## Ruthenium-Catalyzed Redox Isomerization of Trifluoromethylated Allylic Alcohols: Mechanistic Evidence for an Enantiospecific Pathway<sup>\*\*</sup>

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The challenge to generate enantiopure molecules featuring a trifluoromethyl motif at a stereogenic carbon center increasingly stimulates high interest in many laboratories. The recent success of the direct introduction of a CF<sub>3</sub> group by nucleophilic, electrophilic, or radical processes<sup>[1]</sup> nicely complements the equally challenging approach of exploiting prochiral trifluoromethylated substrates.<sup>[2]</sup> The stereoselective construction of an all-C CF<sub>3</sub>-bearing stereogenic tertiary carbon center without any heteroatom substituent undoubtedly belongs to the most fundamental topics in fluorine chemistry and remains highly challenging. For this purpose, a direct  $\alpha$ -trifluoromethylation of carbonyl compounds can be achieved by electrophilic addition to enolates or enol derivatives; however, remote trifluoromethylation at the  $\beta$  position of a carbonyl function is not possible and requires alternative synthetic approaches from  $\beta$ -CF<sub>3</sub>-substituted  $\alpha$ , $\beta$ unsaturated carbonyl compounds, for example, by hydrogenation,<sup>[3]</sup> conjugate reduction,<sup>[4]</sup> and conjugate addition.<sup>[5]</sup> In addition, sigmatropic rearrangements of mixed ketene acetals<sup>[6]</sup> or allyloxy acetates<sup>[7]</sup> have been achieved with high efficiency and complete chirality transfer through welldefined cyclic transition states.

The catalytic redox isomerization is an efficient, selective, atom-economic, one-step process for the isomerization of a C=C bond of O-allylic substrates into saturated carbonyl compounds. In this method, a transition metal assists the migration of the carbon–carbon double bond into an enol, which tautomerizes to the carbonyl compound. It is a conceptually attractive approach, which compares favorably with the more conventional sequential two-step oxidation and reduction reactions or vice versa.<sup>[8]</sup> Ruthenium, rhodium, and iridium have been particularly successful in this transformation, with an emphasis placed on the asymmetric version.<sup>[9]</sup> Surprisingly, the redox isomerization of an allylic alcohol containing a CF<sub>3</sub>-olefin moiety has no precedence in the

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literature, although recent efforts have enabled the incorporation of a fluorine atom into the isomerized product.<sup>[10,11]</sup> Herein, we present a hitherto unknown ruthenium-catalyzed redox isomerization of trifluoromethylated allylic alcohols as a novel synthetic route to enantioenriched trifluoromethyl carbonyl compounds. Several issues were addressed during the search for the optimal reaction conditions including: a) the choice of the catalyst, b) the impact of the highly electron-withdrawing CF<sub>3</sub> group: electronic, steric, and position effects, c) the gain of mechanistic insights, and d) the stereocontrol of the newly created stereogenic center.

A screening of the reaction conditions provided the optimized results compiled in Table 1 (see the Supporting Information for full details). The desired  $\beta$ -CF<sub>3</sub>-substituted saturated ketones were obtained in quantitative yields by using 1 mol% [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>]. The reactions are very clean and the use of more than 1 mol% catalyst is detrimental to the yield because of the persistence of the corresponding enone, which results in an incomplete redox process. In this case, the abstraction of the hydrogen atom  $\alpha$  to the OH group by the metal is not followed by a subsequent 1,4-hydride addition.

