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Homogeneous Catalysis **Hot Paper**

Titanocene(III)-Catalyzed Precision Deuteration of Epoxides

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Abstract: *We describe a titanocene(III)-catalyzed deuterosilylation of epoxides that provides β-deuterated anti-Markovnikov alcohols with excellent D-incorporation, in high yield, and often excellent diastereoselectivity after desilylation. The key to the success of the reaction is a novel activation method of Cp_2TiCl_2 and $(tBuC_5H_4)_2TiCl_2$ with BnMgBr and $PhSiD_3$ to provide $[(RC_5H_4)_2Ti(III)D]$ without isotope scrambling. It was developed after discovering an off-cycle scrambling with the previously described method. Our precision deuteration can be applied to the synthesis of drug precursors and highlights the power of combining radical chemistry with organometallic catalysis.*

Introduction

The preparation and use of deuterated compounds is a highly active field of research.[1] Studying reaction mechanisms through deuteration allows a unique analysis of the pathways of a particular process by analyzing the magnitude and regio- or stereoselectivity of deuterium incorporation (DI).[2] These investigations not only provide insights essential for the understanding of reactions but also offer unique perspectives for improving the performance of the reaction under scrutiny.

One of the attractive applications of deuterated compounds is their use as drugs.[3] While such drugs preserve the biochemical potency and selectivity, their metabolism may be affected by the kinetic isotope effect that imparts different reactivity to C–H and C–D bonds. This can lead to a lower dosage required for the deuterated drug or metabolic shunting resulting in the inhibition of the formation of toxic metabolites from the deuterated drug. Thus, deuterium incorporation can result in safer and more efficient drugs with reduced side effects. To date, the two main approaches towards deuterated drugs are perdeuteration and precision deuteration. In perdeuteration,[1a,c,e] deuterium is incorporated by multiple H/D-exchange reactions or by introduction of perdeuterated groups, such as $-CD_3$ and $-C_6D_5$. Though the perdeuteration approach has been highly successful commercially, there are also disadvantages of this strategy. In perdeuterated compounds, it is not always clear which particular incorporation of deuterium is responsible for the desired pharmaceutical (pharmacokinetic) effects, especially in the case of deuterated alkyl chains.

In contrast, precision deuteration[1b,4] could serve as an approach opening complementary perspectives if deuterium is selectively incorporated at a defined position in a given molecule. By providing selectively deuterated compounds, the potentially most active compound in a series of isotopomers can be identified. Moreover, the amount of the respective deuterium source can also be lowered compared to perdeuteration. Amongst potential deuteration sites, benzylic and tertiary centers are of elevated interest as they are soft-spots for metabolic oxidation via P450 enzymes.[5]

To be practically useful, precision deuteration reactions should be easy to carry out, result in high ratios of deuterium incorporation (>95%) and use readily available, bench-stable deuterating agents in stoichiometric amounts or in slight excess. In this respect, deuterosilanes, such as $PhSiD_3$ or $Ph(Me)SiD_2$, are particularly attractive because they can be easily prepared[6] and do not require storage under anhydrous or oxygen free conditions. Indeed, silanes have been referred to as "liquid hydrogen"[7] because of their ability to store hydrogen that can be liberated in situ by suitable metal catalysts.

Results and Discussion

Here, we report on titanocene catalysis[8] for the activation of deuterosilanes in catalytic epoxide deuterosilylations (Scheme 1). For the success of the precision deuteration it is mandatory that the activation proceeds efficiently and leads to a high DI for the active catalyst [Ti]–D. Moreover, no off-cycle isotope scrambling must occur to ensure high DI for the desired organic products.

