1-Substituted Allenes as Precursors for Stereocontrolled Synthesis of Homoallylic Alcohols

C500 Report

Submitted by

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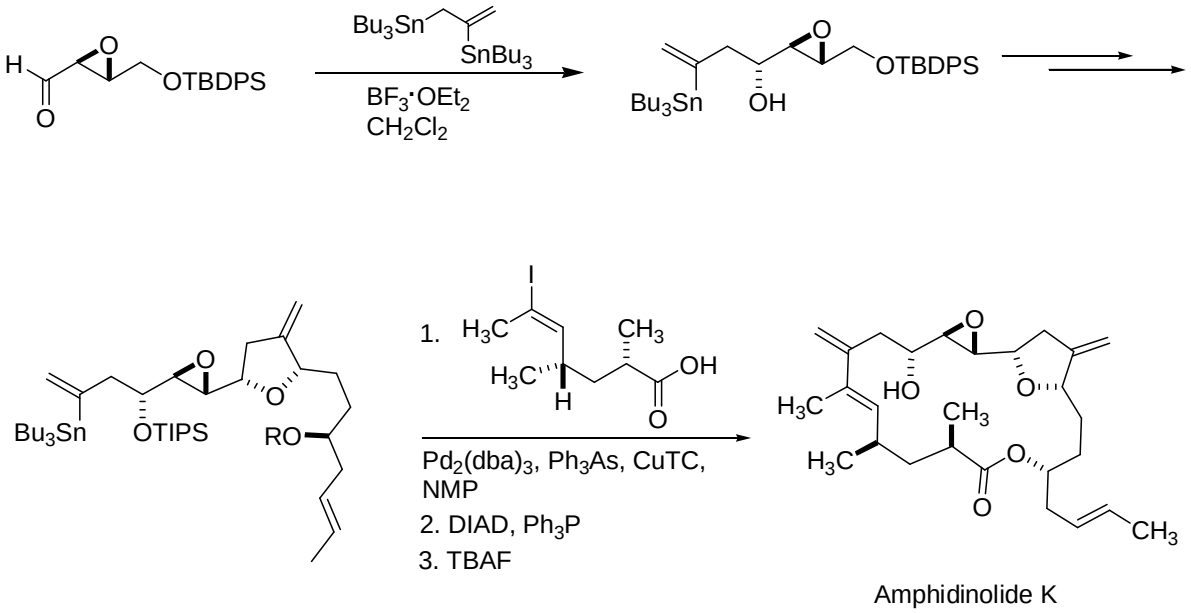
Introduction

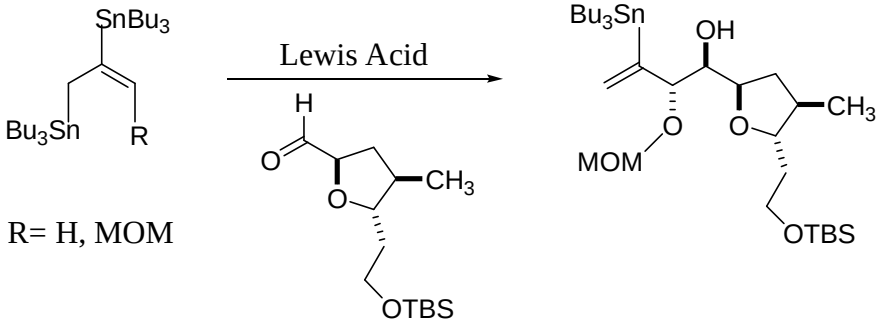
Previous studies in Williams Laboratories have developed a strategy to utilize stereocontrolled allylation reactions in tandem with Pd-catalyzed coupling to efficiently prepare complex dienes as in amphidinolide K[1] (Scheme 1).

