Radical Chemistry

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Catalytic Hydrogen Atom Transfer (HAT) for Sustainable and Diastereoselective Radical Reduction**

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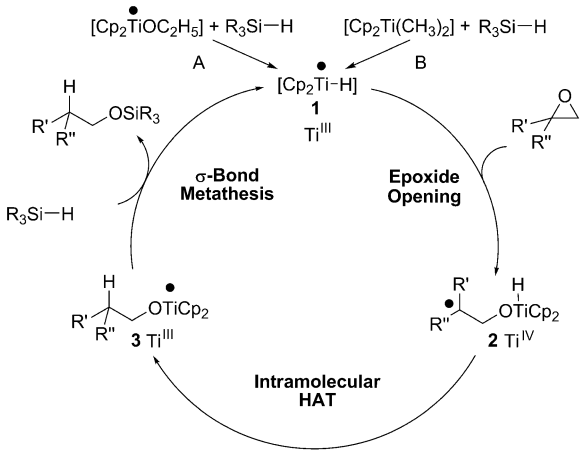
Radical reduction by HAT (hydrogen atom transfer) is an essential step in numerous radical reactions.[1] While transition-metal hydrides are in principle excellent reagents for this purpose because of their low bond dissociation energies,[2] their use in such reactions is attractive only when they serve as catalysts.[2d] The ideal catalyst for such a process should be able to activate a readily available, nontoxic terminal reductant to form the transition-metal hydride, act as a radical-generating agent, and reduce the radical through HAT. A system matching the requirements is the reductive epoxide opening catalyzed by $[Cp_2TiH]$ (**1**; Scheme 1).

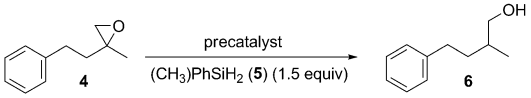


Scheme 1. Catalytic radical reduction featuring intramolecular HAT.

The active catalyst **1** can be generated from $[Cp_2Ti^{III}OC_2H_5]$, which is formed by dissociation of the dimer[3] or formed in situ from $[Cp_2Ti^{IV}(CH_3)_2]$ and silanes.[4] Furthermore, **1** should be able to open epoxides through electron transfer with a regioselectivity similar to that of other titanocene(III) reagents.[5] Radical reduction can subsequently take place through an intramolecular HAT from the weak Ti^{IV}–H bond to the radical center in **2**. The active catalyst **1** is regenerated from **3** by σ-bond metathesis.[6] The intramolecular HAT in this cycle is an appealing step not only because it enables catalysis. First, it should occur with radicals that are otherwise difficult to reduce. Second, it should enable unprecedented catalytic and stereoselective HATs[7] via conformationally well-defined cyclic transition states.

The realization of our catalytic cycle with **4** is summarized in Table 1. Silane **5** was chosen as the terminal reductant because it has been shown to generate titanocene(III) hydrides from dimethyl titanocenes and was used in the preparation of $[(Cp_2TiOC_2H_5)_2]$.[4] While method A provides slightly higher yields than B it should be noted that method B is more convenient, because $[Cp_2Ti^{IV}(CH_3)_2]$ is commercially available as a solution in toluene and somewhat easier to handle than $[(Cp_2TiOC_2H_5)_2]$. For both methods, the catalyst loading can be reduced to 1 mol% under reflux without lowering the yield of **6**. Our novel method requires only a small excess of **5** instead of an equimolar amount of the acid (Coll·HCl; Coll = 2,4,6-trimethylpyridine) and large excesses of Mn or Zn and 1,4-cyclohexadiene.[8]

Table 1: Catalytic reduction of **4** in the presence of **5** (1 M **4**/THF, RT, desilylation with aq K_2CO_3) .



