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Chemoselective preparation of alkynes from *vicinal*- and *geminal*-dibromoalkenes

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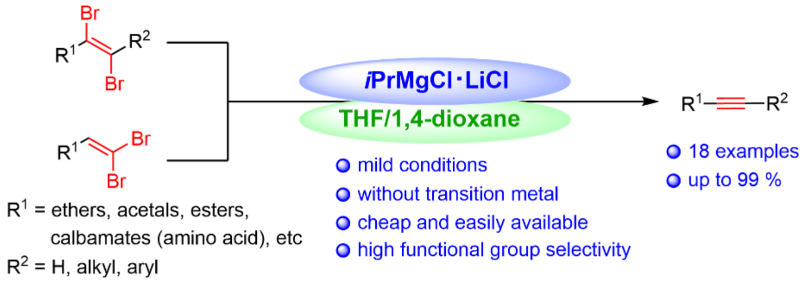
Supporting Information Placeholder



ABSTRACT: Reductive conversion of *vicinal*- and *geminal*-dibromoalkenes into the corresponding alkynes with *i*PrMgCl-LiCl (Turbo Grignard reagent) is described. This reaction proceeded in the presence of various functional groups such as ethers, esters or carbamates under mild conditions in high yields. Due to the selective reactivity, the easily preparable *vic*-dibromoalkene is considered to be a protecting group of alkyne toward an electrophile. Although butyl lithium has been widely used for the conversion of *gem*-dibromoalkenes into alkynes in the Corey-Fuchs alkyne synthesis, we report here alternative mild and chemoselective reaction conditions for alkyne synthesis.

The alkyne functional group is often found in natural products[1,2] and pharmaceuticals[3-5] as well as synthetic intermediates or building blocks such as those for the click reaction.[6-12] Due to the high demand for alkynes, many versatile synthetic methods have been reported. For example, alkyne syntheses from aldehydes are well-known, such as the Corey-Fuchs[13,14] and Seyferth-Gilbert reactions,[15-18] and other methods from various substrates have also been developed to prepare both terminal and internal alkynes.[19-26] The resulting alkyne products are labile toward electrophiles when conversion of alkene or aromatic ring in the alkyne product with electrophile is required. To avoid such undesired reaction pathway, protection-deprotection protocol is desired. Only a few examples are known for the protecting of alkyne; a representative is bis-Cobalt complex. We envisioned a *vic*-dibromoalkene as a protecting group of the alkyne in the view of not only easy conversion to the *vic*-dibromoalkene by well-known procedure but also much less reactivity toward the electrophiles than the original alkyne due to the electron withdrawing property of bromides. However, only small examples of conversion to the original alkyne from *vic*-dibromoalkene have been demonstrated by Malanga with *n*Bu_3SnH/$NidppeCl_2$, [27] and by Mashima and Tsurugi with prepared reagent 1,1'-bis(trimethylsilyl)-1*H*,1'*H*-4,4'-bipyridinylidene (**A**) (Figure 1).[28] Due to the powerful reducing ability of **A**, these reactions were also applied to a reductive preparation of alkenes from the corresponding *vic*-dichloroalkanes, which may induce a side reaction in the presence of other halides. Additionally, only a few substrates were examined for the alkyne synthesis in these two reports.

On the other hand, *gem*-dibromoalkenes are used as intermediates in the Corey-Fuchs alkyne synthesis. Almost all previous works employed *n*BuLi for the bromide-lithium exchange step, although there have been several reports of using strong bases such as LDA or TBAF.[29,30] Due to the strong nucleophilicity and basicity of *n*BuLi and other reagents, functional groups employed in this step are limited. Especially, carbonyl groups must be protected as ether or acetal groups, requiring additional conversion steps. Herein, we describe reductive preparations of alkynes from *vic*-dibromoalkenes with *i*PrMgCl-LiCl (Turbo Grignard reagent)[31-35] in the presence of various functional groups. The Turbo Grignard reagent is also a potential alternative to *n*BuLi in the Corey-Fuchs alkyne synthesis in the presence of carbonyl groups such as esters and carbamates.

