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Ruthenium(II)-Catalyzed Alkenylation of Ferrocenyl Ketones via C−H Bond Activation

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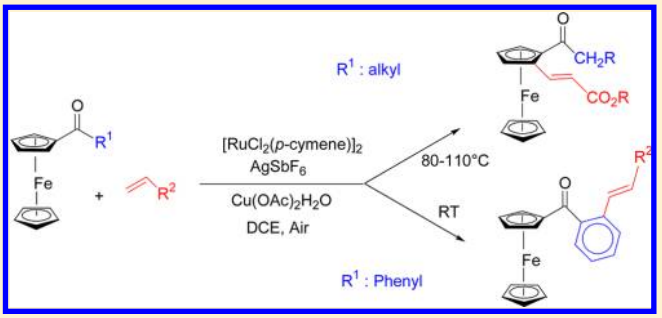
Supporting Information

ABSTRACT: The alkenylation with alkyl acrylates of ferrocenyl alkyl ketones is performed with the $[RuCl_2(p\text{-cymene})]_2$ /$AgSbF_6$ catalytic system and leads, via ferrocene C−H bond activation, to moderate yields of the 1,2-disubstituted ferrocene derivatives in the presence of $Cu(OAc)_2{\cdot}H_2O$ under aerobic conditions at 80−110 °C. The alkenylation of ferrocenyl phenyl ketone, in contrast, takes place at room temperature to afford quantitative yields of the phenyl monoalkenylated product, demonstrating the strong influence of the ferrocenyl group on arene C−H bond functionalization. Small amounts of 2-alkenylferrocenyl 2′-phenyl ketones can also be obtained.



Functional ferrocene derivatives constitute a family of chemicals offering useful properties in several areas. They are the basis of practical ligands,[1] including planar chirality ligands for efficient enantioselective catalysis.[2] They have found applications in material science as metallocene-containing polymers[3] and as materials for optical applications.[4] Most of the synthetic methods functionalizing ferrocene involve either a Friedel−Crafts type electrophilic substitution or a stoichiometric C−H bond metalation followed by coupling with an electrophile.[5] It thus remains a challenge to develop new, general catalytic methods to derivatize the stable ferrocene derivatives.

The direct catalytic sp^2 C−H bond activation/functionalization of arenes and heterocycles has considerably improved synthetic methods via selective C−C bond cross-couplings.[6] In contrast, simple ferrocene derivatives have shown resistance to their catalytic C−H bond functionalization, likely due to the electron richness of this metallocene and its inertness to C−H bond deprotonation via a concerted metalation−deprotonation process.[7] However, several examples of stoichiometric C−H bond activation of ferrocene derivatives leading to cyclometalated complexes have been reported.[8]

Only a few reports have already demonstrated the possibility of catalytic ferrocene C−H bond functionalization leading to arylated and alkenylated products. Ferrocene itself was first alkenylated by Moritani and Fujiwara[9] with $Pd(OAc)_2$ catalyst in dioxane/AcOH solvent in modest yields. A cross-coupling reaction between two C−H bonds of ferrocenyloxazoline and of an arene has been performed using a stoichiometric amount of $Pd(OAc)_2$, but in the additional presence of $Cu(OAc)_2$ the cross-coupling became catalytic and led to a good yield of the diarylated ferrocene.[10] Recently the direct alkenylation of ferrocene with acrylates has been observed with $Pd(OAc)_2$ catalyst in acetic acid, leading only to moderate yields in monoalkenylated ferrocenes.[11] In contrast, in the presence of a directing dimethylaminomethyl group, ferrocene C−H bonds were recently functionalized with Pd(II) catalyst on reaction with diarylacetylenes to give highly arylated naphthalenes,[12] and effective borylation of ferrocene C−H bonds has been performed with iridium catalyst.[13]

Recently it was shown that stable and inexpensive ruthenium(II) catalysts could promote the alkenylation of arene and heterocycle C−H bonds directed by several functional groups[14,15] and that the modification of $RuCl_2Ln$ complexes with silver salts allowed the alkenylation of weakly coordinating aryl ketones at 110 °C.[16] These observations were attractive to explore the direct functionalization of ferrocenyl derivatives with halide-free ruthenium(II) catalysts. Here we report for the first time a ruthenium(II)-catalyzed ferrocene C−H bond alkenylation producing new bifunctional 1,2-disubstituted ferrocene derivatives, although in very moderate yields; surprisingly, the ferrocenyl group favors the ruthenium alkenylation of the phenyl C−H bond of ferrocenyl aryl ketone, which can be performed this time quantitatively at room temperature.

