# Kinetic vs. thermodynamic control in hydrozirconation reactions

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Abstract - Most synthetic applications of organo(chloro)zirconocenes involve the use of *terminal* zirconocenes derived from hydrozirconation of monosubstituted or symmetrical triple or double bonds. In our studies to effect stereoselective hydrozirconations of internal alkynes and alkenes, we have explored the alkoxy-directed hydrozirconation of homoallylic and bis-homoallylic alcohols. The discovery of a new method to prepare zirconocene hydrides *in situ* from readily available, air-stable zirconocene dihydride has allowed us to demonstrate for the first time that kinetic hydrozirconation products of internal, non-functionalized alkenes can be formed in preference over isomerized, thermodynamic products.

Hydrozirconation of alkynes and alkenes generates synthetically useful alkenyl- and alkylzirconocene reagents (ref. 1). In addition to stereocontrolled transmetalation reactions of organozirconocenes, we have applied zirconium complexes for cationic cascade reactions (ref. 2). Our most recent synthetic protocols include the use of alkylzirconocenes in the asymmetric Cu(I)-assisted conjugate addition (eq. 1, ref. 3), the asymmetric synthesis of allylic alcohols via Zr→Zn transmetalation (eq. 2, ref. 4), and oxidative couplings (eq. 3, ref. 5).
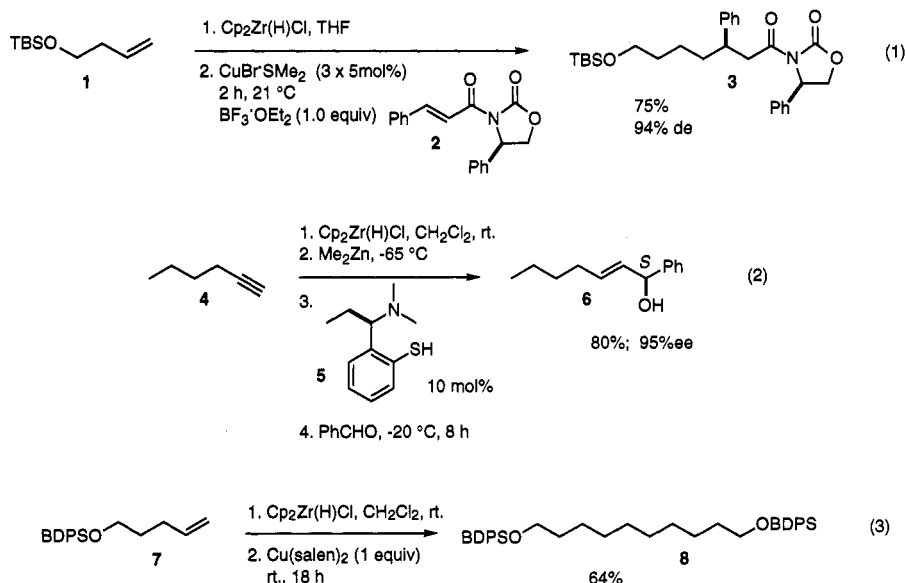

