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Addition of Chloroprene Grignards to Aromatic Aldehydes: Synthesis of Homoallenyl Alcohols

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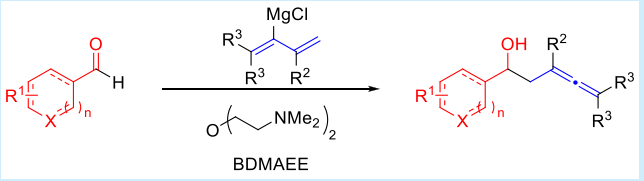
ABSTRACT: A general procedure for the one-pot synthesis of racemic homoallenyl alcohols from the corresponding aldehyde and chloroprene-derived Grignards is described. Employing bis[2-dimethylaminoethyl]ether (BDMAEE) as an additive at low temperatures shifts the selectivity of the chloroprene Grignard addition to aldehydes such that it is almost exclusive toward allene formation. In a set of follow-up experiments, simple and more elaborate methods for further derivatization have been demonstrated, allowing quick access to more complex structures.



Transition-metal-catalyzed allyic addition to allenes has proven to be a high-performing alternative to the related allylic substitution reaction.[1] In particular, the homoallenyl alcohol is a valuable building block in organic synthesis,[2,3] as demonstrated in our recent synthesis of rosuvastatin and pitavastatin.[4] The preparation of homoallenyl alcohols, however, remains challenging, and practical protocols are scarce.[5]

For laboratory purposes, the Crabbé reaction[6] and its further developed forms[7] offer access to a broad range of terminal allenes from the corresponding terminal alkyne. The same can be achieved by chemoselective propargylic substitution with aluminum hydride[8] or via copper catalysis.[9] Quantitative waste and structural prerequisites make these approaches undesirable, yet sometimes necessary because of their flexibility. Conversely, rearrangement reactions allow for the efficient synthesis of homoallenyl esters[10] and aldehydes.[11] However, due to the nature of the rearrangement reaction, the structural flexibility of this approach is limited. More direct homoallenylation protocols of a carbonyl compound with suitable precursors have been recently reported.[12] These partially enantioselective methods rely on toxic stannane or chromium reagents, require a surplus of allenic precursor, or, in case of 2-borylbuta-1,3-dienes, have to be synthesized in an expensive multistep procedure.[13]

Regarding the described problems, we envisioned a simple procedure for the γ-selective addition of a suitable 1,3-diene to a carbonyl compound as the most applicable and straightforward approach for the synthesis of homoallenyl alcohols. Among the typically polymerization labile 1,3-diene pronucleophiles, we chose 2-chlorobuta-1,3-diene (chloroprene), due to its industrial availability,[14] which can be conveniently converted into a Grignard reagent.[15]

2-(1,3-Butadienyl)magnesium chloride (chloroprene Grignard) was reported by Kondo and Matsumoto to react with carbonyl compounds to form a mixture of homoallenyl alcohol **2a** and 1,3-diene **3a** (entry 1, Table 1).[16] A regioselectivity study of the chloroprene Grignard addition reaction by Yamashita and Nunomoto revealed the influence of different parameters, yet a reliable method for selective allene formation in contrast to scarcely separable mixture of isomers was not found.[17]