Scheme 1.Synthesis of Amphidinolide K



Amphidinolide K

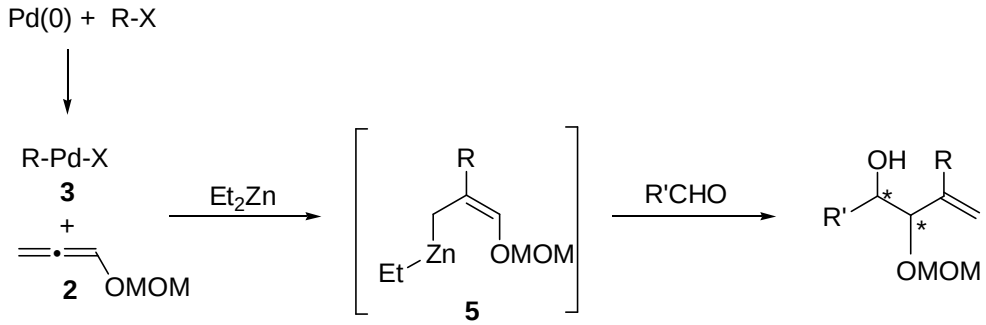
These studies were facilitated by the quantitative and facile bis-stannylation of allene[2] (Scheme 2) and its use in asymmetric allylations.[3] Recent effort has documented the use of 1-alkoxyallene as an effective precursor for regio- and stereocontrolled allylation reactions with aliphatic aldehydes.[4]



R= H, MOM

Most of the reactions involving stereocontrolled allylations have made use of group 13 and group 14 metal alkenyl substituents, using mainly boron, aluminium, tin and silicon, in order to activate the olefin towards carbonyl addition. Relatively few examples have been reported about the effect of zinc-based substituents which may offer lower toxicity but comparable reactivity compared to the metals previously used. The objective of this proposal is to examine use of an allene precursor and a zinc reagent in order to preform allyl zinc species. Reactions with aldehydes, resulting in the stereocontrolled synthesis of homoallylic alcohols, will be explored as illustrated in Scheme 3.

Scheme 3. Stereocontrolled synthesis of homoallylic alcohols

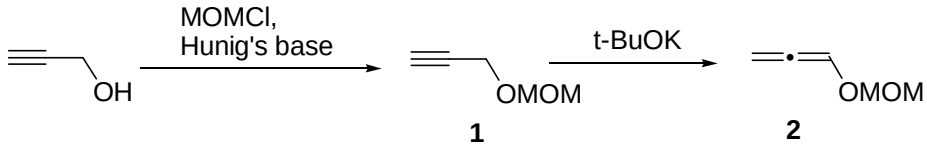


R= alkyl, aryl

Synthesis Approach

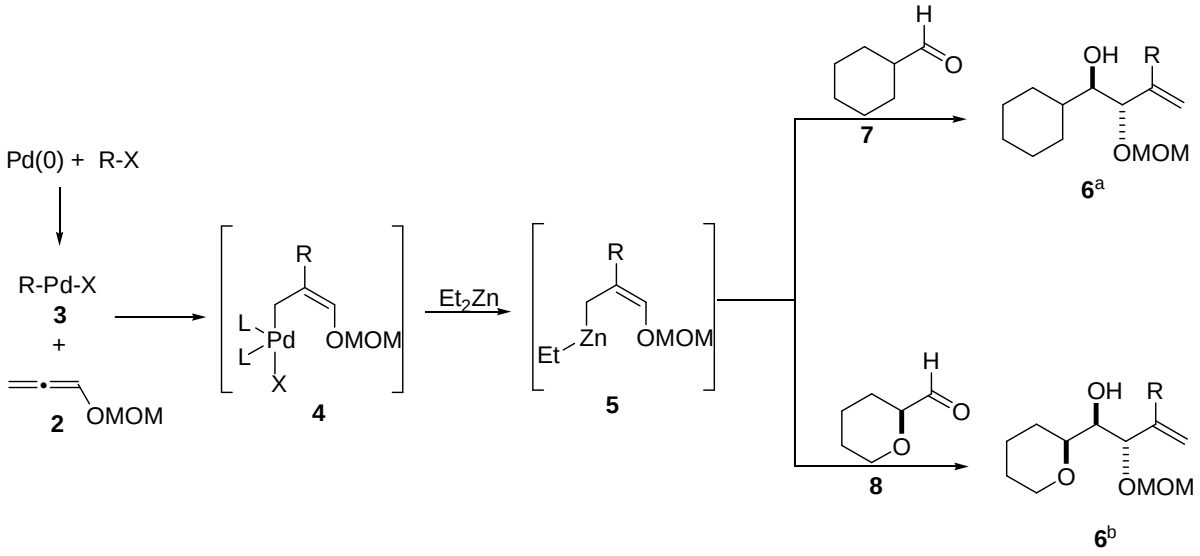
The known allene **2** has been prepared, starting with commercially available propargyl alcohol. Protection of the alcohol with MOMCl is feasible using Hunig's base to provide the MOM-ether in high yields. Treatment of neat acetal **1** with potassium *tert*-butoxide at elevated temperature gives rise to allene **2**.[5,6] (Scheme 4).