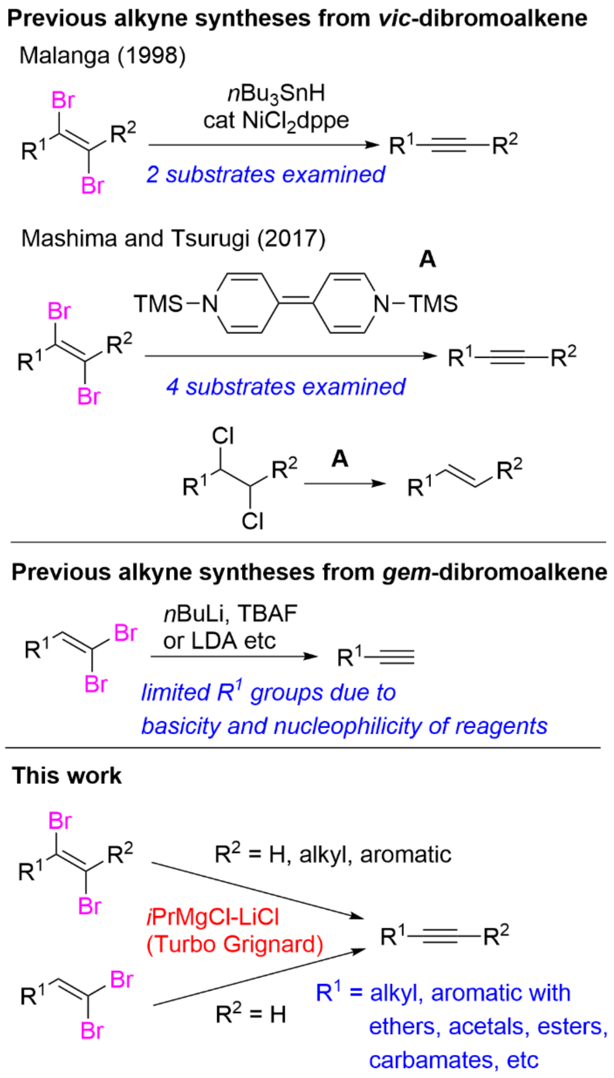
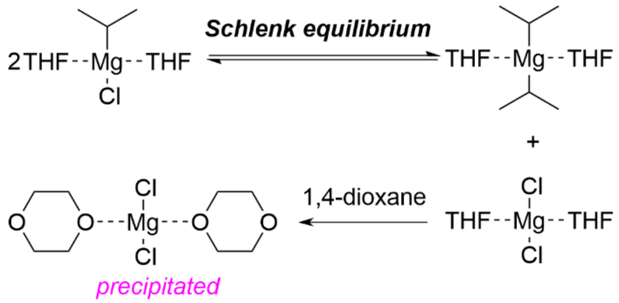


Figure 1 Previous and current syntheses of alkynes from *vic*- and *gem*-dibromoalkenes.