Interestingly, the use of wet toluene doesn't impede the reaction.<sup>[12]</sup> The amount and the nature of the base is another crucial parameter, since in the absence of base no conversion is observed, and inorganic bases, in particular  $Cs_2CO_3$ , give better results than organic ones. Lowering the amount of  $Cs_2CO_3$  should theoretically allow the reaction to go to

| <b>Table 1:</b> Redox isomerization of $\beta$ -CF <sub>3</sub> -substituted allylic alcoh |
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| I. INCLUON       | 130mcmz          | ation of p c  | ing substituted             | a anytic at      | conors.                  |  |
|------------------|------------------|---|-----------------------------|------------------|--------------------------|--|
| R <sup>2</sup>   | ОН               | [RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub> ](1 mol%) |                             | $\mathbb{R}^2$   | O<br>II                  |  |
| F <sub>3</sub> C | ∕⊂R <sup>1</sup> | toluene<br>Cs <sub>2</sub> CO <sub>3</sub> (1 e               | е (0.5 м)<br>equiv), T (°C) | F <sub>3</sub> C | R <sup>1</sup>           |  |
| R <sup>1</sup>   | R <sup>2</sup>   |   | T [°C]                      | <i>t</i> [h]     | Yield <sup>[a]</sup> [%] |  |
| Ph               | Pł               | 1   | 30                          | 2                | 99                       |  |
| Dh               | Ν.4              | •   | 30                          | 1                | 00                       |  |

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[a] Yields were determined by <sup>19</sup>F NMR spectroscopy using trifluorotoluene as an internal standard.

Entry



completion (see Scheme 3), but in practice one equivalent of base is actually needed, probably because of the heterogeneity of the system. These results clearly demonstrate that the steric bulk of the CF<sub>3</sub> group, whose molar volume is similar to that of an isopropyl group, is not detrimental to the reactivity. It is noteworthy that temperatures of 70-100°C are usually required for the isomerization of β-disubstituted substrates with Ru or Rh complexes.<sup>[8c,9e,13]</sup> Attempts to isolate the isomerization product of a primary allylic alcohol ( $R^1 = H, R^2 = Ph$ ) led to the corresponding saturated alcohol as the main product together with aldol condensation products. Indeed, the expected aldehyde is prone to reduction under the



Scheme 1. Isotope-labeling and crossover experiments.

reaction conditions, and its  $\alpha\text{-}CH$  group is susceptible to deprotonation, which generates aldol products.

Next we undertook a comparison of trifluoromethylated allylic alcohols and nonfluorinated substrates (Table 2). When the CF<sub>3</sub> group was replaced by a methyl group (either the E or Z isomer), the corresponding trisubstituted allylic alcohols required a much higher reaction temperature and a longer reaction time but the yields were very poor and some by-products were observed (Table 2, entries 2 and 3 versus entry 1). Even, a disubstituted allylic alcohol (Table 2, entry 4) failed to provide the isomerized product in good yield. These observations indicate that the bulkiness of the CF<sub>3</sub> substituent doesn't affect the reaction and that the electron-withdrawing effect of the CF<sub>3</sub> group significantly enhances the rate of the migratory insertion step (see mechanism in Scheme 3). This finding suggests that the rate-determining step in the redox isomerization of CF3substituted substrates is the  $\beta$ -elimination.

To gain mechanistic insights into this redox isomerization reaction we carried out the reactions illustrated in Scheme 1.<sup>[8e]</sup> Isomerization of deuterium-labeled **1a** ([D<sub>1</sub>]-**1a**) provided valuable information on the mechanism. Although some H-D scrambling occurred during the process (from [D<sub>1</sub>]-**1a** >95% D to [D<sub>1</sub>]-**2a** 81% D), the deuterium was exclusively incorporated at the  $\beta$ -carbon atom, clearly demonstrating a 1,3-migration pathway. The coexistence of catalytic species [Ru(D)Cl(PPh<sub>3</sub>)<sub>3</sub>], [RuDH(PPh<sub>3</sub>)<sub>3</sub>], and [RuD<sub>2</sub>-(PPh<sub>3</sub>)<sub>3</sub>] has been previously discussed by Bäckvall and coworkers, and the mixed hydride [RuDH(PPh<sub>3</sub>)<sub>3</sub>] could cause the H-D scrambling that provides a fraction of the nondeuterated ketone **2a**.<sup>[14]</sup> A crossover experiment with [D<sub>1</sub>]-

Table 2: Fluorinated versus nonfluorinated substrates.