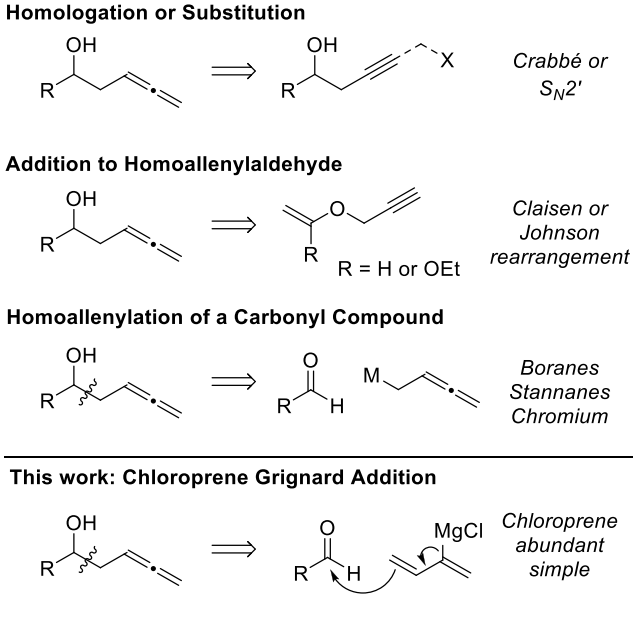


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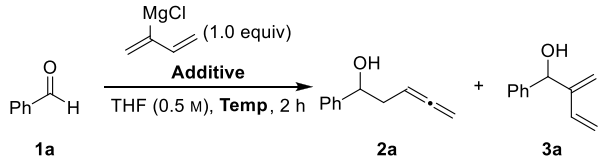
Table 1. Optimization of the Chloroprene Grignard Addition towards Homoallenyl Alcohol Selectivity[a,b]



entry	temp	additive	yield	2a	3a
1[16]	rt		73	1.6	1
2	−78 °C		99	5.7	1
3	−78 °C	BDMAEE (1 equiv)	95	6.7	1
4	−78 °C	BDMAEE (2 equiv)	98	>20	1

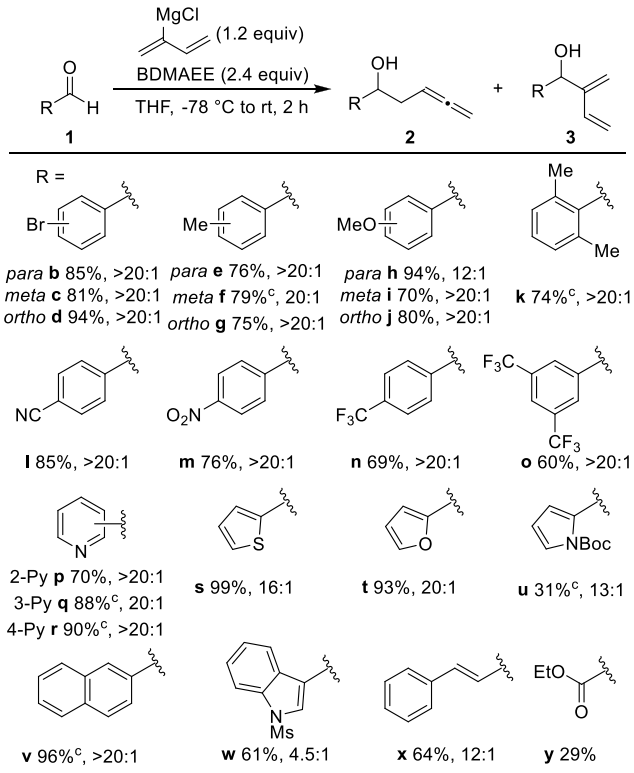
[a]The ratio of isomers **2**:**3** was determined from the crude ^{1}H NMR. [b]Isolated yield.

Taking into consideration that different parameters and additives, such as neutral or anionic ligands, are capable of impacting the reactivity and selectivity of Grignards,[18] we conducted a screening of different additives and reaction conditions to favor allene formation (Table 1).[19] A 2 equiv portion of of bis[2-dimethylaminoethyl]ether (BDMAEE), a well-known additive for decreasing Grignard reactivity by coordination,[20] as well as a reaction temperature of −78 °C, gave the allene **2a** in excellent yields, while the formation of undesired **3a** was suppressed almost entirely (entry 4).

For this reaction, different aromatic aldehydes were tested (Scheme 1). It was found that a slight excess of Grignard and additive further enhances the already good results. Different brominated substrates **1b−d** gave good to very good yields and selectivities. No significant side reaction was observed. For the tolyl aldehydes **1e−g**, the best selectivity was achieved for the *ortho* substrate. The electron rich **1h**, with the strongly donating methoxy group in the *para* position, gave less good regioselectivity. In comparison to the influence of the *meta* and *ortho* substrate, this effect fades. In contrast, **1l−o** performed in the Grignard addition with almost perfect regioselectivity due to their electron-withdrawing character. We were pleased to find the cyano group in **1l** remained intact under the reaction conditions. Trifluoromethyl aryl substituted allenes **2n** and **2o** were obtained in almost perfect selectivity with moderate yield. Next to pyridine carbaldehydes, which gave good results, other heterocycles were subjected to the reaction conditions. The electron rich heterocycles **1s** and **1t** produced excellent yields of allene along with small amounts of diene. Transformation of protected pyrrole **1u** gave only a small amount of allene, partially due to deprotection under the reaction conditions. **1v**, which is similar to **1a**, was converted into the allene **2v** in excellent yield and selectivity. Indole **1w** gave only moderate yields and lacked selectivity. *trans*-Cinnamon aldehyde was found to give moderate yields with a small contamination from **3x**. Aside from ethyl glyoxalate **1y**, which resulted in 29% **2y** without any **3y**, other aliphatic aldehydes did not give a significant amount of allene products. Aliphatic carbonyl compounds, in general, were found to be low-yielding and unselective in the described reaction with chloroprene Grignard.