The alkenylation of ferrocenyl alkyl ketones **1** and **2** was first investigated in the presence of ruthenium(II) catalyst using various additives to modify the Ru−Cl bonds and oxidants to regenerate the ruthenium(II) species. The reaction of ferrocenyl methyl ketone **1** (0.25 mmol) with an excess of ethyl acrylate (4 equiv) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (8 mol %) catalyst precursor in dichloroethane was investigated

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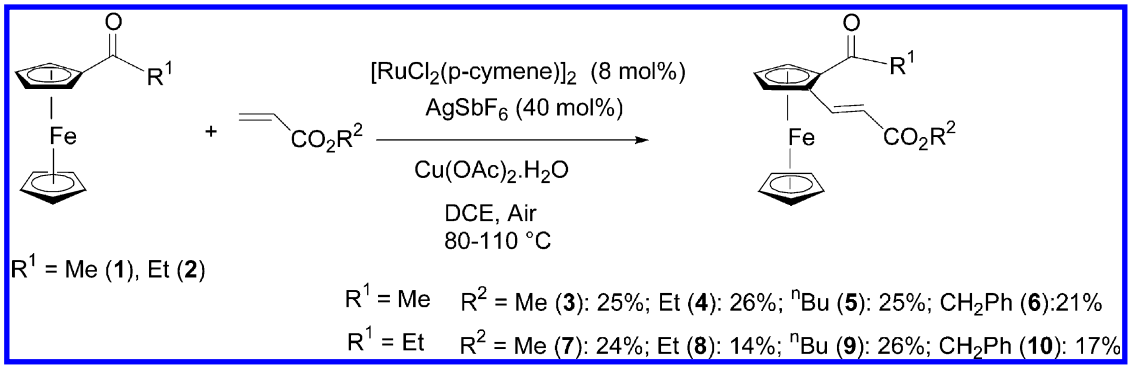
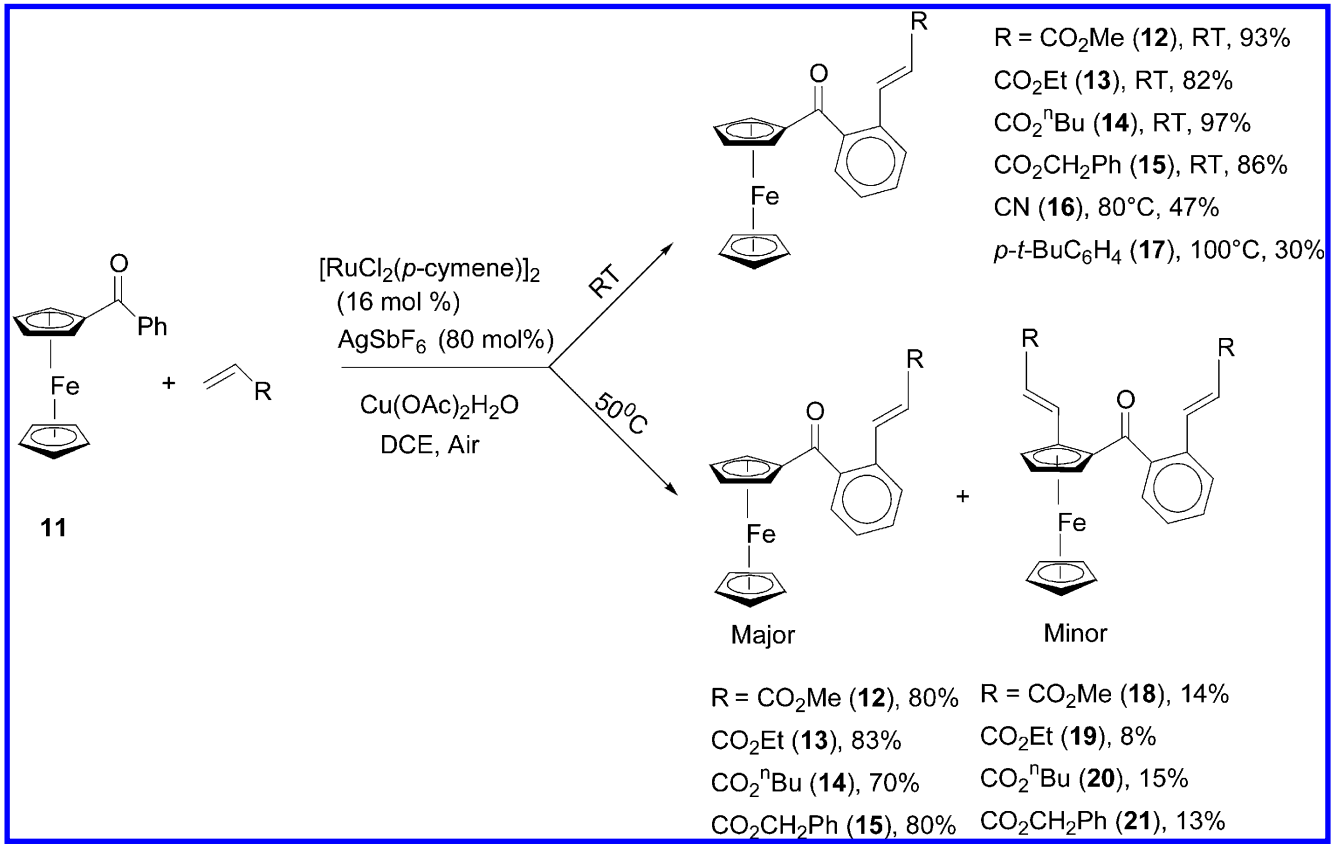
Scheme 1. Ruthenium(II)-Catalyzed Alkenylation of Alkyl Ferrocenyl Ketones 1 and 2



