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$Rh_2(OAc)_4$-catalyzed 2,3-migration of β-ferrocenecarboxyl α-diazocarbonyl compounds: an efficient synthesis of ferrocene-containing α,β-unsaturated esters†

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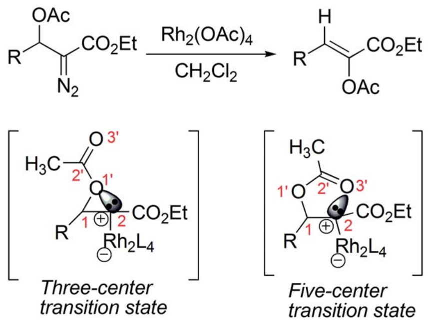
A series of β-ferrocenecarboxyl α-diazocarbonyl compounds were prepared by the reaction of ferrocenoyl chloride with β-hydroxyl α-diazocarbonyl compounds in the presence of pyridine. The diazo decomposition of these ferrocene-containing diazocarbonyl compounds with $Rh_2(OAc)_4$ resulted in 2,3-ferrocenecarboxyl migration to give ferrocene-containing α,β-unsaturated esters in high yields.

Introduction

Since its discovery more than sixty years ago, ferrocene has acquired significant attention[1] as a consequence of its unique physical and chemical properties which allow for its application in many areas such as asymmetric catalysis,[2] materials science,[3] and bioorganometallic chemistry.[4] Among these, the field where ferrocene importance is continuously increasing is bioorganometallic chemistry.[5] Although ferrocene itself is usually considered to be a nontoxic, biologically inert compound, many novel ferrocene derivatives exhibit significant anticancer, antiparasitic, antibacterial, antifungal, and other biological activities.[4,5] Undoubtedly, the design motif and synthesis strategy in ferrocene-based architectures play the most important role to deliver the targeted property. Due to their increasing applications in biology, materials science, and chemistry, there has been an ever increasing demand for the synthesis of novel ferrocenes bearing various functional groups through simple and efficient approaches.

On the other hand, transition-metal-catalyzed diazo decomposition of various substituted diazocarbonyl compounds is a class of important transformation in organic chemistry that has been widely investigated for its intriguing mechanistic features and extensive applications in natural products synthesis.[6] In these diazo decomposition reactions, 1,2-migration is sometimes the dominating pathway, which can compete with the typical reactions of diazo compounds, such as cyclopropanations, X–H (X = C, O, S, N, *etc.*) insertions and ylide formations.[6] Among the transition-metal-catalyzed 1,2-migration reactions of α-diazo carbonyl compounds, the 1,2-hydride migration is usually predominant,[7] but 1,2-aryl, 1,2-alkyl, 1,2-vinyl, 1,2-acetylenyl and 1,2-thio group migrations are also reported.[8] Besides, 1,2-acetoxy group migration of Rh(II)–carbene was also described by Ganem and co-workers in 1981;[9] it is conceived that the 1,2-migration of acetoxy group may proceed through a three-centered or five-centered transition state, where the lone pair electrons of the alkoxy or carbonyl oxygen of the acetoxy group interacts with the electron-deficient Rh(II)–carbene center (Scheme 1). It should be noted that it is actually a 2,3-migration reaction if 1,2-acetoxy group migration proceeds through a five-centered transition state. Wang and co-workers have demonstrated a 2,3-migration reaction of Rh(II)–carbene subtly through installation of an amido group onto the β-position of the α-diazo carbonyl compounds.[10] Inspired by this report, and also as an extension of our interest in the ferrocene and diazo chemistry,[11] we conceived that an α-diazo carbonyl compound bearing a ferrocenecarboxyl group on the β-position may also undergo a similar acyloxy migration in a Rh(II)-catalyzed reaction to give a ferrocene-containing α,β-unsaturated ester. Moreover, if the reaction occurs as predicted, the



Scheme 1 Possible transition state of 1,2-acetoxy migration.

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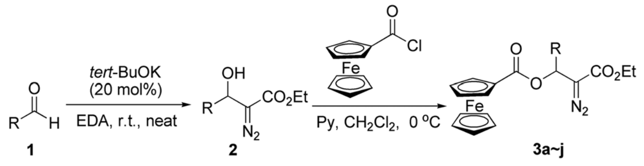
migration should proceed through a five-centered transition state because of the steric effect of the bulky ferrocene group. In this paper, we wish to report the $Rh_2(OAc)_4$ catalyzed decomposition of β-ferrocenecarboxyl α-diazocarbonyl compounds. The results show an efficient 2,3-ferrocenecarboxyl migration leading to the formation of ferrocene-containing α,β-unsaturated esters.