Almost exclusively, these processes involve the use of *terminal* zirconocenes derived from monosubstituted or symmetrical triple or double bonds. A key problem remains the stereoselective hydrozirconation of *internal*, unsymmetrical alkynes and alkenes. Since isomerization of organozirconocenes is generally faster than hydrozirconation, the thermodynamically most stable, e.g. least sterically crowded isomer is rapidly formed. For 2-octene, for example, this results in the exclusive formation of 1-metalated compound (ref. 6). The use of alkylzirconocenes could be considerably expanded if the thermodynamically favored isomerization to the terminus of an alkyl chain could be suppressed.
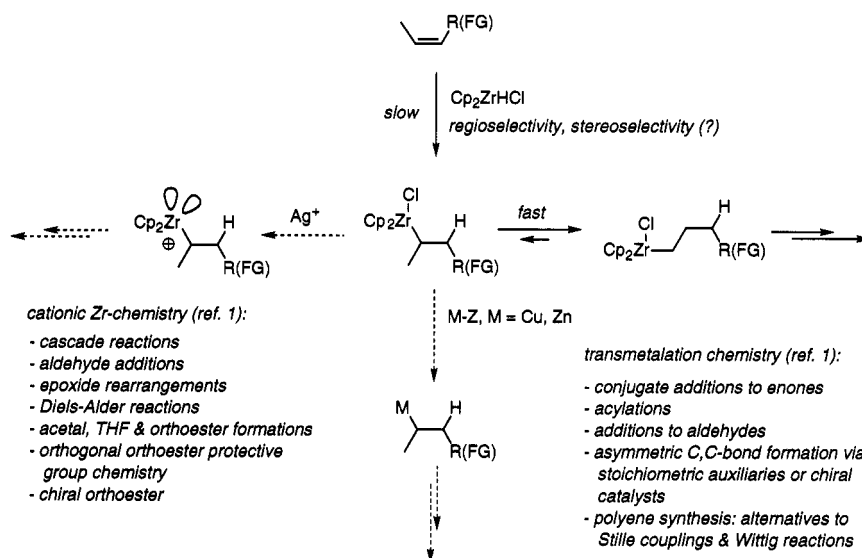
The problem of rapid chain-migrations of secondary or tertiary organometallics is not unique to zirconocenes. Organoboranes isomerize at temperatures from 70 to 200 °C (ref. 7), and, in the presence of transition metal catalysts, hydroalumination of internal alkenes provides only terminal organoalanes at 70 °C (ref. 8). The temperature cutoff for zirconocene migration is not known, and no clear mechanistic understanding has emerged.

Since, in general, only starting alkene and terminal zirconocene are observed in NMR, the initial hydrozirconation with the sparingly soluble Cp$_2$Zr(H)Cl must be considerably faster than subsequent β-elimination and further hydrozirconation. It is unlikely that zirconocene hydrochloride diffuses away from the alkene into solution, even though the π-complexes **9** and **11** offer very little stabilization due to a lack of back-bonding from d^0-zirconium to the alkene. However, the isolation of a mixture of alkenes in the hydrozirconation of (Z)-5-decene with sub-stoichiometric amounts of zirconocene hydrochloride as well as the isotope composition observed in decane after deuteriozirconation provide evidence that a participation by pathway *b* cannot be excluded (ref. 9).
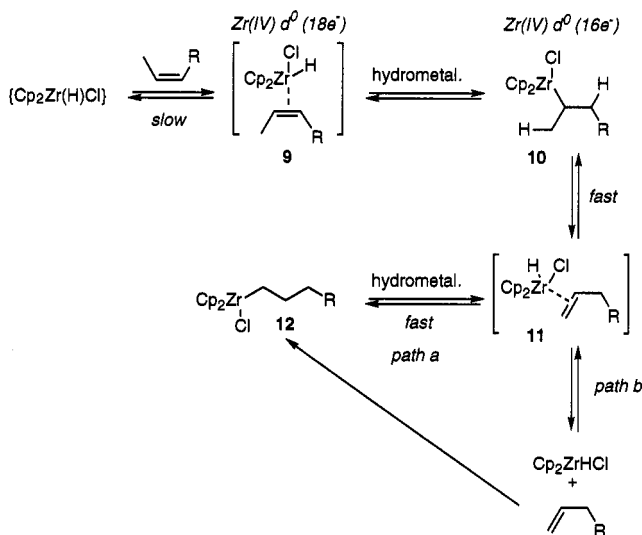

