

Gold(I)-Catalyzed Reaction of Ferrocene and Propargylic Esters: Synthesis of Functionalized Ferrocene Derivatives

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Dedication ((optional))

Abstract: The reaction of propargylic esters with ferrocene in the presence of gold catalysts provided ferrocene derivatives containing a functionalized vinyl moiety. This ferrocene C-H bond functionalization takes place with complete regio- and stereoselectivity. The reaction is proposed to proceed through an electrophilic substitution in which a vinylgold carbene intermediate arising from a 1,2-rearrangement of the starting propargylic ester would behave as the electrophilic counterpart.

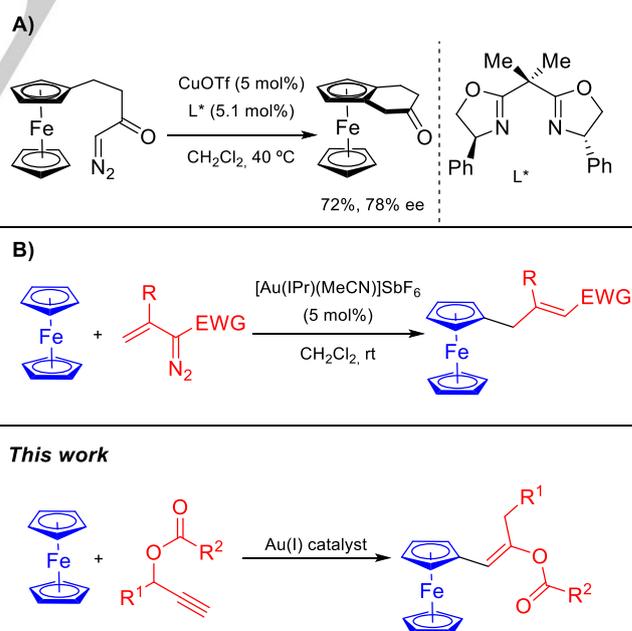
Introduction

C-H bond functionalizations of organic substrates by means of metal carbenoids have become in the last decade a powerful methodology in organic synthesis.^[1] In particular, the transition metal-catalyzed C-H bond functionalization of aromatic compounds involving diazo compounds as the carbene source has been intensively investigated in the last years providing an efficient route to the regioselective synthesis of functionalized benzene derivatives with substitution patterns difficult to access by alternative means.^[2] In most cases, these arene C-H bond functionalizations are proposed to proceed through an electrophilic aromatic substitution mechanism. Surprisingly, despite the large number of useful applications in diverse fields documented for many functionalized ferrocene derivatives,^[3] these well-established methodologies for the functionalization of benzene derivatives based on carbene chemistry have seldom been transferred to ferrocene.^[4] To the best of our knowledge, only two reports on metal-catalyzed C-H bond functionalization of ferrocene involving carbene intermediates have been reported to date (Scheme 1).

A pioneering contribution in this field was made by Siegel and Schmaltz, who in 1997 reported the intramolecular carbene insertion into Cp-H bonds of ferrocene derivatives.^[5] Thus, the decomposition of diazoketones in the presence of both rhodium and copper catalysts allowed the preparation of the cyclization products resulting from the formal insertion of the corresponding electrophilic metal-carbene intermediate into the Cp-H bond. Moreover, this cyclization could be conducted in an enantioselective way when copper(I) triflate (5 mol%) was used in combination with a chiral bis-oxazoline ligand (Scheme 1, A). In 2014, our group reported the gold-catalyzed synthesis of functionalized ferrocene derivatives by reaction of vinyldiazo

derivatives with ferrocene (Scheme 1, B).^[6] This C-H bond functionalization reaction is believed to proceed by means of a vinylgold carbene intermediate which would react regio- and stereoselectively with ferrocene through an electrophilic substitution reaction.