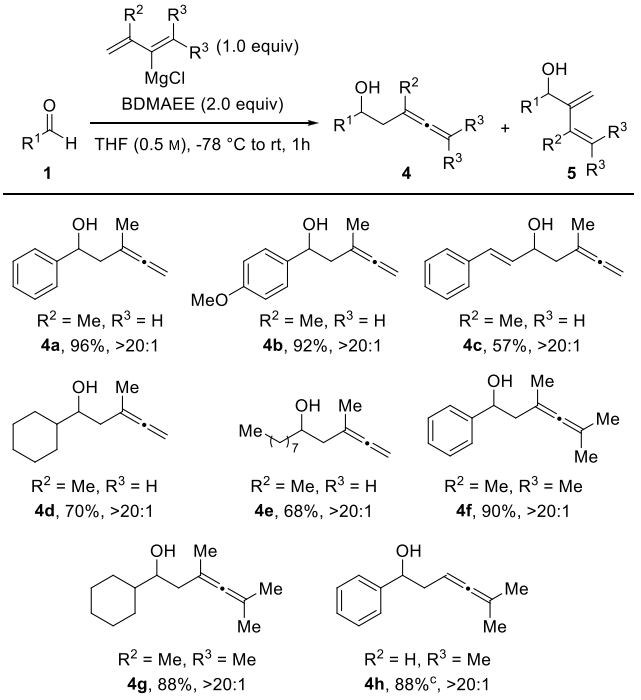
Substituted chloroprene Grignards were synthesized and tested in the reaction with aldehydes (Scheme 2). Compound

Scheme 1. Scope for the Chloroprene Grignard Addition to Different Aldehydes[a,b]



[a]Combined yield. [b]The ratio of isomers **2**:**3** is shown after the yield and is determined from the crude ^{1}H NMR. [c]Grignard (1.0 equiv), BDMAEE (2.0 equiv).

Scheme 2. Addition of Substituted Chloroprene Grignards to Different Aldehydes[a,b]



[a]Major product is depicted showing the combined yield. [b]The ratio of isomers **4**:**5**, shown after the yield, is determined from the crude ^{1}H NMR. [c]BDMAEE (4.0 equiv) was used.

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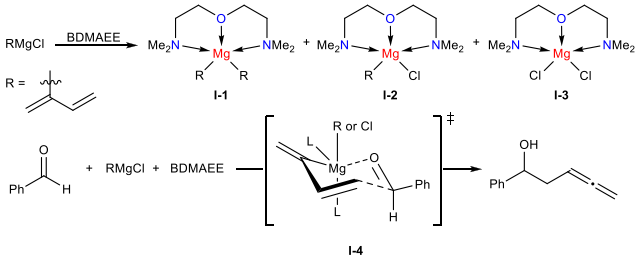
4a was obtained in excellent yield and selectivity from benzaldehyde (**1a**). With the encouragement from these results, challenging substrates **1h** and **1x** were transformed into **4b** and **4c** in excellent allene selectivity. In contrast to unsubstituted chloroprene Grignard, aliphatic allenes **4d** and **4e** were obtained in good yields and excellent selectivity. Following the standard procedure, 1,1,3,3-tetrasubstituted allenes **4f** and **4g** were synthesized in excellent yield and selectivity, with the latter demonstrating compatibility with aliphatic aldehydes. Synthesis of the 3,3-substituted allene **4h** required 4.0 equiv of BDMAEE to push selectivity to almost exclusive allene formation.

