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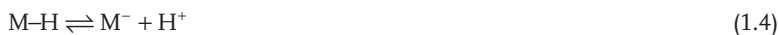
Catalysis Involving the H[•] Transfer Reactions of First-Row Transition Metals

John Hartung and Jack R. Norton

The M–H bonds of transition-metal hydride complexes may be cleaved heterolytically (H⁺, H[−] transfer) or homolytically (H[•] transfer). ΔG for the H⁺ transfer in Equation 1.1 is readily quantified by pK_a measurements (see Chapter 3). Analogous measurements for H[−] transfer, or “hydricities”, are difficult because the loss of H[−] generates a vacant coordination site. However, ΔG for Equation 1.2 can be determined indirectly, from electrochemical and pK_a measurements in the appropriate solvent [1, 2], and we can thus compare the “hydricities” of various hydride complexes (see Chapter 3). The lowest values of ΔG_{H^-} (corresponding to the complexes most eager to transfer H[−]) are found for second- and third-row transition metals¹⁾ [3], which is why those (relatively expensive) metals are good H[−] donors and effective catalysts for reactions like ionic hydrogenation [5–10].



The thermodynamics of the homolytic cleavage of an M–H bond (1.3) are also available from electrochemical and pK_a measurements (the thermodynamic cycle in Equations 1.4–1.6). The oxidation potential is that of the one-electron process in Equation 1.5. If the pK_a is measured in CH₃CN, and the potential is measured relative to ferrocene/ferrocenium in that solvent, ΔG for Equation 1.3 in CH₃CN is given by Equation 1.7 [11, 12], while the bond dissociation energy (BDE) for Equation 1.3 (the traditional gas phase “bond strength”) is given by Equation 1.8²⁾.



1) For $[HM(P-P)_2]^+$, experiments show that ΔG_{H^-} decreases in the order Ni > Pt > Pd; see reference [4].

2) The relative and absolute uncertainties in bond strengths determined in this way are discussed in reference [13].

Table 1.1 Bond dissociation energies of some chromium and vanadium hydrides.

Hydride	M–H BDE, kcal mol ^{–1}
CpCr(CO) ₃ H	62.2
dppm(CO) ₄ VH	57.9
dppe(CO) ₄ VH	57.5
dppp(CO) ₄ VH	56.0
dppb(CO) ₄ VH	54.9

$$\Delta G(\text{M–H})(\text{kcal mol}^{-1}) = 1.37\text{p}K_{\text{a}}(\text{M–H}) + 23.06(\text{M}^{-}/\text{M}^{\bullet}) + 53.6 \quad (1.7)$$

$$\text{BDE}(\text{M–H})(\text{kcal mol}^{-1}) = 1.37\text{p}K_{\text{a}} = 23.06E^{\circ} + 59.5 \quad (1.8)$$

Such measurements show the weakest M–H bonds to be those of first-row transition metals [4], and suggest that these (relatively abundant and cheap) metals are best for catalyzing reactions that involve H[•] transfer. Because most of these metals are nontoxic, their H[•] transfer reactions offer an attractive alternative to the tin-mediated radical chemistry that has become ubiquitous in organic synthesis.

Bond dissociation energies of most M–H bonds lie between 60 and 65 kcal mol^{–1} [4]. A few are much stronger: the Os–H bond of Cp(CO)₂OsH has a BDE ≥82 kcal mol^{–1} [14]. On the other hand V–H bonds are particularly weak. Calculations at the B3LYP level of theory on the hypothetical VH₅ give it the weakest M–H bond (43 kcal mol^{–1}) among neutral “valency-saturated” MH_n (i.e., among complexes where M forms the maximum number of M–H bonds) [15]. Experimentally Table 1.1 [13] shows very weak V–H bonds for (P–P)(CO)₄VH (P–P = Ph₂P(CH₂)_nPPh₂, with *n* = 1 (dppm), *n* = 2 (dppe), *n* = 3 (dppp), and *n* = 4 (dppb) [16, 17].

An H[•] transfer, or hydrogen atom transfer (HAT), reaction has been defined by Mayer as “the concerted movement of a proton and an electron ... in a single kinetic step where both ... originate from the same reactant and travel to the same product.” [18] Mayer considers HAT to be “one type of the broad class of proton-coupled electron transfer (PCET) reactions, which also includes reactions where the proton and electron are separated.” The distinction is a matter of ongoing discussion [19, 20], and other acronyms have been proposed [19, 21], but all the reactions to be considered in this chapter can be satisfactorily described as “H[•] transfer”.

1.1

H[•] Transfer Between M–H Bonds and Organic Radicals

HAT reactions from transition-metal hydrides to organic radicals R[•] (1.9) are characterized by second-order kinetics. Second-order kinetics have been

Table 1.2 Bond dissociation energies and rates of H[•] transfer to tris(*p*-*tert*-butylphenyl)methyl radical (extrapolated to room temperature) of several hydrides.

Hydride	BDE, kcal mol ⁻¹	<i>k</i> _H , M ⁻¹ s ⁻¹
Cp(CO) ₂ Fe–H	57 ^{a)}	1.2 × 10 ⁴
Cp(CO) ₃ Cr–H	62 ^{b)}	335
Cp(CO) ₂ Ru–H	65 ^{a)}	1.03 × 10 ³
(CO) ₄ Co–H	59, ^{c)} 67 ^{a)}	1.6 × 10 ³
(CO) ₅ Mn–H	68 ^{a)}	741
Cp(CO) ₃ Mo–H	69 ^{a)}	514
Cp(CO) ₃ W–H	72 ^{a)}	91
(CO) ₄ OsH ₂	78 ^{d)}	15.7

a) Ref [120].

b) Ref [13].

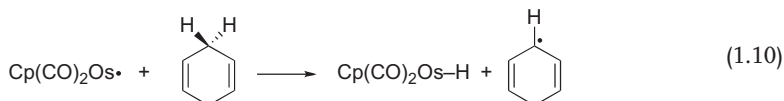
c) Ref [22].

d) Ref [23].

established (the rate constants are shown in Table 1.2) for the transfer of H[•] from a variety of hydrides to the tris(*p*-*tert*-butylphenyl)methyl radical [24–26]. The bulky *t*-Bu substituents keep it entirely monomeric in solution [27, 28]. Additional evidence that H[•] transfers to R[•] obey second-order kinetics is provided by studies of the last step in radical hydrogenation reactions (see Equations 1.14 and 1.15 below). If the hydride L_{*n*}M–H in a transfer such as Equation 1.9 is coordinatively saturated (18 electrons), the metalloradical L_{*n*}M[•] will have a 17 electron configuration.



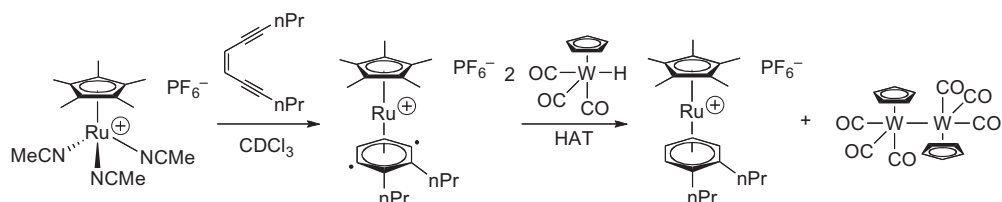
Second-order kinetics have also been established for H[•] transfer in the reverse direction, that is, from R–H to M[•]. The rate constant for Equation 1.10, from 1,4-cyclohexadiene to Cp(CO)₂Os[•], has been measured by time-resolved IR spectroscopy as 2.1 × 10⁶ M⁻¹ s⁻¹ (23 °C, hexane) [14]. Intriguingly, H[•] can be abstracted by a photogenerated osmium metalloradical from even stronger C–H bonds, such as those of toluene and THF; photolysis of [Tp(CO)₂Os]₂ (Tp = tris(pyrazolyl) borate) in either of these solvents gives the osmium hydride. (The C–H bonds of toluene (90 kcal mol⁻¹ for the methyl group) and THF (92 kcal mol⁻¹) are considerably stronger than that of cyclohexadiene (77 kcal mol⁻¹) [14, 29].)