Method	Amount of Ti [mol%]	Precatalyst	*t* [h]	**6** [%]
A	5	$[(Cp_2TiOC_2H_5)_2]$	14	84
A	1	$[(Cp_2TiOC_2H_5)_2]$	16	86[a]
B	5	$[Cp_2Ti(CH_3)_2]$	14	77
B	1	$[Cp_2Ti(CH_3)_2]$	24	78[a]

[a] Reflux.

The scope of the catalytic radical reduction was further explored with aryl-substituted epoxides and 1-dodecene oxide (Table 2). Both types of substrates usually give low yields in titanocene-catalyzed and -mediated epoxide openings.[8] Monosubstituted epoxides mainly give olefins under the previous conditions. Aryl-substituted epoxides are not only prone to nucleophilic ring opening under acidic conditions but also the resulting benzylic radicals are difficult to reduce in general.[1a–c,8]

Our method conducted under neutral conditions gives excellent results for both types of substrates (Table 2). Tertiary benzylic radicals (entries 1–3) are reduced in yields

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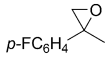
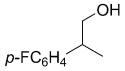
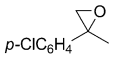
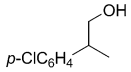
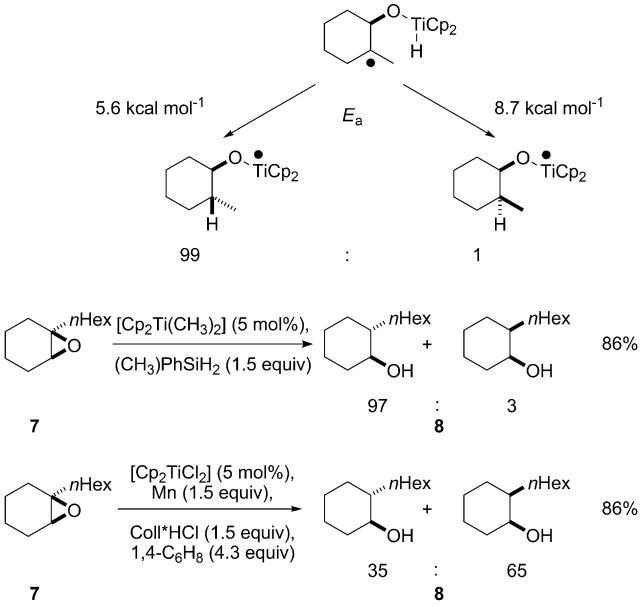
Table 2: Catalytic reduction of aryl- and monosubstituted epoxides (conditions unless otherwise noted: $[Cp_2Ti(CH_3)_2]$ (5 mol%), $(CH_3)PhSiH_2$ /1.5 equiv), 1 M epoxide/THF, reflux, desilylation with aq K_2CO_3).

Entry	Substrate	Product	*t* [h]	Yield [%]
1			16	83
2			14	79
3			36	82
4			16	65
5			18	68
6			16	81[a]
7			18	79[b]

[a] 78:22 mixture of 1- and 2-dodecanol. [b] RT, 80:20 mixture of 1- and 2-dodecanol, $[(tBuC_5H_4)_2Ti(CH_3)_2]$.



Scheme 2. Reduction of cyclohexyl radicals by *syn*- or *anti*-selective HAT. For computational details see the Supporting Information.

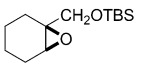
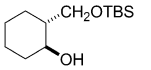
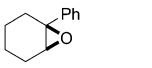
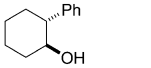
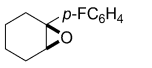
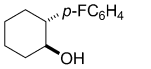
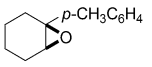
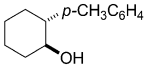
of ca. 80%. Secondary benzylic radicals (entries 4 and 5) give slightly lower yields. 1-Dodecene oxide (entry 6) is opened in 81% yield with $[Cp_2Ti(CH_3)_2]$ as the precatalyst. In reactions with $[Cp_2Ti(CH_3)_2]$ heating is necessary for reasonable reaction times. Gratifyingly, the reaction can be carried out at room temperature with $[(tBuC_5H_4)_2Ti(CH_3)_2]$ with essentially identical results (entry 7). Thus, bulky catalysts are also tolerated by our system and can even lead to improved results.

