai** in good yields.

We next investigated the scope of the allene synthesis with respect to the substituents (R¹–R³) on enynes **1** (Scheme 3). As for the substituent R¹ on the alkyne moiety, the method was suitable for installing various aryl groups including electron-rich (hetero)arenes (for **5aa**, **5ia**, **5ja**, and **5ka**), haloarenes (for **5da**–**5fa**) and sterically demanding ones (for **5ha** and **5ia**). It would be worthy of note that the process was not detrimentally influenced by the presence of alkyl groups as the R¹, providing the corresponding trisubstituted allenes **5la** and **5ma** in good yields. Similarly, the reaction of silyl-substituted enyne **1n** also proceeded smoothly to afford silyl-substituted allene **5na** in an excellent yield. We also found that the present hydromagnesiation was not disturbed by the presence of the substituent R² on the alkene moiety (for **5oc** and **5pc**). Significantly, the protocol was amenable to transform enynes **1q**–**1v** having internal substituent R³ on the alkene, providing tetra-substituted allenes **5qc**–**5vc** in good yields. As for R³, methyl (for **5qc**) and functionalized primary alkyl groups (for **5rc** and **5sc**) as well as sterically bulkier cycloalkyl and *t*-butyl groups (for **5tc**–**5vc**) could be installed.

Having developed a method for the concise construction of functionalized allenes, we next explored derivatization of the representative allene products to other scaffolds of potential use (Scheme 4). One of the highlights in the present synthetic strategy is a facile installation of the silicon-substituent onto the allenes such as **5ah**, **5na** and **5sc**. Therefore, we examined their transformations into other silicon-substituted scaffolds. We

Scheme 3. Scope with respect to enynes **1**. [a] Unless otherwise stated, the reactions were conducted using 0.5 mmol of enynes **1** in THF (2.5 mL, 0.2 M) with NaH (1.5 equiv) and MgI₂ (1.5 equiv) at 100 °C for 2-18 h, followed by CuCN·LiCl (10 mol%) and electrophiles **4a** or **4c** (1.2 equiv) at 0 °C for 2-4 h. [b] 1.5 equiv of MgI₂ was used. [c] The reaction was conducted using 7 mmol (1.31 g) of enyne **1n**.

observed that palladium-catalyzed oxidative arylation of **5na** with arylboronic acids under the Bäckvall's reaction conditions^[25] delivered silicon-substituted 1,3,6-trienes **6** and **7** (Scheme 4A). Iodoarylation of allene **5ah** was found to be facilitated by N-iodosuccinimide (NIS) in MeCN to afford 2-iodo-3-silylindene **8** in excellent yield (Scheme 4B).^[26] In turn, we also attempted desilylative transformations. For example, a facile treatment of silyllallene **5na** with NIS allowed for desilylative propargylic iodination, providing **9** in 62% yield (Scheme 4C). Moreover, bromodesilylation of silylmethylallene **5sc** by the treatment with NBS delivered functionalized diene **10** (Scheme 4D).^[27]

A. Pd-catalyzed oxidative arylation

B. Iodoarylation

C. Iododesilylation for synthesis of propargylic iodide

D. Bromodesilylation for synthesis of 1,3-dienes

Scheme 4. Derivatization of allenes.

Finally, the origin of regioselectivity observed in the present 1,2/1,4-hydromagnesiation of 1,3-enynes was elucidated by the theoretical means (Scheme 5). We recently uncovered that solvothermal treatment of a mixture of NaH and MgI₂ in THF generates highly hydridic MgH₂ in small units,^[14] which should be responsible for the present transformation. To gain insights into the reactivity and selectivity, we carried out the DFT calculations at the ωB97XD/6-311++G**/SMD(THF)//ωB97XD/6-311++G** level of theory using phenyl-substituted enyne **1b** and a MgH₂ dimer as the model substrates. We found that the process is initiated by smooth 1,2-hydromagnesiation of **1b** via **TS_{A-1}** (ΔG[‡] +16.2 kcal/mol), where the Mg–H moiety comes from the upper side of the alkene plane to afford the corresponding propargylmagnesium species **INT_{A-2}** (i.e. **A** in Scheme 2A) (Scheme 5A). We observed that the energy barrier of the isomerization from propargylmagnesium **INT_{A-2}** to allenylmagnesium **INT_{A-3}** is reasonably small (ΔG[‡] +5.0 kcal/mol) and so is their energy difference (ΔΔG 5.3 kcal/mol), indicating that these species should exist in an equilibrium, where the presence of allenyl **INT_{A-3}** should be predominant over propargyl **INT_{A-2}**. We also examined another 4,1-hydromagnesiation pathway, that should be initiated by hydromagnesiation of the alkyne moiety (Scheme 5B). In this case, the hydride was forced to access the alkyne from the same plane of the benzene ring. Therefore, the large distortion was observed in **TS_{B-1}**, resulting in larger deformation energy (DEF_{enyne}: 18.8 kcal/mol) than that for **TS_{A-1}** (DEF_{enyne}: 5.1 kcal/mol) and thus higher activation energy (ΔG[‡] +22.2 kcal/mol). In this event, the magnesium cation instantly moved to the C1, giving the homoallenylmagnesium species **INT_{B-2}** in one step. These theoretical outcomes well corroborated the experimental observations.^[28]

A. 1,4-Hydromagnesiation pathway

B. 4,1-Hydromagnesiation pathway

Scheme 5. DFT calculations for model reactions of **1b** with dimeric MgH₂•thf species. Energy changes and bond lengths at the ω B97XD/6-311++G**/SMD(THF)// ω B97XD/6-311++G** level of theory are shown in kcal/mol and Å, respectively. thf = tetrahydrofuran.

The key enabling advance in the present method takes advantage of the unique hydridic reactivity of magnesium hydride for regio-controlled hydromagnesiation of 1,3-enynes without the aid of transition-metal catalysts and directing groups. Thus, the present protocol demonstrates potential of s-block metal hydrides for the selective functionalization of various π -conjugated organic molecules. Further studies in this direction are currently in progress at our laboratory.

Acknowledgements

This work was supported by funding from Nanyang Technological University (NTU) (for S.C.) and the Singapore Ministry of Education (Academic Research Fund Tier 2:

MOE2019-T2-1-089 for S.C.) as well as JSPS KAKENHI grant JP19K06992 (for R.T.) and the Naito Foundation (for R.T.). Computational calculations were performed using the resources of the Research Center for Computational Science at Okazaki, Japan.

Keywords: allenes • enynes • magnesium hydride • sodium hydride • hydromagnesiation

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Entry for the Table of Contents

Regio-controlled hydromagnesiation of 1,3-enynes was enabled by magnesium hydride and subsequent downstream alkylation and silylation allowed for construction of tri- and tetra-substituted allenes.