Steric factors can be important in H[•] transfer reactions. The rate constant (*k*_H) of H[•] transfer to tris(*p*-*tert*-butylphenyl)methyl radical decreases by a factor of 37 from Cp(CO)₃MoH to Cp^{*}(CO)₃MoH (which has an Mo–H bond of comparable

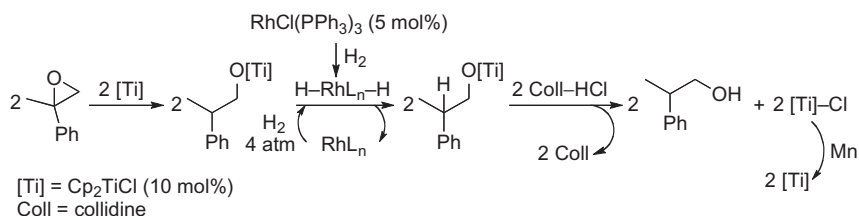
strength) [24, 25]. There is a smaller rate difference between Cp/Cp* with the more reactive 5-hexenyl radical; radical clock methods have shown that the rate constant for H[•] transfer decreases by a factor of two from Cp(CO)₃MoH to Cp*(CO)₃MoH at 298 K [30]. The considerable primary:secondary:tertiary selectivity of Cp*(CO)₃MoH in these radical clock studies (26:7:1) arises from steric interactions with the radical substituents [30].

However, the strength of an M–H bond is particularly important in determining the rate of its H[•] transfer reactions. Moving from Cp(CO)₃MoH to the (structurally similar) Cp(CO)₃WH in Table 1.2 produces a 5.6-fold decrease in *k*_H to tris(*p*-*tert*-butylphenyl)methyl as the bond strength increases by 3 kcal mol^{–1}. Consideration of M–H bond strengths has enabled O'Connor and coworkers to employ an H[•] donor that works effectively with their Ru cycloaromatization catalyst. In Scheme 1.1 Cp(CO)₃WH donates H[•] only to the diradical intermediate, whereas the weaker M–H bond in Cp(CO)₃CrH transfers H[•] to the enediyne before cycloaromatization [31].



Scheme 1.1 Ruthenium mediated Bergman cycloaromatization.

Gansäuer and coworkers have developed a tandem catalytic approach to reductive epoxide opening that employs H[•] transfer from a dihydride complex (Scheme 1.2) [32, 33]. The carbon-centered radical that arises from rate-determining epoxide opening with Cp₂TiCl abstracts H[•] from the H₂ adduct of Wilkinson's catalyst. Manganese or zinc metal regenerates the active Ti^{III} species and makes the reaction catalytic.



Scheme 1.2 Tandem catalytic epoxide opening.

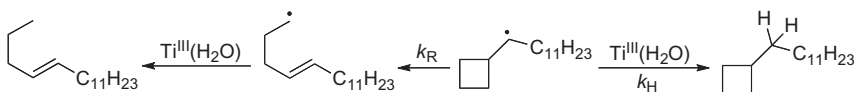
1.2

H[•] Transfer Between Ligands and Organic Radicals

The transfer of H[•] to organic radicals is not limited to hydride complexes. Although free N–H and O–H bonds have high bond dissociation enthalpies, they are weak-

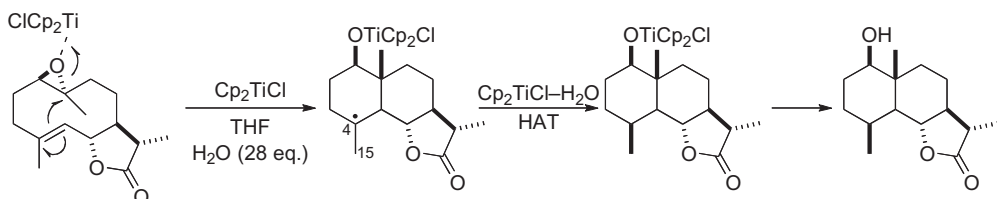
ened substantially by coordination of the N or O to a metal center. Such complexes, often of inexpensive transition metals, have been able to accomplish synthetically useful transformations.

Newcomb has measured the rate of H[•] transfer to carbon-centered radicals from the water and methanol complexes of Cp₂TiCl [34]. The rate constant (k_H) for HAT to the radical below (determined by the radical clock method, Scheme 1.3) in THF at room temperature is $1.0 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.



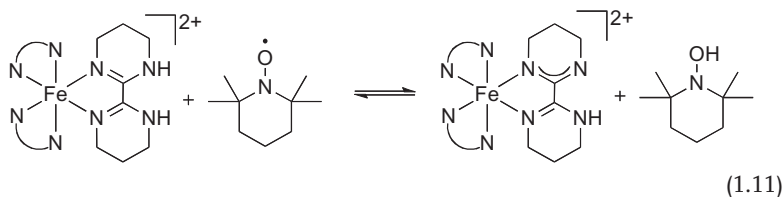
Scheme 1.3 Determination of k_H from Cp₂TiCl(H₂O) to a secondary alkyl radical.

In an investigation related to the total synthesis of (+)-3 α -hydroxyreynosin, Cuerva and Oltra discovered that the products of a Ti(III)-mediated epoxide-opening/cyclization cascade varied with the presence or absence of water. In dry THF they obtained the product originally desired, with an exocyclic Δ [3, 14] double bond, but the addition of water resulted in the formation of the reductively cyclized product in Scheme 1.4. Apparently H[•] is transferred from the titanium–water complex to the cyclized radical [35–37].

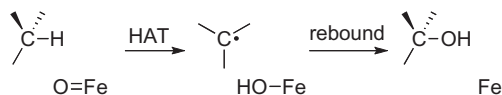


Scheme 1.4 Epoxide opening/reductive cyclization cascade.

Mayer has observed transfer of H[•] to TEMPO from an N–H bond in the tris iron(II) complex of 2,2'-bi(tetrahydropyrimidine) (1.11), and has shown that the Marcus cross relation accurately models its negative enthalpy of activation [38]. As previously suggested in another context [39], the high point on the enthalpy surface appears to occur before the transition state.

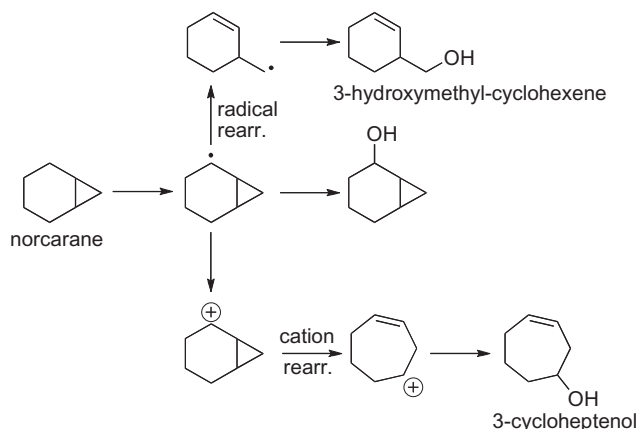


The abstraction of H[•] from organic substrates by oxo ligands occurs in the chemistry of cytochrome P450 and related biological oxidants [40, 41]. In most cases the resulting hydroxyl ligand is transferred to the organic radical (a “rebound” mechanism), giving an alcohol (Scheme 1.5).