Scheme 2. Ruthenium(II)-Catalyzed Alkenylation of Ferrocenyl Phenyl Ketone 11



(Scheme 1). With additional $Cu(OAc)_2{\cdot}H_2O$ alone or $AgSbF_6$ alone no reaction occurred, but with both additives the 2-monoalkenylated acetylferrocene complex **4** was isolated in a moderate yield of 26% after 24 h of reaction at 100 °C (Scheme 1). The replacement of $AgSbF_6$ by AgOTf or KPF_6 did not lead to an active catalyst, and the use of $Ru(O_2CCF_3)_2(p\text{-cymene})$ as catalyst precursor with $Cu(OAc)_2{\cdot}H_2O$ was not efficient. Among the evaluated oxidants, $Cu(OAc)_2{\cdot}H_2O$ was found to be effective in air. In the absence of air a very low conversion to the desired product was obtained. Optimal reaction conditions were found with 5 equiv of $AgSbF_6$ with respect to $[\{RuCl_2(p\text{-cymene})\}_2]$ for the generation of dicationic active ruthenium(II) species. These experiments revealed that the oxidant $Cu(OAc)_2{\cdot}H_2O$ is operative but that only $AgSbF_6$ leads to an active catalyst, likely by efficient chloride abstraction in the presence of noncoordinating anion (SbF_6^- vs OTf^-), and that even if very moderate yields are obtained, the ferrocene ortho C−H bond activation, directed by a weakly coordinating ketone group, can be promoted for the first time by ruthenium(II) catalyst.

