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Iron(II) complexes are suitable catalysts for the isomerization of trifluoromethylated allylic alcohols. Synthesis of trifluoromethylated dihydrochalcones

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ABSTRACT

We demonstrated that iron(II) complexes can substitute platinum metals as well as iron(0) carbonyls for the isomerization of γ -trifluoromethylated allylic alcohols into β -trifluoromethylated ketones. In particular, iron(II)-tetra(isonitrile) complexes were employed for the synthesis of a series of trifluoromethylated dihydrochalcones variously decorated on each aromatic ring.

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1. Introduction

The isomerization of allylic alcohols into the corresponding saturated carbonyl compounds, often referred to as redox isomerization is an efficient, selective, redox- and atom-economical, one-pot isomerization process [1]. Second- and third-row transition metals, such as Ru, Rh, and Ir, have been widely used in isomerization of allylic alcohols [2]. Faced with an ever-increasing demand for precious metal, their replacement by abundant, less expensive and environmentally benign first-row transition metals is eagerly sought after. In this context, iron salts, which are very abundant on Earth and usually non-toxic, are the subject of current intense research [3]. It has been demonstrated that various iron(0) carbonyls that include homoleptic $[\text{Fe}(\text{CO})_5]$ [4], $[\text{Fe}_2(\text{CO})_9]$ [5], $[\text{Fe}_3(\text{CO})_{12}]$ [6] as well as heteroleptic $[(\text{bda})\text{Fe}(\text{CO})_3]$ (bda = *trans*-benzylideneacetone) [7] and $[(\text{COT})\text{Fe}(\text{CO})_3]$ (COT = cyclooctatetraene) [7] are catalytically active in the isomerization of allylic alcohols under irradiation conditions. Good evidence was provided that photodissociation of these complexes gave $[\text{Fe}(\text{CO})_3]$ that would act as the true catalytic species [8]. However, as a source of

carbon monoxide, iron(0) carbonyls are toxic and not really appropriate for the development of an asymmetric variant of the isomerization reaction. Consequently, we focused our attention on iron(II) catalysts which we could not find precedence in the literature as far as isomerization of allylic alcohols is concerned. In addition, a number of chiral iron(II)-catalysts have been successfully applied in asymmetric transfer hydrogenation and would be definitely evaluated in the isomerization reaction that is also a hydride transfer reaction [9,10,11]. We recently reported the first involvement of trifluoromethylated allylic alcohols in ruthenium-catalyzed isomerization [12]. The presence of the CF_3 group is beneficial to accelerate the hydride insertion step and thus allows higher reactivity in particular for trisubstituted $\text{C}=\text{C}$ bond of allylic alcohols which isomerizations are conducted under mild conditions. We and others demonstrated that a ruthenium hydride intermediate is generated from an allylic alcohol and a ruthenium complex in basic medium with concomitant formation of the corresponding α,β -unsaturated carbonyl derivative [13]. Thus, we hypothesized that: (i) such a discrete metal hydride might be an intermediate in iron-catalyzed allylic alcohol isomerization and (ii) iron complexes, able to catalyze transfer hydride reduction, might also be active in isomerization of allylic alcohols. For this study, we focused on three types of iron(II) complexes. One of the most efficient and easily amenable to structural modification type of iron complexes are the modular Morris complexes **C1–C3** (Fig. 1)

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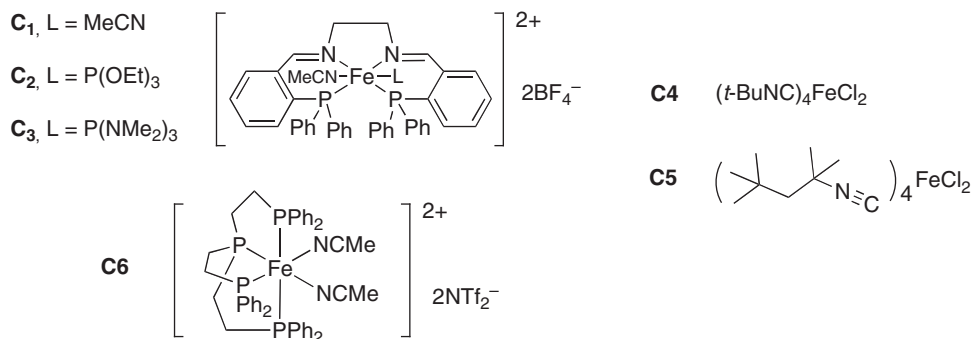


Fig. 1. Iron(II) catalysts.