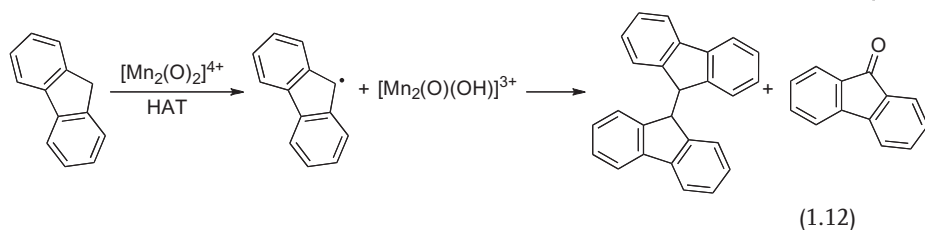
Scheme 1.5 Oxygen rebound mechanism.

Groves has demonstrated that norcaradiene functions as a mechanistic probe when oxidized by two bacterial enzymes P450_{cam} and P450_{BM3}, two mammalian enzymes CYP2B1 and CYP2E1 [42], and the monooxygenase AlkB from the soil organism *Pseudomonas oleovorans* [43]. In all cases (although the yield was lower with CYP2B1) an appreciable amount of the radical rearrangement product 3-(hydroxymethyl)-cyclohexene was formed, and relatively little of the product (3-cyclohepten-1-ol) expected from a cationic rearrangement (Scheme 1.6). In contrast, no radical rearrangement product was observed after the oxidation of spiro[2.5]octane by P450_{cam}, P450_{BM3}, CYP2B1, and CYP2E1 [42]; the radical generated by H[•] abstraction rearranges four times more slowly than that from norcaradiene.

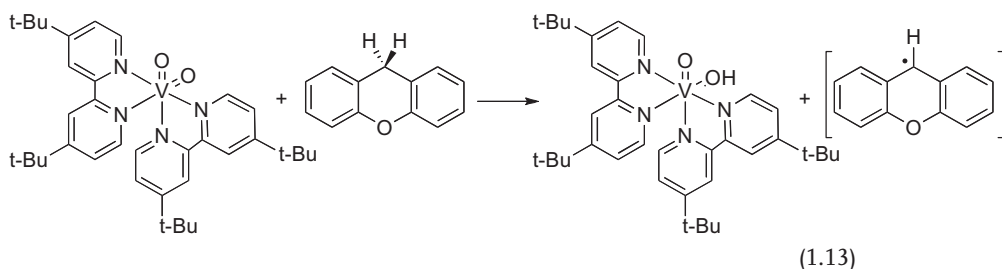


Scheme 1.6 Rearrangements available to norcaradiene during the oxygen rebound mechanism.

The oxo ligands in a number of model compounds have proven capable of removing H[•] from C–H bonds [44]. For example, the oxo ligands of [(phen)₂Mn(μ-O)₂-Mn(phen)₂] [4+] remove H[•] from fluorene (1.12) and xanthene, forming fluorenyl and xanthenyl radicals that dimerize or are oxidized to ketones (by radical addition to the bridging oxo ligand and subsequent oxidation) [45]. The rate of H[•] transfer in these systems is, to a first approximation, determined by ΔH, that is, by the strength of the O–H bond being made and the C–H bond being broken [44].



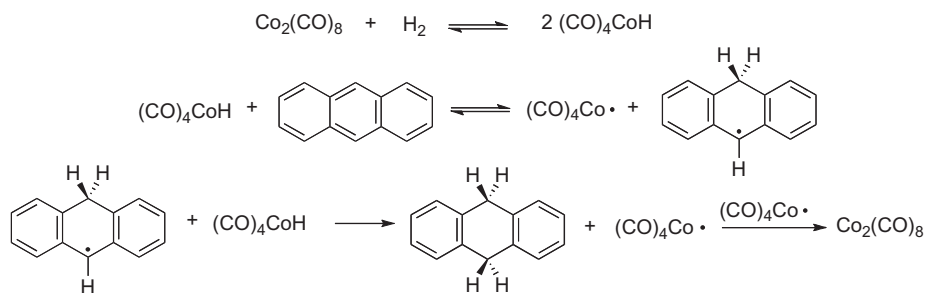
The H' transfer in Equation 1.13, to a vanadium oxo ligand, is surprisingly slow. The transfer requires a great deal of structural reorganization, as the V–O distance increases by 0.264 Å when V=O is converted to V–OH. The barrier to transfer of an H' from V–OH to V=O (in Marcus theory, the “intrinsic barrier” to self-exchange) is thus large, and its size is reflected in the size of the barrier to the C→O H' transfer in Equation 1.13 [46].



1.3

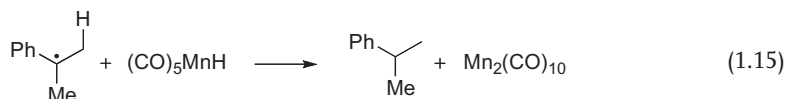
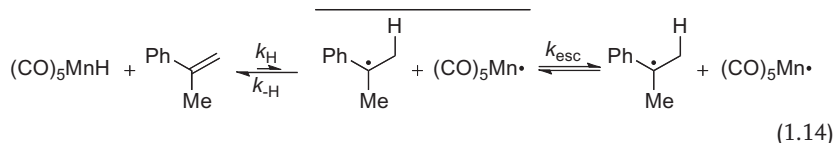
H' Transfer Between M–H and C–C Bonds

In the early 1950s reports appeared of the $\text{Co}_2(\text{CO})_8$ -catalyzed hydrogenation of polycyclic aromatic hydrocarbons in the presence of synthesis gas (CO/H_2). In 1975 Halpern proposed that these reactions occurred by sequential H' transfer from a cobalt hydride formed *in situ* (Scheme 1.7) [47]. This transfer must be reversible, because treatment of anthracene with $(\text{CO})_4\text{CoD}$ leads to deuterated anthracene [48]. (Syn addition of Co–D would not lead to H/D exchange.)



Scheme 1.7 Reduction of anthracene by $\text{Co}_2(\text{CO})_8$ under syngas.

In 1977 Sweany and Halpern reported the hydrogenation of α -methylstyrene by $(\text{CO})_5\text{MnH}$ and proposed that it began with a similar step, the reversible transfer of H[•] from Mn–H to the olefin (1.14) [49]. They established reversibility by showing that exchange between $(\text{CO})_5\text{MnH}$ and α -methylstyrene was faster than the overall reaction.



