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Selective Oxidation of Zirconocyclopentenes via Organoboranes

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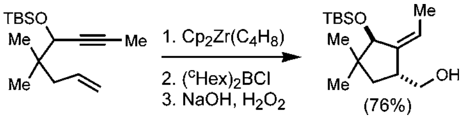
ABSTRACT



A new, convenient, one-pot protocol is described for oxidation of zirconocyclopent-2-enes selectively at the sp^3 carbon by efficient transfer to electrophilic (^{c}Hex)$_2$BCl followed by oxidation with H$_2$O$_2$/NaOH to afford 1-alkylidene-2-hydroxymethylcyclopentanes. Results with several substrates show that overall reaction efficiencies for the zirconocene-mediated enyne cyclization, boron transmetalation, and oxidation sequence are generally comparable to yields obtained from protonation of intermediate zirconocycles. The formation of E/Z olefin isomers from the cyclization-oxidation sequence and an acid-catalyzed pinacol-type rearrangement of a vinylsilane are described.

In the 1980s several groups reported the reductive cyclization of 1,7-enynes (and related systems) mediated by low valent zirconocene that was generated in situ by the reduction of Cp$_2$ZrCl$_2$.[1,2] The most straightforward method for accessing an equivalent "free zirconocene" (i.e., Cp$_2$Zr) consists of treating Cp$_2$ZrCl$_2$ with 2 equiv of *n*-BuLi at low temperatures.[2] These disclosures resulted in a subsequent flourish of zirconocene research that ultimately led to widespread adoption of zirconocene as a useful synthetic reagent for many interesting transformations.[3,4] Zirconocene has proved surprisingly effective for converting various dienes and enynes to zirconocyclopentanes and pentenes, and these intermediates can be subsequently functionalized by ligand transfer to reactive electrophiles.[5] Selective functionalizations of zirconocyclopentenes have been reported with preferential reaction at the sp^3 carbon (methanol,[6−9] aldehydes,[10] allenyl carbenoids,[11] halogens,[7,8,12] chlorostannanes,[7] isonitriles,[7,13] and oxygen[9]) and at the sp^2 carbon (enones,[14] halogens,[7,8,12] and allyl chloride[15]) often via transmetalation with Cu(I).[16] However, the synthetic impact of Zr(II)-mediated enyne

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cyclizations is constrained by the limited synthetic transformations available with which to functionalize the weakly nucleophilic carbon–zirconium bonds.[17]

We were interested in achieving a selective zirconocyclopentene oxidation (Scheme 1), but to the best of our knowledge such a zirconocene-mediated transformation has not been described.[9,18] Oxidations of zirconocyclopentanes or alkyl zirconium species generated by the Wailes–Schwartz reaction have been reported that used molecular oxygen or other chemical oxidants (e.g., H_2O_2, *m*-CPBA) to produce alcohols or aldehydes.[19] The malonate-derived enyne **1b** was selected as a model substrate to evaluate the viability of a direct oxidation of a carbon–zirconium bond generated by reductive cyclization, and the results are summarized in Table 1. Not surprisingly, hydroperoxides resulted primarily in protonation, with only 4–20% of oxidation products being formed. Aprotic oxidants such as *N*-methylmorpholine *N*-oxide, trimethylamine *N*-oxide, TEMPO, and benzoyl peroxide were equally disappointing (entries 5–8). Molecular oxygen caused decomposition (entry 9), in contrast to successful oxidations of zirconocyclopentanes under identical conditions.[9,19a,20]

Scheme 1

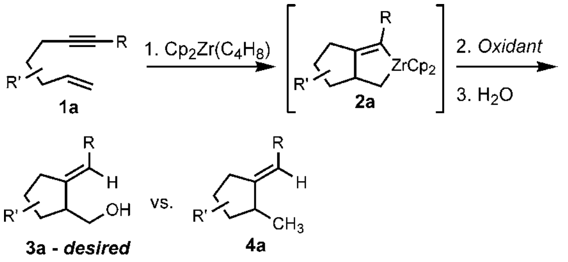
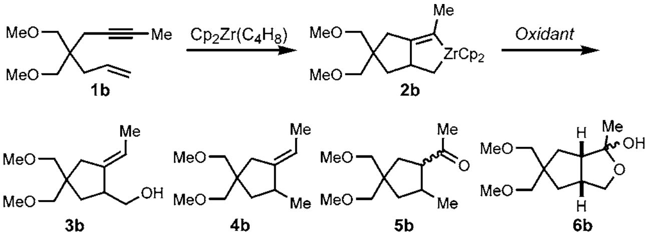