If these conditions can be met, this investigation will not only allow us to gain further insight into the mechanism of epoxide hydrosilylation but will also result in a precision deuteration of epoxides with high diastereoselectivity and a regioselectivity opposite to that of S_N2 reactions.[9] In this manner, anti-Markovnikov alcohols with a D-label at the epoxides' more substituted C-atom are obtained. Cp_2TiCl_2

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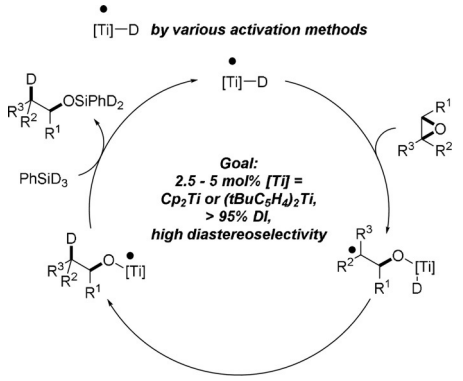
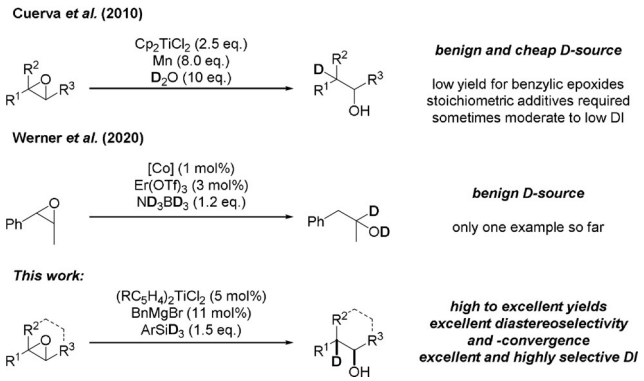


Scheme 1. Concept of the titanocene-catalyzed epoxide precision deuteration.

and $(t\mathrm{BuC_5H_4})_2\mathrm{TiCl_2}$ are attractive precatalysts. $\mathrm{Cp_2TiCl_2}$ is readily available and easy to handle. $(t\mathrm{BuC_5H_4})_2\mathrm{TiCl_2}$ is an attractive substitute if the diastereoselectivity of epoxide deuteration with $\mathrm{Cp_2TiCl_2}$ is low.

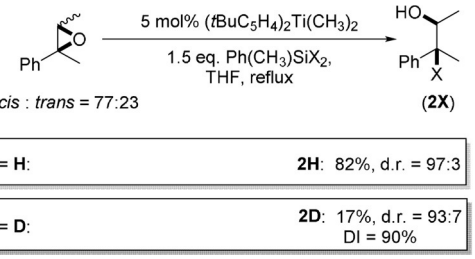
Two anti-Markovnikov openings under deuterating conditions have been described (Scheme 2): Justicia's and Cuerva's titanocene-mediated (2.5 equiv. $\mathrm{Cp_2TiCl_2}$, 8 equiv. Mn) or catalyzed (0.2 equiv. $\mathrm{Cp_2TiCl_2}$, 8 equiv. Mn, 2.0 equiv. Coll*DCl) epoxide deuteration with $\mathrm{D_2O}$ (10 equiv.) provides the deuterated alcohols typically in 35–90 % yield and 55–90 % DI (stoichiometric) and 40–60 % yield and 60–85 % DI (catalytic).[10] Werner's Er- and Co-catalyzed reactions proceed via a Meinwald rearrangement[11] and ensuing reduction of a carbonyl group with $\mathrm{ND_3BD_3}$ (1.2 equiv.).[12]



Scheme 2. Previously reported anti-Markovnikov openings of epoxides under deuterating conditions.

We employed $(t\mathrm{BuC_5H_4})_2\mathrm{TiMe_2}$ as catalyst precursor first (Scheme 3).[13] This is because the complex can be stored in solution for extended periods of time and can activate silanes through the formation of titanocene hydrides by simple heating.