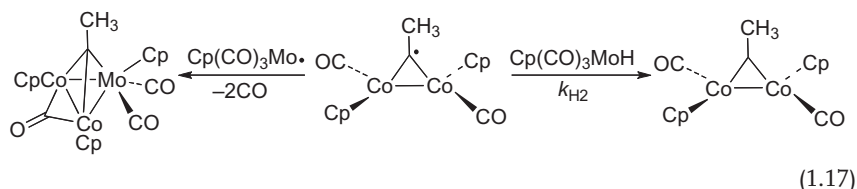
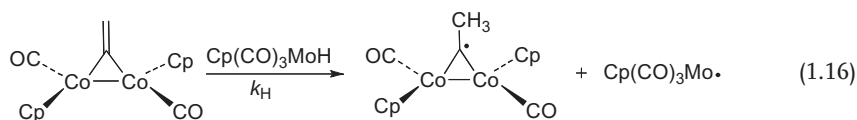
Convincing evidence for the radical products in Equation 1.14, and therefore for H[•] transfer, was offered by the observation of enhanced and/or distorted peaks in the ¹H NMR known as CIDNP (chemically induced dynamic nuclear polarization) for ¹H nuclei possessing significant coupling to unpaired electrons. This phenomenon requires that the pair of radicals formed in Equation 1.14 be contained within a solvent cage, with competition between back transfer (k_{-H}) and escape from the cage (k_{esc}). The changes due to CIDNP are smaller at the higher magnetic fields now in general use, making this phenomenon less commonly observed.

An inverse isotope effect (about 0.4 at 65 °C) was observed for the hydrogenation of α -methylstyrene according to Equations 1.14 and 1.15. (Cage escape, k_{esc} in Equation 1.14, appears to be the rate-determining step.) Sweany and Halpern wrote that an inverse effect in Reaction (1.14) was “not unexpected” in view of the “low initial frequency of the Mn–H bond ($\approx 1800\text{ cm}^{-1}$) relative to that of the C–H bond ($\approx 3000\text{ cm}^{-1}$)” [49]. By assuming 60 kcal mol^{-1} for Mn–H they estimated that ΔH° for H[•] transfer from $(\text{CO})_5\text{MnH}$ to styrene would be $+15\text{ kcal mol}^{-1}$ [50], making Equation 1.14 significantly endothermic³). A similar ΔH° , $+15\text{--}16\text{ kcal mol}^{-1}$, is implied by our BDE ($52.4\text{ kcal mol}^{-1}$) for the α -methylbenzyl radical [50–52] and the Mn–H BDE in Table 1.2 (68 kcal mol^{-1})⁴). Our C–H BDE is consistent with the strengths of C–H bonds next to other radical centers [54]. Inverse isotope effects often result from the presence of pre-equilibria that are less unfavorable for D than for H [55], but it is not clear whether such a pre-equilibrium is established inside the cage in Equation 1.14. It is possible that the inverse isotope effect observed for Equation 1.14 is the result of a late transition state for k_H [56]. It would be useful to know the vibrational frequencies of the α -methylbenzyl radical so that the equilibrium isotope effect could be calculated.

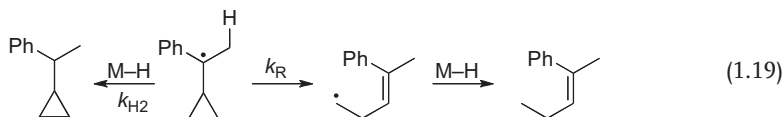
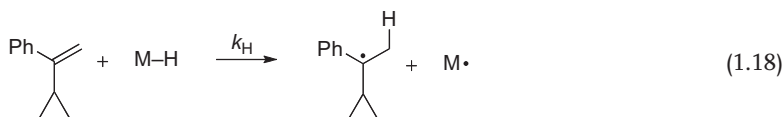
3) The fact that such reactions are thermodynamically uphill was pointed out in reference [24].

4) An incorrect estimate of ΔH° for H[•] transfer from $(\text{CO})_5\text{MnH}$ to styrene, “ $+8\text{--}10\text{ kcal mol}^{-1}$ ”, is given in reference [23] of reference [53].

In 1985 Jacobsen and Bergman proposed a similar H[•] transfer mechanism for the reaction of the dicobalt complex $(\mu\text{-CCH}_2)(\text{CpCoCO})_2$ with $\text{Cp}(\text{CO})_2(\text{L})\text{MoH}$ ($\text{L} = \text{CO}, \text{PMe}_3, \text{PPh}_3$) (1.16). They reported that H/D exchange was faster than the overall reaction, and that the isotope effect was inverse. (It became more inverse as the solvent viscosity increased, which they explained by suggesting that the greater viscosity made escape slower, increased the ratio of k_{H} to k_{esc} , and allowed the H[•] transfer equilibrium within the cage more time to establish itself prior to escape [57].)



Bullock determined the rate constant k_{H} for the transfer in Equation 1.18 from the overall rate of hydrogenation, and used the rearrangement of the cyclopropylbenzyl radicals as a clock to determine k_{H_2} in Equation 1.19 [58]. The reversibility of Equation 1.18 was demonstrated by the observation that, with $\text{Cp}(\text{CO})_3\text{CrD}$, H/D exchange was faster than the overall reaction; an inverse isotope effect (0.55 at 100 °C) was obtained with $\text{Cp}(\text{CO})_3\text{WH}/\text{Cp}(\text{CO})_3\text{WD}$. The relative values of k_{H} in Equation 1.18 (which is generally endothermic) were largely determined by the strengths of the M–H bonds, while the relative values of k_{H_2} in Equation 1.19 (which is relatively exothermic) were largely determined by steric effects.



Our group has determined the rate constants for H[•] donation from $\text{Cp}(\text{CO})_3\text{CrH}$ and related Cr hydrides to methyl methacrylate and styrene [51, 52], and compared them to the rates at which the various $(\text{P-P})(\text{CO})_4\text{VH}$ donate H[•] to the same substrates [13]. The strength of the Cr–H bond in $\text{Cp}(\text{CO})_3\text{CrH}$ (62.2 kcal mol^{−1} in Table 1.1) is surely one reason why its H[•] transfer to styrene is relatively slow. The V–H bonds in $(\text{P-P})(\text{CO})_4\text{VH}$ transfer H[•] more rapidly, although the difference is

Table 1.3 M–H bond dissociation energies and rates of H[•] transfer to styrene.

Hydride	BDE, kcal mol ^{−1}	10 ^{−3} × <i>k</i> _H , M ^{−1} s ^{−1}
dppm(CO) ₄ VH	57.9	≥17
dppe(CO) ₄ VH	57.5	≥9.0
dppp(CO) ₄ VH	56.0	7.0
dppb(CO) ₄ VH	54.9	5.7
Cp(CO) ₃ CrH	62.2	0.85

not as large as would be expected from the decrease in bond strength between these and the Cr hydrides. The vanadium hydride dppe(CO)₄VH transfers H[•] to styrene about 10 times more rapidly than does Cp(CO)₃CrH [13].

As Table 1.3 shows, *k*_H becomes *slower* as the V–H bonds in (P–P)(CO)₄VH become *weaker*; presumably the steric effect of the chelating ligand undermines the effect of the weaker bond. It is worth noting a precedent for the fast transfer of H[•] from vanadium: *k*_H from the anionic hydride Cp(CO)₃VH[−] to a hexenyl radical has been reported to be “more than an order of magnitude larger than that measured for Bu₃SnH” [59].