It is well-precedented that, in the presence of gold complexes, propargylic esters can undergo 1,2- and 1,3-acyloxy rearrangements to generate vinylgold carbene and Au(I)-coordinated allene intermediates, respectively, that can subsequently undergo a wide range of useful transformations.^[7] In particular, the trapping of α,β -unsaturated Au(I) carbenes arising from propargylic esters by electron-rich arenes was reported in 2007 by Echavarren et al.^[8] Inspired by this work and continuing with our interest in the synthesis of functionalized ferrocene derivatives through C-H bond functionalization involving carbene intermediates, we envisaged that trapping of the resulting vinylgold carbene intermediate by ferrocene could allow the synthesis of functionalized ferrocene derivatives with a substitution pattern otherwise difficult to achieve. Herein, we disclose the successful realization of this goal. Specifically, we report the synthesis of ferrocene derivatives containing a functionalized vinyl moiety by reaction of ferrocene with propargylic esters in the presence of gold catalysts.



Scheme 1. Functionalization of ferrocene derivatives based on carbene chemistry.

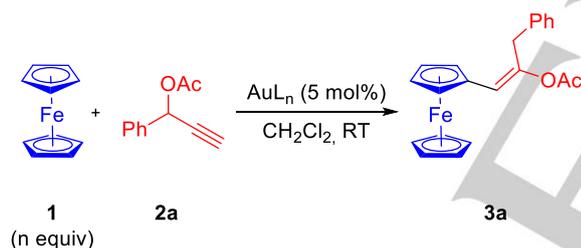
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Results and Discussion

On the outset, we studied the reaction of an excess of ferrocene (**1**) with 1-phenylprop-2-yn-1-yl acetate (**2a**) in the presence of 5 mol% of a series of gold catalysts in dichloromethane as solvent at room temperature. A subset of our screening results are summarized in Table 1. To our delight, various gold complexes proved capable of promoting the formation of ferrocene derivative **3a**. Among them, phosphite complex (ArO)₃PAuNTf₂ (Ar = 2,4-di-tert-butylphenyl) was identified as the most efficient catalyst, providing **3a** as an orange solid in 73% yield after chromatographic purification.

This gold-catalyzed C-H bond functionalization process comprises some significant features: 1) in contrast to previous results involving the use of electron-rich arenes as the trapping reagents or those involving vinyldiazo compounds as carbene source, the ferrocene derivative **3a** isolated in our model reaction does not feature a functionalized allyl but a vinyl group, 2) clearly a 1,2-migration of the acetoxy group took place, which points to the participation of a gold-alkenyl carbene intermediate resulting from a 1,2-acyloxy rearrangement of the starting propargylic ester,^[9] 3) the reaction proceeded with complete regioselectivity with exclusive coupling through the carbenic carbon atom of the postulated gold-alkenyl carbene intermediate,^[10] and, 4) the reaction proceeded with total stereoselectivity because the *E*-isomer is formed exclusively.

Table 1. Summary of catalyst screening^[a]



entry	AuL _n	n	3a (%) ^[b]
1	[IPrAu(CH ₃ CN)][SbF ₆]	3	54
2	IPrAuNTf ₂	3	55
3	JohnPhosAuNTf ₂	3	29
4	[IPrAu(CH ₃ CN)][SbF ₆]	3	54
5	(ArO) ₃ PAuNTf ₂	3	66
6	(ArO) ₃ PAuNTf ₂	3	60 ^[c]
7	(ArO)₃PAuNTf₂	2	73

[a] Unless otherwise stated, these exploratory experiments were performed using 5 mol% of the corresponding gold complex. [b] Isolated yields after chromatography. [c] Reaction performed with 2.5 mol% of the gold complex.

The regio- and stereochemistry of compound **3a** were ascertained by NMR methods (including COSY and NOESY experiments). Moreover, single crystals of ferrocene **3a** were obtained from *n*-pentane/dichloromethane at -20°C. X-ray crystal

structure analysis unambiguously confirmed our initial structural assignment (Figure 1).^[11]

