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Synthetic transformation of homopropargylic selenides to conjugated diene-substituted alcohols and amines using diisopropoxy(η^2-alkyne)titanium intermediates

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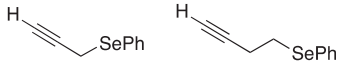
ABSTRACT

The reaction of homopropargylic selenides with the low-valent titanium reagent, derived from Ti(O-*i*-Pr)$_4$ and 2 equiv of *i*-PrMgCl, proceeded via titanium–alkyne complexes, followed by the reaction with electrophiles, such as aldehydes and imines to afford allylic alcohols and amines having a phenylseleno group in moderate to high yields with excellent regioselectivity (up to >99:1). Especially, the reaction of the silyl-substituted alkynes with imines provided the desired products in almost complete regioselectivity. The resulting products were subjected to oxidation with H_2O_2 to lead conjugated diene-substituted alcohols and amines via selenoxide elimination in high yields. In addition, the isomer ratio of products was nearly completely maintained under the oxidative deselenation conditions.

1. Introduction

Titanium–alkyne complexes are very valuable intermediates in organic synthesis.[1] In 1995, Sato and co-workers reported that the titanium complexes known as diisopropoxy(η^2-alkyne)titaniums are readily prepared from internal alkynes and the low-valent titanium reagent, generated in situ from Ti(O-*i*-Pr)$_4$ and 2 equiv of *i*-PrMgCl. These complexes can react with various electrophiles, such as aldehydes,[2] ketones,[2] imines,[3] and so on,[4] to afford a variety of di-, tri-, and tetrasubstituted alkenes. Internal alkynes are suitable substrates for this reaction, and the reports of the use of terminal alkynes are limited.[5] In addition, for a titanium complexes arising from an unsymmetrical alkyne, the reaction with ketones, unsaturated, and aromatic aldehydes indicated generally significantly high regioselectivity, which raised with increasing the steric hindrance when saturated aldehydes was used.[2]

On the other hand, organoselenium chemistry has become a very powerful tool in organic synthesis.[6] In particular, 3-phenylseleno-1-propyne **1** (propargylic selenide) and 4-phenylseleno-1-butyne **2** (homopropargylic selenide) are expected to be versatile intermediates for synthesis of polyfunctionalized compounds (Scheme 1), because several reactive moieties of them will play important roles in functional group transformations.[7,8] Those are (1) carbon–carbon bond formation via hydrometallation of a terminal triple bond, (2) formation of olefins and allylic alcohols via selenoxide elimination and [2,3]-sigmatropic rearrangement, respectively, and (3) elongation of carbon chain via abstraction of acidic protons.



1 2

Scheme 1. Terminal alkynes having a phenylseleno group.

Especially, the CH_2CH_2SePh moiety of **2** can be converted into the $CH{=}CH_2$ functional group via selenoxide elimination by oxidation, and thus is regarded as a vinylic equivalent. On the other hand, it has been reported that the reaction of conjugated enyne–titanium alkoxide complex with aldehydes gave the allenyl alcohol derivatives.[9] In this reported reaction, conjugated diene derivatives are not obtained. We herein present the efficient and facile synthetic procedure of conjugated dienes having an allylic alcohol or amine moiety, in combination with titanium–alkyne

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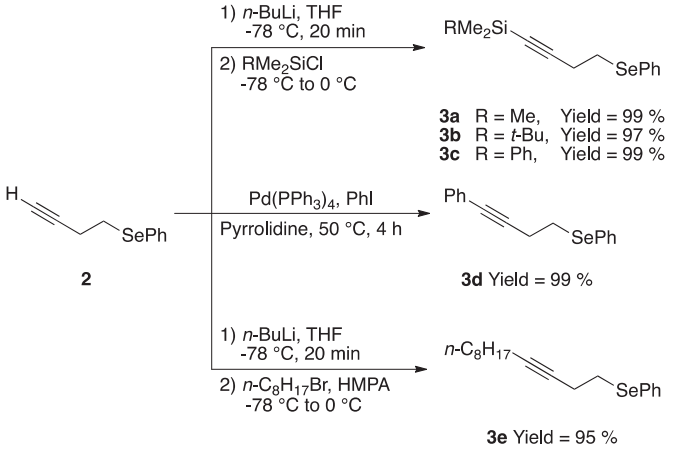
complex formation by the reaction of homopropargylic selenide derivatives with the low-valent titanium reagent and selenoxide elimination via oxidation of phenylseleno group.