Results and discussion

At the outset of this investigation, we first converted the β-hydroxyl group in diazo compound **2** into β-ferrocenecarboxyl group to afford β-ferrocenecarboxyl substituted diazo compounds **3a–j** (Scheme 2). The β-hydroxy α-diazo esters **2** were prepared by *tert*-BuOK-catalyzed condensation of ethyl diazoacetate (EDA) with aldehyde under solvent-free conditions recently developed by our group with the yields ranging from 69% to 92%.[12] Then ferrocenoyl chloride in anhydrous CH_2Cl_2 was added dropwise to a solution of β-hydroxy α-diazo ester **2** with pyridine in anhydrous CH_2Cl_2 at 0 °C. The esterification reaction was completed within 3 h, and the β-ferrocenecarboxyl substituted α-diazo carbonyl compounds **3a–j** were obtained in moderate to good yields (Table 1).

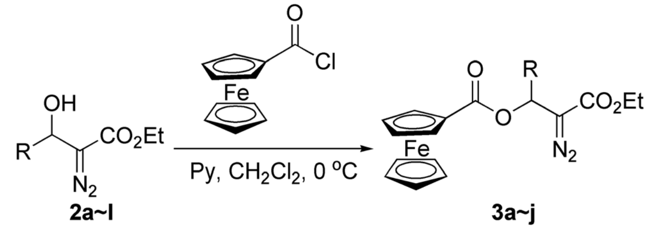
It is worthwhile to note that the reaction should be quenched with saturated $NaHCO_3$ at 0 °C in order to avoid the oxidation of ferrocene as well as the decomposition of the diazo compound under acidic conditions. Most aromatic or aliphatic substituents could be tolerated, and the reaction gave moderate to good yields of the products **3a–j** (Table 1, entries 1–10). However, when R was a *p*-methoxyphenyl or 2-furyl group, we were disappointed to find that the reaction gave a complex mixture and no desired β-ferrocenecarboxyl substituted α-diazo ester product was detected (Table 1, entries 11 and 12). Moreover, the pure ferrocene-containing diazo compounds **3a–j** obtained above are relatively stable and can be kept at 0 °C for several days without any change.

With the β-ferrocenecarboxyl substituted α-diazo esters in hand, we then proceeded to investigate their diazo decomposition behavior using $Rh_2(OAc)_4$ as catalyst. First, diazo compounds **3a–g** with an aromatic ring on the β-position were investigated. The diazo decomposition proceeded smoothly in the presence of 0.1 mol% of $Rh_2(OAc)_4$ in anhydrous CH_2Cl_2 at room temperature to afford the stereoisomeric mixture of products **4a–g** in excellent total yields (Table 2, entries 1–7). It was found that substrates with a halogen or electron-donating substituent on the phenyl ring, such as methyl group, gave slightly lower stereoselectivities (Table 2, entries 1–5), while substrates with a phenyl ring bearing a strong electron-withdrawing group generally gave slightly higher stereoselectivities (Table 2, entries 6 and 7). More interestingly, when R was an aliphatic group, the reaction gave only one isomer whose absolute configuration was not identified from the ^1H NMR



Scheme 2 Synthesis of β-ferrocenecarboxyl α-diazocarbonyl compounds.

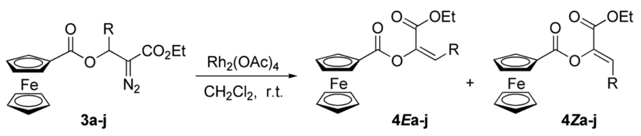
Table 1 Reaction of β-hydroxy α-diazo esters with ferrocenoyl chloride[a]



Entry	R	Time (h)	Yield[b] (%)
1	**2a**, C_6H_5	2	**3a**, 56
2	**2b**, *p*-ClC_6H_4	2	**3b**, 55
3	**2c**, *p*-BrC_6H_4	2	**3c**, 57
4	**2d**, *o*-ClC_6H_4	2.5	**3d**, 70
5	**2e**, *p*-$CH_3C_6H_4$	1	**3e**, 65
6	**2f**, *p*-$NO_2C_6H_4$	3	**3f**, 66
7	**2g**, *o*-$NO_2C_6H_4$	3	**3g**, 61
8	**2h**, H	1.5	**3h**, 70
9	**2i**, CH_3	1.5	**3i**, 60
10	**2j**, $CH_3CH_2CH_2$	1.5	**3j**, 50
11	**2k**, *p*-$CH_3OC_6H_4$	3	nd[c]
12	**2l**, 2-furyl	3	nd[c]

[a] Reactions were carried out with 1.0 mmol of **2**, 1.1 mmol of ferrocenoyl chloride, and 2.0 mmol of pyridine at 0 °C. [b] Yield of isolated product after chromatography. [c] No β-ferrocenecarboxyl substituted α-diazo ester product was detected.