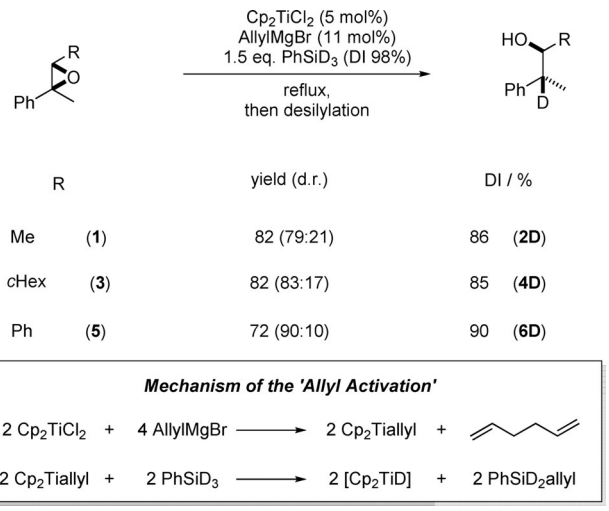
Compared to the hydrosilylation with $(t\mathrm{BuC_5H_4})_2\mathrm{TiMe_2}$ with $\mathrm{Ph(CH_3)SiH_2}$, the use of $\mathrm{Ph(CH_3)SiD_2}$ (98 % DI) results in a sluggish and incomplete reaction (17 % yield of **2D**). Moreover, **2D** is not even fully deuterated (90 % DI). Thus, an H/D-isotope scrambling is occurring during catalysis. While the exact mechanism of this process is unclear, it is



Scheme 3. Hydro- and deuterosilylation of **1** with $(t\mathrm{BuC_5H_4})_2\mathrm{TiMe_2}$.

clear that using $(t\mathrm{BuC_5H_4})_2\mathrm{TiMe_2}$ is not promising for a precision deuteration.

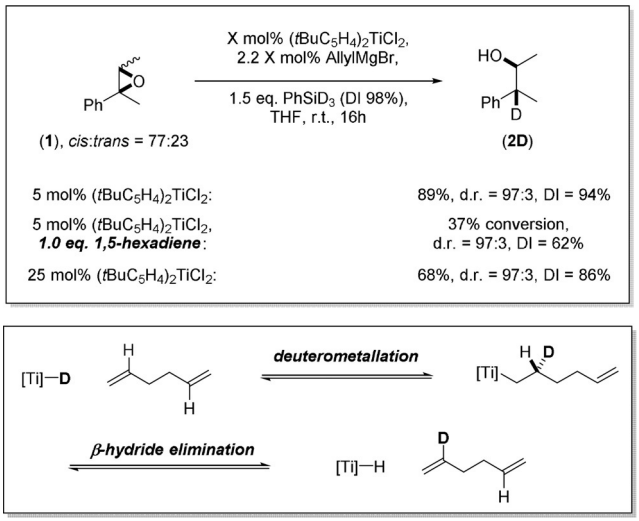
A milder method for the in situ generation of $[\mathrm{Cp_2TiH}]$ from bench stable $\mathrm{Cp_2TiCl_2}$ employs allylMgBr for the preparation of $[\mathrm{Cp_2Tiallyl}]$[14] (allyl activation).[15] This species is then transformed into $[\mathrm{Cp_2TiH}]$ by σ-bond metathesis with $\mathrm{PhSiH_3}$. Some of our initial results with $\mathrm{Cp_2TiCl_2}$ of the allyl activation for precision deuteration with $\mathrm{PhSiD_3}$ (98 % DI) are summarized in Scheme 4.



Scheme 4. Attempted precision deuteration after allyl activation and mechanism of the allyl activation.

The experiments with substrates **1**, **3**, and **5** show that acceptable to high yields of the desired products **2D**, **4D**, and **6D** were obtained with diastereoselectivities typical of the titanocene-catalyzed epoxide hydrosilylation. However, DI varies between 85 and 90 % and is far from ideal for a precision deuteration. The result that DI is dependent on the epoxides' substitution pattern suggests that $[\mathrm{Cp_2TiD}]$ undergoes an H-D-exchange faster than epoxide opening because bulkier epoxides are opened slower. To identify this off-cycle isotope scrambling and to show that low DI also occurs with $(t\mathrm{BuC_5H_4})_2\mathrm{TiCl_2}$, we performed the experiments shown in Scheme 5.

An increase in catalyst loading results in a reduced yield of **2D** as well as a reduced DI. This led us to postulate that 1,5-hexadiene and $\mathrm{PhSiH_2allyl}$ that are formed as by-products of



Scheme 5. Dependence of DI on catalysts loading and the amount of 1,5-hexadiene with allyl activation.

the allyl activation might be responsible for isotope scrambling.