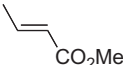

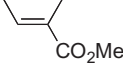


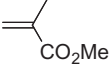
The influence of the double bond substituents on *k*_H has been determined by treating a series of olefins with Cp(CO)₃CrH and its D analogue. Comparing the reactivity of the various olefins requires that we estimate *k*_H (for H[•] transfer from Cp(CO)₃CrH) when we have measured *k*_D (from Cp(CO)₃CrD). As stated previously, inverse isotope effects are generally observed for the transfer of H[•] from M–H to a carbon–carbon double bond [56, 60]. To date, the only isotope effect reported for Cp(CO)₃CrH, by Bullock *et al.* [58], is *k*_H/*k*_D = 0.45 ± 0.10 for its reaction with 2-cyclopropylpropene at 68°C. We have used 0.45 (the effect of the temperature difference is negligible compared to the uncertainty) to estimate the *k*_H values for hydrogen atom transfer to olefins; we have then calculated the relative rates from these *k*_H values to deduce the chemoselectivity of this step [61]. Some of the olefins in Table 1.4 undergo hydrogenation, some undergo H/D exchange, but in either case it is straightforward to estimate *k*_H (Table 1.4)⁵⁾.

A substituent on the carbon that receives the H[•] slows *k*_H by a factor of about a thousand (compare entries 1 and 2). Substituents that stabilize the resulting radical increase *k*_H (CH₃<CO₂Me<Ph) [61].

5) Deducing *k*_H from the rate constant for H/D exchange requires that we estimate the isotope effect for back transfer—the relative rate at which H and D transfer back to the Cr from the organic radical initially formed. In most cases the

resulting *k*_H is not very sensitive to this isotope effect estimate (which we have, from the results quoted after Equation 1.27, taken as 3 in references [62] and [63]).

Table 1.4 Rates of H[•] transfer from Cp(CO)₃CrH to various olefins at 49.8 °C.

Entry	Olefin	$10^{-3} \times k_H \text{ (M}^{-1} \text{s}^{-1}\text{)}$	Relative rate
1		0.59 (2)	1
2		460 (60)	780
3		79 (3)	134
4		$\leq 3.2 \times 10^{-4}$	$\leq 5 \times 10^{-4}$
5		$\leq 1.1 \times 10^{-4}$	$\leq 2 \times 10^{-4}$
6		$(0.8 \text{ to } 1.6) \times 10^{-2}$	≈ 0.02
7		$\leq 3.2 \times 10^{-3}$	≤ 0.005
8		15.8 (6)	27
9		14 (3)	24

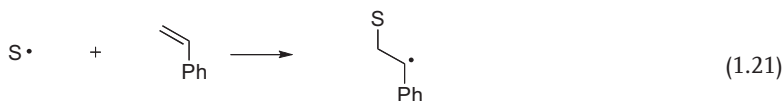
1.4

Chain Transfer Catalysis

H[•] transfer *from* the α carbon of an organic radical *back* to a metalloradical (the reverse of 1.18) is a key step in CCT (catalytic chain transfer), a process that can be used to control radical polymerizations. Many of the effective CCT catalysts contain inexpensive and abundant transition metals; the first catalysts all contained cobalt.

Suess [64] and Schulz [65] observed that the presence of solvents during the polymerization of styrene lowered the molecular weight. In the case of CCl₄, Mayo suggested that the chain-carrying radical abstracted Cl[•] from CCl₄ (1.20), terminating the chain but leaving CCl₃[•], which added to monomer and initiated a new chain (1.21).

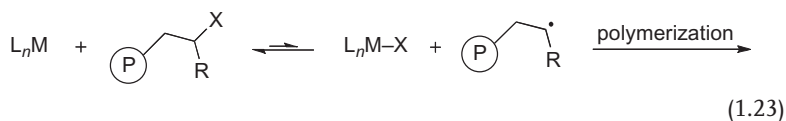




Mayo defined a chain transfer constant that could be empirically determined by Equation 1.22. \bar{P} is the degree of polymerization, S and M are concentrations of solvent and monomer respectively, and \bar{P}_0 is the degree of polymerization in the absence of solvent. Thiols are particularly effective (albeit stoichiometrically as in 1.20 and 1.21) reagents for chain transfer [66].

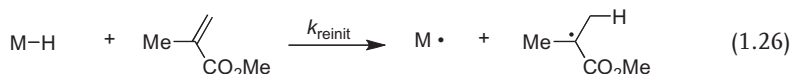
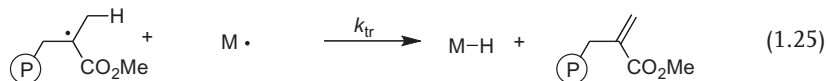
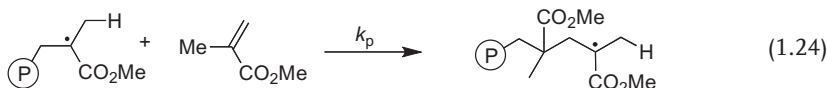
$$\frac{1}{\bar{P}} = C \frac{(S)}{(M)} + \frac{1}{\bar{P}_0} \quad (1.22)$$

It is possible to carry out chain transfer *catalytically*. The process is related to atom transfer radical polymerization (ATRP) [67, 68] and related “living” polymerizations which keep the concentration of chain-carrying radicals low. ATRP employs a halide complex (often $\text{Ru}^{\text{III}}\text{X}$) that is subject to facile one-electron reduction; that complex reversibly donates X^\bullet to the chain-carrying radical (1.23) and thereby decreases the concentration of the latter [69, 70].



In CCT a metalloradical reversibly *abstracts H[•]* from the chain-carrying radical and starts a new chain. Early work on CCT during radical polymerizations employed cobalt porphyrins during the polymerization of methyl methacrylate, and was carried out in the USSR (Smirnov, Marchenko in 1975; Enikolopyan in 1977). Gridnev discovered in Moscow in 1979 that cobaloximes were effective CCT catalysts, then moved to the US in 1992 (Wayland laboratory, University of Pennsylvania) and joined DuPont in 1994. The basic features of CCT have been described in a series of patents (at first Russian, then largely DuPont) that appeared in the 1980s [71], and in a comprehensive review that appeared in 2001 [72]. The mechanism in Scheme 1.8 has become generally accepted, and CCT has been successfully applied to other monomers (styrene, methacrylonitrile) and comonomers.

In Scheme 1.8, propagation (1.24) occurs by the addition of the chain-carrying radical to the double bond of the monomer. Chain transfer requires that hydrogen atoms shuttle from the growing polymer chain to the same (monomer) double bond. In the first step, Equation 1.25, H^\bullet is removed from the chain-carrying radical; in Equation 1.26 its transfer to fresh monomer begins a new chain [72]. The competition of H^\bullet removal (1.25) with propagation (1.24) reduces the chain length and molecular weight of the polymer. (During a free radical polymerization the rate constant for propagation is chain length dependent [73].)



Scheme 1.8 Catalytic chain transfer polymerization.

The efficiency of a chain transfer catalyst has traditionally been measured by its chain transfer constant (C_s), which is the ratio of the rate constant for chain transfer (k_{tr}) to that for propagation (k_p). Values of C_s are generally determined from the slope of a plot of $1/\text{DP}_n$ vs. $[\text{CTA}]/[\text{M}]$ (the Mayo method, Equation 1.27 [74]), in which DP_n is the degree of polymerization, CTA is the chain transfer agent, and M is monomer.

$$\frac{1}{\text{DP}_n} = \frac{1}{\text{DP}_{n0}} + \frac{k_{tr}[\text{CTA}]}{k_p[\text{M}]} \quad (1.27)$$

By comparing the termination rate constant during a MMA- d_0 polymerization with that during a MMA- d_5 polymerization, the isotope effect $k_{tr(\text{H})}/k_{tr(\text{D})}$ can be estimated as 2.93 at 60°C [62]. It can also be estimated as 3.5 (between 40 and 80°C) by comparing the efficiency of a cobalt catalyst for chain transfer during MMA polymerization to the efficiency of the same catalyst during the polymerization of MMA- d_8 [63].