While the positive impact of BDMAEE for the selectivity in the chloroprene Grignard addition to aldehydes has been clearly demonstrated, the role of the additive in the reaction remains unconfirmed. Da[20b] and Wang[20d] assigned BDMAEE the role of a chelating ligand for magnesium to form the intermediates **I-1**, **I-2**, and **I-3** from the Schlenk equilibrium. As a consequence, the overall reactivity is decreased, primarily due to the reduced catalytic potential of $MgCl_2$ (Scheme 3).

Scheme 3. Proposed Mechanism

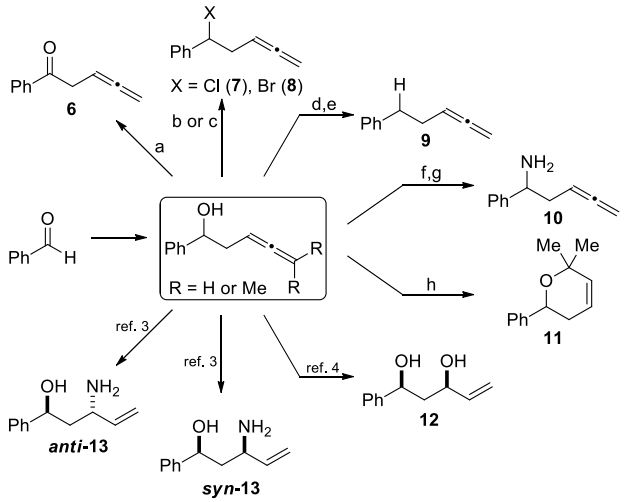


The decrease in reaction rates[21] and better differentiation of competing transition states[22] lead to the observed increase of selectivity. In accordance with recent studies,[22c] a six-membered transition state **I-4** is proposed that results in selective allene formation by allylic addition.

Finally, substrates **2a** and **4h** were subjected to different follow-up reactions (Scheme 4). Selective oxidation with DMP gives ketone **6**. Chlorination with $SOCl_2$ or bromination with PBr_3 afforded halides **7** and **8** in good yields. From the procedure reported by Barton and McCombie, deoxygenation was achieved leaving the allene functionality intact.[23] The transformation of the alcohol group into amine **10** was achieved by the Mitsunobu reaction towards the corresponding azide, which is followed by Staudinger reduction to the primary amine **10**. A gold-catalyzed cycloisomerization of **4h** according to Krause yielded dihydropyran **11** in 90% yield.[24] Furthermore, our group previously described methods that employ the alcohol group for the formal diastereoselective introduction of an amine[3] or alcohol[4] group, leading to the valuable *syn*-allylic alcohol **12** or the aminoalcohols *syn*- and *anti*-**13**.

In summary, we successfully developed a cheap, facile, and high-yielding method for the synthesis of homoallenyl alcohols and substituted homoallenyl alcohols from abundant aromatic aldehydes and the chloroprene-derived Grignard reagents. The obtained racemic homoallenyl alcohols were demonstrated to be further modified easily and therefore allow access to structural motives that are far more difficult to obtain following classical procedures.

Scheme 4. Follow-Up Reactions for Homoallenyl Alcohols[a]



[a]Reaction conditions: (a) DMP (1.1 equiv), DCM, 0 °C to rt, 16 h, 86%; (b) $SOCl_2$ (1.05 eqiv), $CHCl_3$, rt, 12 h, 85%; (c) PBr_3 (1.05 equiv) $CHCl_3$, rt, 18 h, 68%; (d) NaH (1.2 equiv), CS_2 (1.5 equiv), MeI (2.0 equiv), DCM, −78 °C to rt, 2 h, then NaH (1.2 equiv), rt, 16 h, 66%; (e) nBu_3SnH (2.5 equiv), AIBN (17 mol %), DCM, 60 °C, 3 h, 57%; (f) PPh_3 (1.2 equiv), $(PhO)_2P(O)N_3$ (1.2 equiv), DIAD (1.2 equiv), THF, 0 °C to rt; then (g) PPh_3 (1.5 equiv), THF/water (2:1), rt, 16 h, 45% in two steps; (h) PPh_3AuCl (5.0 mol %), $AgSbF_6$ (5.0 mol %), toluene, rt, 1 h, 90%.

Further studies aim to expand the applicability of the chloroprene Grignard addition to different electrophiles and to develop an asymmetric version of this reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00527.

Synthetic procedures for new compounds and their analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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(19) An extended table of screening experiments is attached in the Supporting Information.
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