Scheme 4. Preparation of allene



Oxidative addition (Scheme 5) of a suitable organic halide with a Pd (0) complex will result in generation of palladium intermediates of type **3**.[7,8,9] The insertion reaction of **3** with a C=C double bond of the allene **2** will yield the л-allylpalladium complex **4**, which upon treatment with diethyl zinc, will result in formation of the allylzinc intermediate **5**. Subsequent treatment with aldehydes will give the homoallylic alchohols **6** having vicinal anti-diol arrangement.

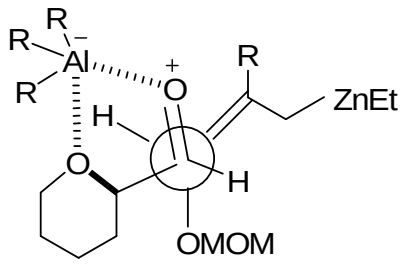
Scheme 5. Stereoslecetive synthesis of homoallylic alcohols



Two classes of aliphatic aldehydes, simple aldehydes and α-alkoxy aldehydes arerepresented as **7** and **8**. Formation of **6** is believed to occur via open transition states **9**

and **10** (Figure 1). Our studies will examine the reactivity and stereoselectivity of the overall process.

Fig.1. Proposed transition states



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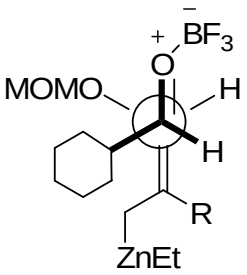

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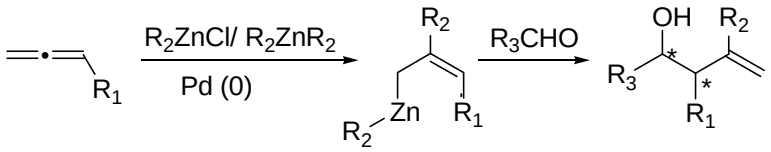
Results and discussions

The initial plan (Scheme 6) concentrated on palladium-mediated addition of alkyl zinc across the unsubstituted C=C of allene to yield the allyl zinc intermediate which upon treatment with aldehydes will stereoselectively give the homoallylic alcohol.