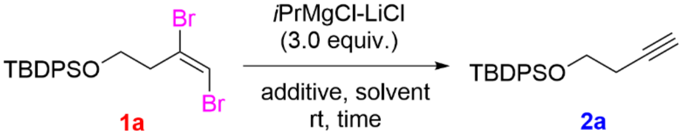
Results and discussion

First, the reaction conditions were optimized with *E*-*vic*-bromoalkene **1a** as a model substrate (Table 1). Solvents and additives were screened using 3.0 equivalents of Turbo Grignard reagent at room temperature. THF, a standard solvent in the Grignard reaction, showed high activity even in a short reaction time (10 min, entry 1), although running the reaction for a longer time (60 min) did not result in complete consumption of **1a** (entry 2). Solvents such as Et_2O, cyclopentylmethyl ether (CPME) and CH_2Cl_2, possessed less activity than THF (entries 3-5). For complete consumption of **1a**, additives were investigated based on the pioneering works by Knochel.[32] Crown ethers (1.0 equivalent) did not improve the reaction efficiency (entries 6 and 7). When a mixed solvent of THF/1,4-dioxane was used, only a trace amount of **1a** could be detected in the ^{1}H NMR spectrum of the crude product along with almost pure alkyne **2a** (entry 8). According to the previous report, the generation of a dialkyl magnesium species in the Schlenk equilibrium becomes dominant through coordination of 1,4-dioxane to magnesium dichloride to precipitate (Scheme 1). It has been shown that the dialkyl magnesium species is an active species for the bromide-magnesium exchange reaction. According to this pathway, more than two equivalents of the Turbo Grignard reagent are expected to be necessary for higher conversion. However, it is noted that this reaction with *E*- *vic*-dichloroalkene, prepared by our previous method,[36] did not give alkyne to recover only the starting material.



Scheme 1 Schlenk equilibrium.

Table 1. Optimization of reaction conditions. [a]



1a **2a**

Entry	Solvent	Additive	Time (min)	Ratio (**1a**:**2a**) [b]
1	THF	none	10	12:88
2	THF	none	60	4:96
3	Et_2O	none	10	28:72
4	CPME	none	10	80:20
5	CH_2Cl_2	none	10	34:66
6	THF	15-crown-5 [c]	10	26:74
7	THF	18-crown-6 [c]	10	35:65
8	THF	1,4-dioxane [d]	10	1:99

[a] 0.200 mmol of **1a** was used. [b] The ratio was estimated by ^{1}H NMR. [c] 1.0 equivalent of crown ether was used. [d] 10 volume% to THF was used

With the optimized conditions in hand, various substrates were subjected to the reductive alkyne synthesis by Turbo Grignard reagent as shown in Figure 2. Some optimizations for the amount of Turbo Grignard reagent, reaction time and temperature were required for higher yield. *vic*-Dibromoalkenes **1a**-**c** having benzyl or silyl ether groups were converted to the corresponding terminal alkynes in high yields. To our delight, the current reaction with *vic*-dibromoalkenes **1d**-**g**, including acetal, ester or carbamate groups, proceeded in high yields (73-90%). Lower temperature was required for higher yield when substrates having carbonyl groups were employed; reactions at room temperature resulted in around 50% yield along with side products. This reaction could also be applied to **1h**-**n** for the preparation of internal alkynes in the presence of various functional groups, revealing high efficiency of the reaction. Phenylacetylene derivatives were also synthesized from dibromides **1o**-**p** in high yields.

We next compared the reactivity of alkynes and *vic*-dibromoalkenes towards electrophiles to reveal the utility of the *vic*-dibromoalkene as a protecting group of alkynes. The results are shown in Figure 3. First, enyne **3**, prepared through Wittig olefination reaction with our previous phosphonium salt for the danicalipin A synthesis,[37] was treated with 1.0 equivalent of the NCS-PPh_3 system developed by Yoshimitsu.[38] This resulted in a complex mixture due to the similar reactivities of the alkene and alkyne toward electrophile. Diene **4** was next examined. The dichlorination reaction proceeded at the disubstituted olefin to furnish **5** in 69% yield. The subsequent debromination reaction with the Turbo Grignard reagent afforded *vic*-dichloroalkyne **6** as the sole product in high yield. The alkyne could be regenerated by the Turbo Grignard reagent without loss of the *vic*-dichloride moiety, which was reduced in the previous reports mentioned in the introduction. The *vic*-dibromoalkene moiety in **7** was tolerated in the electrophilic aromatic substitution reaction to give **8**, and the alkyne was regenerated in high yield without loss of the aromatic bromides.