At least for functionalized alkenes, there is encouraging literature evidence for the existence of internal zirconocene products (ref. 1). Styrenes give both secondary benzyl alcohols and primary alcohols upon hydrozirconation/oxidation (ref. 10), and heteroatoms present in oxazoline **17** and homoallylic alcohol **19** can stabilize internal zirconocenes through complexation (refs. 11,12).
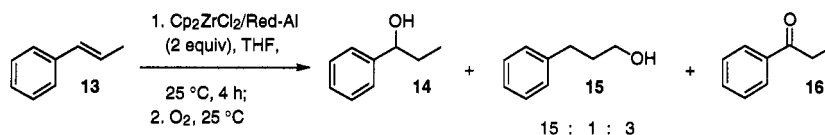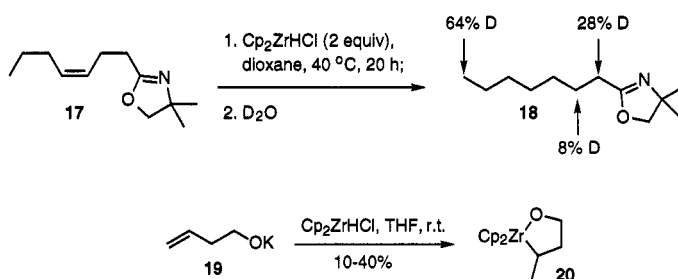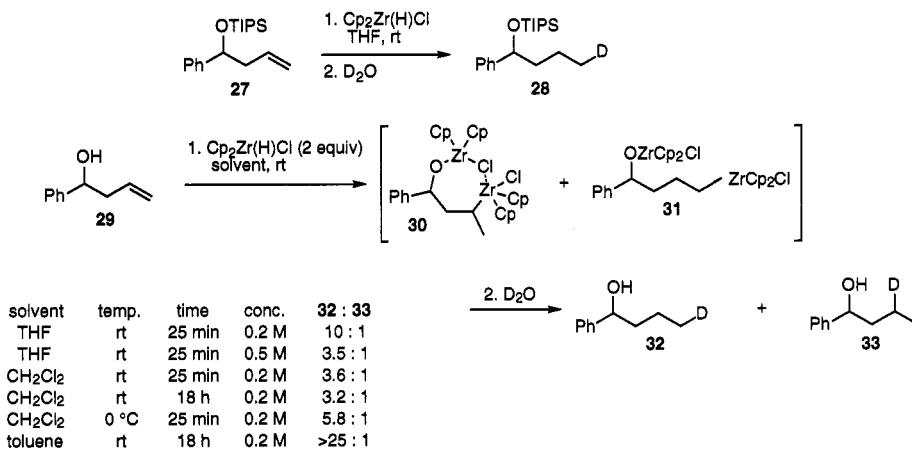
In our own work, we have observed that hydrozirconation of silyl ether **21** followed by copper(I)-assisted acylation with benzoyl chloride provided the *trans*-cyclohexyl ketone **22** as the major isomer (ref. 13). Presumably, axial attack *anti* to the bulky silyl ether is favored due to steric hindrance, and subsequent isomerizations might be disfavored by the inductive effect of the oxygen substituent. We were interested to determine if related neighboring group participations were effective in suppressing zirconocene isomerization in acyclic alcohols.
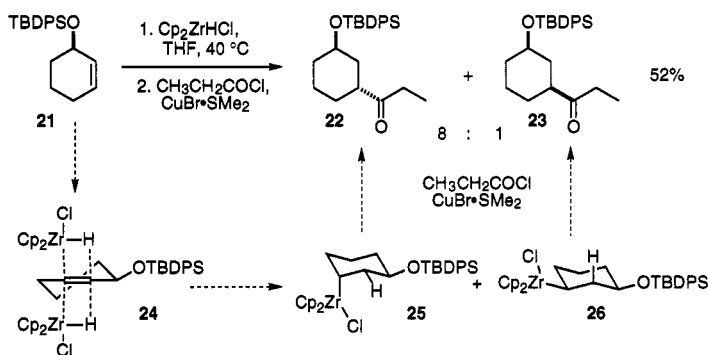
Hydrozirconation/deuteration of homoallylic ether **27** provided terminally labeled **28** as the sole detectable isomer. The deprotected homoallylic alcohol **29** exerted a more interesting neighboring group effect. The ratio of terminal to internal deuterides was highly depended on solvent and concentration (ref. 14). In THF, a 10 : 1 ratio of terminal deuteride **32** and secondary deuteride **33**, possibly derived from the bis-zirconocenes **30** and **31**, was isolated from a standard 0.2 M reaction mixture. At a higher concentration, the relative amount of terminal to internal zirconocene was decreased to 3.5 : 1. A similar ratio was obtained in CH_2Cl_2 at room temperature. Lowering the reaction temperature is likely to decrease the solubility of Schwartz reagent and thus its concentration in the reaction mixture, and at 0 °C the ratio of **32** to **33** increased to 5.8 : 1. The ratio observed after 25 min in CH_2Cl_2 was largely unchanged after 18 h, and since toluene provided a >25 : 1 ratio of products after the same reaction time, we conclude that the kinetic barrier toward isomerization is unusually high due to the coordinating alkoxide ligand. No combination of solvent, reaction time, and temperature provided the internal deuteride **33** as the major product.