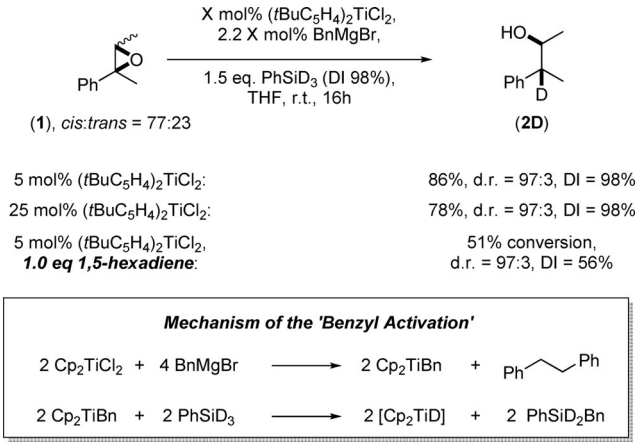
Indeed, upon deliberate addition of 1.0 equiv. of 1,5-hexadiene the conversion decreases dramatically and DI drops to 62%. Under these conditions, isotope scrambling can occur via a deuterometallation-β-hydride elimination sequence that not only leads to the formation of $[(t\text{BuC}_5\text{H}_4)_2\text{TiH}]$ from $[(t\text{BuC}_5\text{H}_4)_2\text{TiD}]$ but also to a competitive inhibition of epoxide opening. Similar considerations apply to $PhSiH_2$allyl that also contains a double bond.

This proposal readily explains that the diastereoselectivity of epoxide hydrosilylation and deuterosilylation are identical. The reactions of $[(t\text{BuC}_5\text{H}_4)_2\text{TiD}]$ from $[(t\text{BuC}_5\text{H}_4)_2\text{TiH}]$ proceed via identical mechanisms. Moreover, it also rationalizes the higher DI with $(t\text{BuC}_5\text{H}_4)_2\text{TiCl}_2$ compared to Cp_2TiCl_2 because the bulkier ligands lead to a slower hydrometallation.

To prevent isotope scrambling, it is necessary to find a group R that results in a complex $\text{Cl}(t\text{BuC}_5\text{H}_4)_2\text{Ti}-\text{R}$ that can be formed at room temperature in THF from $(t\text{BuC}_5\text{H}_4)_2\text{TiCl}_2$ and RMgBr and that allows formation of $[(t\text{BuC}_5\text{H}_4)_2\text{TiCl}]$ and R· at room temperature or slightly elevated temperatures. To this end, we investigated BnMgBr[16] because the benzyl radical formed by homolysis of $[\text{Cl}(t\text{BuC}_5\text{H}_4)_2\text{Ti}-\text{Bn}]$ is of similar stability than the allyl radical formed by thermal homolysis of $[\text{Cl}(t\text{BuC}_5\text{H}_4)_2\text{Ti}-\text{allyl}]$.

Gratifyingly, the use of BnMgBr in the activation of $(t\text{BuC}_5\text{H}_4)_2\text{TiCl}_2$ results in a clean conversion of **1** to **2D** with an almost complete diastereoselectivity that is superior to the use of Cp_2TiCl_2 and an excellent DI of 98%. The synthetically attractive diastereoconvergence is in line with the radical mechanism of epoxide hydrosilylation (Scheme 1) and highlights the power of combining organometallic catalysis with radical chemistry.[17]

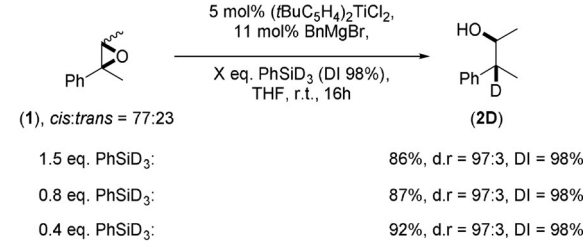
The benzyl activation does not lead to a decrease of DI with an increase of catalyst loading because 1,2-diphenyl ethane cannot be deuterometallated (Scheme 6). The slightly



Scheme 6. Precision deuteration after benzyl activation.

