Communication

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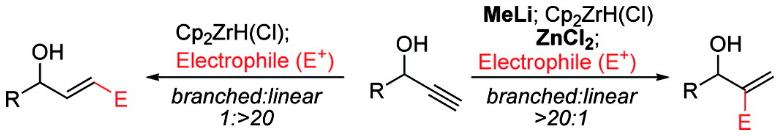

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Directed Hydrozirconation of Propargylic Alcohols

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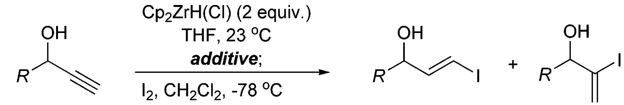
Hydrozirconation of alkynes with $Cp_2ZrH(Cl)$ (Schwartz reagent) generates vinyl zirconium species reliably, stereospecifically, and regioselectively. These organometallic reagents can participate in cross-coupling reactions, conjugate and nucleophilic additions, and can undergo carbonylation and halogenation.[1] 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 $Cp_2Zr(OR)H$ might be formed under the reaction conditions through 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 equiv of $ZnCl_2$, only the internal vinyl iodide was formed, marking a 1000-fold change in regioselectivity from standard hydrozirconation conditions (entry

Table 1. Hydrozirconation/Iodination of Alkyne **1a**[a]

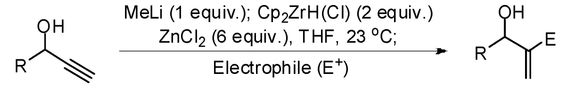


1a: *R* = *n*-C_9H_{19} **2a** **3a**

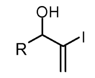
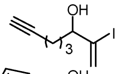
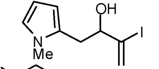
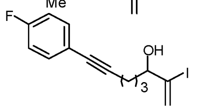
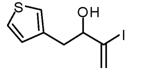
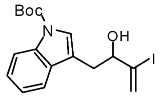
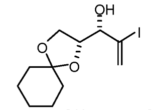
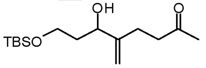
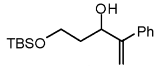
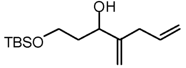
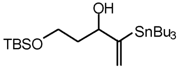
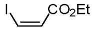
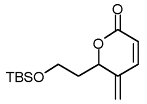
entry	additive[b]	**2a**:**3a**[c]
1	none	>50:1
2	MeLi (1 equiv)	1:1
3	MeLi (1 equiv), LiCl (3 equiv)	1:2
4	MeLi (1 equiv), $ZnCl_2$ (3 equiv)	1:10
5	MeLi (1 equiv), $ZnCl_2$ (6 equiv)	1:>50 (70% yield)
6	$ZnCl_2$ (6 equiv)	*d*

[a] Conversion >95% except as noted. [b] MeLi added prior to introduction of $Cp_2ZrH(Cl)$. [c] Determined by ^1H NMR analysis of crude reaction mixture. [d] 35% conversion; <5% iodide (**2a** + **3a**) formed.

Table 2. Hydrozirconation/Electrophilic Trapping of Propargylic Alcohols[a]



branched:linear
>20:1

entry	trapping reagent	product	yield (%)[b]
1	I_2	 R = CH_2OBn	71
2	I_2	R = $(CH_2)_2Ph$	73
3	I_2	R = $(CH_2)_8Cl$	74
4	I_2	R = $(CH_2)_2OTBS$	66
5	I_2	R = *c*-Hex	73
6	I_2	R = $(CH_2)_8CHCH_2$	75
7	I_2		68
8	I_2		70
9	I_2		70
10	I_2		75
11	I_2		68
12[c]	I_2		86
13	$CuCN\cdot 2LiCl$, MVK[d]		68
14	PhI, $Pd(PPh)_4$ (cat.)		72
15	$CuCN\cdot 2LiCl$ Allyl bromide		70
16	Bu_3SnCl		66
17	$Pd(PPh)_4$ (cat.) 		63

[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] Diastereomeric ratio >99:1. [d] MVK = methyl vinyl ketone.

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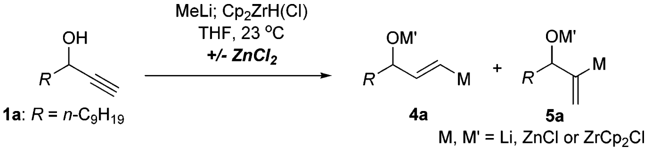
Table 3. Kinetic and Thermodynamic Selectivity in the Hydrozirconation of **1a**



entry	equiv of $Cp_2ZrH(Cl)$	equiv of $ZnCl_2$	**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

[a] Determined by ^{1}H 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.

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 $Cp_2ZrH(Cl)$ (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, $Cp_2ZrH(Cl)$ is sparingly soluble in THF. In the presence of $ZnCl_2$, however, solutions with [Zr] > 1 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 $Cp_2ZrH(Cl)$ and $ZnCl_2$. Alternatively, a zinc hydride may arise from this combination.[14] Structural data for the active species have proved elusive to date; NMR spectra of the solution formed from adding $ZnCl_2$ to $Cp_2ZrH(Cl)$ in THF reveal several Cp-containing species and at least two metal hydrides. Irrespective of structure, the various metal hydrides must be unreactive toward 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**, M = 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.

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Note Added after ASAP Publication. After this paper was published ASAP on September 13, 2007, ref 5f was added. The corrected version was published ASAP on September 18, 2007.

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

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(7) (a) Et_2Zn provided similar results as $ZnCl_2$, indicating that the effect is from zinc rather than chloride. (b) BuLi is as effective as MeLi. (c) Deprotonation with EtMgCl or $AlMe_3$ led to **2a** as the major product. (d) The major side products are 1,2-dodecadiene and 2-dodecene.
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(11) Internal propargylic alcohols yield allenes. Details will be reported separately.
(12) Excess Schwartz reagent is required to reach equilibrium. See ref 2a.
(13) Deprotonation of the alkyne is also not observed.
(14) Gao, Y.; Harada, K.; Hata, T.; Urabe, H.; Sato. F. *J. Org. Chem.* **1995**, *60*, 290−291. Preparations of IZnH by this procedure do not yield reagents capable of hydrozincation in the presence or absence of Cp_2ZrCl_2. Deprotonation of the alkyny C−H is observed.
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