Table 2 Rh(II)-catalyzed reaction of diazo compounds **3a–j**



Entry	Diazo compounds **3**	Time (min)	Yield of **4** ($E + Z$)[a] (%)	Ratio ($E : Z$)[b]
1	**3a**	40	95	66 : 34
2	**3b**	40	94	68 : 32
3	**3c**	40	93	65 : 35
4	**3d**	40	94	65 : 35
5	**3e**	40	94	57 : 43
6	**3f**	60	96	73 : 27
7	**3g**	60	94	81 : 19
8	**3h**	40	92	—
9	**3i**	40	90	—[c]
10	**3j**	40	92	—[c]

[a] Yields after column chromatographic purification with silica gel. [b] Ratio determined by ^1H NMR (500 MHz) of the crude product. [c] Only one isomer was obtained.

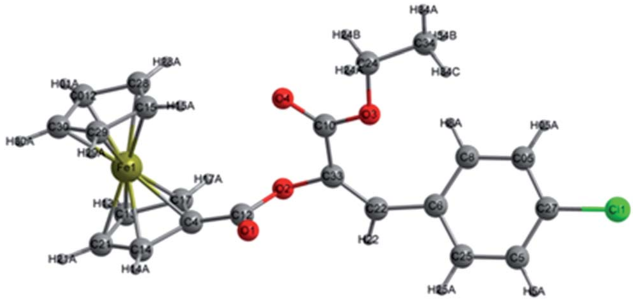
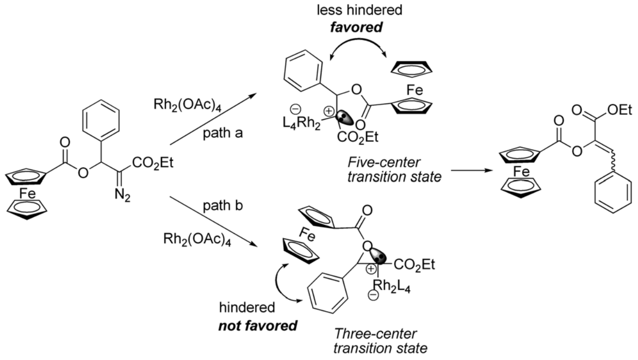


Fig. 1 X-ray structure of **4*E*b**.



Scheme 3 Possible pathway for $Rh_2(OAc)_4$-catalyzed migration reaction of β-ferrocenecarboxyl α-diazocarbonyl compound.

spectra (Table 2, entries 9 and 10). Moreover, the stereochemistry of the *E* product was further confirmed by X-ray structure of **4*E*b** (Fig. 1).[13]

Based on the experimental results above and the X-ray structure of **4*E*b** as well as previous understanding of this type of reactions,[9,10] we conceived that this reaction was performed through a facile 2,3-ferrocenecarboxyl migration of the Rh(II)–carbene. Considering the steric effect of the bulky ferrocene group, the 2,3-migration in this Rh(II)-catalyzed reaction is considered to be the favorable conformation of the five-centered transition state as depicted in Scheme 3. The formation of three-centered transition state may be highly unfavorable due to the steric interaction of the phenyl ring with the ferrocene skeleton. Thus, the current study supports the five-centered transition state that was proposed by Ganem and Wang for 1,2-acetoxy and 2,3-trifluoroacetamido migration.

Conclusions

In conclusion, we have observed an efficient 2,3-ferrocenecarboxyl migration leading to the formation of ferrocene-containing α,β-unsaturated esters under mild reaction conditions. Mechanistically, the reaction is thought to proceed through a five-centered transition state. Moreover, this reaction may find synthetic application as a new entry to these novel ferrocene derivatives.

Experimental

General procedure for the preparation of β-ferrocenecarboxyl substituted diazo compounds 3

In a dried three-necked round-bottom flask, ferrocenoyl chloride (1.1 mmol) in 2 mL of anhydrous CH_2Cl_2 was added dropwise to a solution of β-hydroxy α-diazo ester **2** (1.0 mmol) with pyridine (2.0 mmol) in 5 mL of anhydrous CH_2Cl_2 at 0 °C under N_2. The resulting mixture was stirred at 0 °C and the progress of the reaction was monitored by TLC. After completion of the esterification reaction, saturated $NaHCO_3$ was added at 0 °C. the organic phase was dried using Na_2SO_4, and solvent was removed under reduced pressure. Next, the residue was subjected to chromatography on silica gel to afford the products **3a–j**.

General procedure for the $Rh_2(OAc)_4$-catalyzed reaction of 3a–j

In a dried three-necked round-bottom flask, $Rh_2(OAc)_4$ (0.1 mol%) was dissolved into 5 mL of anhydrous CH_2Cl_2. A solution of diazo substrates **3a–j** in anhydrous CH_2Cl_2 was added dropwise at 0 °C over the course of 30 min. The reaction mixture was stirred until TLC analysis indicated the complete disappearance of the diazo compound. The solvent was then removed under reduced pressure, and the crude residue was purified by column chromatography to give the corresponding 2,3-migration products.

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