

Das Reagenz · The Reagent

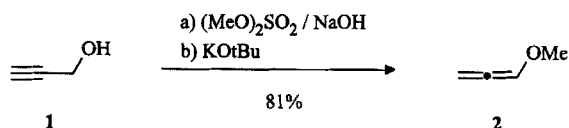
Methoxyallene: A Reagent of Versatile Applications in Organic Synthesis

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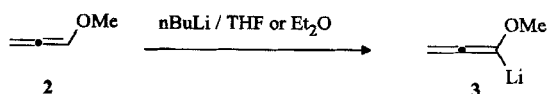
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Since the first preparation of methoxyallene (**2**) by Hoff, Brandsma and Arens in 1968 [1], this compound with cumulated C=C bonds has emerged as a useful and convenient C3-building block for many transformations commonly performed in organic synthesis [2]. Methoxyallene (**2**) is easily accessible by a two-step reaction sequence starting from propargyl alcohol (**1**) [1, 3]. The compound is a colourless liquid (bp. 51–52 °C/760 Torr), and its chemical behaviour is similar to a „normal“ enol ether (e.g. the sensitivity towards acidic hydrolysis). In the meantime, methoxyallene (**2**) is a commercially available reagent.



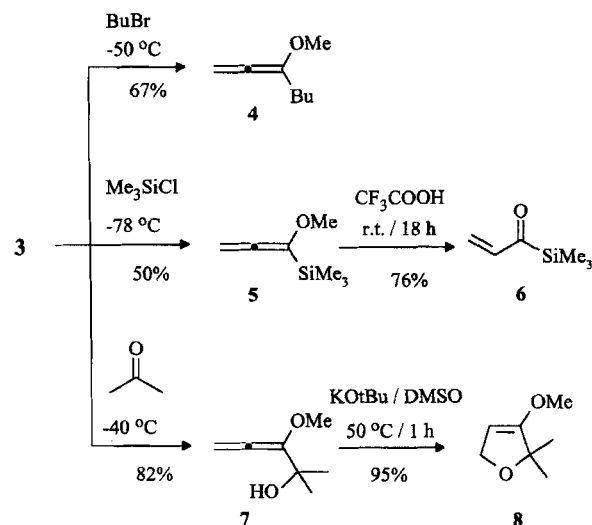
One of the key features of methoxyallene (**2**) is the smooth deprotonation of the hydrogen atom at C-1 leading to the 1-lithio-1-methoxyallene (**3**) [3, 4]. The broad utility of the lithiated intermediate **3** for synthesis is apparent from the wide ranging applications that are known in the literature [2]. The species **3** is reactive enough towards a variety of electrophiles, like alkyl halides, chlorotrimethylsilane or carbonyl compounds etc. [1, 5, 6]. A subsequent hydrolysis of methoxyallene derivatives can be easily performed under acidic conditions to produce an α,β -unsaturated carbonyl compound (**5**→**6**) [5]. On the other hand, C-1-hydroxyalkylated methoxyallene derivatives like **7** are cleanly cyclised to the corresponding 2,5-dihydro-3-methoxyfuran [7]. This methodology has been successfully applied to the



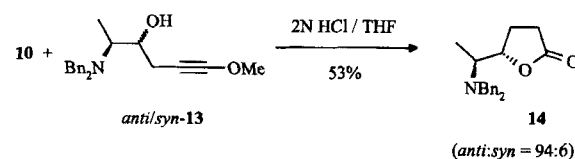
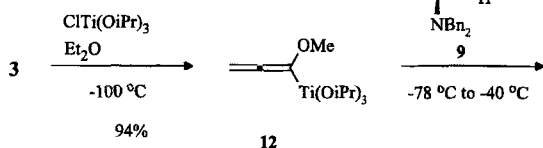
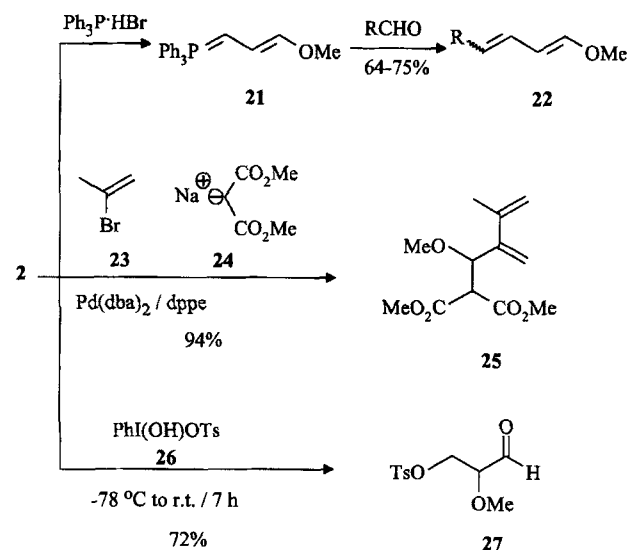
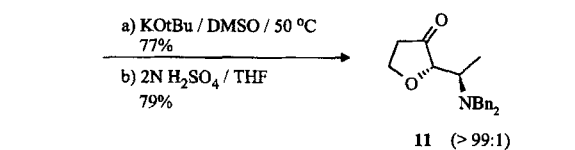
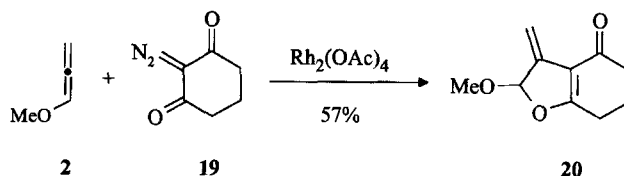
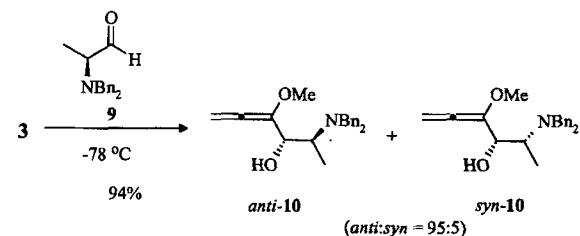
stereoselective synthesis of 3(2H)dihydrofurans, e.g. **3**→**10**→**11** [8].