| solvent	temp.	time	conc.	32 : 33
THF	rt	25 min	0.2 M	10 : 1
THF	rt	25 min	0.5 M	3.5 : 1
CH_2Cl_2	rt	25 min	0.2 M	3.6 : 1
CH_2Cl_2	rt	18 h	0.2 M	3.2 : 1
CH_2Cl_2	0 °C	25 min	0.2 M	5.8 : 1
toluene	rt	18 h	0.2 M	>25 : 1

Since the *in situ* prepared zirconocene alkoxide failed to shift the regioselectivity of the intermolecular hydrozirconation of the homoallylic alcohol in favor of the secondary zirconocene, we investigated the use of zirconocene dihydride to induce an intramolecular metalation pathway. In CH_2Cl_2 and THF we obtained indeed a 1 : 1 mixture of deuterides **32** and **33**, presumably formed via the cyclic zirconocenes **34** and **35**, respectively. Longer reaction times in THF and toluene provided ca. 2 : 1 mixtures.
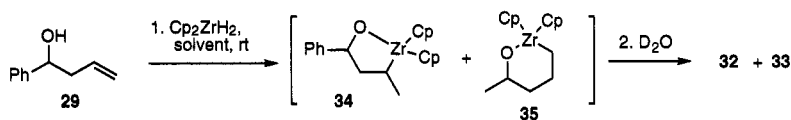

solvent	temp.	time	conc.	**32 : 33**
THF	rt	4 h	0.2 M	1 : 1
THF	rt	18 h	0.2 M	2.4 : 1
CH_2Cl_2	rt	4 h	0.2 M	1 : 1
toluene	rt	18 h	0.2 M	2 : 1

Hydrozirconation of the potassium alkoxide did not provide any further improvements in the formation of the internal deuteride; the ratio of **32** to **33** ranged from 3 : 1 in THF to 8 : 1 in CH_2Cl_2. Generation of the lithium alkoxide by deprotonation of **29** with BuLi at -78 °C, followed by addition of zirconocene hydrochloride and warming to room temperature, provided for the first time the internal deuteride as the major isomer. Comparable results were obtained in the hydrozirconation of the tertiary homoallylic alcohol **36**. Use of 2 equivalents of zirconocene hydrochloride provided the terminal deuteride **37** in >25 : 1 selectivity. In contrast, this regioselectivity was shifted in favor of the internal deuteride **38** with the *in situ* prepared lithium alkoxide.
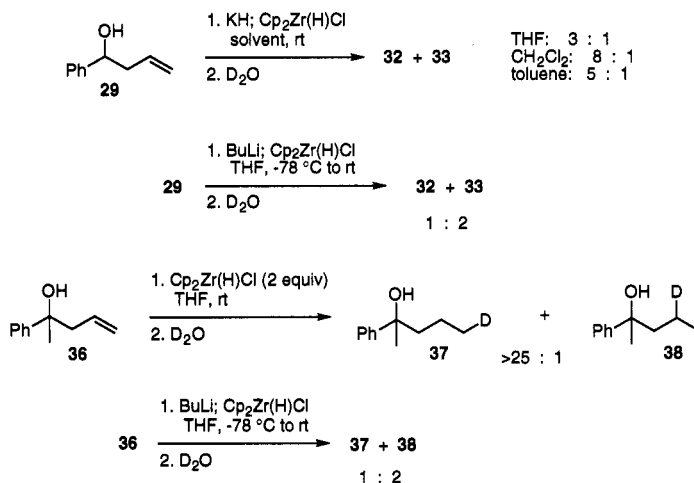

