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Highly Diastereoselective Synthesis of Homoallylic Alcohols Bearing Adjacent Quaternary Centers Using Substituted Allylic Zinc Reagents

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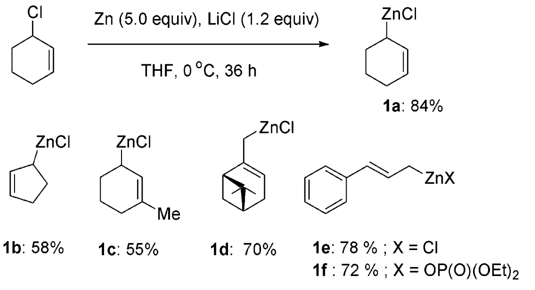
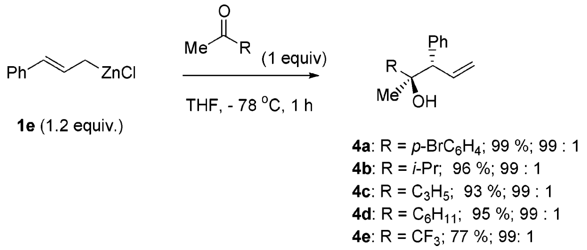
The stereoselective generation of quaternary centers is one of the major challenges in asymmetric synthesis.[1] The addition of highly substituted allylic organometallics to carbonyl derivatives[2] offers a straightforward synthesis of homoallylic alcohols bearing quaternary centers. This approach requires a convenient preparation of the allylic organometallics.[3] Although allylic lithium and magnesium reagents are highly reactive, they are difficult to prepare and are unstable.[3e] Allylic zinc reagents are much more readily available. Thus, allylzinc bromide is produced in high yield by the direct zinc insertion to allyl bromide.[4] The zinc insertion to *substituted* allylic bromides is less satisfactory, and increased amounts of homocoupling products are formed. Thus, cyclohexenylzinc bromide can only be prepared by the direct zinc insertion in 65% yield[5] and is best obtained by an indirect route via an allyltributylstannane.[6,7] Recently, we have reported a LiCl-mediated insertion of zinc dust into alkyl, aryl, and heteroaryl iodides leading to organozincs in good yields.[8] Herein, we wish to report that this method allows also the preparation of di- and trisubstituted allylic zinc reagents starting from the corresponding allylic chlorides, with a moderate formation of homocoupling products. Thus, the dropwise addition of cyclohexenyl chloride (1.0 equiv) to a suspension of zinc dust (5.0 equiv) and dry LiCl (1.2 equiv) in THF provides, after 36 h at 0 °C, cyclohexenylzinc chloride (**1a**) in 84% yield (Scheme 1).

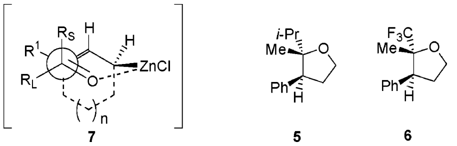
Scheme 1. LiCl-Mediated Preparation of Substituted Allylic Zinc Chlorides by the Direct Insertion of Zinc Dust (Yields Determined by Iodinolysis)



Scheme 2. Reaction of the Allylic Zinc Reagent **1e** with Various Methyl Ketones



Scheme 3. Chair-like Transition State **7** and Substituted Tetrahydrofurans **5** and **6**



This procedure can be successfully extended to previously unknown allylic zinc reagents, such as cyclopentenylzinc chloride (**1b**, 58% yield) and the trisubstituted 3-methylcyclohexenylzinc chloride (**1c**, 55% yield). Starting from 2-(1-chloromethyl)apopinene, the allylic zinc reagent **1d** is obtained in 70% (25 °C, 24 h). Importantly, the preparation of aryl-substituted allylic zinc reagents (such as **1e** or **1f**) can be achieved starting either from the corresponding allylic chloride (X = Cl; 20 °C, 1 h, 78%) or from the corresponding allylic phosphate (X = $OP(O)(OEt)_2$; 20 °C, 18 h, 72%). The addition of these highly reactive allylic organometallics to various aldehydes and ketones was then studied (Table 1 and Scheme 2). This reaction proceeds diastereoselectively and regioselectively under exceedingly mild conditions (−78 °C, 1 h). Aromatic ketones **2a,b** afford, regardless of the substitution pattern of the aromatic ring, the homoallylic alcohols **3a,b** bearing a quaternary center (dr >99:1, entries 1 and 2). Related ketones, such as 6-methoxy-1-tetralone (**2d**) or the ferrocenyl ketone (**2e**), are leading to the homoallylic alcohols (**3d,e**) with dr >96:4 (entries 4 and 5). Interestingly, this organometallic reaction is compatible with the presence of a free NH_2 group. Thus, the addition of **1a** to the benzaldehyde **2c** furnishes the amino alcohol **3c** (dr >99:1; 94% yield, entry 3). This allylic addition is also highly chemoselective.[9] Thus, a chloromethyl ketone such as **2f** or a ketone bearing an azido function in an α-position such as **2g** reacts with cyclohexenylzinc chloride (**1a**), providing the tertiary homoallylic alcohols **3f** and **3g** (dr >98:2, 93−97% yield, entries 6 and 7). The structure of **3g** was confirmed by X-ray analysis of its 1,2,3-triazole derivative.[10]

