



Synthesis of Substituted Allenes: A decade updates

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Abstract

The development of efficient strategy for the synthesis of allene moiety is much more challenging due to its unstable in nature. This scaffold is found in many natural products and pharmacologically active compounds. Herein, we report a review on the synthesis of this scaffold employing different starting materials such as propargyl acetates, -benzoates, -carbonates, -carboxylates, -bromides, -alcohols, -amines, *etc.*

Keywords: *Syntheis, Allene, Propargyl derivatives*

1. Introduction

Allenes are cumulated unsaturated hydrocarbons found in various natural compounds and in marketed drugs.¹ These are the building blocks for a variety of potentially useful carbocycles and heterocycles.² Functionalized allenes are showing various activities as mechanism-based enzyme inhibitors, cytotoxic or antiviral agents.^{1b} These allenes are also important synthetic target because of their prevalence in huge number of optoelectronic materials.³ Moreover, functionalized allenes are the potent precursors of various valuable hydrocarbons.^{4,5} Generally, allene group contains three C-atoms in which one *sp* carbon atom is attached with two *sp*² carbon atoms. In terms of the stereochemical aspect the molecule possesses an axis of chirality if attached four groups are different as shown in Fig 1.

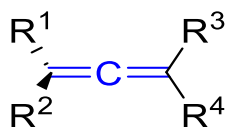


Fig. 1 Stereochemical aspects of allene core moiety

In addition, functionalized allenes are obtained from various natural sources (Fig. 2) such as heterocycles containing quinone and furan derivative of allenes are obtained from the bark of the tree *Brosimum acutifolium* and roots of the tree *Carlina acaulis* respectively. Moreover, allenic nucleoside analogues containing cytallene and adenallene act as cytotoxic and antiviral agents.^{1b}

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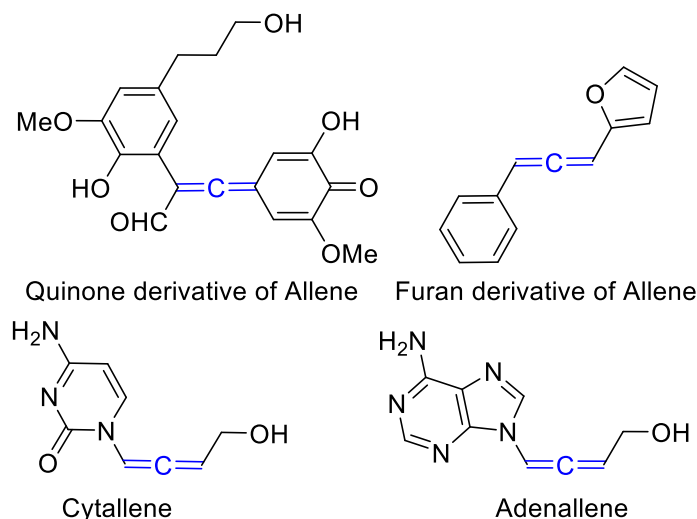


Fig. 2 Naturally occurring heterocycles containing allene core moiety

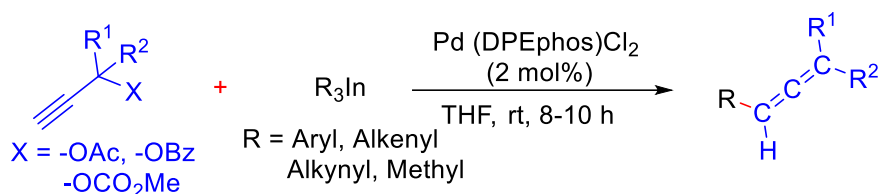
Synthesis of multi-substituted allenes has been gained much interest due to their wide range of applications in the fields of medicinal as well as industrial aspects among the researchers for a long period. The development of a novel and efficient strategy for the synthesis of this moiety is much more challenging due to its unstable in nature. A brief review is discussed herein for the formation of multi-substituted allenes and the results are summarized according to the type of reactant.