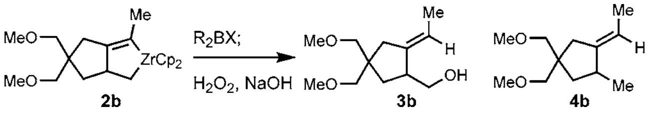
Table 1. Oxidation of Zirconocyclopentenes[a]



entry	oxidant	GC ratio **3**:**4**:**5**:**6**
1	H_2O_2, NaOH	4:96:0:0
2	$NaBO_3$	4:96:0:0
3	${}^tBuOOH$	19:81:0:0
4	*m*-CPBA	20:80:0:0
5	NMO	21:72:7:0
6	Me_3NO	5:95:0:0
7	TEMPO	5:95:0:0
8	$(BzO)_2$	2:90:8:0
9	O_2	decomposition

[a] Conditions: THF, rt to reflux.

Table 2. Affect of Boron Reagent on Zirconocyclopentene Transmetalation-Oxidation[a]



entry	boron source	isolated yield (ratio)[b]	
		3b, oxidation	**4b**, protonation
1	BCl_3	5	11
2	BBr_3	0	75
3	Bu_2BOTf	57	8
4	BrB(catechol)	25	62
5	9-BBNBr	11	79
6	$(Ipc)_2BCl$	24	59
7	$({}^cHex)_2BCl$	83	8

[a] Conditions: THF, rt to reflux. [b] Calibrated GC yields were within ±10%.

Zirconium alkyl and alkenyl ligands readily transfer to boron and other main group elements.[21] In synthetic studies on borolanes, Cole elegantly demonstrated the viability of oxidizing alkyl boranes generated by alkyl migration from zirconium to boron.[22] Our experimental results for the oxidation of zirconocyclopentene **2b** employing a similar transmetalation and oxidation strategy with a variety of electrophilic boranes are summarized in Table 2. The transmetalation was monitored by GC analysis of an oxidized aliquot (H_2O_2, NaOH), and the reaction was allowed to proceed until no further change in the ratio of products was observed (typically 4 h). Transmetalation efficiency proved to be relatively insensitive to extended reaction times, excess boron reagent, solvents, or lowered/elevated temperatures. Product yields were similar whether H_2O_2 or $NaBO_3$ was used to oxidize the intermediate borane. In the reaction with BCl_3 methyl ether cleavage accompanied transmetalation (entry 1), whereas no transmetalation appeared to occur with BBr_3 (entry 2). Reaction with Bu_2BOTf consistently gave the alcohol **3b** as the major product, but yields averaged only 57% (entry 3). Bromocatechol borane, 9-BBNBr, and di-

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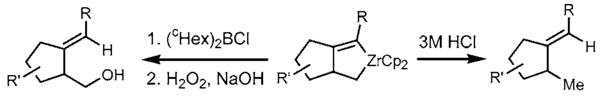
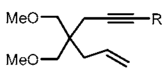
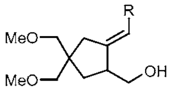
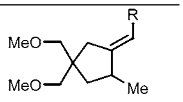
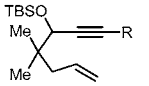
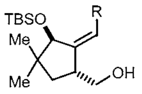
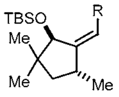
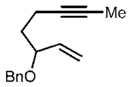
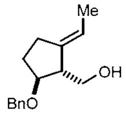
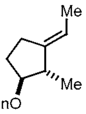
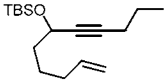
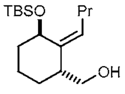
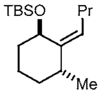
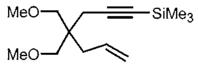
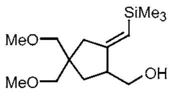
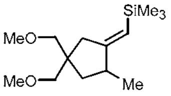
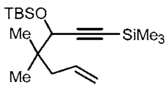
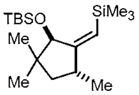
isopinylcamphenylboron chloride gave the alcohol as the minor product in each case (entries 4−6). Reaction with dicyclohexylboron chloride gave the highest isolated yield of alcohol **3b** (83%, entry 7).

