Sustainable Radical Reduction through Catalytic Hydrogen Atom Transfer

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Owing to their high versatility, selectivity, and compatibility with densely functionalized substrates, radical reactions are frequently employed in the synthesis of complex molecules.[1] However, limitations also exist. One of the unresolved problems is constituted by catalytic and environmentally benign reduction of carbon-centered radicals.[2] Water or alcohols have been introduced as stoichiometric reductants to address the second issue.[3] Here, we demonstrate that H_2 constitutes an attractive hydrogen atom source for at least two reasons. First, the reduction will proceed under complete atom economy.[4] Second, after activation by a transition metal complex, the powerful arsenal of catalytic hydrogenation methods can be made accessible for radical reduction.[5] The use of stoichiometric amounts of stannanes, silanes, or cyclohexadienes can be avoided.[2]

Here, we describe a process exploiting these features. It is based on the combination of the catalytic cycles outlined in Scheme 1. The radical intermediates are generated by titanocene-catalyzed epoxide opening via electron transfer.[6] Radical reduction proceeds through hydrogen atom transfer from Wilkinson's catalyst, one of the most common hydrogenation catalysts.[7] In this manner, the well-established advantages of both radical chemistry and hydrogenation methods can be combined for efficient radical reduction. Through our decoupling of radical generation and reduction, the kinetic constraints of the $CpCr(CO)_3$-catalyzed radical chain cyclizations using H_2 are circumvented.[8]

To be effective, the radical reducing hydrogen atom abstraction from both **1** and **2** should be exothermic and faster than epoxide opening. It is reasonable to assume that both conditions can be fulfilled. Usually, hydrogen atom abstractions by carbon-centered radicals from transition metal hydrides are highly exothermic due to the weakness of M−H bonds compared to C−H bonds. In the case of rhodium(III) hydrides, these BDEs are about 58 kcal mol^{-1}.[9] The rate constants k of these processes[10] may be as high as 10^9 M^{-1} s^{-1}.[11] Thus, even for sterically shielded β-titanoxy radicals, these reactions will be much faster than titanocene-mediated epoxide openings ($k \approx 0.5-2$ M^{-1} s^{-1}).[12]

Our approach can only be successful if the cycles of Scheme 1 do not interfere. We were optimistic that this could be achieved for two reasons. First, Wilkinson's catalyst is stable toward strong Lewis acids, such as BF_3*Et_2O.[13] It should therefore tolerate the mildly acid protic conditions of the titanocene-catalyzed oxirane opening. Second, titanocenes are stable under typical hydrogenation conditions and activate H_2 only slowly after reaction with alkyl lithium reagents.[14] Hence, the titanium(III) complexes involved in epoxide opening should not be affected by the any of the Rh species or H_2 and vice versa.

The relative rates of the two cycles were adjusted to avoid an accumulation of reactive intermediates such as **2** or the titanocene-bound radicals as summarized in Table 1.

Without $RhCl(PPh_3)_3$, a complex mixture containing **6** and unidentified side products was obtained in only 20% yield (entry

Scheme 1. Sustainable Radical Reduction through Catalytic Hydrogen Atom Transfer

[Ti] = Cp₂TiCl
[Rh] = RhCl(PPh₃)₂ or ₃ generated from RhCl(PPh₃)₃
[Ti] = Cp₂TiCl
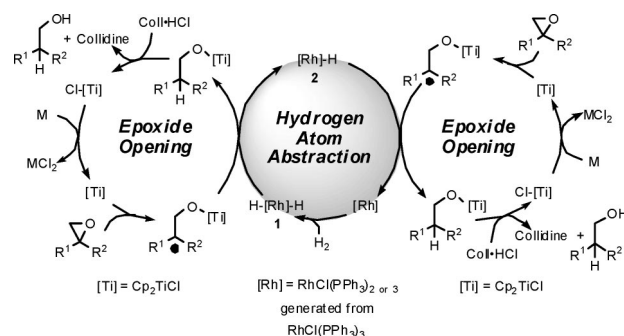
Table 1. Optimization of the Catalytic Hydrogen Atom Transfer in THF (See Supporting Information for Details) at 4 bar H_2

entry	**4**/mol %	**5**/mol %	T/°C	concn/ M	reductant	**6**/%
1	10		25	0.2	Mn	<20[a]
2		5	25	0.2		0
3	10	5	25	0.2	Mn	68[b]
4	10	5	25	0.2	Mn	84
5	10	5	25	0.2	Zn	81
6	10	2.5	25	0.2	Mn	81
7	5	2.5	25	0.2	Mn	72
8	5	1	25	0.2	Mn	73
9	5	1	25	0.4	Mn	55
10	5	1	50	0.2	Mn	46
11	10	5	0	0.2	Mn	34

[a] Obtained with two other unknown compounds. [b] With 1 bar H_2.