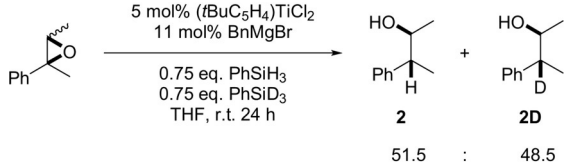
reduced yield of **2D** is due to an increase in the formation of a polymeric material that is more difficult to remove than with a catalyst loading of 5 mol%. When 1.0 equiv. of 1,5-hexadiene are added to the reaction mixture, conversion and DI decrease in line with the results of Scheme 5. This lends further support to our hypothesis of deuterometallation and β-hydride elimination for isotope scrambling in the allyl activation.

The benzyl activation allows a reduction of the amount of $PhSiD_3$ to 0.4 equiv (Scheme 7). We attribute the increase in the yields of **2D** with lower amounts of deuterosilane to a reduced formation of polymeric material that exacerbates purification of **2D**.



Scheme 7. Reduction of the amount of $PhSiD_3$ in the precision deuteration after benzyl activation.

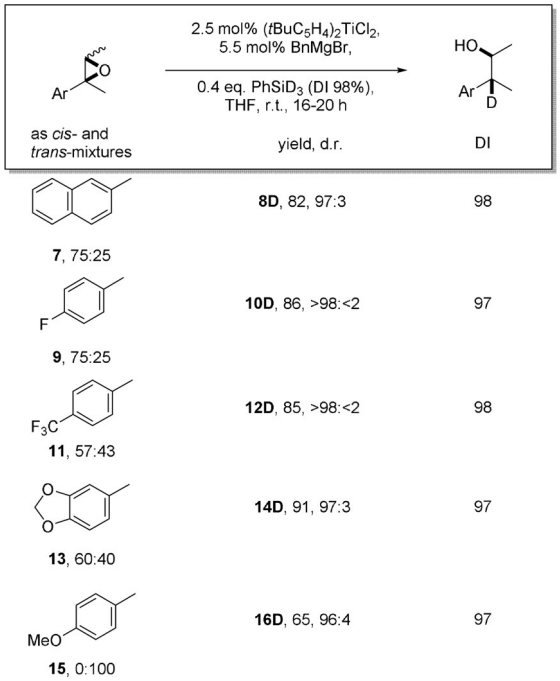
To check if a kinetic isotope effect is operating in the HAT step, we performed the following competition experiment (Scheme 8) in the presence of a mixture of 0.75 equiv. of $PhSiH_3$ and 0.75 equiv. of $PhSiD_3$. **2** and **2D**, were obtained in essentially equal amounts (51.5:48.5 based on the ^{1}H-NMR



Scheme 8. Competition experiment to determine the reaction's KIE.

spectrum of the isolated product). Therefore, a KIE in the H-/D-atom transfer and σ-bond metathesis is very low and too low to be determined by ^{1}H-NMR-spectroscopy.

We investigated substrate scope by varying the substitution of the arene (Ar-) in epoxides similar to **1** (Scheme 9) next. Catalyst loading can be reduced further to 2.5 mol% of $(t\mathrm{BuC_5H_4})_2\mathrm{TiCl_2}$ without reduction of yield, diastereoselectivity or DI. Electron withdrawing groups as well as electron



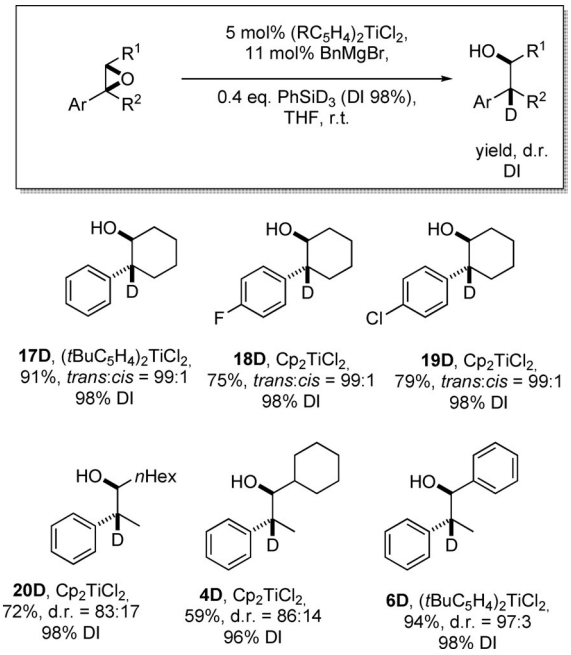
Scheme 9. Precision deuteration of benzylic epoxides similar to **1** in the presence of 2.5 mol% $(t\mathrm{BuC_5H_4})_2\mathrm{TiCl_2}$.

donating groups are tolerated. We used 0.8 equiv. of $\mathrm{PhSiD_3}$ to ensure a complete conversion in 16–20 h.

