C–H Activation

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

Enol López,[a] Tatiana Suárez,[a] Alfredo Ballesteros,*[a] and Luis A. López*[a]

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 proceeded with complete regio- and stereoselectivity. The reaction was proposed to proceed through electrophilic substitution, in which a vinylgold carbene intermediate arising from 1,2-rearrangement of the starting propargylic ester would behave as the electrophilic counterpart.

Introduction

In the last decade, C–H bond functionalization of organic substrates by means of metal carbenoids has become a powerful method 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 and has provided 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 documented for many functionalized ferrocene derivatives in a variety of fields,[3] these well-established methods 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 intramolecular carbene insertion into the Cp–H bonds (Cp = cyclopentadienyl) of ferrocene derivatives.[5] Thus, the decomposition of diazo ketones in the presence of both rhodium and copper catalysts allowed the preparation of the cyclization products resulting from formal insertion of the corresponding electrophilic metal–carbene intermediate into the Cp–H bond. Moreover, this cyclization could be conducted in an enantioselective way if copper(I) triflate (CuOTf, 5 mol-%) was used in combination with a chiral bisoxazoline 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 AuI-coordinated allene intermediates, respectively, which can subsequently undergo a wide range of useful transformations.[7] In particular, the trapping of α,β-unsaturated AuI 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 in-
termedes, we envisaged that trapping the resulting vinylgold carbene intermediate by ferrocene would 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.

Results and Discussion

At the outset, we studied the reaction of an excess amount of ferrocene (1) with 1-phenylprop-2-yn-1-yl acetate (2a) in the presence of various gold catalysts at a loading of 5 mol-% in dichloromethane as the solvent at room temperature. A subset of our screening results is summarized in Table 1. To our delight, various gold complexes proved capable of promoting the formation of ferrocene derivative 3a. Among them, the phosphite complex (2,4-

Table 1. Summary of catalyst screening.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>AuL&lt;sub&gt;n&lt;/sub&gt; (equiv.)</th>
<th>Yield [%]</th>
<th>[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[IPrAu(CH&lt;sub&gt;3&lt;/sub&gt;CN)][SbF&lt;sub&gt;6&lt;/sub&gt;]&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>IPrAuNTf&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>JohnPhosAuNTf&lt;sub&gt;2&lt;/sub&gt;[c]</td>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>[IPrAu(CH&lt;sub&gt;3&lt;/sub&gt;CN)][SbF&lt;sub&gt;6&lt;/sub&gt;]&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>(2,4-tBu&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;O)&lt;sub&gt;3&lt;/sub&gt;PAuNTf&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>(2,4-tBu&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;O)&lt;sub&gt;3&lt;/sub&gt;PAuNTf&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3</td>
<td>60[b]</td>
</tr>
<tr>
<td>7</td>
<td>(2,4-tBu&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;O)&lt;sub&gt;3&lt;/sub&gt;PAuNTf&lt;sub&gt;2&lt;/sub&gt;</td>
<td>2</td>
<td>73</td>
</tr>
</tbody>
</table>

[a] Unless otherwise stated, these exploratory experiments were performed by using 5 mol-% of the corresponding gold complex. [b] Yield of isolated product after chromatography. [c] JohnPhos = 2-(di-tert-butylphosphino)bi-phenyl. [d] Reaction performed with 2.5 mol-% of the gold complex.

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, ferrocene derivative 3a isolated in our model reaction does not feature a functionalized allyl group but a vinyl group; (2) clearly, 1,2-migration of the acetoxy group took place, which points to the participation of a gold–alkenyl carbene intermediate resulting from 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] (4) the reaction proceeded with total stereoselectivity because the E isomer was formed exclusively.