Cyclopentenylzinc chloride (**1b**) reacts similarly with the aromatic ketone **2h**, affording the homoallylic alcohol **3h** (dr >99:1; 95% yield, entry 8). In the case of 3-methyl-2-cyclohexenylzinc chloride (**1c**), a regiospecific addition is observed. The new carbon−carbon bond is formed exclusively from the most substituted end of the allylic system, leading to the homoallylic alcohols **3i,j** in 98−99% yield (dr >97:3, entries 9−10). Noticeably, the alcohol **3j** bearing two adjacent quaternary centers was obtained with a dr >98:2 (entry 13). Similarly, the 2,3-disubstituted allylic zinc species (**1d**) adds to pivaldehyde (**2k**), affording the homoallylic alcohol **3k**[10] (dr >98:2, 96% yield, entry 11). Interestingly, the cinnamylzinc chloride (**1e**) displays high diastereoselectivities[11] (Scheme 2). Thus, the addition of various methyl ketones, such as 3-methylbutan-2-one, 1-cyclopropylethanone, 1-cyclohexylethanone, or even 1,1,1-trifluoropropan-2-one, led to the corresponding alcohols with dr >99:1 (**4a**−**e**, 77−99% yield). The structures of the homoallylic alcohols resulting from the addition to aromatic ketones could be

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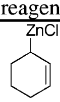
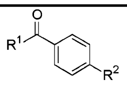
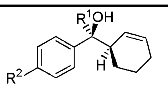
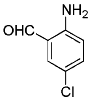
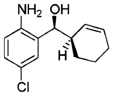
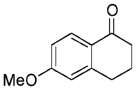
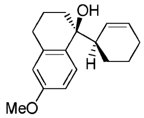
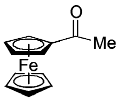
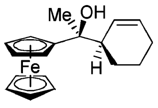
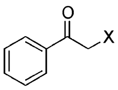
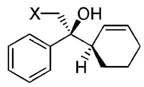
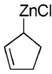
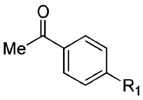
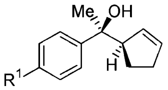
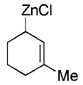
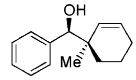
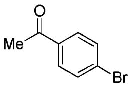
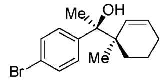
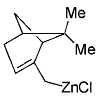
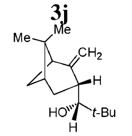
Table 1. Diastereoselective Preparation of Homoallylic Alcohols of Type **3** Using Allylic Zinc Reagents of Type **1**

entry	zinc reagent	ketone	product of type **3**	yield (%)[a]; dr[b]
				
1	**1a**	**2a**:R^1= Me; R^2 = CN	**3a**	97; 99 : 1
2[c]	**1a**	**2b**: R^1 = *i*-Pr; R^2 = H	**3b**	94; 99 : 1
				
3	**1a**	**2c**:	**3c**	94; 99 : 1
				
4	**1a**	**2d**	**3d**	97; 96 : 4
				
5	**1a**	**2e**	**3e**	95; 98 : 2
				
6	**1a**	**2f**: X = Cl	**3f**: X = Cl	97; 98 : 2
7	**1a**	**2g**: X = N$_3$	**3g**: X = N$_3$	93; 98 : 2
				
8	**1b**	**2h**: R^1 = CO$_2$Me	**3h**	95; 99 : 1
		PhCHO		
9	**1c**	**2i**	**3i**	98; 97 : 3
				
10	**1c**	**2j**	**3j**	99; 98 : 2
		*t*-BuCHO		
11	**1d**	**2k**	**3k**	96; 98 : 2

[a] Isolated yield of analytically pure products. [b] The diastereoselectivity was determined by ^{1}H NMR analysis. [c] Reaction conditions: −30 °C, 12 h.

readily established by literature comparison[2d] or X-ray analysis. In the case of *i*-PrCOMe or MeCOCF$_3$, no direct assessment could be made, and the alcohols **4b** and **4e** were converted to the tetrahydrofurans **5** and **6**,[12] confirming the generality of the cyclic chair-like transition state **7** (Scheme 3).

In conclusion, we have described a convenient method for preparing new allylic zinc chlorides using a LiCl-mediated zinc dust insertion to allylic chlorides. These add with remarkable diastereoselectivity and regioselectivity to various aldehydes or ketones, affording homoallylic alcohols bearing quaternary centers. Extensions of this work are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The crystal structures of **3e** and the derivatives **3g′** and **3k′** (CCDC-629595 (**3e**), CDCC-629596 (**3g′**), and CCDC-629597 (**3k′**)) can be obtained free via www.ccdc.cam.ac.uk/data-request/cif.

(11) Similar yields and diastereoselectivities are obtained with **1f**.

(12) Via a hydroboration, oxidation, and cyclization sequence.

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