While macrocyclic cobalt(II) complexes are effective catalysts for chain transfer (see above), the hydrides they form during the catalytic cycle are unobservable, presumably because they are so efficient in transferring H^\bullet back to monomer (1.26) [72]. Chromium and vanadium metalloradicals offer the advantage that their hydrides are stable enough to be observed. For the polymerization of methyl methacrylate, $(\text{C}_5\text{Ph}_5)(\text{CO})_3\text{Cr}^\bullet$ is a good chain transfer catalyst, $\text{Cp}(\text{CO})_3\text{Cr}^\bullet$ (in equilibrium with its dimer) is a much better one [75], and the vanadium metalloradical $\text{dppe}(\text{CO})_4\text{V}^\bullet$ shows respectable activity [76]. This effectiveness implies that the corresponding hydrides $((\text{C}_5\text{Ph}_5)(\text{CO})_3\text{CrH}$, $\text{Cp}(\text{CO})_3\text{CrH}$, and $\text{dppe}(\text{CO})_4\text{VH}$) transfer H^\bullet back to methyl methacrylate.

The ratio between the metalloradical and the corresponding hydride during chain transfer catalysis is determined by the balance between H^\bullet transfer from the chain-carrying radical to M^\bullet (as in 1.25) and reinitiation by transfer from M-H to the monomer (as in 1.26). We can define a $C_s(\text{true})$ in terms of the apparent C_s (from the slope of a Mayo plot) by Equation 1.28, where $[\text{M}]_{\text{st}}$ is the concentration at steady state. For the various Cr hydrides, with their relatively strong Cr-H bonds, the balance lies slightly on the side of H^\bullet transfer to Cr^\bullet , so $[\text{Cr-H}] > [\text{Cr}^\bullet]$,

and from Equation 1.28 $C_s(\text{true}) > C_s(\text{app})$. For Co(II) chain transfer catalysts, the balance lies completely on the side of the Co(II) “metalloradical”, and $C_s(\text{true})$ is equal to $C_s(\text{app})$ [77].

$$C_s(\text{app}) = C_s(\text{true}) \times \frac{[\text{M}^\bullet]_{\text{st}}}{[\text{M}^\bullet]_0} \quad (1.28)$$

The characteristics of an effective chain transfer catalyst are now clear [75]. First, M^\bullet must be stable under the conditions of polymerization. Second, the metal center must be crowded enough to discourage (i) the dimerization of M^\bullet , (ii) the formation of a bond between M^\bullet and the chain-carrying radical R^\bullet , and (iii) the hydrogenation of R^\bullet by the transfer of H^\bullet from $\text{M}-\text{H}$. (Dimerization of M^\bullet will interfere with its ability to abstract H^\bullet from R^\bullet ; formation of $\text{M}-\text{R}$ bonds will also deplete M^\bullet ; transfer of H^\bullet to R^\bullet will terminate growing chains.) Finally, the BDE of the $\text{M}-\text{H}$ bond in the corresponding hydride should be as close as possible to the BDE of the $\text{C}-\text{H}$ bond in the chain-carrying radical. (If the substrate is methyl methacrylate, the $\text{C}-\text{H}$ BDE formed by the H^\bullet transfer in Equation 1.26 will be 50 kcal mol^{-1} [51, 52].)

Cobalt(II) macrocyclic complexes (Figure 1.1, Table 1.5) are the best available chain transfer catalysts [78].

There is a possibility that, during chain transfer catalysis, H^\bullet transfer occurs not only to monomer but also to the vinyl-terminated oligomers generated by chain transfer. Wayland and coworkers have reported that the degree of polymerization increases with the extent of conversion during the polymerization of MMA and

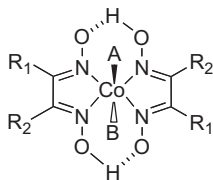


Figure 1.1 Cobaloxime.

Table 1.5 Effect of substituents on cobaloximes: methyl methacrylate polymerization.

R_1	R_2	A	B	C_s
Me	Me	Cl	Py	5 000
Me	Me	PPh_3	PPh_3	20 000
Ph	Ph	Cl	Py	30 000
Ph	Ph	Cl	PPh_3	100 000

methacrylic acid [79] with a Co porphyrin as a chain transfer catalyst. This result suggests that reinitiation can occur by H \cdot transfer to these oligomers.

Treatment of Cp*(CO) $_3$ CrD with a large excess of MMA *dimer* allows the measurement of k_{reinit} by monitoring the increase in the hydride resonance due to H/D exchange [80]. This method gives a value of $3 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, which is much smaller than the k_{reinit} for MMA itself ($1.74 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$) [51].

1.5

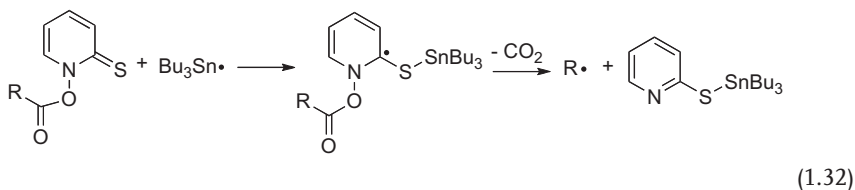
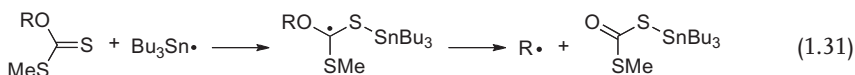
Catalysis of Radical Cyclizations

Methods involving carbon-centered radicals are used extensively in synthesis [81–83]. The cyclization of such radicals forms the rings common in natural products, and tolerates functional groups—for example, unprotected hydroxyls—that cannot be present during some heterolytic transformations.

Generally, cyclizations begin with the photo- or initiator-stimulated formation of a tin radical, which abstracts X \cdot from R–X (1.29); where X is Br, I, occasionally Cl, or PhSe or PhS [84]. The resulting R \cdot then undergoes cyclization or rearrangement to R' \cdot before abstracting H \cdot from a tin hydride (typically Bu $_3$ SnH), which regenerates the tin radical (1.30) and continues the chain. Such methods are necessarily stoichiometric both in tin and in another heavy element (Br, I, Se, S).



Related methods begin with the addition of a radical Rad \cdot to the C=S double bond in a xanthate (1.31) or thiohydroxamate (1.32) ester [84, 85]. (Rad \cdot is often R $_3$ Sn \cdot but in initial investigations *t*-BuS \cdot and CCl $_3\cdot$ were also used [86, 87].) The resulting intermediates give R \cdot by β scission (31 and 32) and decarboxylation (1.32).

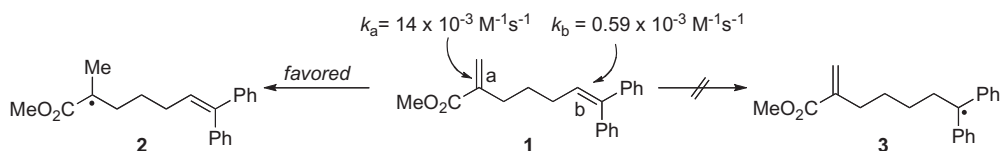


Special care is required to handle trialkyltin hydrides and the waste they generate, and standard laboratory purification techniques often leave toxic levels of tin compounds in the product [88]. The industrial application of these methods has been hindered by the need to remove these tin-containing contaminants. Methods catalytic in tin have been developed [89–91], and tin hydride reagents modified to make their removal easier [92–98], but the need for alternatives to tin

remains [99–101]. A review entitled “Flight from the Tyranny of Tin” has appeared [102].