The generality of this new oxidation protocol was established by successful reaction with a representative set of enynes (Table 3). Reaction yields from separate protonolysis control experiments listed in Table 3 provide a reference point for evaluating the impact of the transmetalation/oxidation steps on overall reaction efficiency. Gratifyingly, isolated yields of alcohols were within 10% of those obtained from protonation in all cases examined but for one exception (entry 6) in which oxidation was 20% less efficient.

Table 3. Oxidation or Protonation of Zirconocyclopentenes[a]



entry	enyne	isolated products, yield	
		oxidation	protonation
			
1	R = Ph	83%	89%
2	R = Me	75%	84%
			
3	R = Ph	70%	74%
4	R = p-ClC$_6$H$_4$	60%	61%
5	R = Me	76%[b]	83%[b]
			
6		64%[c]	82%[c]
			
7		49%	56%
			
8		64%	95%[d]
		See Scheme 2	
9			86%

[a] Zirconocycles generated in situ. [b] 1.5:1 ratio *trans*:*cis*. [c] 8:1 ratio. [d] 1 M H_2SO_4; H_2O (64%); 3 M HCl (multiple products).

A general procedure for oxidation was developed that consisted of treating the zirconocyclopentene (prepared in situ) in THF with $({}^c\text{Hex})_2$BCl (1.5−2 equiv) at room temperature.[23] After 5 h the borane was oxidized with alkaline hydrogen peroxide, and the product alcohol was isolated by flash chromatography. It is important to note that securing reproducible yields for this oxidation sequence necessitates that freshly prepared $({}^c\text{Hex})_2$BCl be employed.[24]

Malonate-derived 1,6-enynes with either phenyl- or methyl-substituted alkynes (entries 1 and 2) are excellent substrates for the cyclization and oxidation sequence, as are the geminal dimethyl substituted enynes in entries 3−5. In these cases oxidation efficiency closely mirrors that observed from protonation of the intermediate zirconocycles. In entry 5, a 1.5:1 ratio of diastereomers was obtained from both the protonation and oxidation reaction sequences.[20] The example in entry 6 illustrates that a substrate lacking a propensity for cyclization endowed by Thorpe−Ingold or reactive rotamer effects can be successfully oxidized,[25] but in this one case the yield of the alcohol (64%) lagged behind that for protonation (84%). Cyclization to form six-membered rings was achieved in moderate yields (entry 7), but reassuringly, oxidation efficiency (49%) was only slightly lower than for simple protonation (56%).

The product vinyl silane in entry 8 was not affected by the conditions employed to oxidize the intermediate borane, although conditions for concomitant Tamao−Fleming-type oxidation are under investigation. Protonation results with the enyne in entry 8 were peculiar in that yields greatly depended upon the acid source employed (e.g., 95% with 1 M H_2SO_4, 64% with H_2O, decomposition with 3 M HCl).

In contrast to the preceding results, reaction of enyne **7** (Scheme 2 and Table 3, entry 9) under the boron transmetalation-oxidation conditions with 1.5 equiv of $({}^c\text{Hex})_2$BCl resulted in formation of the expected *Z* product **8** (54%) along with the unusual *E* isomer **9** (31%). The assignment of the *E* configuration in **9** is based on single-crystal X-ray analysis (Figure 1). The olefin configuration and trans ring substituents of the remaining products were assigned on the basis of NOE data. Additionally, cleavage of the silyl ether in **8** and **11** with HF·pyridine gave the expected diols **10** and **9**, respectively, without *E*/*Z* isomerization.[26] When the amount of electrophilic borane was increased to 2.5 equiv, duplicate experiments showed that none of the diols **9** or **10** formed in the cyclization/oxidation reaction (Scheme 2).