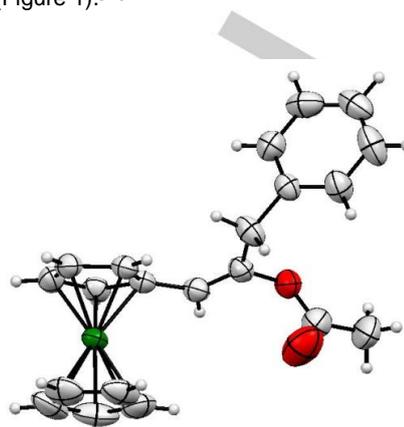


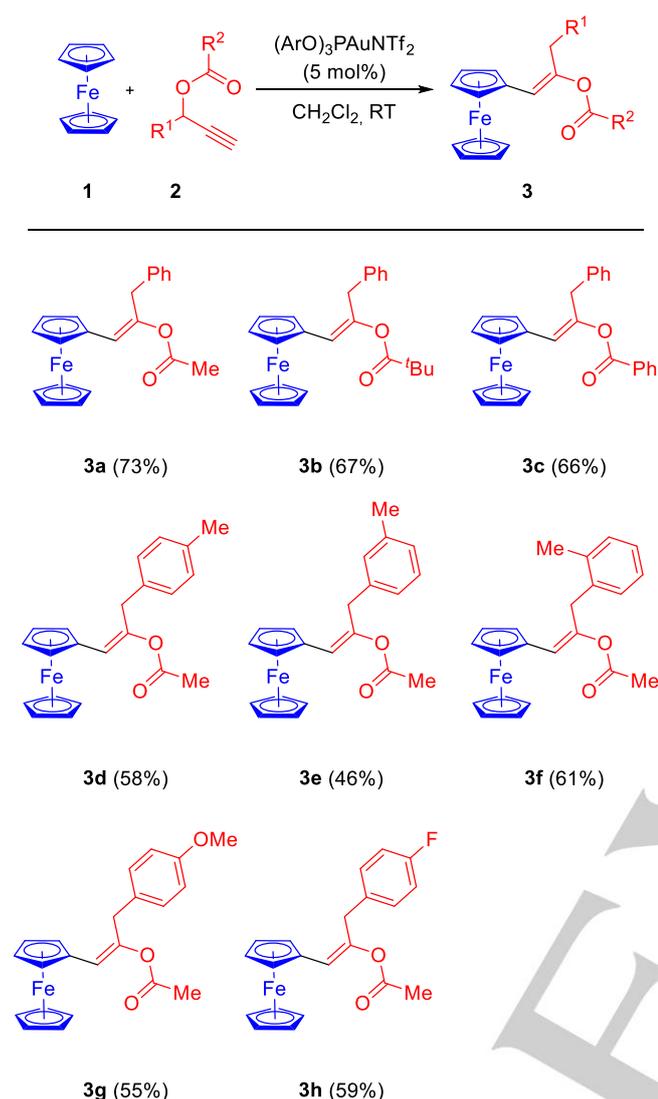
Figure 1. X-ray structure of ferrocene derivative **3a**.

With optimized reaction conditions in hand, the substrate scope of this gold-catalyzed C-H bond functionalization was assessed using a range of propargylic esters (Scheme 2).

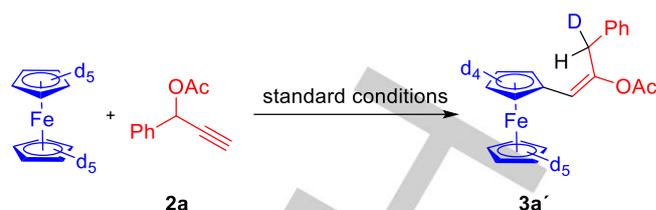
First, we examined the effect of the ester moiety on the reaction outcome. Thus, propargylic pivalate (**2b**; R¹ = Ph, R² = ^tBu) undergoes this gold-catalyzed C-H bond functionalization affording the corresponding ferrocene derivative **3b** in comparable yield and without affecting the regio- and stereoselectivity of the process. Likewise, the use of propargylic benzoate (**2c**; R¹ = R² = Ph) delivered the expected product **3c** in moderate yield.