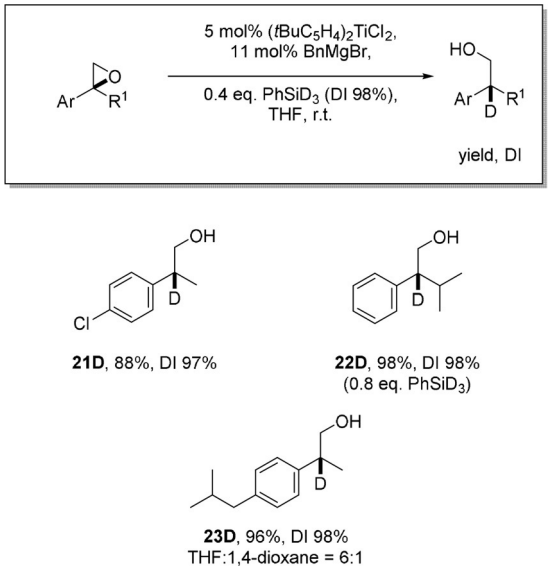
The precision deuterations to give the cyclic alcohols **17D**, **18D** and **19D** all proceed in high yields, and with excellent diastereoselectivity and DI (Scheme 10). As shown for **18D** and **19D** it is not even necessary to use the bulky $(t\mathrm{BuC_5H_4})_2\mathrm{TiCl_2}$. $\mathrm{Cp_2TiCl_2}$ yields very high diastereoselectivities, too. For **20D** and **4D**, employing $\mathrm{Cp_2TiCl_2}$ is mandatory, however. With $(t\mathrm{BuC_5H_4})_2\mathrm{TiCl_2}$ no products were obtained indicating that the *n*hexyl (**20D**) and *c*hexyl (**4D**) groups prevent substrate binding. For the diphenyl substituted **6D** this is not the case and $(t\mathrm{BuC_5H_4})_2\mathrm{TiCl_2}$ leads to substantially higher diastereoselectivity than $\mathrm{Cp_2TiCl_2}$ (90:10, not shown).

Finally, we investigated the use of 2,2-disubstituted substrates (Scheme 11). Alcohols **21D** and **22D** could be prepared under the standard conditions in excellent yield and with high DI.

The conditions necessary for **23D** require comment. In earlier studies, this epoxide was found to be prone to undergo a Meinwald rearrangement to the corresponding aldehyde. Addition of 1,4-dioxane results in the precipitation of $\mathrm{MgX_2}$



Scheme 10. Substrate scope of precision deuteration of benzylic epoxides.

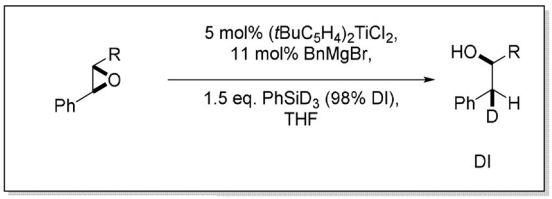


Scheme 11. 2,2-disubstituted benzylic epoxides in the precision deuteration.

(X = Cl or Br) that causes the rearrangement and leads to a clean precision deuteration.

For substrates like styrene oxide and β-methyl styrene oxide conversion is incomplete without elevated temperature (Scheme 12). However, in refluxing THF polymeric byproducts are formed that could not be removed during purification.