The current reaction was next applied to *gem*-dibromoalkenes as intermediates of the Corey-Fuchs alkyne synthesis. As described in the introduction, almost all previous works have employed *n*BuLi, which shows strong basicity and nucleophilicity toward carbonyl groups, limiting the substrates employed in this step. The Turbo Grignard reagent is a mild and chemoselective reagent for the bromine-metal exchange reaction. The reaction with benzyl and silyl ethers **10a** and **10b** proceeded to give alkyne **11** in high yields (Scheme 2). To our delight, Boc-proline having both ester and carbamate groups afforded alkyne **11c** in 92% yield at lower temperatures.

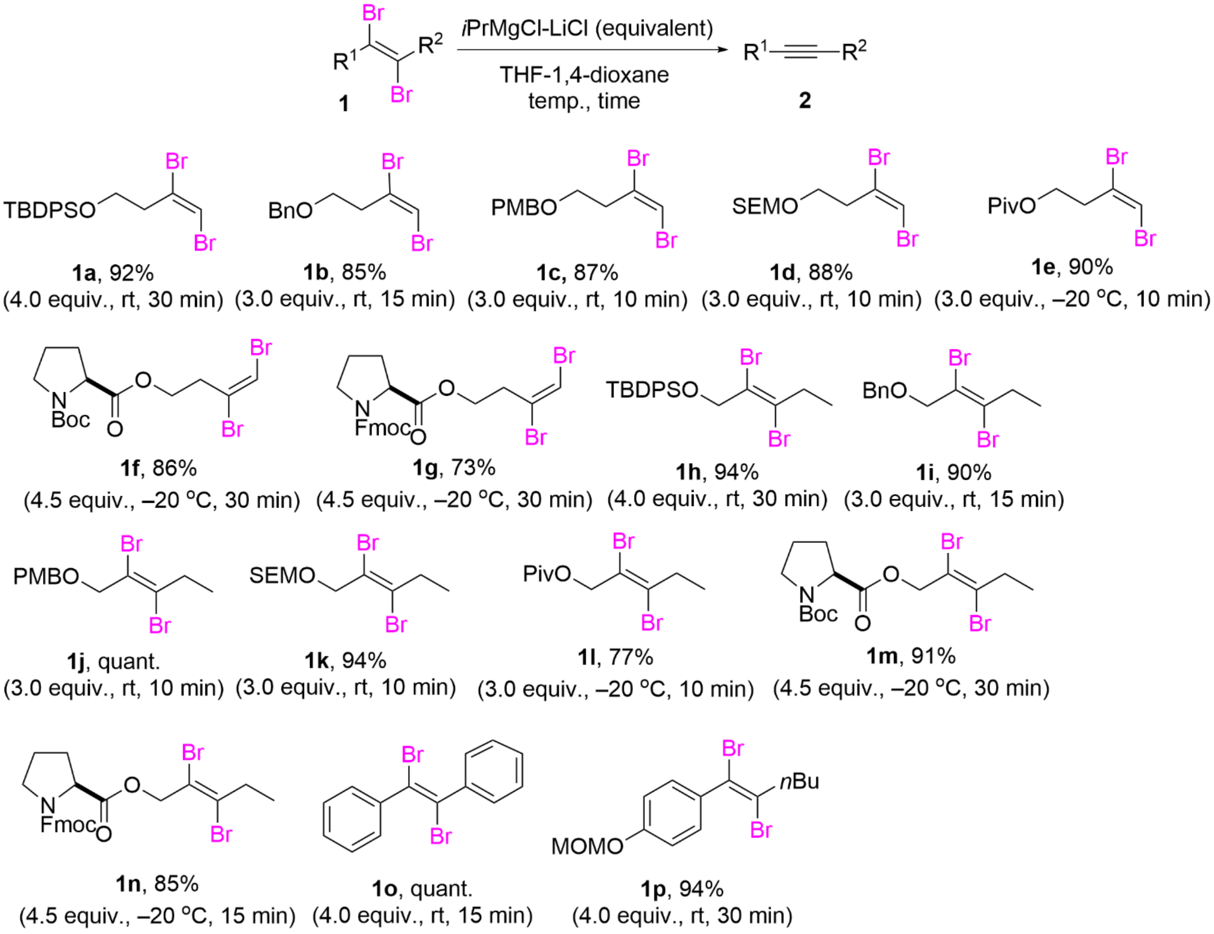


Figure 2 Substrate Scope. [a,b]