The modest levels of regioselectivity for the internal secondary zirconocene obtained in the directed hydrozirconation of homoallylic alcohols **29** and **36** could not be extended to the disubstituted alkene **39** and the bis-homoallylic alcohols **41**, **43** and **45**. Only terminal deuterides were obtained under a range of reaction conditions.
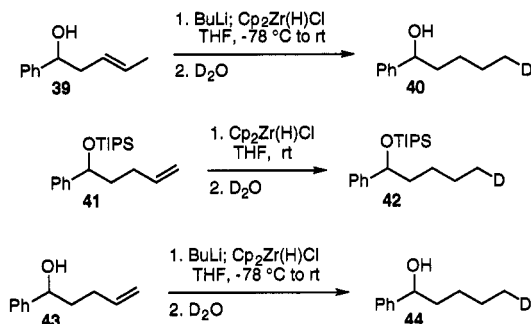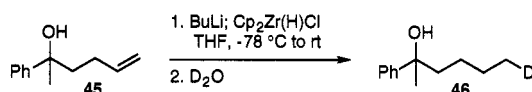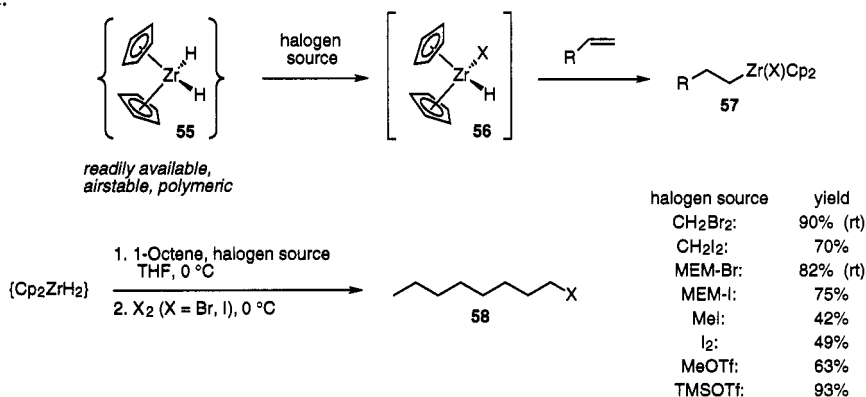
Our early attempts to control the regioselectivity of the hydrozirconation of internal, unfunctionalized alkenes were unsuccessful. Hydrozirconation-acylation of cyclopentene **47** led to a mixture of five isomeric ketones (ref. 13). The isolation of the methylene ketone **54** implies that at the reaction temperature necessary to effect hydrozirconation of the trisubstituted alkene even the tertiary zirconocene **50** is formed transiently.

(52+53)/54 ≡ 12 : 1
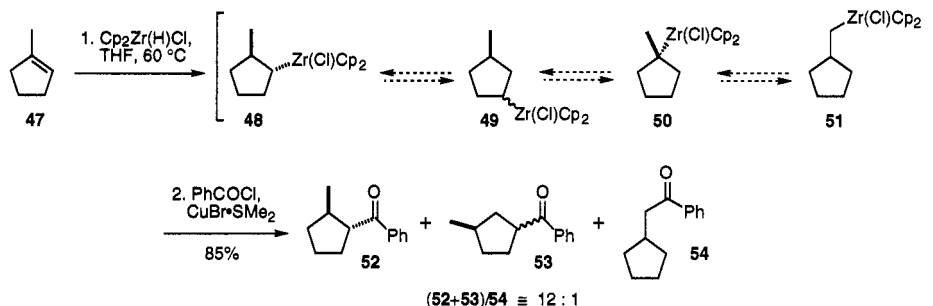
A decrease in the temperature necessary for hydrozirconation would likely inhibit any undesired thermodynamic equilibration and allow the isolation of kinetic products. However, the insolubility of zirconocene hydrochloride in organic solvents effectively limits the lower temperature range for hydrozirconation of alkynes and terminal alkenes at 0 °C to room temperature. Internal alkenes are less reactive and require higher temperatures such as refluxing THF for reasonable reaction rates. Since chloride is an excellent bridging ligand and thus facilitates zirconocene oligomerization, we investigated next the rate of hydrozirconation of alkenes with derivatives $Cp_2Zr(H)X$, where X=Br, I, and OTf. These studies were greatly facilitated by our discovery that treatment of the readily available, highly polymeric and air-stable Cp_2ZrH_2 with halogen sources such as CH_2Br_2, MEM-I, and others, converts the dihydride *in situ* into the desired monohydrides, which are much more effective hydrozirconating agents than Cp_2ZrH_2 (ref. 15). In spite of the heterogeneous nature of this reaction, only stoichiometric amounts of halogen sources are required. Trapping of the terminal zirconocene derived from 1-octene with Br_2 or I_2 led to high yields of 1-halooctanes. Methylene bromide and TMS-triflate were among the most effective reagents in this process. In the absence of an electrophilic partial quenching of the zirconocene dihydride, no monohalogenated product was isolated.