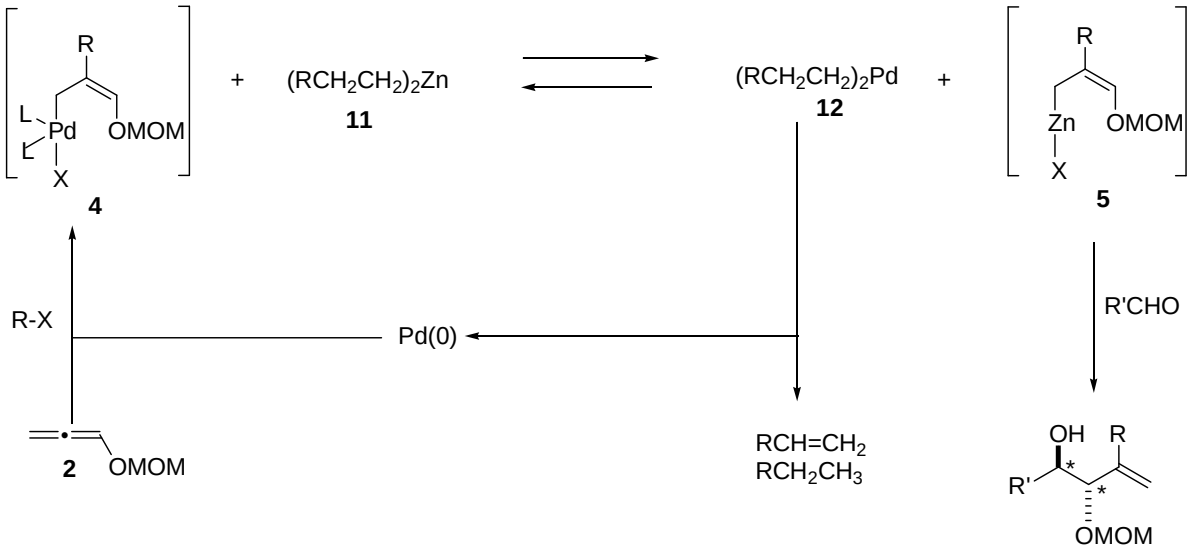
Scheme 6. Stereocontrolled synthesis of homoallylic alcohols



R_1 = alkyl, OMOM

The reaction of allene (1 equivalent) and dimethyl zinc (1 equivalent) in the presence of catalytic amount of Pd (0) at room temperature for 6 hrs resulted in no reaction and the starting material was recovered. Change in reaction conditions i.e., at 0ºC for 24 hrs, at 40ºC for 6 hrs, at 60ºC for 24 hrs had no effect on reaction outcome. Alternative use of diethyl zinc had no effect. Thus, keeping these observations in mind with related work,[11] a modified route of preparation of allyl zinc species was formulated (Scheme 5).

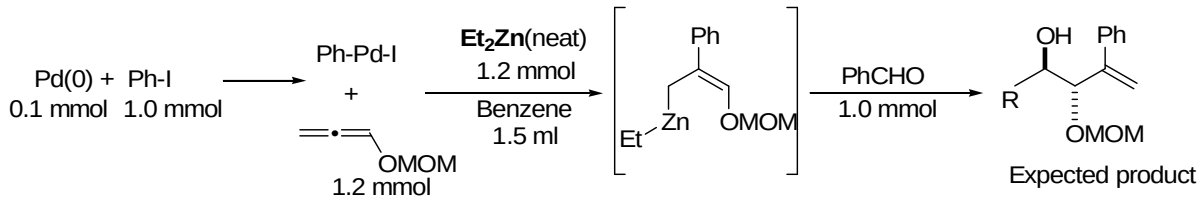
Scheme 7. Proposed Mechanism



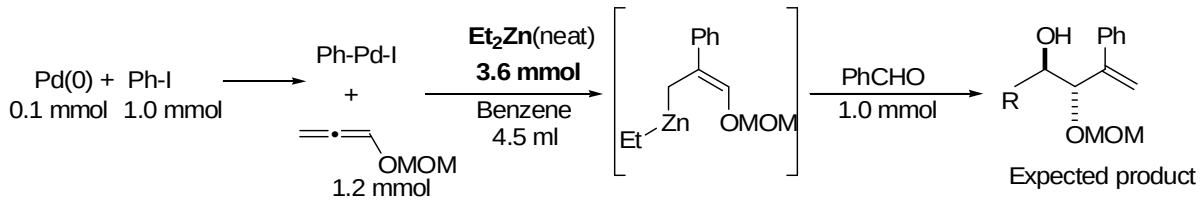
Allyl zinc species **5** is an active agent that is generated by an alkyl-allyl exchange reaction between alkyl zinc reagent **11** and л-allyl palladium species **4**. If one takes into account high thermodynamic stability of л-allyl palladium species, the equilibrium shown above will be to the left and may shift to the right either by fast consumption of alkyl palladium species **12** or allyl zinc species **5** or in the presence of excess amount of alkyl zinc.[10]

We propose to drive the equilibrium to the right by modifying the ligand X group or by making the Pd-allyl complex less stable. Following this protocol, less electron-donating ligands or more sterically hindered ligands would destabilize the palladium-allyl complex **4**. One can use Pd(o-tolPPh$_3$)$_2$ as this is a bulky ligand and may decrease the stability of Pd-allyl complexes favoring transmetallation with zinc. Another possibility may be to use Pd(PAr$_3$)$_4$ complexes where Ar = F-Ph or CF$_3$-Ph. This fine-tuning of reaction conditions could help improve the reaction. The allyl zinc intermediate **5** formed on treatment with aldehydes will stereoselectively give the homoallylic alcohols **6** having the vicinal anti diol arrangement.

