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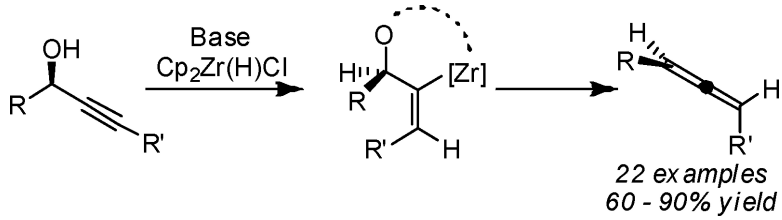

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Direct and Stereospecific Synthesis of Allenes via Reduction of Propargylic Alcohols with $Cp_2Zr(H)Cl$

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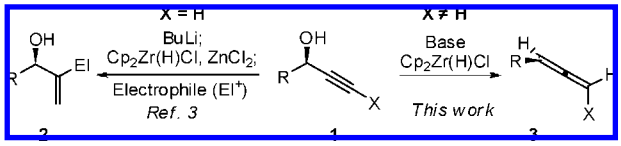
Hydrozirconation of alkynes with the Schwartz reagent [$Cp_2Zr(H)Cl$] provides vinyl zirconium species in a stereospecific and regioselective fashion. These intermediates can react with a variety of electrophiles or participate in cross-coupling reactions.[1] The least hindered vinyl zirconium product usually dominates under either kinetically or thermodynamically controlled conditions.[2] However, we recently discovered that lithium alkoxides can alter the regioselectivity of these reactions. In particular, hydrozirconation of *terminal* propargylic alcohols (**1**, X = H) occurs with complete selectivity for the branched products in the presence of BuLi and $ZnCl_2$ (Scheme 1, **1** → **2**).[3,4] In contrast, when *internal* propargylic alcohols were treated under similar reaction conditions, substantial quantities of disubstituted allenes were isolated in addition to branched allylic alcohols (Scheme 1, **1** → **3**). Here we demonstrate that this direct synthesis of allenes is high-yielding, general, and stereospecific.

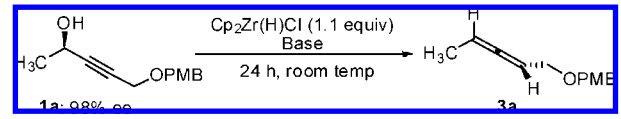
Scheme 1



Allenes can be prepared via S_N2' addition to propargylic alcohols or their derivatives.[5] Conceptually, hydride addition is one of the most attractive routes to disubstituted allenes. Indeed, traditional hydride reagents have been used,[6] and transition metal catalyzed methods have been developed as well.[7] Unfortunately, S_N2 addition often competes with S_N2' addition. Furthermore, when scalemic propargylic alcohols are used as substrates, substantial deterioration of optical purity accompanies reduction.[6] An alternative approach, developed by Myers and co-workers,[8] involves a Mitsunobu reaction between a propargylic alcohol and a sulfonyl hydrazine. The allene is generated through a sigmatropic elimination of N_2. While stereospecific and high-yielding in many cases, this protocol requires an unstable hydrazine and all the accoutrements of a Mitsunobu reaction; additionally, it has not proved generally effective for allylic, benzylic, or tertiary propargylic alcohols.[9]

To address some limitations of existing methodology we optimized the reaction of internal propargylic alcohols with $Cp_2Zr(H)Cl$. Initial experiments utilized alcohol **1a** (98% ee) and revealed that both the yield and optical purity of the product depended strongly on the base and solvent (Table 1). For example, under conditions originally optimized for terminal propargylic alcohols,[3] conversion was low (entry 1). We observed increased reactivity in hydrocarbon solvents, but inorganic salts still affected both the selectivity and efficiency of the reaction. With zinc or aluminum bases, **3a** was formed in reasonable yields but in unacceptable enantiomeric excess (entries 3, 4). Alternatively, the

