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Directed Hydrozirconation of Propargylic Alcohols

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Abstract

Hydrozirconation of terminal alkynes with Cp₂ZrH(Cl) (Schwartz reagent) usually proceeds with high selectivity to yield the terminal vinyl zirconium. Under standard hydrozirconation conditions, terminal propargylic alcohols are no exception. However, we report that the sense of regioselectivity is completely reversed when the hydrozirconation is performed on the lithium alkoxide of terminal propargylic alcohols in the presence of ZnCl₂. Only the more hindered, branched products are observed. The reaction tolerates silyl and alkyl ethers, aromatic and heteroaromatic rings, and even terminal olefins and alkynes. The intermediate vinyl organometallic reagent can be trapped with I₂, enones, allyl bromide and can participate directly in cross-coupling reactions. Products are isolated in good yields as single regioisomers. We provide evidence that the presence of ZnCl₂ alters the kinetic selectivity such that the internal product is favored. More importantly, ZnCl₂ inhibits isomerization of the vinyl metal species, likely through transmetalation to a vinyl zinc chloride.

Hydrozirconation of alkynes with Cp₂ZrH(Cl) (Schwartz reagent) generates vinyl zirconium species reliably, stereospecifically and regioselectively. These organometallic reagents can participate in cross-coupling reactions, conjugate and nucleophilic additions and can undergo carbonylation and halogenation.¹ Hydrozirconation of terminal alkynes often proceeds with >50:1 selectivity to form the terminal vinyl zirconium product. Addition to internal alkynes often displays lower selectivity, but the initial kinetic distribution of products can reach equilibrium via β-hydride elimination from a dizirconium intermediate.² The least hindered product is always observed. For these reasons hydrozirconation has become a staple of modern synthetic chemistry. It was thus of interest to determine if the regioselectivity of hydrometalation could be reversed. While unprecedented, such an accomplishment would provide access to synthetically valuable reagents and might reveal fundamental aspects of organozirconium chemistry.

As part of a program to exploit directing groups in alkyne functionalization reactions^{3,4} we explored the hydrozirconation of propargylic alcohols.⁵ We initiated our studies with the most challenging class of propargylic alcohols, namely terminal alkynes. Thus, consistent with literature reports, terminal alkyne **1a** provided, after iodination, the terminal vinyl iodide **2a** as a single regioisomer (Table 1, entry 1).⁶ In contrast, hydrozirconation of the lithium alkoxide of **1a** yielded an equal distribution of regioisomers (entry 2). We hypothesized that an (alkoxy) zirconium hydride species Cp₂Zr(OR)H might be formed under the reaction conditions through

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Supporting Information Available: Complete experimental procedures and characterization data. This material is available free of charge at <http://pubs.acs.org>.

chloride displacement by lithium alkoxide. However when prepared independently such complexes were not competent intermediates in the hydrozirconation. While failing to support our original hypothesis, these experiments did suggest that chloride was important for the hydrozirconation reactions. Accordingly, we evaluated the effect of exogenous chloride sources. Additional lithium chloride proved marginally beneficial with respect to regioselectivity (entry 3) and zinc chloride yielded substantial improvements. Thus, in the presence of 6 equivalents of ZnCl_2 only the internal vinyl iodide was formed, marking a thousand-fold change in regioselectivity from standard hydrozirconation conditions (entry 5).⁷ Control experiments revealed that both MeLi and ZnCl_2 were required for branched-selective hydrometalation (entry 6).

The scope of the directed hydrozirconation displays several noteworthy features (Table 2). Substantial functionality is tolerated in the transformation, including protected alcohols, heterocycles and, remarkably, olefins (entry 6) and alkynes (entries 7, 9). Unsurprisingly optically active substrates retain stereochemical integrity during the reaction (entry 12). Electrophilic trapping is not limited to iodination: the intermediate organometallic reagent can participate in conjugate additions (entry 13),⁸ allylation (entry 15),⁹ stannylation (entry 16), and catalytic cross coupling (entries 14, 17).^{10,11}

A series of experiments helped elucidate the effect of ZnCl_2 on the kinetics and thermodynamics of hydrozirconation. For example, in the absence of ZnCl_2 , hydrozirconation of the lithium alkoxide of **1a** proceeds with moderate kinetic selectivity (Table 3, entry 1) and little thermodynamic selectivity (entry 2).¹² In contrast, reaction in the presence of ZnCl_2 displays high selectivity for the branched product with either substoichiometric or excess $\text{Cp}_2\text{ZrH}(\text{Cl})$ (entries 3–4). Finally, when alkyne **1a** was treated with Schwartz reagent in the absence of ZnCl_2 (as in entry 2) and ZnCl_2 was added subsequently, substantial isomerization to the internal organometallic was not observed. We conclude that in the absence of ZnCl_2 , the initially-formed branched product isomerizes to a thermodynamic product ratio approximating unity. In the presence of ZnCl_2 , high kinetic selectivity is observed for the internal product, and equilibration is prevented.