2. Synthesis of Multi-Substituted Allenes in terms of the reactants

2.1. From Propargyl Esters

2.1.1. From Propargyl -acetates/-benzoates/-carbonates

In 2006, Sestelo *et al.* reported the synthesis of tri-substituted allene from propargylic esters (*e.g.* propargylic acetates, -benzoates and -carbonates) with triorganoindium reagents in the presence of dichlorobis(diphenylphosphinophenyl)-ether palladium [Pd(DPEphos)Cl₂] as catalyst in THF solvent at room temperature for 10-12 h (Scheme 1).⁶ The reaction was followed by the S_N2' type pathway *via* palladium-catalyzed cross-coupling reaction of triorganoindium compounds with propargylic esters.

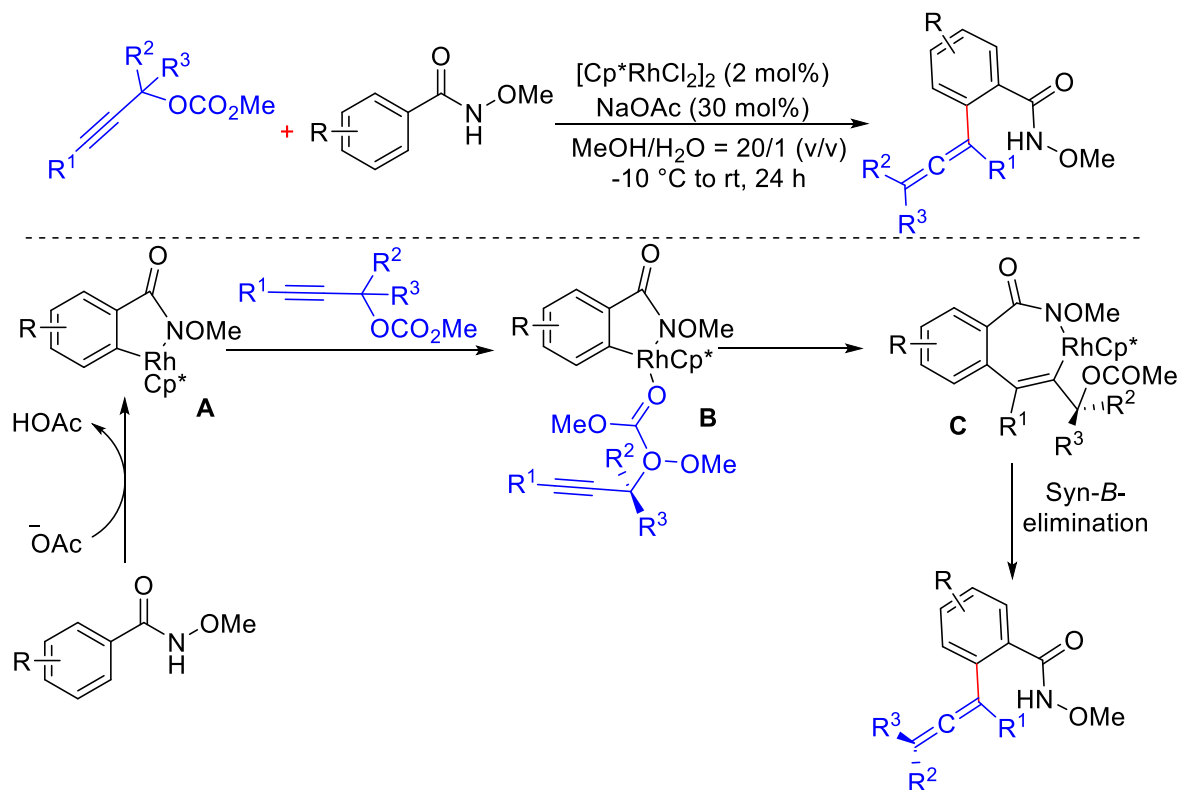


Scheme 1. Synthesis of allene from propargylic esters

2.1.2. From Propargyl Carbonates

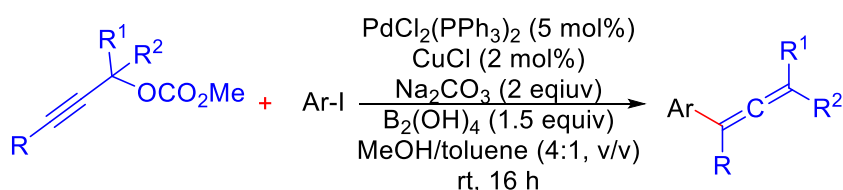
In 2015, Ma group developed an approach for the synthesis of tetra-substituted chiral allenes from propargyl carbonates and *N*-methoxybenzamide with [Cp*₂RhCl₂]₂ and NaOAc in

MeOH/H₂O (v/v 20:1) at -10 °C to room temperature for 24 h (Scheme 2).