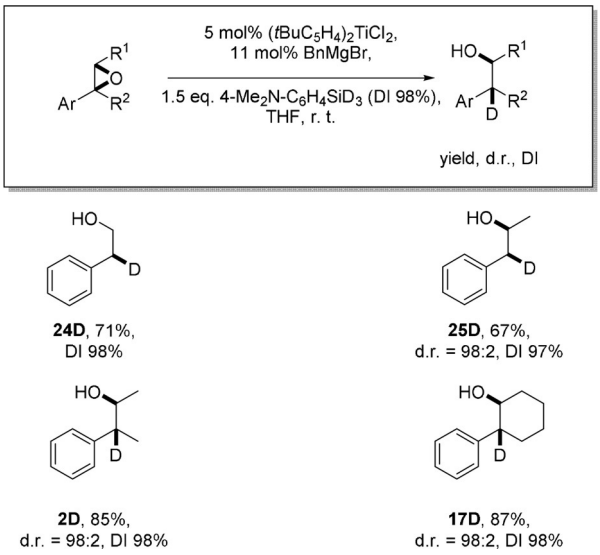
Therefore, we have chosen 4-$\mathrm{Me_2N}$-$\mathrm{C_6H_4SiD_3}$ as a substitute for $\mathrm{PhSiD_3}$ because it should be possible to remove sideproducts from the N-substituted deuterosilane by a simple acid extraction. Moreover, 4-$\mathrm{Me_2N}$-$\mathrm{C_6H_4SiD_3}$ is a solid compound that is bench stable, easy to handle, and especially



R = H: r.t., 62% conversion, 96% DI; reflux, 100% conversion, 96% DI

R = CH_3: r.t., 50% conversion, d.r. = 98:2, 96% DI; reflux, 100% conversion, d.r. = 98:2, 96% DI

Scheme 12. Critical substrates for the precision deuteration with $PhSiD_3$.



Scheme 13. Use of 4-Me_2N-$C_6H_4SiD_3$ in the titanocene-catalyzed precision deuteration.

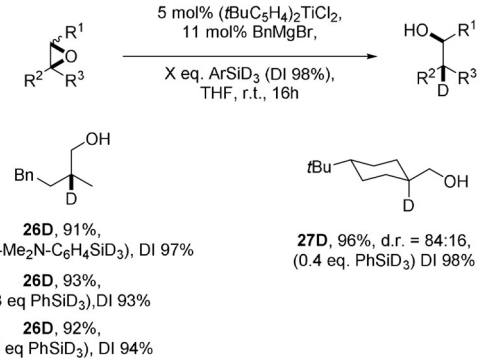
convenient to use on small scale. Gratifyingly, its use allowed the isolation of **24D** and **25D** in pure form (Scheme 13).

Furthermore, the yields of **2D** and **17D** obtained with 4-Me_2N-$C_6H_4SiD_3$ are similar to those obtained with $PhSiD_3$. Thus, 4-Me_2N-$C_6H_4SiD_3$ constitutes a practical alternative $PhSiD_3$ when purification of the products by chromatography is difficult due to the formation of polymeric by-products. In unproblematic cases, the yields are similar to those obtained with $PhSiD_3$.

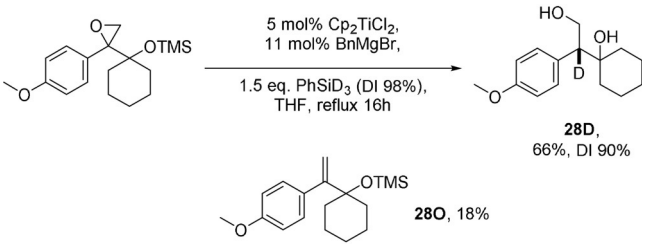
The examples investigated so far led to the formation of benzylic C–D bonds. We chose these substrates because in titanocene catalysis, the reduction of benzylic radicals is often problematic and because they are more easily oxidized than aliphatic C–H bonds. However, our conditions are also suitable to the reduction of simple alkyl radicals (Scheme 14).

The examples show that the precision deuteration also works very well for alkyl substituted epoxides. The yields are high and DI essentially complete.