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(23) **General Experimental Procedure.** To a solution of Cp_2ZrCl_2 (1.05 mmol) in THF (3 mL) cooled to −78 °C was added *n*-BuLi (2.1 mmol), and the dry ice bath was removed. The reaction mixture was allowed to warm until homogeneous (∼0 °C), at which point the mixture was cooled to −78 °C. A solution of enyne (1 mmol) in THF (1.5 mL) was added, and the dry ice bath was replaced with an ice bath. After 1 h the ice bath was removed, and the reaction was allowed to warm to room temperature. Neat $({}^c\text{Hex})_2$BCl was added 12−18 h later, and after 5 h the borane was oxidized by treatment with aqueous NaOH (2 mL, 7.5 M, 15 mmol) and H_2O_2 (30% aqueous solution, 2 mL), using a water bath to control the exotherm. The resultant reaction mixture was then heated at 50 °C for 1 h; allowed to cool; extracted with EtOAc; washed with 10% aqueous $Na_2S_2O_3$ (2 × 10 mL), saturated aqueous $NaHCO_3$, and brine; dried ($MgSO_4$); filtered; and purified by chromatography. See: Pagenkopf, B. L.; Lund, E. C.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 4421.

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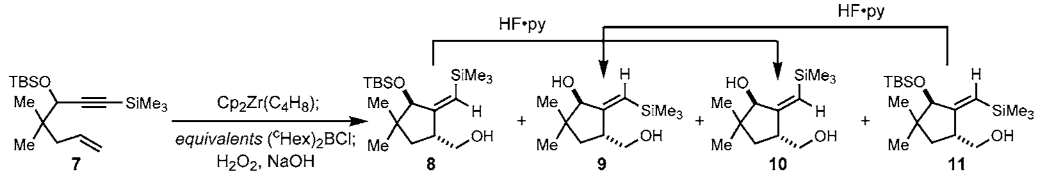
(26) This isomerization will be described elsewhere.

Scheme 2



1.5 equivalents R_2BCl, (85% yield), ratio: 1.7 : 1 : 0 : 0

2.3 equivalents R_2BCl, (83% yield), ratio: 2.6 : 0 : 0 : 1

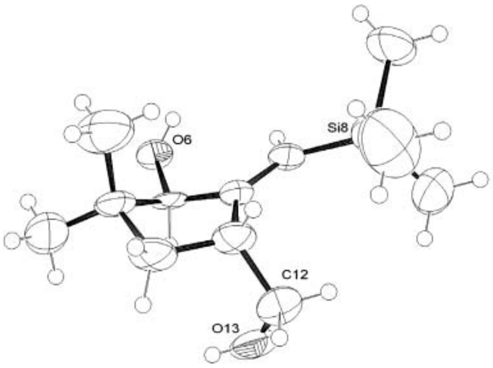
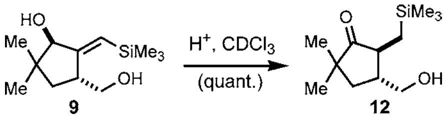


Figure 1. X-ray structure of **9**.

Scheme 3



The diol **9** was prone to undergo an interesting silicon-accelerated acid-catalyzed pinacol-type rearrangement (Scheme 3), and ketone **12** was obtained when a sample of vinylsilane **9** was stored in $CDCl_3$ at room temperature for several days (quantitative yield by ^1H NMR, 92% isolated yield).[27] Transition metal catalyzed isomerizations of allylic alcohols to carbonyl compounds have been extensively studied.[28]

In summary, a new method for the selective and efficient oxidation of zirconocyclopentenes to 1-alkylidene-2-hydroxymethylcyclopentanes featuring ligand migration from zirconium to boron has been described. The method is successful with a variety of enynes representative of those typically employed in zirconocene-mediated reductive cyclizations. This new oxidation protocol enhances the synthetic utility of reductive cyclizations by providing products with a functional handle suitable for further synthetic manipulations.

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Supporting Information Available: Characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036031R

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