Table 1. Effect of Additives on the Reduction of Propargylic Alcohols with $Cp_2Zr(H)Cl$



entry	base	equiv	solvent	yield[a] (%)	ee (%)
1	MeLi + $ZnCl_2$	1/6	THF	<5	–
2	Me_2Zn	1	THF	15	–
3	Me_2Zn	1	benzene	58	64
4	Me_2AlCl	1	benzene	~50	78
5[b]	None	–	benzene	40	93
6	MeLi	1	benzene	15	95
7	NaH	1	benzene	<20	90
8	EtMgCl	1	benzene	70[d]	98
9	**EtMgCl**	**1**	**toluene**	**70[d]**	**98**
10[c]	**Et_2Zn + $ZnCl_2$**	**0.5/0.5**	**toluene/THF[e]**	**72[d]**	**90**

[a] Yield determined by ^1H NMR except as indicated. [b] 2 equiv of $Cp_2Zr(H)Cl$. [c] 1.6 equiv of $Cp_2Zr(H)Cl$. [d] Isolated yield. [e] 30:1 Tol/THF.

zirconium, lithium, and sodium alkoxides reacted sluggishly but selectively (entries 5−7). Finally, we identified two conditions that provided the allene in good yield and excellent optical purity: deprotonation of **1** with either EtMgCl or EtZnCl (formed in situ from Et_2Zn and $ZnCl_2$) in toluene prior to hydrozirconation (entries 9, 10). Further studies revealed that the two protocols were complementary. In general, for allenes bearing two sp^3-hybridized substituents, optimal results were obtained when the propargylic alcohol was deprotonated with EtMgCl. As indicated by the difference between entries 9 and 10 in Table 1, lower ee was observed when EtZnCl was used to deprotonate these substrates.

For allenes connected to one or two sp^2-hybridized carbons, deprotonation of the propargylic alcohol with EtZnCl was preferred. The use of only 1 equiv of EtZnCl was critical as racemization of the allene was observed in the presence of excess zinc salts.[10] Additionally, the use of EtMgCl with aryl- or vinyl-substituted substrates led to over-reduction of the allene. For both procedures, toluene was found to offer the optimal balance of reactivity and selectivity; halogenated solvents displayed higher reactivity, but the allenes were isolated with lower ee. Finally, under optimized conditions, little or no allylic alcohol was isolated, indicating that the regioselectivity of the hydrometalation is high.

Having identified conditions to convert propargylic alcohols into enantiomerically enriched allenes, we evaluated the generality of the reduction (Figure 1). Benzyl and silyl ethers were tolerated under the reaction conditions (**3a**−**3c**), as were acetals and aminals (**3d**−**3f**). Neither carbamates (**3f**, **3h**, **3r**) nor silyl esters (**3m**) interfered with the reduction. Various aromatic and heteroaromatic rings remained intact. Additionally, we detected no hydrozirconation of olefins (**3g**, **3j**, **3l**) or other alkynes (**3o**) present in the substrates.