The ferrocenyl ketones **1** and **2** were reacted with several alkyl acrylates. In a typical reaction, ferrocenyl alkyl ketone (0.25 mmol) reacts with alkyl acrylate (0.1 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (8 mol %)/$AgSbF_6$ (40 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2 equiv) in DCE at 110 °C for 24 h to provide the oxidative dehydrogenative coupling products (Scheme 1, Table SI-2 (Supporting Information)). The acetylferrocene **1** leads to monoalkenylated acetyl ferrocenes **3**−**6** in 21−26% isolated yields. Analogously, the ferrocenyl ethyl ketone **2** leads to the alkenylated products **7**−**10** in 14−26% isolated yields. This reaction proceeds in almost equal efficiency in a dioxane/acetic acid solvent mixture or DCE but not in pure acetic acid. A decrease of reaction temperature to

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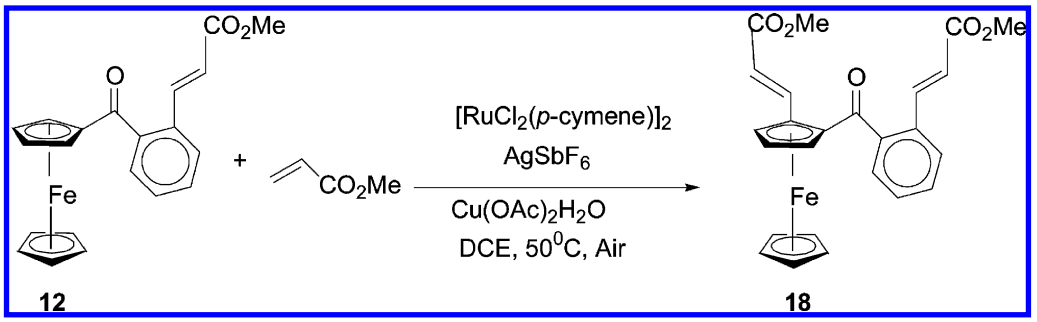
Scheme 3. Ruthenium(II)-Catalyzed Alkenylation of Ferrocenyl Phenyl Ketone 11 with Acrylate



80 °C but for a longer time results in similar yields (see Table SI-2 in the Supporting Information).

The structures of derivatives **3**−**10** are consistent with those of 1,2-disubstituted ferrocene derivatives, as shown by ^{1}H NMR. All compounds show, in addition to the COR and CH═CHCO$_2$R proton signals, a singlet for the C_5H_5 ligand at δ ~4.1−4.2 ppm and for the disubstituted cyclopentadienyl group three C_5H_3 consecutive coupled protons with the central proton appearing as a pseudotriplet. For example, the ^{1}H NMR spectrum of compound **3** shows the C_5H_3 protons at δ 4.66, 4.86, and 4.90 for H_3, H_4, and H_5, respectively, with an integral ratio of 1:1:1, as compared with two multiplets at 4.50 and 4.70 ppm observed for the starting ketone $(C_5H_5)Fe(C_5H_4COCH_3)$ (**1**). The ^{13}C NMR spectral data of **3** showed signals at 80.20, 78.48, 74.38, 72.64, and 70.28 ppm assignable to the carbons of the disubstituted cyclopentadienyl ring, as compared to only three signals observed for the starting ferrocenyl methyl ketone **1**.

This 1,2-disubstitution in compounds **3**−**10** is consistent with the directing capability of the ketone group to activate the neighboring ortho C−H bond. In addition, the C−H bonds of the acyl cyclopentadienyl group are expected to be more acidic than those of the C_5H_5 ring and thus both higher C−H bond acidity and a directing coordinating ketone group favor ortho C−H bond deprotonation/functionalization of the C_5H_4COR ring only and formation of bifunctional 1,2-disubstituted ferrocenes.

The oxidative dehydrogenative cross-coupling of methyl acrylate with the ketone FcCOPh (**11**) has then been investigated to compare the competitive alkenylation of the ferrocenyl versus the phenyl ring. When the reaction of **11** (0.125 mmol) and methyl acrylate was performed in the presence of $[RuCl_2(p\text{-cymene})]_2$ (0.02 mmol, 16 mol %) and $AgSbF_6$ (0.1 mol) *at room temperature in air* for 18 h, it resulted in the quantitative formation of the phenyl monoalkenylated compound **12** exclusively, isolated in 93% yield (Scheme 2). When the catalyst loading was decreased to 8 mol %, the reaction needed 36 h at room temperature to reach complete conversion and **12** was then isolated in 80% yield. A further decrease of catalyst loading to 4 mol % with a reaction time of 48 h led to compound **12** in 74% yield, showing that a high loading of 16 mol % of catalyst is required to reach a complete transformation in 18 h.