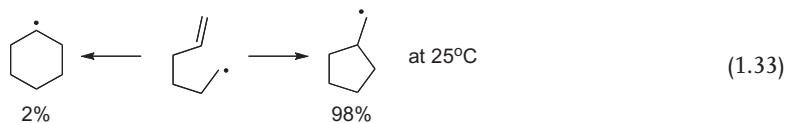
Substitutes such as *N*-ethylpiperidinium hypophosphite [103], (Me₃Si)₃SiH [104], Bu₃GeH [105], HGaCl₂ [106], and HInCl₂ [107] contain bonds to hydrogen stronger than that of 78 kcal mol⁻¹ in Bu₃SnH [29] and are, therefore, likely to be less reactive in H[•] transfer. Studer has remarked that “transition metal based hydrides are promising alternatives to the tin hydrides” [108], and Cp₂Zr(H)Cl has been used for the cyclization of halo acetals [109].

Radicals that will undergo cyclization can be generated *without the use of tin* by the transfer of H[•] from M–H to one C=C in an appropriate 1,6 diene. The two C=C in the diene must, however, perform different functions: one must accept H[•] quickly; the other must undergo facile intramolecular attack by the radical thus generated. Table 1.4 [61] predicts that the “a” double bond in **1** should be kinetically favored for H[•] transfer (25 times faster), yielding radical **2** rather than radical **3** (Scheme 1.9).



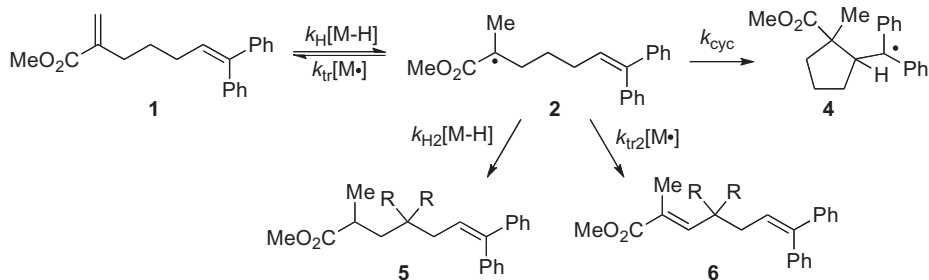
Scheme 1.9 H[•] transfer to diene **1**.

The ethyl ester analogous to **2** cyclizes rapidly to a five-membered ring with $k_{\text{cyc}} > 10^5 \text{ s}^{-1}$ [110]. In general, the cyclization of 5-hexenyl radicals to five-membered rings is favored over their cyclization to six-membered rings. For the 5-hexenyl radical itself the rate constant at 25 °C for 5-exo cyclization is $2 \times 10^5 \text{ s}^{-1}$, and the rate constant for 6-endo cyclization is $4 \times 10^3 \text{ s}^{-1}$ (1.33). These reactions have often been used as “radical clocks”, to determine the rate constants of competing reactions [111]. The synthetic utility of a particular radical cyclization reaction is often a matter of how successfully its k_{cyc} can compete with other rate constants.



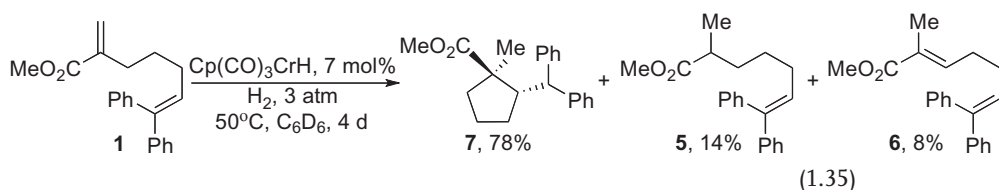
All the reactions to which **2** is subject are shown in Scheme 1.10. In addition to cyclization it can undergo back transfer ($k_{\text{tr}}[\text{M}^{\bullet}]$), hydrogenation ($k_{\text{H}_2}[\text{M}-\text{H}]$), and isomerization by H[•] abstraction ($k_{\text{tr}2}[\text{M}^{\bullet}]$) from the carbon adjacent to the radical center.

Back transfer and isomerization require M[•], and can be avoided if M[•] is converted back to M–H rapidly enough—a transformation that has the advantage of making the overall reaction *catalytic*. Cp(CO)₃Cr[•] is converted back to Cp(CO)₃CrH with modest hydrogen pressures (3 atm H₂, Equation 1.34). (This transformation



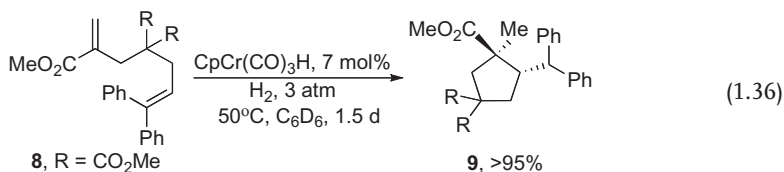
Scheme 1.10 Pathways available to radical **2**.

was reported by Fischer and coworkers in 1955, but under a pressure of 150 atm at 70 °C [112].) Thus Reaction 1.35 is catalytic as well as tin-free, forming **7** in 78% yield together with relatively small amounts of the hydrogenation product **5** and the isomerization product **6**.



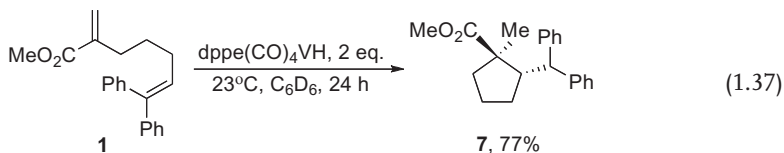
Increasing the concentrations of $\text{CpCr}(\text{CO})_3\text{H}$ and **1**, or heating the reaction, shortens the reaction time but increases the extent of hydrogenation to **5**. Increasing the hydrogen pressure increases the rate at which $\text{CpCr}(\text{CO})_3\cdot$ is converted to $\text{CpCr}(\text{CO})_3\text{H}$ and thus increases (as we expect from Scheme 1.10) the ratio of the hydrogenation byproduct **5** to the isomerization byproduct **6**.

When we increase k_{cyc} by placing two substituents on the γ carbon to take advantage of the Thorpe–Ingold effect, the reaction (**8**→**9**) becomes quantitative (1.36) [113].