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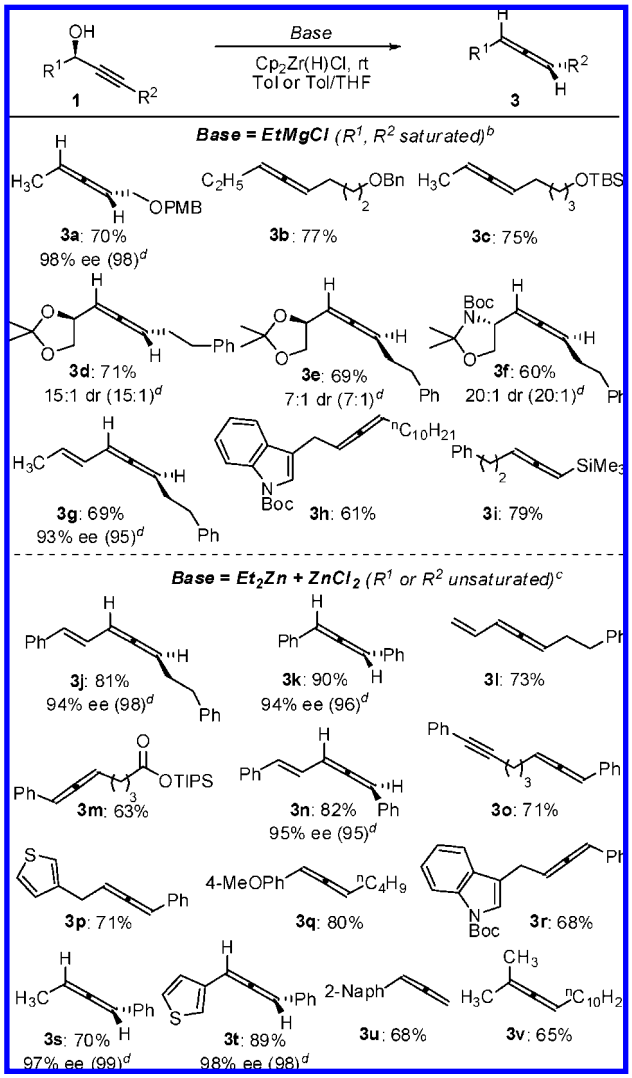
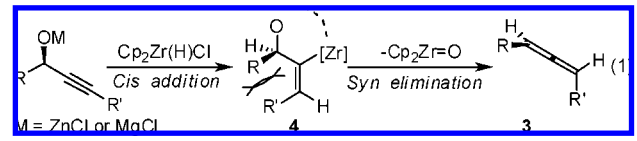


Figure 1. Synthesis of allenes from propargylic alcohols. [a]Isolated yields. Allenes are drawn such that the original alkyne substituent (R^2) is on the right. See Supporting Information for experimental details. [b]1 equiv of EtMgCl; 0.2 M in toluene; 1.1 equiv of Cp_2ZrHCl. [c]0.5 equiv each of Et_2Zn, $ZnCl_2$; 0.2 M in toluene/THF 30:1; 1.6 equiv of Cp_2ZrHCl. [d]Values in parentheses represent ee or dr of starting material.

Finally, we have used the hydrozirconation to prepare silyl-substituted allenes (**3i**), allenes derived from tertiary alcohols (**3v**), and terminal allenes (**3u**), although the latter showed some evidence of polymerization under the reaction conditions.

About half of our substrates were optically active[11] and in every case studied to date, the allenes were isolated with nearly the same optical purity as the starting propargylic alcohols (Figure 1). The absolute stereochemistry of the allenes was assigned based on optical rotation.[12] The conversion of central chirality to axial chirality is consistent with a *cis* addition of Zr−H to the alkyne followed by a *syn* elimination of Cp_2ZrO (eq 1).[13]

The difference in reactivity between terminal and internal propargylic alcohols is noteworthy. Our previous study demonstrated that the vinyl metal species derived from terminal propargylic alcohols is sufficiently stable to be trapped with various electrophiles (Scheme 1).[3] In contrast, we demonstrate here that the corresponding vinyl metal species formed from internal propargylic alcohols (**4**) eliminates rapidly to form allene. We interpret this difference as a manifestation of $A^{1,3}$ strain as indicated in eq 1. Furthermore, substrates with weaker C−O bonds (e.g., benzylic alcohols) suffer elimination even in the context of terminal alkynes (see **3u**).



In summary, we have identified two complementary sets of conditions that generate allenes in high yield and with high stereochemical purity. The method provides access to dialkyl-, aryl-alkyl-, and diaryl-substituted allenes in excellent enantiomeric or diastereomeric ratios. This approach provides direct and stereospecific access to allenes from free propargylic alcohols and therefore represents an attractive alternative to nonselective reductive methods and substitution of propargylic esters.

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Supporting Information Available: Complete experimental details and characterization data for new compounds. Time-course experiments related to racemization studies. This material is available free of charge via the Internet (http://pubs.acs.org).

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