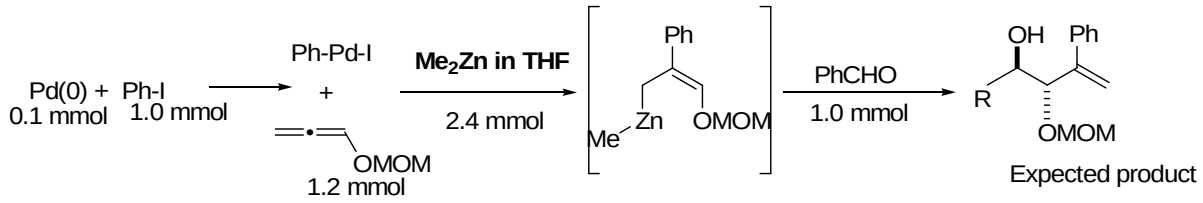
In a typical reaction procedure, the Pd (0) catalyst was added to a flame dried round bottomed flask under argon. This was followed by addition of solvent and iodobenzene, which was kept for 30 minutes at room temperature. This step was followed by addition of allene, alkyl zinc and benzaldehyde. Reactions were quenched with saturated NH$_4$Cl after 4 h and extracted with ether. The reactions were performed under three different stoichiometries as shown below: (reaction condition changes in bold)



Reaction Condition 1



Reaction Condition 2



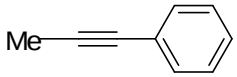
Reaction Condition 3

A common product was isolated from all the three reactions above. Diagnostic experiments were performed which are highlighted below:

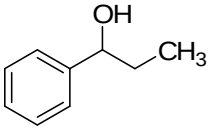
IR spectra shows a distinct broad peak at 3421 cm^{-1} indicating the presence of a **hydroxy group.**

NMR spectra shows peaks at δ 4.48 and δ 3.12 which indicates the presence of the OMOM protecting group of the starting allene. The allene has participated in a reaction as shown by the fact that the doublets at δ 5.41 corresponding to the geminal hydrogens at one terminus of the allene and the triplet corresponding to the hydrogen at the other terminus at δ 6.63 are absent. Multiplets at δ 7.3 indicates the presence of the phenyl substituent.

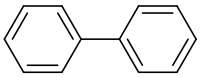
Mass Spectra show that following side products are also produced –



prop-1-ynylbenzene



1-phenylpropan-1-ol
formed by reaction of benzaldehyde with diethyl zinc



biphenyl
probably formed by free radical mechanism

Final analysis and full characterization of the compound are in progress.

Future work

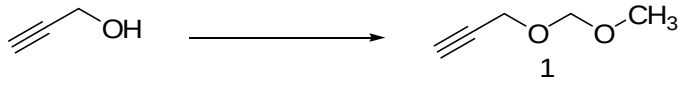
Allyl zinc derivatives can play a significant role in the stereoconvergent synthesis of natural products as exemplified by Amphidinolide K and C. Our investigations will attempt to perform *in situ* allylation reactions using reactive allylzinc species preformed from allene derivatives. Parameters which control the stereoselectivity of these reactions will be studied.

Experimental Procedures

General

Nuclear magnetic resonance spectra were obtained on either a Varian I-400 or Varian VXR-400 NMR spectrometer. All samples were dissolved in $CDCl_3$ and are reported in parts per million (δ), using residual $CHCl_3$ (δ7.26) as the internal standard.