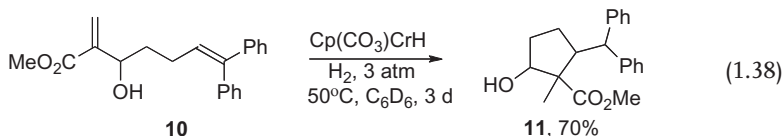


In view of the speed with which the weak V–H bonds in $(\text{P}-\text{P})(\text{CO})_4\text{VH}$ transfer $\text{H}\cdot$ to styrene (Table 1.3 above), we have tried these hydrides with the cyclization substrates **1** and **8**. *Stoichiometrically* they give similar results, but *more quickly, even at lower temperatures* [13]. For example, treatment of **1** with $\text{dppe}(\text{CO})_4\text{VH}$

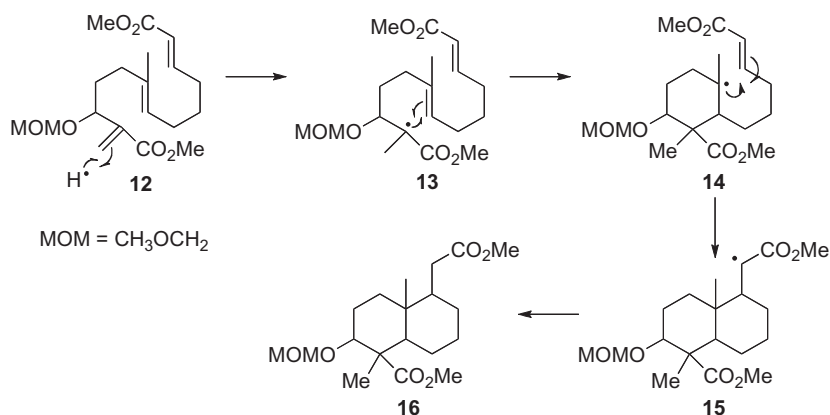
gives **7** in 77 % yield (1.37), while treatment of **8** with any of the vanadium hydrides gives **9** quantitatively. Unfortunately, these vanadium hydrides cannot be regenerated from the corresponding vanadoradicals, at least at 50 °C and 80 psi, so they can only be used as *stoichiometric* reagents.



Additional α -substituted acrylates related to our original substrate **1** are readily assembled by the Morita–Baylis–Hillman reaction [114, 115], but necessarily bear an additional hydroxyl group. However, that substituent appears to have little influence on k_{cyc} . Treatment of diene **10** with a *catalytic* amount (7 mol%) of $\text{Cp}(\text{CO})_3\text{CrH}$ in C_6D_6 under 3 atm H_2 generated the substituted cyclopentanol **11** after three days at 50 °C (1.38), while treatment of **10** with a *stoichiometric* amount of $\text{dppe}(\text{CO})_4\text{VH}$ gave **11** in 77% yield after 3 h at room temperature [53].



This chemistry can be used to initiate *sequential* (cascade) cyclizations. From a Morita–Baylis–Hillman reaction and protection of the resulting hydroxyl we have prepared the triene **12**. Treatment of **12** with a catalytic amount of $\text{CpCr}(\text{CO})_3\text{H}$ under H_2 for 6 d gave the cyclization product **16** in 23% isolated yield, presumably by the mechanism in Scheme 1.11 [53].



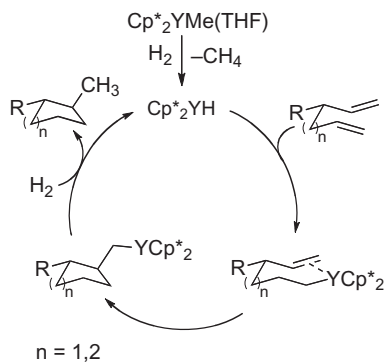
Scheme 1.11 Proposed 6-endo/6-exo cascade cyclization of **12** to **16**.

The initial H^\bullet transfer will occur to the α -substituted acrylate, giving radical **13**. The 6-endo-trig cyclization of **13** gives tertiary radical **14**, which forms the decalin **15** by intramolecular addition to its *E* double bond.

1.6

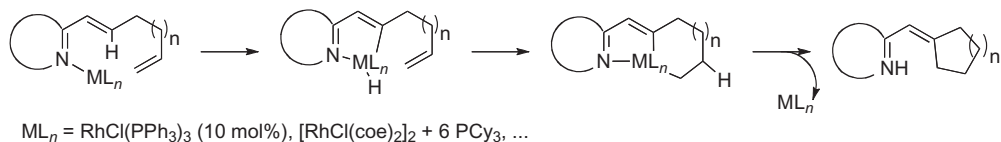
Competing Methods for the Cyclization of Dienes

A number of other organometallic species cyclize 1,5- and 1,6-dienes to five- and six-membered rings. In an early example Molander used 5 mol% $\text{Cp}^*_2\text{YMe}(\text{THF})$ under H_2 (Scheme 1.12) [116]. Sigma-bond metathesis releases methane and forms a Y-H bond. Sequential insertion of the two double bonds into the Y-H bond gives cyclization; hydrogenolysis of the resulting Y-C bond releases the product and reforms the yttrium hydride.



Scheme 1.12 Cyclization of 1,5- and 1,6-dienes by $\text{Cp}^*_2\text{YMe}(\text{THF})$ under H_2 .

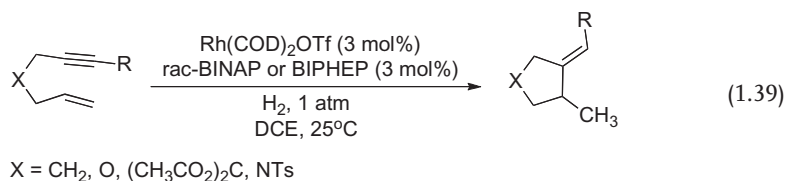
Other methodologies capable of cyclizing 1,6 dienes require the use of precious metals. Pd allyls cyclize these dienes to unsaturated products [117], and Ru and Rh catalysts cyclize heterocycle-substituted dienes [118]. Murai's method functions by the mechanism proposed in Scheme 1.13).



Scheme 1.13 Cyclization of heterocycle-substituted dienes.

Initial coordination to the nitrogen of the heterocycle guides insertion into the alkenyl C–H bond to form the transition metal hydride. Insertion into the pendant olefin gives the metallobicycle, which reductively eliminates to regenerate the catalytic species and form the cycloalkane.

Rh(I) catalysts under H₂ effect the reductive cyclization of diynes and enynes [119]. In the example below (1.39), Rh(COD)₂OTf (COD = 1,5-cyclooctadiene) is converted by H₂ gas to a Rh hydride, which is thought to undergo oxidative cyclization to produce a rhodacyclopentene intermediate. Cleavage of the Rh–C bonds by reductive elimination to form a vinyl rhodium species, and hydrogenolysis of that intermediate, forms the Rh hydride and the cyclized product.



1.7

Summary and Conclusions

Steric as well as electronic factors affect the rate at which H[•] is transferred between a transition metal and the carbon of a double bond. However, the weak M–H bonds of the first-row metals, particularly vanadium, make them uniquely effective in this regard.

Such reactions can be used in the catalysis of *chain transfer* during radical polymerizations. In this process a metalloradical abstracts H[•] from a chain-carrying radical, transfers it to the double bond of a monomer, and starts a new chain. The resting state of traditional cobalt chain-transfer catalysts is the Co(II) metalloradical, but both the metalloradical and the hydride are present during the operation of newer (Cr) catalysts. Success in catalyzing chain transfer requires (i) that the M–H bond be not too much stronger than the 50 kcal mol^{–1} C–H bond in chain-carrying radicals, and (ii) that M[•] be stable enough to discourage the formation of bonds other than that to hydrogen.

Cp(CO)₃CrH and (P–P)(CO)₄VH can be used to initiate radical *cyclizations* by transferring H[•] to activated terminal olefins. However, the resulting radicals must cyclize quickly; competing reactions include transfer of a second H[•] (resulting in hydrogenation) and removal of an H[•] (resulting in isomerization) (Scheme 1.10). Cp(CO)₃CrH is relatively slow at H[•] transfer, but can be regenerated with H₂ gas, enabling it to carry out reductive cyclizations catalytically; vanadium hydrides (P–P)(CO)₄VH are faster but operate stoichiometrically.

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