1).[15] No formation of **6** was observed without Cp_2TiCl_2 (entry 2), and **3** was reisolated in >85% yield. This rules out alernative pathways, such as epoxide isomerization to an allylic alcohol and hydrogenation or radical reduction by adventitious water. When applying only 1 bar of H_2 (entry 3), a 68% yield of **6** was obtained compared to 84% with 4 bar pressure (entry 4). As desired, this suggests that radical reduction is fast. Hydrogen activation hence constitutes the slowest step in the central catalytic cycle. With 10 mol % of **4** and 5 mol % of **5**, yields of more than 80% of **6** can be obtained with either Mn or Zn as reductant (entries 4 and 5). Decreasing the amount of **5** to 2.5 mol % resulted in a slightly reduced yield of **6** (81%, entry 6). A similar trend was observed when lowering the loading of both **4** to 5 mol % and **5** to 2.5 or 1 mol %, respectively (entries 7 and 8). This suggests that epoxide opening constitutes the rate-determining step of our process. An increase in the concentration results in a deterioration of the isolated yield of **6** (entry 9). This is also the case for changing the temperature (entries 10 and 11).

Table 2. Functional Group Tolerance under Optimized Conditions

entry	substrate	product	yield/%[a]
1	**3** PhCOMe	**6** PhCOMe	81 / 87
2	**7**	**8**	82
3	**9**	**10**	71
4	**11**	**12**	67
5	**13**	**14**	79
6	**15**	**16**	66
7	**17** tBuO—OtBu	**18** tBuO—OtBu	57

[a] See Supporting Information for details.

Table 3. Catalytic Enantioselective Epoxide Opening

RO—epoxide—OR, 10 mol% **19**, Mn, Coll*HCl, **5**, H$_2$ → RO—CH(OH)—OR

R = nPr: **20**
R = Et : **22**

19 =

R = nPr: **21**
R = Et : **23**

entry	substrate	**5**/mol %	product	yield	(R):(S)[a]
1	**17**	10	**18**	60	93:7
2	**20**	5	**21**	64	97:3
3	**22**	5	**23**	75	96:4

[a] Measured by GC analysis of the isolated products (see Supporting Information).

We next turned our attention to the compatibility of our reaction conditions with different functional groups and epoxide substitution patterns. These results are summarized in Table 2.

The reaction conditions tolerate sensitive functionality. Acetophenone can be reisolated in 87% yield when added to the reduction of **3**, while the yield of **6** remains essentially unchanged (81%, entry 1). Tosylates (entry 2), esters (entry 3), and chlorides (entry 4) remain unaffected. Silyl groups can also be submitted to our conditions (entry 5). The reaction of **15** is especially noteworthy. In titanocene-based methodology, the reduction of benzylic radicals is notoriously difficult and requires thiols or selenols (entry 6).[6a] Bulky ethers in the close vicinity of a secondary radical center are tolerated (entry 7).

To probe the sensitivity of our reaction toward the substitution pattern of the titanocene catalyst, we investigated the enantioselective opening of three *meso*-epoxides[16] by Kagan's complex **19**[17] (Table 3). Alcohols **18**, **21**, and **23** were isolated with enantioselectivities identical to those of the reactions performed with 5 equiv of 1,4-cyclohexadiene as radical reductant.[17] Thus, radical genera-

tion by the titanocene(III) reagents and radical reduction by the rhodium hydrides are fully compatible. For both **4** and **19**, the isolated yields of the products are similar to the reactions with 5 equiv of the hydrogen atom donors such as cyclohexadienes.[15] Thus, radical reduction by rhodium hydrides is as efficient as titanocene-catalyzed radical generation.

In summary, we have presented the first system of combined catalytic cycles for a sustainable reduction of radicals. Our approach unites titanocene-catalyzed reductive epoxide opening with the powerful rhodium-catalyzed H$_2$ activation and hydrogen atom transfer. Because of their different affinities toward the substrates and ligands, the early and late transition metal catalysts are mutually compatible. Epoxide opening tolerates a number of functional groups incompatible with nucleophilic ring opening by hydride reagents. The regioselectivity of ring opening is complementary to S$_N$2 reactions. Moreover, opening of *meso*-epoxides occurs with high enantioselectivity.

Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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