[10]. Such complexes are able to reduce carbonyl functions through hydride transfer hydrogenation in high yields. Moreover, it is worth mentioning that reduction of enones in the presence of such iron complexes led to the corresponding saturated alcohols through reduction of the activated C=C double bond [10d,e]. Variation of the apical ligand nature (L = MeCN, P(OEt)₃, P(NMe₂)₃...) can also modify the reactivity of the iron complex. The second family of iron complexes are achiral analogues of the chiral iron-tetra(isonitrile) complexes reported by Reiser and coworkers (complexes **C4–C5**, Fig. 1) [11]. We also evaluated the complex [(PP₃)Fe(NCMe)₂][NTf₂]₂ (PP₃ = P(CH₂CH₂PPh₂)₃) **C6** [14].

Obviously, switching from ruthenium to iron in isomerization of allylic alcohols would create a fully cost-effective reaction. In order to demonstrate the ability of iron(II) complexes to catalyze the isomerization reaction, we targeted trifluoromethylated dihydrochalcones as fluoro analogues of these members of the flavonoid family [15]. Indeed, dihydrochalcones are key intermediates for the synthesis of bioactive molecules that possess a wide range of properties including anticancer, antiviral, antibacterial, antioxidant among others [16]. The search for novel substitution patterns for dihydrochalcones also included fluorinated motifs. Towards this goal, Surya Prakash, Mathew and coworkers have recently described a synthetic route to CF₃-dihydrochalcones through intermolecular Friedel-Crafts acylation and alkylation of 4,4,4-trifluorocrotonic acid with various arenes in the presence of excess triflic acid (Fig. 2, top) [17]. However, this methodology is limited in that only CF₃-dihydrochalcones bearing identically substituted aryls at C₁ and C₃ positions can be synthesized. Moreover, in this synthetic approach, dihydrochalcones are sometimes accompanied by other regioisomers. Konno and coworkers obtained some CF₃-dihydrochalcones through asymmetric rhodium-catalyzed 1,4-conjugate arylation

of 4,4,4-trifluoro-1-phenyl-2-buten-1-one, and hence aryl variety was generated only at C₃ (the aryl at C₁ was constantly a phenyl group) [18]. We herein propose an alternative route to single regioisomers of CF₃-dihydrochalcones that feature variously decorated aromatic rings through iron(II)-catalyzed isomerization of γ -CF₃ allylic alcohols (Fig. 2, bottom).

2. Results and discussion

In a first series of experiments, we examined the reaction conditions optimized for the ruthenium-catalyzed isomerization: 1 mol% catalyst and 1 equivalent of Cs₂CO₃ in toluene (0.5 M) at 25–50 °C. Under these conditions in the presence of allylic alcohol **1a**, the isomerization took place in the presence of iron(II) catalysts **C1–C5** but failed with **C6** (Table 1). With catalyst **C6**, we recovered the starting material quantitatively without any isomerized product. With Morris type catalysts **C1–C3**, the isomerization required a temperature of 50 °C to obtain full conversion of **1a**. The isomerization performed best with the tetra(isonitrile) catalysts **C4** and **C5** at 25 °C for 22 h providing the desired β -trifluoromethylated ketone **2a** in up to 72% yield after silica gel column chromatography (Table 1, entry 5). When the reaction was run at 50 °C with **C5**, full conversion was reached within 7 h, albeit in a much lower isolated yield due to the concomitant formation of ketolisation byproducts that were favoured at higher temperature (Table 1, entry 6). Advantageously, catalysts **C4** and **C5** are easily synthesized by treatment of the corresponding isonitriles with FeCl₂·4H₂O in methanol. We selected the iron(II)-tetra(isonitrile) catalyst **C5** for further investigation of reaction parameters and substrate scope.

The solvent effect was evaluated next (Table 2, entries 1–6). The reaction failed in CHCl₃ and MeOH but the isomerization reaction

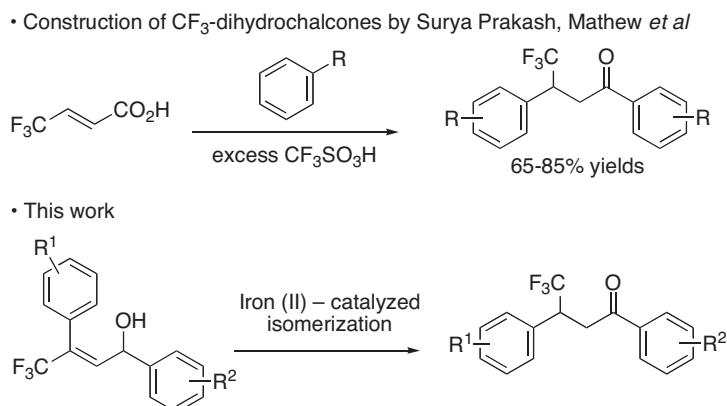


Fig. 2. Proposed investigation.

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