|       | $R^1 OH$            | $\frac{[RuCl_2(PPn_3)_3](1 \text{ mol}\%)}{toluono (0.5 \text{ w}) Co. CO. (1 oguin)} = 2 \frac{1}{2}$ |   |                       |                          |  |  |  |
|-------|---------------------|--|---|-----------------------|--------------------------|--|--|--|
|       | R <sup>2</sup> ~ Ph | toluerie (0.c  | (m), CS <sub>2</sub> CO <sub>3</sub> (1 | equiv) R <sup>2</sup> | ∽ Ph                     |  |  |  |
| Entry | R <sup>1</sup>      | R <sup>2</sup>   | T [°C]                                  | <i>t</i> [h]          | Yield <sup>[a]</sup> [%] |  |  |  |
| 1     | Ph                  | CF <sub>3</sub>  | 30                                      | 2                     | 98                       |  |  |  |
| 2     | Ph                  | Me   | 100                                     | 15                    | 10                       |  |  |  |
| 3     | Me                  | Ph   | 100                                     | 15                    | 21                       |  |  |  |
| 4     | Н                   | Ph   | 30                                      | 9                     | 33                       |  |  |  |

<sup>[</sup>a] Yields of pure isolated products.

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**1a** and **1b** resulted in no deuterated ketone  $[D_1]$ -**2b** being detectable, thus establishing that the redox isomerization is an intramolecular process. Furthermore, to evaluate the impact of a noncoordinated enone as a possible intermediate resulting from a dissociation from the metal, we carried out a reaction between **1a** and **3**. The enone **3** was consumed, but the formation of ketone **2b** was not observed, and **2a** was found to be the major product with significant amounts of aldol condensation products. This result indicates that the intermediate enone remains coordinated to the metal center in the redox isomerization process.

We next examined the stereochemistry of the 1,3-hydride shift. Optically enriched starting allylic alcohols were successfully prepared from the corresponding enones by Noyori's ruthenium(II)-catalyzed transfer hydrogenation using [RuCl- $(p-\text{cym})\{(R,R)-\text{Tsdpen}\}\}$  (p-cym = p-cymene, Tsdpen = N-(ptoluenesulfonyl)-1,2-diphenylethylenediamine) and the azeotropic formic acid/triethylamine mixture.<sup>[15]</sup> This reaction raised the problem of the selective reduction of the keto group in the  $\alpha,\beta$ -unsaturated enones, and the present result constitutes a rare example of the chemoselective transfer hydrogenation of  $\alpha,\beta$ -unsaturated enones<sup>[16]</sup> and a unique case with CF<sub>3</sub>-substituted enones. Furthermore, the enantioselectivity of the transfer hydrogenation was very high for enones having an aryl ketone moiety, but only moderate in the case of enones having an alkyl ketone moiety and preparative HPLC was required to reach high ee values (Table 3, alcohols in entries 4 and 5). However, we studied the particular case of a poor ee value (Table 3, entry 2). When  $[RuCl_2(PPh_3)_3]$  was used as the catalyst, we were delighted to observe that the initial alcohols and the saturated ketones had very similar ee values,, with a very high enantiospecificity  $(es)^{[17]}$  ranging from 97 to 100% [% es = 100 (product ee)/ (reactant ee)].<sup>[18]</sup> These results indicate an excellent transfer of chirality during the redox isomerization, but this reaction is not as easy as it first seems because other ruthenium catalysts do not behave similarly. For example, the transfer of chirality is not complete with  $[RuCl_2(C_6H_6)]_2$  (82% es),  $[RuCl_2(p-$ (79% es), and  $[RuCp*(MeCN)_3]PF_6$  (42% es; Cp\* = $C_5Me_5$ ).

Of special interest is the experiment described in Table 3, entry 3, for which we chose a  $\beta$ -CF<sub>3</sub>-substituted secondary

Table 3: Enantiospecific redox isomerization.