With an operating catalytic system in hand, we turned our attention to the diastereoselective reduction of epoxide-derived radicals. The postulated intramolecular HAT should result in ordered cyclic transition states. For cyclic radicals this leads to an unprecedented and highly selective catalytic formation of *trans* products by means of a *syn*-selective radical reduction[9] as verified by both computational and synthetic results (Scheme 2).

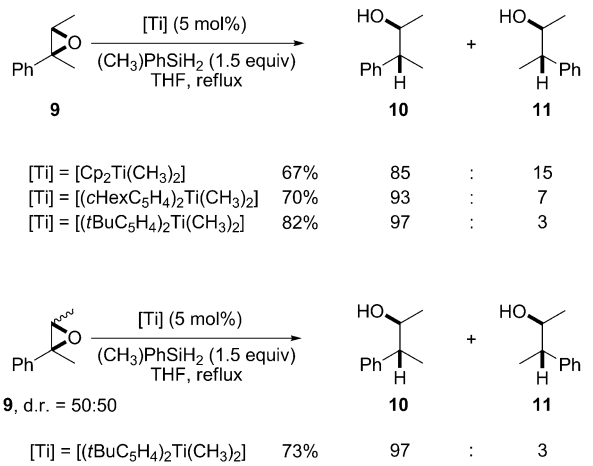
The computational study (Scheme 2, top) demonstrates that the transition state for the *syn* HAT is lower in energy than the transition state for *anti* HAT by 3.1 kcal mol^{-1}. This prediction is in excellent agreement with the synthetic diastereoselectivity of radical reduction (*syn*/*anti* = 97:3; Scheme 2, middle). With an external HAT reagent, such as 1,4-C_6H_8 (1,4-cyclohexadiene), the *cis* product is predominantly obtained by an *anti*-selective HAT. However, the selectivity is disappointingly low (35:65; Scheme 2, bottom) in agreement with the results of Giese et al.[7b] Thus, our concept of an intramolecular *syn*-selective HAT through binding of the HAT catalyst to the radical provides a unique opportunity for controlling the diastereoselectivity of radical reduction. The examples in Table 3 highlight the validity of our concept. In reactions with aliphatic as well as aromatic substituents at the radical center high yields and diastereoselectivities are obtained, in the latter case, even at elevated temperatures. A silyl protecting group (TBS) was tolerated.

An even greater challenge is the diastereoselective reduction of acyclic radicals. We chose **9** either diastereomerically pure or as 1:1 mixture of *cis* and *trans* isomers as a substrate to investigate the influence of the *syn*-selective HAT on this issue (Scheme 3). The $[Cp_2Ti(CH_3)_2]$-derived catalyst gave only a moderate diastereoselectivity of 85:15. Introduction of bulky substituents resulted in higher selectivity. With $[(tBuC_5H_4)_2Ti(CH_3)_2]$ as the precatalyst an excellent selectivity of 97:3 was obtained even in refluxing THF. Gratifyingly, with this system the highest yield of **10** was obtained (82%), too. Moreover, our process is diastereoconvergent as exemplified in the reaction of **9** as 1:1 mixture of diastereomers. The diastereoselectivity in the formation of **10** was the same as that observed for pure *trans*-**9**. This finding demonstrates that after epoxide opening the intramolecular HAT is slower than rotation around the C–C bond adjacent to the radical center. As an explanation for the high diastereoselectivity (Figure 1), we suggest that in transition state **A** the interactions between the cyclopentadienyl ligands and the

Table 3: Catalytic diastereoselective reduction of substituted cyclohexene oxides ($[Cp_2Ti(CH_3)_2]$ (5 mol%), 1.5 equiv $(CH_3)PhSiH_2$, in THF, desilylation with aq K_2CO_3).