[a] 0.100-0.200 mmol of **1** was used. [a] Isolated yield

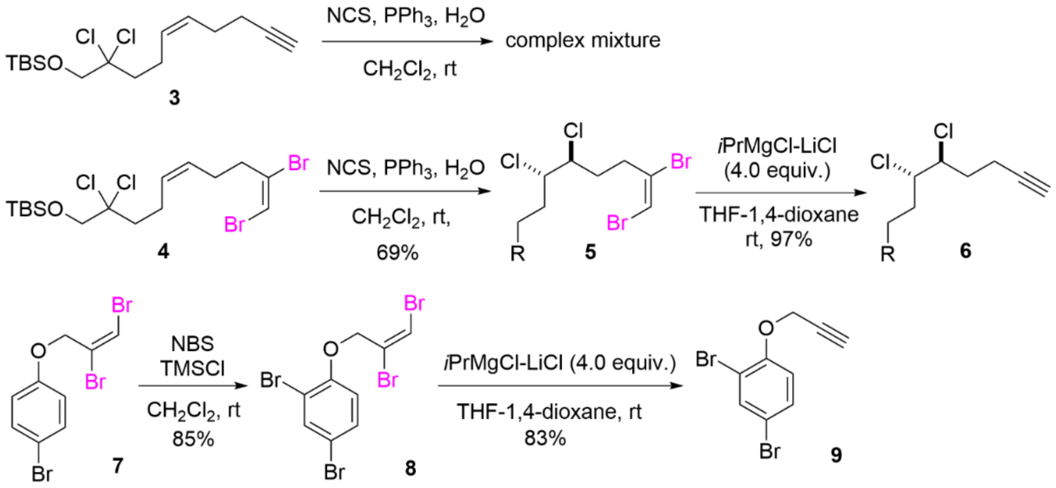
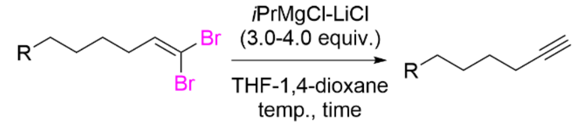


Figure 3 Reactivity of *vic*-dibromoalkenes toward electrophiles and regeneration of alkyne.



R = OBn (**10a**) **11a** 93%, rt, 10 min
$CH_2CH_2OTBDPS$ (**10b**) **11b** 86%, rt, 10 min
CH_2CH_2O-L-BocPro (**10c**) **11c** 92%, –20 °C, 30 min

Scheme 2. Reaction of Turbo Grignard reagent with *gem*-dibromoalkenes.

Conclusions

In summary, we have achieved conversion of *vic*-dibromoalkenes to alkynes through reduction of bromide by the Turbo Grignard reagent. The reaction efficiency was improved by the addition of 1,4-dioxane. Due to the mild and chemoselective reactivity of the Turbo Grignard reagent, various functional groups were tolerated, even an ester, a labile functionality toward nucleophiles. Using the current reaction, *vic*-dibromoalkenes, prepared from the corresponding alkynes, are expected to act as protecting groups of alkynes toward electrophiles. The utility of the Turbo Grignard reagent was further explored by the transformation of *gem*-dibromoalkenes, intermediates for the Corey-Fuchs reaction, to alkynes without using highly reactive *n*BuLi. Synthetic studies of natural products using the current reaction are underway in this laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Procedures for the preparation of all new compounds and their structural characterization data and copies of their NMR spectra (PDF)

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Author Contributions

Hyuga Okumura: conceptualization; data curation. Nurcahyo Iman Prakoso: conceptualization; writing – review & editing. Tatsuya Morozumi: writing – review & editing. Taiki Umezawa: conceptualization; funding acquisition; supervision; writing – original draft.

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