The regio- and stereochemistry of compound 3a were ascertained by NMR spectroscopy (including COSY and NOESY experiments). Moreover, single crystals of ferrocene 3a were obtained from n-pentane/dichloromethane at –20 °C. The X-ray crystal-structure analysis unambiguously confirmed our initial structural assignment (Figure 1).[11]

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

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

Table 2. Scope of the gold-catalyzed reaction of ferrocene (1) with propargylic esters (2).[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>tBu</td>
<td>73 (66%)</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>tBu</td>
<td>66 (66%)</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>tBu</td>
<td>60 (66%)</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>tBu</td>
<td>54 (66%)</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>tBu</td>
<td>55 (66%)</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>tBu</td>
<td>29 (66%)</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>tBu</td>
<td>54 (66%)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1 (0.4 mmol), 2 (0.2 mmol), (2,4-tBu<sub>2</sub>C<sub>6</sub>H<sub>3</sub>O)<sub>3</sub>PAuNTf<sub>2</sub> (5 mol-%), CH<sub>2</sub>Cl<sub>2</sub>, room temperature. Values in parenthesis are the yields of the isolated products.
underwent this gold-catalyzed C–H bond functionalization to afford corresponding ferrocene derivative 3b in comparable yield and without affecting the regio- or stereoselectivity of the process. Likewise, the use of propargylic benzoate (2c; R1 = R2 = Ph) delivered expected product 3c in moderate yield.

Next, the substrate scope of the propargylic ester 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 the para (2d; R1 = p-MeC6H4, R2 = Me), meta (2e; R1 = m-MeC6H4, R2 = Me), or ortho position (2f; R1 = o-MeC6H4, R2 = Me) were viable substrates, and they afforded ferrocene derivatives 3d–f in moderate yields (46–61%). Moreover, a strong electron-releasing group (2g; R1 = p-MeOC6H4, R2 = Me) was also well tolerated, and ferrocene derivative 3g was thus afforded in moderate yield. Finally, the presence of a fluorine atom on the aryl group (2h; R1 = p-FC6H4, R2 = Me) posed no problems, and ferrocene derivative 3h was furnished in a 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-labeling 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 position (Scheme 2).

![Scheme 2. Deuterium-labeling experiment.](image)

On the basis of 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 3. Initial coordination of the gold complex to the alkyne triggers a 1,2-acyloxy rearrangement to furnish vinylgold carbene intermediate II (through 5-exo-dig cyclization/ring opening). Attack of ferrocene to the carbenic electrophilic carbon atom of intermediate II generates gold allyl intermediate III. This intermediate evolves into the final products by simultaneous demetalation and intramolecular 1,4-proton transfer. This mechanistic picture would satisfactorily account for both the results of the deuterium-labeling 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 (TSIII–III) in the final step.

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 4).

![Scheme 4. Gold-catalyzed reaction involving propargylic ester 2i.](image)

**Conclusions**

In summary, we developed an atom-economical C–H bond functionalization of ferrocene by trapping gold carbene intermediates generated from propargylic esters. This process, which takes place under very mild conditions, proceeded with complete regio- and stereoselectivity. A deuterium-labeling experiment pointed to an electrophilic aromatic substitution mechanism, in which the gold carbene resulting from 1,2-rearrangement acts 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 under investigation in our group.
Experimental Section

Synthesis of 3a as a Representative Procedure: (2,4-tBuC6H3O)3PAuNTf2 (11 mg, 0.001 mmol, 5 mol-%) was added to a solution of 1 (74 mg, 0.4 mmol) and propargylic ester 2a (34.8 mg, 0.2 mmol) in dichloromethane (2 mL). The mixture was stirred at room temperature for 15 min (disappearance of 2a checked by TLC). The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate, 40:1). 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 an orange solid. Crystallization from pentane/dichloromethane (10:1) afforded orange crystals suitable for X-ray analysis.

Acknowledgments

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Keywords: Homogeneous catalysis · Gold · Carbenes · C–H activation · Sandwich complexes

[9] The preference of terminal propargylic esters for 1,2-acyloxy rearrangement in the presence of gold catalysts is well documented. See ref.[7] for specific examples.
[10] 1,4-Additions of nucleophiles were also reported for α,β-unsaturated Au carbenes arising from propargylic esters (see ref.[6]).
[11] CCDC 1491628 (for 3a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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