readily available,
airstable, polymeric

halogen source	yield
CH_2Br_2:	90% (rt)
CH_2I_2:	70%
MEM-Br:	82% (rt)
MEM-I:	75%
MeI:	42%
I_2:	49%
MeOTf:	63%
TMSOTf:	93%

Application of these new preparations for modified Schwartz reagents to (*E*)-2-octene provided, for the first time, the kinetic, internal trapping products. In the presence of 0.5 equiv of CH_2Br_2, trapping of a mixture of 1.0 equiv of Cp_2ZrH_2 and 0.83 equiv of 2-octene in THF with Br_2 provided only traces of terminal bromide in addition to the major compound, dibromide **60**, which was formed from unreacted 2-octene. A slightly better ratio was obtained with 1 equiv of CH_2I_2, however, the use of 0.5 equiv of TMS-triflate resulted in the formation of the internal trapping product 2-bromooctane as the major isomer. With (*E*)-4-octene, *in situ* prepared zirconocene hydrotriflate led to a 1 : 1.8 ratio of 1-bromo- to 4-bromooctane.

Interestingly, independently prepared Cp2Zr(H)OTf (ref. 16) did not provide any kinetically controlled internal trapping product, and no 2- or 3-brominated octanes were detected in any reaction mixture.
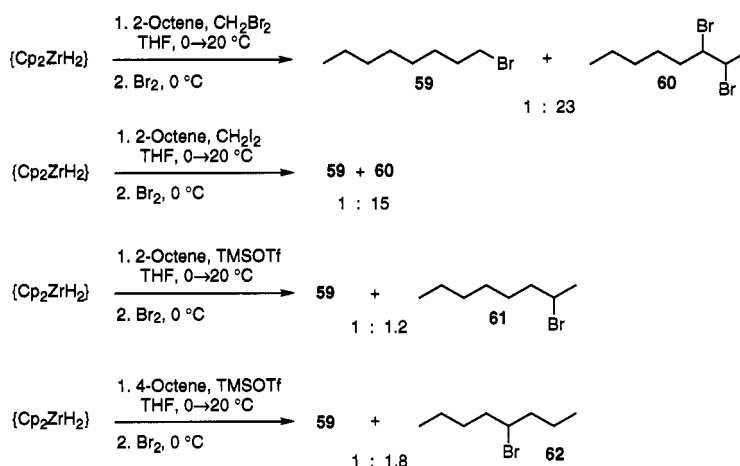
In conclusion, lithium alkoxide-directed hydrozirconation or *in situ* prepared zirconocene hydrotriflate allow for the formation of internal, secondary zirconocenes in preference over the primary isomers obtained by migration along the carbon chain. With unfunctionalized internal alkenes, the thermodynamically preferred isomerization to the terminal position can be partially suppressed at 0 °C by the use of zirconocene dihydride and TMS-triflate, and electrophilic trapping of kinetically formed internal zirconocenes has been achieved. Further studies will be directed at low-temperature (-78 °C) hydrozirconation protocols that should allow for the exclusive formation of kinetic hydrozirconation products.

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14. In this and all subsequent deuteration experiments, the internal deuteride **33** was isolated as a 1 : 1 to 1 : 10 mixture of diastereomers. No attempts to assign the relative stereochemistry of the major isomers were made.
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