The preparation of **28D** (Scheme 15) that has been transformed into the antidepressant venlafaxine in two steps[18] deserves comment. This is our only example where a DI with less than 95% was observed with the benzyl



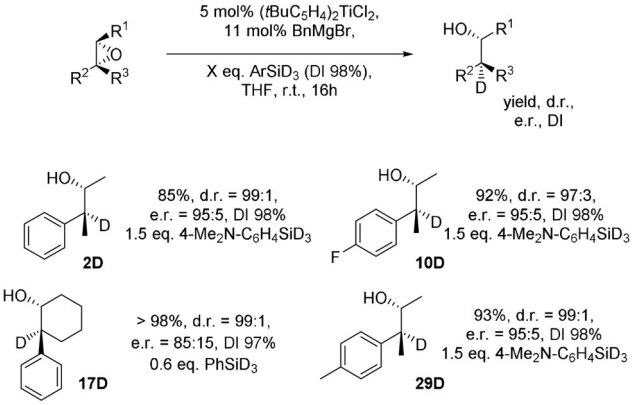
Scheme 14. Precision deuteration of alkyl-substituted epoxides.



Scheme 15. Precision deuteration for synthesis of the venlafaxine precursor **28D**.

activation. As opposed to all other reactions, the transformation requires heating and the use of Cp_2TiCl_2 as catalyst precursor. With $(tBuC_5H_4)_2TiCl_2$ (reflux or room temperature) no **28D** is obtained. ^{2}H-NMR spectroscopy of **28D** revealed that DI had occurred only at the benzylic C. Thus, no Meinwald rearrangement had taken place.

The formation of the unusual olefinic by-product **28O** suggests that the minor isotope scrambling occurs via the deuterometallation-β-hydride elimination sequence shown above (Scheme 5). The formation of **28O** through deoxygenation reveals that the presence of very bulky tertiary substituents requires the use of the less hindered Cp_2TiCl_2 as precatalysts and heating to enable substrate binding. Moreover, in such cases deoxygenation can compete with D-atom transfer.[19]



Scheme 16. Precision deuteration of enantiomerically enriched epoxides.

Finally, we investigated if the precision deuteration is also suitable for the preparation of enantiomerically enriched compounds (Scheme 16). The alcohols were obtained in high enantiomeric excesses that correspond to the e.r. of the epoxides obtained by the Shi-epoxidation.[20] Thus, the precision deuteration is also a suitable method for the enantio- and diastereoselective two-step anti-Markovnikov addition (epoxidation and ensuing deuterosilylation)[16] of HOD to olefins.

Conclusion

We have developed a novel [Cp_2TiD] or [$(t BuC_5H_4)_2TiD$]-catalyzed precision deuterosilylation of epoxides. It relies on a regioselective ring opening via electron transfer and an intramolecular D-atom transfer from a Ti–D bond to an organic radical to form the pivotal C–D bond. Surprisingly, the previously developed method for the in situ generation of [Ti–H] failed to deliver high deuterium incorporation when the terminal reductant $PhSiH_3$ was replaced by $PhSiD_3$. The isotope scrambling was found to take place in an off-cycle deuterometalation-β-hydride elimination sequence with olefinic compounds generated during catalyst activation. We resolved this issue with a novel olefin-free activation method featuring the formation of [$(RC_5H_4)_2Ti(III)Bn$] from $(RC_5H_4)_2Ti(IV)Cl_2$ and BnMgBr. After σ-bond metathesis of [$(RC_5H_4)_2Ti(III)Bn$] with $PhSiD_3$, the crucial [$(RC_5H_4)_2Ti(III)D$] is obtained in situ and leads to high deuterium incorporation (DI typically 97–98% from $PhSiD_3$ with a D content of 98%) at pharmaceutically significant benzylic and tertiary positions[5] with excellent diastereoselectivity. The reaction can be carried out with substrates pertinent to the synthesis of drugs and can also be applied to the synthesis of enantiomerically pure compounds. $(t BuC_5H_4)_2TiCl_2$ typically results in an excellent diastereoselectivity of deuteration and only needs to be replaced by Cp_2TiCl_2 in the reactions of sterically demanding substrates. Our precision deuteration is a case example for highlighting the power of combining the advantages of organometallic catalysis with those of radical chemistry.

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Conflict of Interest

The authors declare no conflict of interest.

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