⁷ Plausible mechanism was proposed as the arenes would form rhodabicyclic intermediate **A** which is followed by coordination with the carbonyl oxygen of the carbonate forming intermediate **B**. Then alkyne moiety was directed by the carbonyl group in propargyl carbonate *via* 'reversed' regioselective insertion to prepare intermediate **C** with the carbonyl oxygen-coordinated rhoda-tricyclic. Finally intermediate **C** formed the final allenylated product *via* *syn*- β -oxygen elimination.



Scheme 2. Synthesis of allene from propargyl carbonates.

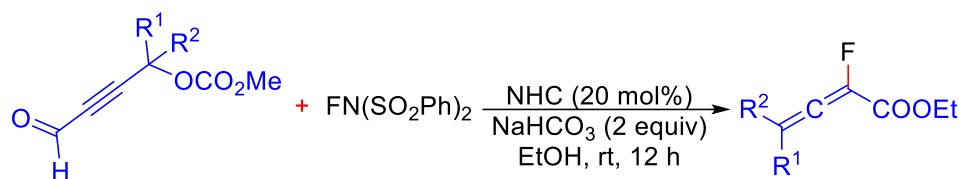
In the same time, Szabá *et al.* reported the synthesis of allenes by Pd and Cu catalyzed coupling of propargyl carbonates with aryl iodides in presence of diboron species.^{5a} The reaction was performed between propargyl carbonates, aryl iodides and diboron with 5 mol% PdCl₂(PPh₃)₂, 2 mol% CuCl and Na₂CO₃ as base in MeOH:Toluene (4:1) at room temperature for 16 h (Scheme 3).



Scheme 3. Synthesis of allene from propargyl carbonates.

In the next year, Wang group developed α -fluoroallenoate synthesis *via* *N*-heterocyclic carbene (NHC)-catalyzed reaction of alkynals.^{5b} This reaction was performed between

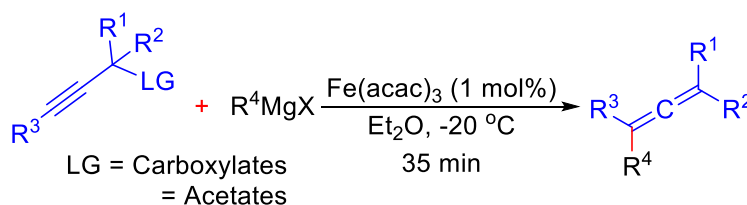
propargyl carbonates and NFSI with pre-catalyzed *N*-heterocyclic carbene and NaHCO₃ as base in ethanol at rt for 12 h (Scheme 4).



Scheme 4. Synthesis of allene from propargyl carbonates.