Starting from methoxyallene (**2**) the methoxyalkyne derivative **13** can be prepared by lithiation under standard conditions, transmetalation with $\text{TiCl}(\text{OiPr})_3$ followed by addition of the in situ generated titanium species **12** to the α -aminoaldehyde **9** [9]. The observed regioselectivity is good (**13**:**10** = 91:9), and the resulting *anti/syn*-selectivity of **13** is high (94% *anti*). The subsequent cyclisation of **13** under acidic reaction conditions yielded the γ -lactone **14** [9].

Furthermore, methoxyallene (**2**) can also serve as the dienophile component in inverse electron demand hetero-Diels-Alder reactions with different heterodienes **15** to give regioselectively the corresponding heterocycles **16** [10]. For example, using the in situ generated nitrosoalkene **17**, the [4+2]-cycloaddition leads to the trifluoromethyl substituted 1,2-oxazine **18** in excellent yield [10c]. On the other hand,

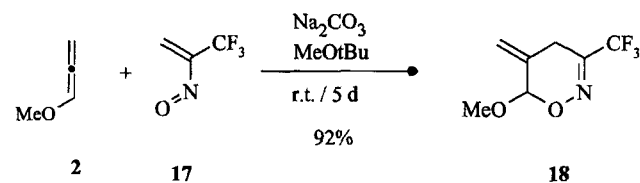


employing the diazocyclohexane-1,3-dione (**19**) allows the dipolar cycloaddition of **2** to produce regioselectively the tetrahydrobenzofuran derivative **20** in 57% yield [11].



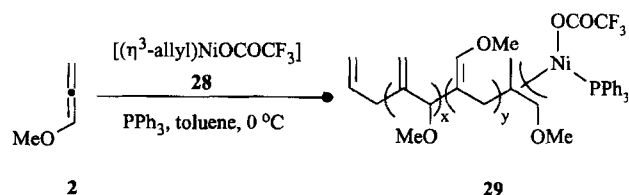
X, Y = C atom; A, B = C atom or heteroatom

For example:



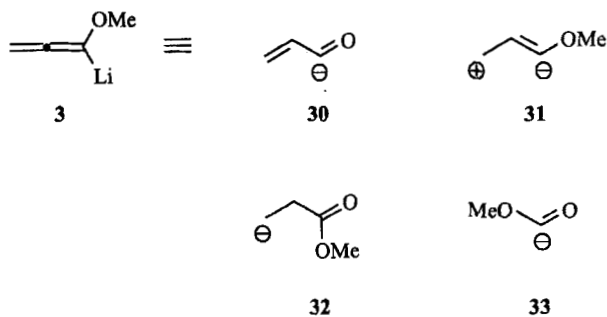
A number of other reactions involving methoxyallene (**2**) as reagent are well known [2]. 4-Substituted 1-methoxy-1,3-dienes **22** (R = Ph, n-Hex, cyclohexyl) are synthesized as a geometric mixture from **2** by sequential treatment with triphenylphosphonium bromide followed by the reaction

with an aldehyde [12]. Carbopalladation of **2** has been achieved with 2-bromo propene (**23**), dimethyl malonate **24** and catalytic amounts of a palladium catalyst [13]. Recently, it has been demonstrated that the allene **2** can be transformed into the 2-methoxy-3-tosyloxypropanal (**27**) by oxidation with the hypervalent iodine compound **26** [14].



Finally, methoxyallene (**2**) is also an attractive monomer to produce reactive polymers bearing exo-methylene moieties in the side chain [15]. For example, in the polymerisation of **2** at the feed ratio of $[\mathbf{2}/\mathbf{28}] = 205$, polymer **29** was obtained in 90% yield, and its number-average molecular weight (M_n) was established as 18 100.

In summary, the methoxyallene (**2**) has found wide applications in synthetic organic chemistry as a useful reagent leading to a number of interesting products such as dihydrofuran derivatives or α,β -unsaturated carbonyl compounds. Besides this, compound **2** serves also as a potent 2π -component in cycloaddition reactions to give synthetically interesting six-membered heterocycles. The lithiated methoxyallene intermediate **3** represents a useful equivalent for several synthons, e.g. **30** (α,β -unsaturated acyl anion equivalent), **31** (dipolar synthon), **32** (homoenolate equivalent), and **33** (formyl ester anion synthon) etc.



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