[a] Yields of pure isolated products.

allylic alcohol bearing a bromoaryl moiety because its prochiral trigonal  $\beta$  carbon center can serve as a convenient probe for the detection of the 1,3-chirality transfer and the bromine atom can facilitate the determination of the absolute configuration of the newly created stereogenic center by X-ray analysis (Scheme 2).<sup>[19]</sup>

The (R)-allylic alcohol (97% ee) was fully converted into the (R)-saturated ketone (94 % ee) by a process that was 97 %enantiospecific, with the ruthenium center acting almost exclusively on the Si face of the alkene moiety of the (R)allylic alcohol. The overall reaction can occur within the coordination sphere of the ruthenium center through a suprafacial enantiospecific 1,3-hydrogen atom transfer. This is a unique demonstration of the stereochemical course of a redox isomerization of an acyclic substrate.<sup>[20]</sup> In light of all these observations and literature precedence,<sup>[21]</sup> we propose the mechanism depicted in Scheme 3. Cesium carbonate facilitates the formation of a 16-electron ruthenium alkoxide complex that is further coordinated to the double bond to account for the reactivity observed. Subsequent  $\beta$ -hydride elimination produces the enone-hydride complex, in which the enone remains coordinated until the 1,3-migratory insertion of the hydride takes place from a single face of the trigonal carbon center. The resulting ruthenium enolate is then protonated by an incoming allylic alcohol and tautomerizes into the final saturated ketone concomitantly with the release of the catalyst.

Our approach allows a CF<sub>3</sub>-bearing stereogenic carbon center at a remote position of a carbonyl function to be controlled with excellent enantiospecificity (up to 99% *ee* and 100% *es*). It compares favorably with the unique example



Scheme 2. Suprafacial enantiospecific 1,3-chirality transfer.

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Scheme 3. Mechanism rationale for enantiospecific redox isomerization.

of ruthenium-catalyzed isomerization of nonfluorinated secondary allylic alcohols described by Ikariya et al. which gives an intermediate with 74% *ee* during the synthesis of muscone.<sup>[9a]</sup>

To illustrate the usefulness of our approach, we prepared the (*S*)-CF<sub>3</sub> analogue of citronellol, which has olfactory properties dissimilar to those of the natural product. This synthetic fragrance compound was previously synthesized by Seebach and co-workers by a multistep process involving a resolution.<sup>[22]</sup> We herein report a shorter and enantioselective route to (*S*)-CF<sub>3</sub>-citronellol in which the key step is an enantiospecific redox isomerization (Scheme 4).

In summary, we have disclosed a new approach to prepare enantioenriched carbonyl compounds featuring a  $\beta$ -trifluoromethylated stereogenic carbon center that is notable for its simplicity of execution and enantiospecificity. We have also described a unique example of chemo- and enantioselective transfer hydrogenation of  $\beta$ -CF<sub>3</sub>- $\alpha$ , $\beta$ -unsaturated enones. With regard to the issue of the mechanism, we have conducted experiments that afford the first experimental evidence in support of an intramolecular suprafacial enantio-



**Scheme 4.** Reaction conditions for the asymmetric synthesis of (S)-CF<sub>3</sub>-citronellol: a) [RuCl(p-cym){(R,R)-Tsdpen}], Et<sub>3</sub>N/HCO<sub>2</sub>H; b) [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>], toluene, Cs<sub>2</sub>CO<sub>3</sub>; c) Beckmann rearrangement through the corresponding oxime, then hydrolysis and reduction.



specific 1,3-hydrogen transfer. This new synthetic approach was applicable to the asymmetric synthesis of a  $CF_3$  analogue of citronellol.

## **Experimental Section**

General procedure:  $\beta$ -Trifluoromethylated allylic alcohol (1 mmol), degassed toluene (2 mL), cesium carbonate (325.8 mg, 1 mmol), and [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>] (9.6 mg, 10<sup>-2</sup> mmol) were added to a Schlenk tube under an inert atmosphere. The mixture was heated at a temperature of 30 to 70 °C for 1 to 12 h (see Table 1), until <sup>19</sup>F NMR spectroscopic analysis showed full conversion. The reaction mixture was then filtered through celite, concentrated under reduced pressure, and purified by column chromatography on silica gel (petroleum ether/ ethyl acetate: 99:1) to give the corresponding  $\beta$ -trifluoromethylated ketone.

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