Next, the propargylic ester substrate scope was further expanded by investigating the effect of substitution on the aryl group. First, we found that propargylic esters with an aryl group featuring a methyl group in either *para*- (propargylic ester **2d**; R¹ = *p*-MeC₆H₄, R² = Me), *meta*- (propargylic ester **2e**; R¹ = *m*-MeC₆H₄, R² = Me) or *ortho*-position (propargylic ester **2f**; R¹ = *o*-MeC₆H₄, R² = Me) were viable substrates affording ferrocene derivatives **3d-f** in moderate isolated yields (46-61%). Moreover, a strong electron-releasing group (propargylic ester **2g**; R¹ = *p*-MeOC₆H₄, R² = Me) was also well tolerated, thus affording ferrocene derivative **3g** in moderate isolated yield. Finally, the presence of a fluorine atom on the aryl group (propargylic ester **2h**; R¹ = *p*-FC₆H₄, R² = Me) posed no problems furnishing ferrocene derivative **3h** in synthetically useful yield.

Unfortunately, the present C-H bond functionalization process seems to be limited to the use of terminal propargylic esters bearing an aromatic group at the propargylic position. Indeed, alkyl- and dialkyl-substituted substrates as well as propargylic esters featuring an internal alkyne failed to produce the corresponding coupling products (See the Supporting Information for the complete list of propargylic substrates screened).

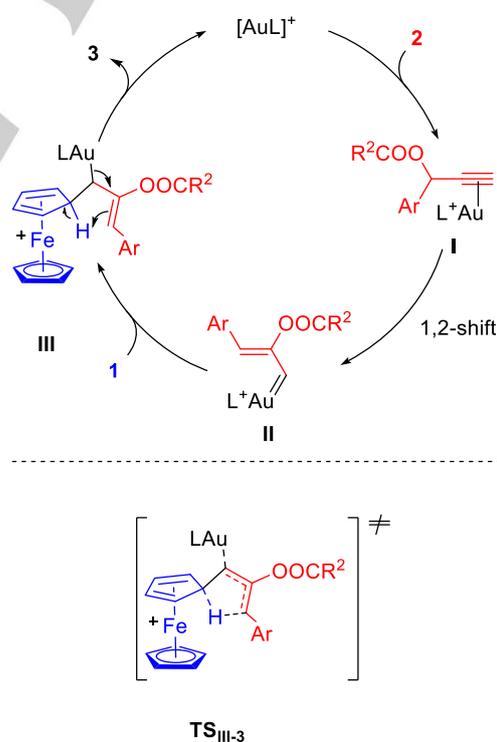


To obtain information about the mechanism of this gold-catalyzed ferrocene C-H bond functionalization, we performed a deuterium-labelling experiment. Thus, the reaction of propargylic ester **2a** with deuterated ferrocene under the standard conditions resulted in the formation of the corresponding ferrocene derivative with exclusive incorporation of deuterium at the benzylic methylene (Scheme 3).



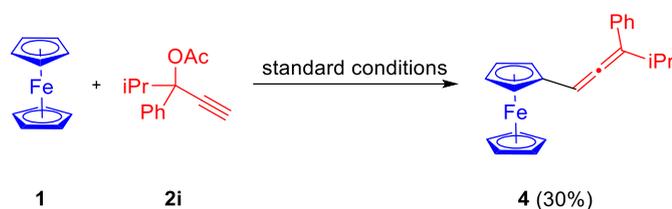
Scheme 3. Deuterium-labelling experiment.

Based on the well-established rearrangement chemistry of propargylic esters in the presence of gold catalysts, a mechanistic proposal for the formation of functionalized ferrocene derivatives **3** is depicted in Scheme 4. Initial coordination of the gold complex to the alkyne would trigger a 1,2-acyloxy rearrangement furnishing vinylgold carbene intermediate **II** (via 5-exo-dig cyclization/ring opening). Attack of ferrocene to the carbenic electrophilic carbon atom of intermediate **II** would generate gold allyl intermediate **III**. This intermediate would evolve to the final products by simultaneous demetalation and intramolecular 1,4 proton transfer. This mechanistic picture would satisfactorily account for both the deuterium-labelling experiment and the observed stereochemistry. In particular, the *E*-configuration of the final products would be very likely a consequence of a cyclic transition state (TS_{III-3}) in the final step.