2.1.3. From Propargyl Carboxylates/Acetates

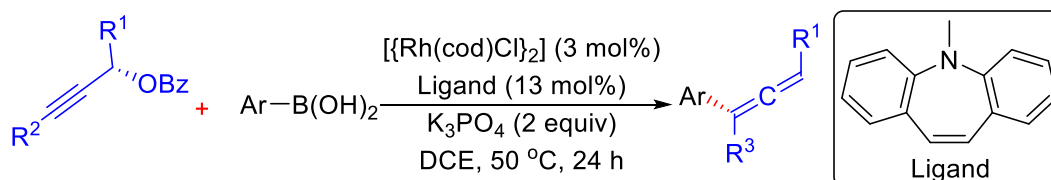
In 2016, Bäckvall group communicated iron-catalyzed cross-coupling reaction between propargyl esters (carboxylates or acetates) and Grignard reagents for the synthesis of substituted allenes.^{1a} The reaction was performed in the presence of Fe(acac)₃ as catalyst, in diethyl ether (Et₂O) at -20 °C for 35 minute (Scheme 5). The reaction pathway is proposed as syn or anti S_N2' attack by an organoiron intermediate.



Scheme 5. Synthesis of allene from propargyl esters

2.1.4. From Propargyl Benzoates

At the similar time, Carreira group communicated Rh-catalyzed synthesis of allenes from propargyl benzoates and arylboronic acids.^{5c} The reaction was carried out using catalytic amount of [{Rh(cod)Cl}₂] and K₃PO₄ as a base in DCE at 50 °C for 24 h (Scheme 6).

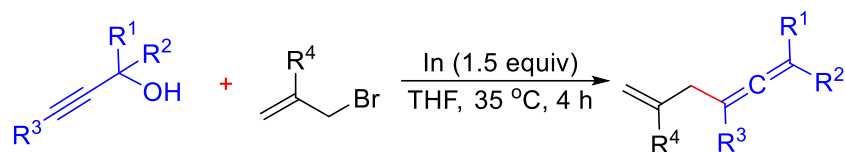


Scheme 6. Synthesis of allene from propargyl benzoates with aryl boronic acids

2.2. From Propargyl Alcohol

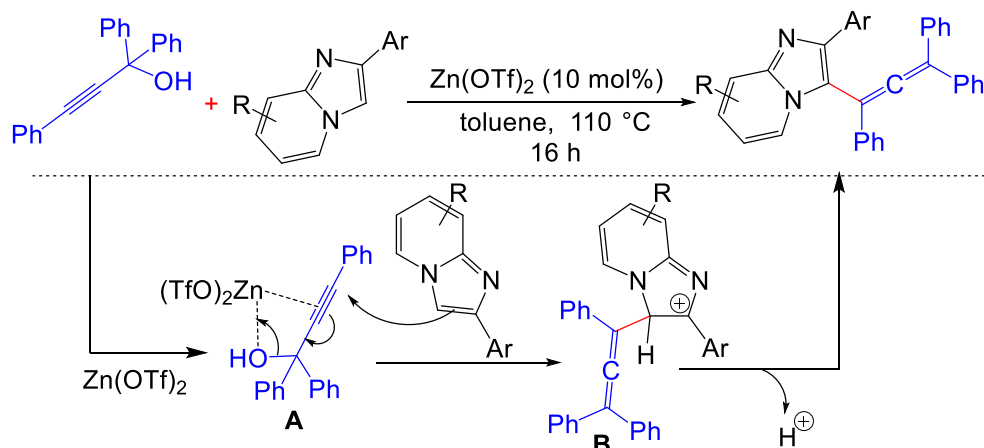
In 2008, Lee group reported the synthesis of multi-substituted allenes having an allyl and methallyl group from propargylic alcohol with allylic halide in the presence of Indium

catalyst in THF at 35 °C for 4 h (Scheme 7).⁸ The mechanistic pathway for this methodology was predicted through S_N2' nucleophilic substitutions of propargylic electrophiles with organometallic reagents.