With the above optimized reaction conditions based on $[RuCl_2(p\text{-cymene})]_2$ (16 mol %), in air *at room temperature*, the ketone **11** reacts with various alkyl acrylates, leading to the isolation of the phenyl monoalkenylated derivatives **13**−**15** isolated in 82, 97, and 86% yields after 24, 24, and 30 h at room temperature, respectively. The monoalkenylations of **11** with acrylonitrile and *p-tert*-butylstyrene were more difficult to perform, and 47% of **16** after 24 h at 80 °C and 30% of **17** after 30 h at 100 °C were obtained (Scheme 2). The ^{1}H NMR showed that the phenyl group was monoalkenylated and that the C_5H_5 and C_5H_4COR group signals were retained.

The alkenylation of arene sp^2 CH bonds catalyzed by a ruthenium(II) complex in the presence of silver salt was recently reported for aryl alkyl ketones at 110 °C for 12 h.[16] Here the alkenylation of the phenyl group of the ferrocenyl phenyl ketone is performed under much milder reaction conditions at room temperature for 18−30 h. In order to give more evidence for the profitable influence of the ferrocenyl group on the alkenylation of arenes, the reaction of benzophenone with methyl acrylate was carried out under the same conditions as in Scheme 2. Benzophenone reacts with 4 equiv of methyl acrylate in the presence of $[RuCl_2(p\text{-cymene})]_2$/5 $AgSbF_6$ catalyst, leading to the isolation of ortho-monoalkenylated benzophenone **22** in 13% yield after 24 h at room temperature. These results show that, in the alkenylation of ferrocenyl phenyl ketone **11**, the ferrocenyl group actually activates the alkenylation of the phenyl group such a way that it allows the dehydrogenative alkenylation of an aromatic ketone to occur for the first time at room temperature. A possible explanation is that, in the presence of an oxidant, the ferrocenyl group can be oxidized into ferrocenium ion,[1,12] an electron-withdrawing group facilitating alkenylation of the arene group.

The partial dialkenylation of FcCOPh (**11**) with an excess of alkyl acrylates was attempted by increasing the temperature and time to 50−60 °C for 24−48 h. The reaction leads to only small amounts of dialkenylated products **18**−**21** that were separated in low yields of 14, 8, 15, and 13%, respectively, from the previous monoalkenylated products **12**−**15** isolated in 80, 83, 70, and 80% yields, respectively (Table SI-3 in the Supporting Information). The dialkenylated compounds **18**−**21** can also be obtained by the reaction of **12**−**15** with the corresponding acrylate in the presence of $[RuCl_2(p\text{-cymene})]_2$ and $AgSbF_6$. For example, compound **18** has been prepared and isolated in only 13% yield by reacting **12** with methyl acrylate in the presence of $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ at 50 °C for 48 h (Scheme 3).

Compounds **18**−**21** have been isolated by column chromatography and characterized by spectroscopic data. The identity of compounds **18**−**21** was confirmed by NMR analysis (^{1}H and ^{13}C). The proton NMR spectrum of **21** showed signals at 5.00 and 4.22 ppm and a triplet at 4.66 ppm with integral ratios of 1:1:1, indicating the presence of a 1,2-disubstituted ferrocene ring.

In conclusion, we have described for the first time the still difficult to perform ruthenium(II)-catalyzed alkenylation of ferrocenyl alkyl ketone with alkenes via ferrocene C−H bond

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activation. New bifunctional 1,2-disubstituted ferrocenes were thus prepared in moderate yields. The reaction takes place under aerobic conditions by oxidative dehydrogenative coupling in the presence of the $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ catalytic system with $Cu(OAc)_2{\cdot}H_2O$ as oxidant. We have especially shown that the monoalkenylation of ferrocenyl phenyl ketone occurs at room temperature and takes place on the phenyl ring, demonstrating that the ferrocenyl group can be used as a promoting group for the difficult to perform C−H bond alkenylation of aromatic ketones.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, and tables giving general experimental procedures, characterization data (^1H, ^{13}C) of all compounds, and ^1H and ^{13}C NMR spectra for compounds **6**, **7**, and **12**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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