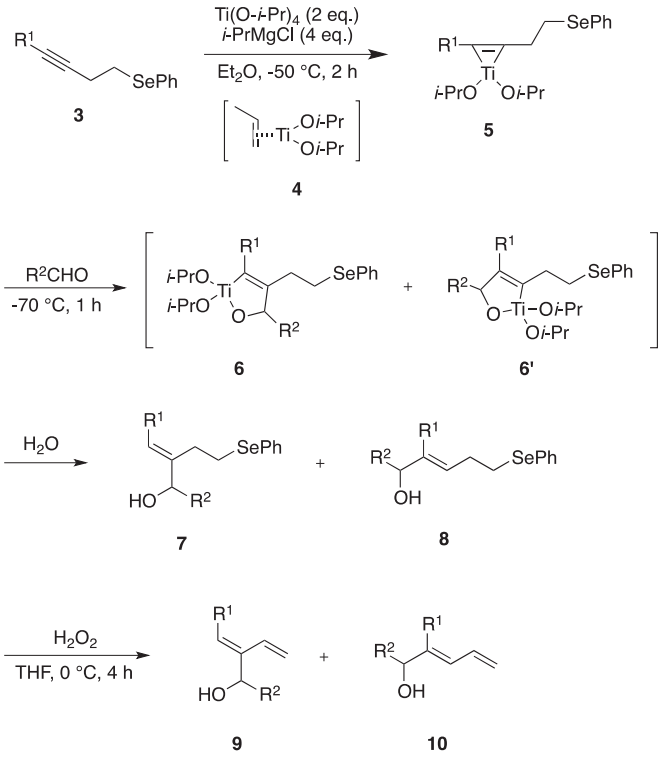
2. Results and discussion

The internal alkynes **3a**–**e** were prepared by the introduction of some groups to the terminal alkyne carbon of 4-phenylseleno-1-butyne **2** (Scheme 2). Treatment of **2** with 1.1 equiv of *n*-BuLi in THF at −78 °C generated the alkynyl anion, followed by reacting with silyl chlorides to give the corresponding silyl-substituted alkynes **3a**–**c** in excellent yields. According to Linstrumelle's procedure, the phenyl-substituted alkyne **3d** was prepared by the reaction with iodobenzene in the presence of 5 mol % of $Pd(PPh_3)_4$ in pyrrolidine at 50 °C in 99% yield.[10] The alkyl-substituted alkyne **3e** was obtained in 95% yield by abstraction of terminal acidic proton on **2** and the subsequent reaction with *n*-octyl bromide in the presence of hexamethylphosphoric triamide (HMPA).



Scheme 2. Introduction of some groups to the terminal alkyne carbon of 4-phenylseleno-1-butyne **2**.

The internal alkynes **3a**–**d** reacted with the low-valent titanium reagent **4**, generated in situ from $Ti(O\text{-}i\text{-}Pr)_4$ (2 equiv) and *i*-PrMgCl (4 equiv), in Et_2O at −50 °C for 2 h to produce titanium–alkyne complexes **5**, which were then reacted with various aldehydes at −70 °C for 1 h to give allylic alcohols **7** and **8** via oxatitanacyclopentene intermediates **6** and **6′**, respectively (Scheme 3, Table 1).[11] However, when the octyl-substituted alkyne **3e** was used as a substrate, the reaction did not proceed and the starting alkyne **3e** was completely recovered. These results are summarized in Table 1. The regioselectivity of giving products **7** and **8** was depended on both the substituent groups (R^1) of internal alkynes **3** and the steric hindrance of aldehydes. Namely, the silyl-substituted alkynes **3a**–**c** selectively underwent the addition of aldehydes at β-carbon to the silyl group to lead intermediates **6**, whereas the phenyl-substituted alkyne **3d** preferentially reacted at α-carbon to the phenyl group to give allylic alcohols **8** via intermediates **6′**, accompanying the regioisomer **7**. It was revealed that the combination of the alkynes **3a**–**c** bearing a silyl group and sterically hindered aldehydes provided allylic alcohols **7** in extremely high regioselectivity, but the selectivity decreased when primary aliphatic aldehyde was used (entries 2, 5, and 8). In the case of the alkyl-substituted alkyne **3e**, the starting alkyne was completely recovered (entries 13 and 14). This may be due to no stabilizing advantages arising from alkyl substituent influences for the complex **5**. Accordingly, the alkyne complex **5** substituted by an alkyl group was not formed from the treatment of the low-valent titanium reagent and **3e**, and the subsequent quench by H_2O afforded the starting alkyne **3e**.



Scheme 3. Synthetic transformation to conjugated diene-substituted alcohols from **3**.

The plausible mechanism for the carbotitanation of **3** with benzaldehyde is shown in Scheme 4. The titanium–alkyne complex **5** is formed by ligand exchange of coordinated propene in the low-valent titanium reagent **4** with the internal alkyne **3** (**3a**: R^1=$SiMe_3$, **3d**: R^1=Ph). When the carbonyl group of aldehydes inserts to one of the two carbon–titanium bonds, a couple of presumable oxatitanacyclopentene intermediates **A** and **B** are possible. When the silyl-substituted alkyne **3a** was used, the addition of a carbonyl carbon to the C–Ti bond at β-position to the silyl group would selectively proceed via the intermediate **A1** to prevent forming **B1** because of steric interruption between silyl and phenyl groups, followed by the treatment with H_2O to obtain the corresponding allylic alcohol **7aa**. In contrast, the complex **5** from phenyl-substituted alkyne **3d** preferentially reacted with benzaldehyde at the carbon having the phenyl group to give the intermediate **B2**, followed by treatment with H_2O to afford mainly the allylic alcohol **8da**. This notable regioselectivity is consistent with the previous reports using unsymmetrical alkynes.[1e,2]

In this way, the resulting products **7** and **8** having a phenylseleno group were oxidized by H_2O_2 in THF to give conjugated diene derivatives **9** and **10** bearing an allylic alcohol moiety in high to excellent yields via *syn* elimination of the corresponding selenoxides without isomerization of alkene (Scheme 3). The results are shown in Table 2. The structure of products **9** and **10** was identified by ^{1}H NMR analysis and that ratio of the isomers (**9**, **10**) was almost completely maintained under the oxidative deselenation conditions.

The results on the reaction of alkynes **3** with various imines instead of aldehydes as electrophiles using the low-valent titanium reagent were summarized in Table 3. In this reaction, two possible allylic amine derivatives **11** and **12** were produced. Similar to the above results using aldehydes, the reaction of the silyl-substituted alkynes **3a**–**c** with imines showed excellent regioselectivity (>96:4), of which titanium–alkyne complexes underwent electrophilic addition by imines at β-carbon to the silyl group regardless of the size of imines, to give the corresponding allylic amines **11**