Scheme 4. Proposed mechanism for the formation of ferrocene derivatives **3**.

Finally, the reaction of ferrocene with propargylic ester **2i** featuring both alkyl and aryl groups at the propargylic position provided an unexpected result. Notably, under otherwise identical conditions, treatment of this propargylic derivative with ferrocene did not afford the expected vinyl-substituted ferrocene derivative. Instead, ferrocenylallene derivative **4** was isolated in modest yield (Scheme 5).



Scheme 5. Gold-catalyzed reaction involving propargylic ester **2i**.

Conclusions

In summary, we have developed an atom economical C-H bond functionalization of ferrocene by trapping of gold carbene intermediates generated from propargylic esters. This process, that takes place under very mild conditions, proceeded with complete regio- and stereoselectivity. A deuterium-labelling experiment pointed to an electrophilic aromatic substitution mechanism in which the gold carbene resulting from a 1,2-rearrangement would act as the effective electrophile through its carbenic carbon atom. This transformation further demonstrates the potential of metal carbene intermediates for accessing functionalized ferrocene derivatives through C-H bond functionalization reactions, a field that remains underdeveloped. Follow-up research focused on the synthetic applications of the reported functionalized ferrocene derivatives is currently pursued in our group.

Experimental Section

Representative Procedure (3a). To a solution of **1** (74 mg, 0.4 mmol) and propargylic ester **2a** (34.8 mg, 0.2 mmol) in dichloromethane (2 mL) was added (2,4- $\text{Bu}_2\text{C}_6\text{H}_3\text{O}$) $_3\text{PAuNTf}_2$ (11 mg, 0.001 mmol, 5 mol%). The mixture was stirred 15 minutes at room temperature (disappearance of **2a** checked by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO_2 , 40:1 hexanes/ethyl acetate). Two fractions were collected. The first fraction was unreacted ferrocene and the second one was found to be pure functionalized ferrocene derivative **3a** (52.6 mg, 73%). Compound **3a** was isolated as a orange solid. Crystallization from pentane/dichloromethane (10:1) afforded orange crystals suitable for X-ray analysis.

Acknowledgements

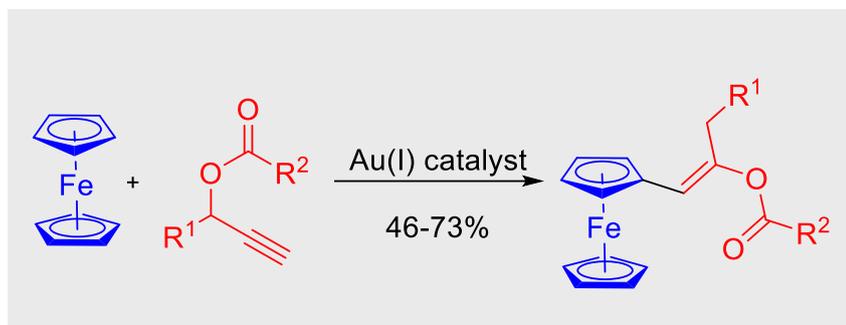
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Keywords: carbene • C-H bond functionalization • ferrocene • gold-catalysis • propargylic esters •

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- [10] 1,4-Additions of nucleophiles have been also reported for α,β -unsaturated Au(I) carbenes arising from propargylic esters (see reference 8).
- [11] CCDC-1491628 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Entry for the Table of Contents

SHORT COMMUNICATION

Ferrocene functionalization**Enol López, Tatiana Suárez, Alfredo Ballesteros,* Luis A. López***Page No. – Page No.***Gold(I)-Catalyzed Reaction of Ferrocene and Propargylic Esters: Synthesis of Functionalized Ferrocene Derivatives**

The gold-catalyzed reaction of ferrocene with propargylic esters provides a convenient route to ferrocene derivatives featuring a functionalized vinyl moiety. This transformation is supposed to proceed through initial 1,2-acyloxy rearrangement with generation of a gold carbene intermediate, which may be subsequently involved in an electrophilic aromatic substitution. This method demonstrates the potential of carbene intermediates in the C-H bond functionalization of ferrocene.