Precoated glass backed silica gel plates (0.25 mm thick) were used for thin layer chromatography. Visualization was done with the help of Ethanolic *para*-anisaldehyde, ethanolic potassium permanganate and/or short wave UV light. Flash chromatography was performed using Kieselgel-60 (230-400 mesh) silica gel. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were freshly distilled from sodium benzophenone ketyl under Nitrogen atmosphere. Dichloromethane, hexanes, triethyl amine, diisopropyl ethyl amine and ethyl acetate were freshly distilled prior to use. All reactions were performed in flame dried glassware under an argon atmosphere unless otherwise indicated.



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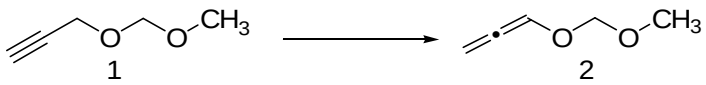
3-(methoxymethoxy)-1-propyne:

To a solution of methylene chloride (100.0ml) and methylmethoxy chloride (21.40g, 266 mmol) cooled to OºC, freshly distilled diisopropyl ethyl amine (34.4 g, 266 mmol) was added dropwise. This was stirred was stirred for 10 min before a solution of propargyl alcohol (14.91g, 266 mmol) in methylene chloride (12.5 ml) was slowly added. This was allowed to react at 0ºC and warmed to room temperature. After 16 h the reaction was quenched with water (50ml). The crude product was then washed with three 62.5-mL portions of water and three 62.5-mL portions of brine. The separated organic extract was then dried over sodium sulfate, filtered and then subjected to a fractional distillation . The fraction between 115-117ºC was collected as a yellow oil: yield 19.66g

(74%); ^{1}H NMR (400MHz, $CDCl_3$) δ 4.72 (s, 2H), 4.23 (d, J=2.4 Hz, 2H), 3.38 (s, 3H), 2.44 (t, J=2.4 Hz, 1H).



1-(methoxymethoxy)-1,2-propadiene

Potassium tert-butoxide (0.36g, 3.22 mmol) was dried under vacuum at 50ºC overnight. Protected alcohol **1** (3.22g, 32.2 mmol) was syringed in and left to stir for 1 h at 70ºC. Ice water (60 mL) and diethyl ether (30 ml) was used to quench the reaction. The crude product was then washed with three 75-mL portions of saturated aqueous sodium bicarbonate and three 75-mL portions of brine. The separated organic extract was then dried over sodium sulfate and filtered. The diethyl ether was pulled off under high vacuum using an ice bath (0ºC) and a dry ice bath (-78ºC to trap the product). The remaining reaction was not purified any further. The vacuum was removed leaving the crude product **:** yield 1.83 g (57 %) ; ^{1}H NMR (400MHz, $CDCl_3$) 6.63 (t, J= 6 Hz, 1H), 5.41 (d, J=6 Hz, 2H), 4.80 (s, 2H), 3.43 (s, 3H).

References.

1. Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765.

2. Mitchell, T. N.; Kwetkat, K.; Rutschow, D.; Schneider, U. *Tetrahedron* **1989**, *45*, 969.

3. (a) Corey, E. J.; Yu, G. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (b) Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Clark, M. P. *Tetrahedron Lett.* **1998**, *39*, 7251.

4. Williams, D. R.; Fultz, M. W. *J. Am. Chem. Soc.* **2005**, *127*, 14550.

5. Hoff, S.; Brandsma, L.; Arenes, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1967.

6. Bee, C.; Tius, M. A. *Org. Lett.* **2003**, *5*, 1681.

7. Negishi, E *Handbook of organopalladium chemistry for organic synthesis*, **Vol. 1;** Wiley-Interscience, **2002**.

8. Fitton, P.; Johnson, M. P.; McKeon, J. E. *Chem. Comm.* **1968**, 6.

9. Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233.

10. Yasui, K.; Goto, Y.; Yajima, T.; Taniseki, Y.; Fugami, K.; Tanaka, A.; Tamaru, Y. *Tetrahedron Lett.* **1993**, *34*, 7619.

11. Subburaj, K.; Montgomery, J. *J. Am. Chem. Soc.* **2003**; *125*, 11210.