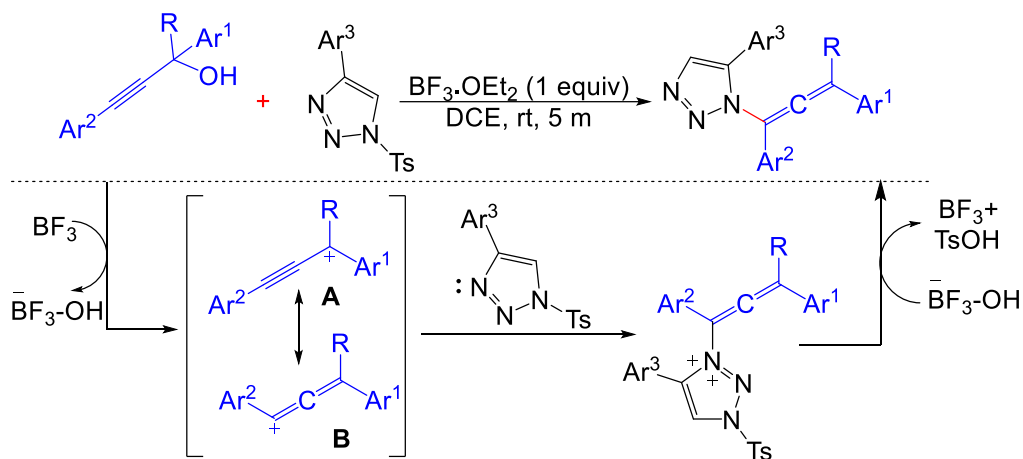
Scheme 7. Synthesis of allene from propargylic alcohol and allylic halide

In 2016, Hajra group disclosed a metal catalyzed synthesis of tetra-substituted allenes. The reaction was carried out by taking 8-methyl-2-phenylimidazo[1,2-*a*]pyridine and 1,1,3-triphenylprop-2-yn-1-ol in presence of Zn(OTf)₂ as catalyst in toluene at 110 °C for 16 h (Scheme 8).⁹ The methodology is successfully extended to other heterocyclic scaffolds like imidazo[1,2-*a*]pyrimidine, imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]thiazole. The reaction pathway of this protocol is mentioned as initially the intermediate **A** is formed from 1,1,3-triphenylprop-2-yn-1-ol in the presence of Zn(OTf)₂. Subsequently imidazoheterocycles reacted with the intermediate **A** to form the intermediate **B** through S_N2' type attack. Finally corresponding allenylated product was obtained from the intermediate **B** by the elimination of proton.



Scheme 8. Synthesis of tetra-substituted allene from propargylic alcohol

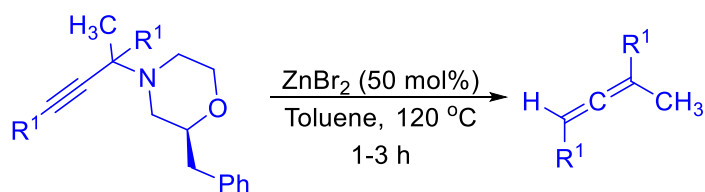
Very recently, in 2017, Lu and Wang *et al.* disclosed metal free synthetic approach for the preparation of multi-substituted allenes from propargyl alcohol and 1-sulfonyl-4-aryl-1,2,3-triazoles with BF₃·OEt₂ in DCE at room temperature for 5 minute (Scheme 9).¹⁰ A plausible mechanism is proposed as BF₃ could polarize the C–O bond of propargylic alcohol and to form stable propargylic carbocation intermediate **A** which can stabilize allenic carbocation **B** by resonance. After that intermediate **B** was trapped by 1-tosyl triazole to generate intermediate **C**. Finally, the desired allenylated product was formed by the elimination of TsOH.