Two observations indicate that Schwartz reagent reacts with ZnCl_2 directly. First, $\text{Cp}_2\text{ZrH}(\text{Cl})$ is sparingly soluble in THF. In the presence of ZnCl_2 , however, solutions with $[\text{Zr}] > 1\text{M}$ can be prepared. Second, as hinted at by entry 7 in Table 2, ZnCl_2 inhibits the hydrozirconation of unfunctionalized alkynes. For instance, whereas hydrozirconation of dodecyne proceeded rapidly and quantitatively in the absence of ZnCl_2 , we observed <20% conversion in its presence.¹³

A heterobimetallic complex may be formed on mixing $\text{Cp}_2\text{ZrH}(\text{Cl})$ and ZnCl_2 . Alternatively, a zinc hydride may arise from this combination.¹⁴ Structural data for the active species has proved elusive to date: NMR spectra of the solution formed from adding ZnCl_2 to $\text{Cp}_2\text{ZrH}(\text{Cl})$ in THF reveal several Cp-containing species and at least two metal hydrides. Irrespective of structure, the various metal hydrides must be unreactive towards unfunctionalized alkynes, but may coordinate to propargylic alkoxides to force proximity between the hydride and the alkyne.¹⁵ Directed hydrometalation and, if necessary, subsequent transmetalation, would yield a branched vinyl zinc (**5a**, $\text{M} = \text{ZnCl}$). Critically, the vinyl zinc species may not isomerize to the less hindered, linear product via hydrozirconation/ β -hydride elimination.¹⁶ Thus ZnCl_2 appears to prevent both linear-selective hydrozirconation and isomerization in the presence of excess Schwartz reagent.

The observation that alkoxides can direct hydrozirconation to the contrasteric products suggests that other directing groups might behave similarly and that related Zr-mediated reactions might be subject to similar influences. Both prospects are subjects of current investigations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Hydrozirconation/Iodination of alkyne **1a**.^a

Entry	Additive ^b	2a:3a ^c
1	None	>50:1
2	MeLi (1 equiv)	1:1
3	MeLi (1 equiv), LiCl (3 equiv)	1:2
4	MeLi (1 equiv), ZnCl_2 (3 equiv)	1:10
5	MeLi (1 equiv), ZnCl_2 (6 equiv)	1:>50 (70% yield)
6	ZnCl_2 (6 equiv)	<i>d</i>

^aConversion >95% except as noted.^bMeLi added prior to introduction of $\text{Cp}_2\text{ZrH}(\text{Cl})$.^cDetermined by ^1H NMR analysis of crude reaction mixture.^d35% conv.; <5% iodide (**2a** + **3a**) formed.

Table 2Hydrozirconation/electrophile trapping of propargylic alcohols.^a

Entry	Trapping reagent	Product
1	I_2	 $\text{R} = \text{CH}_2\text{OBn}$
2	I_2	$\text{R} = (\text{CH}_2)_2\text{Ph}$
3	I_2	$\text{R} = (\text{CH}_2)_8\text{Cl}$
4	I_2	$\text{R} = (\text{CH}_2)_2\text{OTBS}$
5	I_2	$\text{R} = c\text{-Hex}$
6	I_2	$\text{R} = (\text{CH}_2)_8\text{CHCH}_2$
7	I_2	
8	I_2	
9	I_2

Entry	Trapping reagent	Product
10	I_2	
11	I_2	
12 ^c	I_2	
13	$\text{CuCN} \cdot 2\text{LiCl}$, MVK^d	
14	PhI , $\text{Pd}(\text{PPh})_4$ (cat.)	
15	$\text{CuCN} \cdot 2\text{LiCl}$ Allyl bromide

Entry	Trapping reagent	Product
16	Bu_3SnCl	
17	$\text{Pd}(\text{PPh})_4$ (cat.)

^a Reactions carried out on a 0.5 mmol scale, 0.2 M in THF. See supporting information for details. Conversion >95% in all cases.

^b Isolated Yield.

^c d.r > 99:1.

^d MVK = methyl vinyl ketone.

Table 3Kinetic and thermodynamic selectivity in the hydrozirconation of **1a**

Entry	Equiv. $\text{Cp}_2\text{ZrH(Cl)}$	Equiv. ZnCl_2	4a:5a ^a
1	0.5	0	1:6
2	2.0	0	1:1
3	0.5	6	1:>10
4	2.0	6	1:>50
5 ^b	2.0	6; after hydrozirconation	1:1–2

^aDetermined by ^1H NMR analysis of the crude reaction mixture following addition of DCl. See supporting information for details.

^b ZnCl_2 was added after alkyne was completely consumed.