Entry	Substrate	Product	d.r.	*t* [h]	Yield [%]
1			96:4	22	80[a]
2			96:4	16	86[b]
3			96:4	4	76[b]
4			94:6	16	81[b]

[a] $[(Cp_2TiOC_2H_5)_2]$ (2.5 mol%), RT, 0.17 M epoxide. [b] Reflux, 1 M epoxide.



Scheme 3. Diastereoselective reduction of acyclic radicals by reductive opening of **9**.

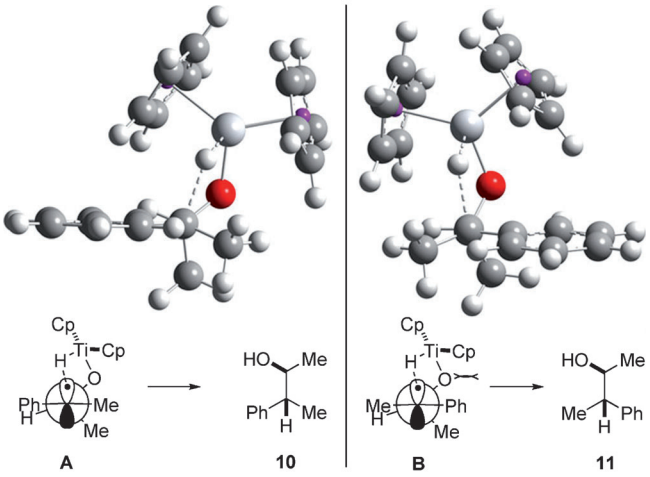


Figure 1. Transition states for radical reduction through *syn*-selective HAT after ring opening of **9**.

methyl group at the radical center are substantially weaker than the interactions between the cyclopentadienyl ligands and the phenyl group in **B**. This will be even more pronounced with the $(t\mathrm{BuC_5H_4})_2$Ti-bound radical.

Thus, our catalytic system featuring the catalytic intramolecular *syn*-selective HAT is also suitable for unprecedented and highly selective reductions of acyclic radicals. It should be noted that in related studies the opposite diastereoselectivity was observed by Giese et al. for intermolecular *anti*-selective HAT from TTMSS (tris(trimethylsilyl)silane).[10]

In summary, we have devised a novel, sustainable, and highly efficient catalytic system for the activation of readily available, nontoxic $(\mathrm{CH_3})\mathrm{PhSiH_2}$ towards reduction of epoxide-derived radicals. The catalytically active species, a titanocene(III) hydride, serves a dual role as a radical-generating species and as a HAT catalyst for the radical formed. The crucial HAT proceeds in an intramolecular manner and is therefore *syn*-selective. This unprecedented catalyst control of radical reduction allows highly diastereoselective HAT with cyclic and acyclic radicals. In the latter case the reaction can even be conducted stereoconvergently. The experimental results are in agreement with a preliminary computational study of the proposed mechanism.

Experimental Section

$[(\mathrm{Cp_2TiOC_2H_5})_2]$ (11.2 mg, 25.0 μmol, 1 mol% [Ti]) and **5** (917 mg, 7.50 mmol, 1.50 equiv) were dissolved in THF (5 mL) under Ar. After the mixture had been stirred for 5 min, **4** (811 mg, 5.0 mmol, 1.0 equiv) was added and the mixture was heated at reflux for 16 h. The solution was added to acetone (5 mL) and aq K_2CO_3 (25 wt% in H_2O, 100 mL, and stirred for 16 h. The organic solvents were concentrated under reduced pressure and the remaining solution was extracted with Et_2O (1 × 100 mL). The organic phase was washed with sat. NaCl solution (1 × 20 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography (SiO_2, eluent cyclohexane/ethyl acetate 9:1) gave 706 mg (4.30 mmol, 86%) of **6**.

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