Scheme 9. Synthesis of substituted allene from propargyl alcohol

2.3. From Propargyl Amines

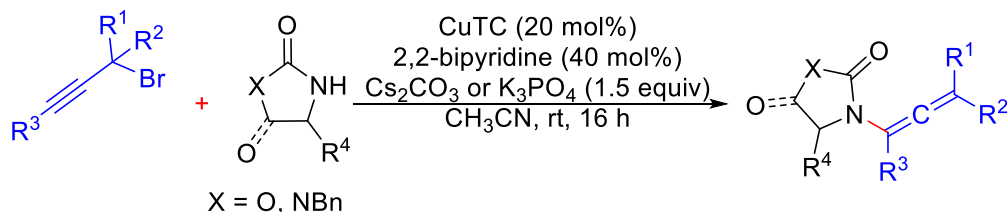
In 2016, Periasamy *et al.* communicated synthesis of trisubstituted chiral allenes by chiral propargyl amines.¹¹ The reaction was carried out between chiral propargyl carbonates with ZnBr₂ in dry toluene at 120 °C between 1-3 h (Scheme 10).



Scheme 10. Synthesis of allene from propargyl amines

2.4. From Propargyl Bromides

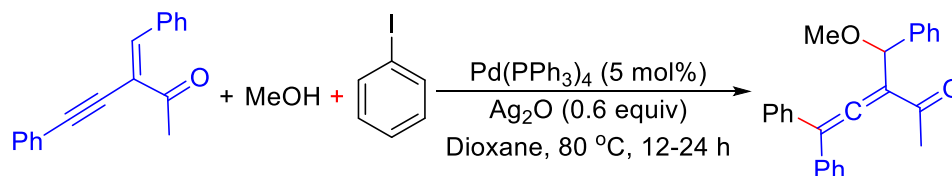
In the same year (2016), Evano *et al.* reported Cu-catalyzed synthesis of substituted allenamides.^{5d} Substituted allenamides were synthesized by the coupling between propargyl bromides and nitrogen nucleophiles with catalytic amount of CuTC, 40 mol% 2,2-bipyridine as ligand and 1.5 equiv of base such as Cs₂CO₃ or K₃PO₄ in acetonitrile at room temperature for 16 h (Scheme 11).



Scheme 11. Synthesis of allene from propargyl bromide

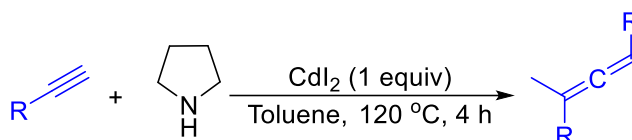
2.5. From other Sources

Zhang group developed the synthesis of tetra-substituted allenes *via* Pd catalyzed three components tandem Michael addition/cross-coupling reaction in 2009.^{5e} In this methodology allenes were prepared by electron-deficient enynes with nucleophiles and aryl halides. The reaction was catalyzed by Pd(PPh₃)₄ with Ag₂O as base in 1,4-dioxane solvent at 80 °C for 12- 24 h (Scheme 12).



Scheme 12. Synthesis of allene from three component tandem Michael addition reaction

In 2015, Ma *et al.* reported the synthesis of trisubstituted allenes having a methyl group from terminal alkyne and cadmium iodide in toluene at 120 °C for 4 h.^{5f} Trisubstituted allenes were prepared by tandem reaction involving two molecules of terminal alkynes and imine *via* methyl ketoniminium and propargylic amine formation (Scheme 13).



Scheme 13. Synthesis of allene from terminal alkyne

3. Conclusion and Future Research Agenda

During the last decade significant developments have been made on the synthesis of tetra-substituted allenes. Most of these methods have been carried out employing with propargyl acetates/-carbonates/-benzoates/-bromides/-alcohol and in few cases electron deficient enynes and alkynes are also used as the coupling partner to produce allene scaffold. All of these developed methodologies exhibit high efficiency and selectivity. Therefore, the syntheses of allenes having different substituents have been drawn much attention of chemists over a long period. We believe that the strategies of these methodologies will be very useful for the construction of the allene moiety.

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