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Synthesis of allene ferrocenes through CuI-mediated Crabbé homologation reaction†

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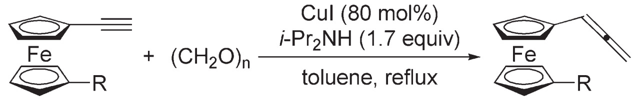
A concise and efficient method for the synthesis of bifunctional allene ferrocenes based on the modified Crabbé homologation reaction of ferrocenylacetylenes with paraformaldehyde promoted by CuI was developed. The presented synthesis proceeded readily with high compatibility of sensitive functional groups on the cyclopentadiene ring providing good to excellent yields of the desired products.

Introduction

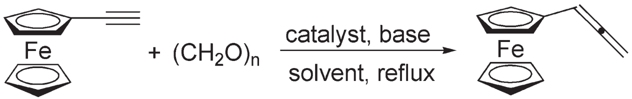
Recently, there has been a resurgence of interest in the chemistry of ferrocene and its derivatives[1] due to their increasing applications in many areas such as material science,[2] asymmetric catalysis,[3] and bioorganometallic chemistry.[4] Undoubtedly, the design motif and synthesis strategy for ferrocene-based architectures play the most important roles in delivering the required properties. Although ferrocene derivatives are classical aromatic compounds, traditional methods for the derivatization of aromatic compounds may not work for ferrocene due to its specific geometric and electronic properties.[5] In view of the importance of ferrocene derivatives, there has been a continuing interest in developing efficient methods for their synthesis under mild reaction conditions.

On the other hand, the chemistry of allenes is currently a field of interest because of the diverse reactivities that these compounds exhibit in organic synthesis.[6] Furthermore, allene moieties have also been found in many natural products and pharmacologically active compounds.[7] Thus, the development of efficient methods to synthesise novel structured allene derivatives from commonly used starting materials is highly desirable. Over the past decades, enormous efforts have been devoted to the development of highly efficient allene synthesis.[8] Among which, the Crabbé homologation reaction and its modifications are widely used in the synthesis of simple allenes.[9,10] For example, Ma and co-workers have reported a modified Crabbé reaction of terminal 1-alkyne that generates terminal allene products with moderate to high yields by using CuI and Cy_2NH.[9g]



Scheme 1 Synthesis of allene ferrocenes.

Table 1 Optimization of reaction conditions[a]



1a **2a**

Entry	Cat. (mol%)	Base	Solvent	Time (h)	Yield (%)[b]
1	CuBr (200)	i-Pr_2NH	Dioxane	5.5	56
2	CuCl (200)	i-Pr_2NH	Dioxane	5.5	58
3	CuI (200)	i-Pr_2NH	Dioxane	5.5	78
4	$CuCl_2$ (200)	i-Pr_2NH	Dioxane	6	Trace
5	$Cu(OAc)_2$ (200)	i-Pr_2NH	Dioxane	6	Trace
6	ZnI_2 (200)	i-Pr_2NH	Dioxane	4	Trace
7	CuI (150)	i-Pr_2NH	Dioxane	5.5	82
8	CuI (100)	i-Pr_2NH	Dioxane	5.5	81
9	CuI (80)	i-Pr_2NH	Dioxane	5.5	84
10	CuI (50)	i-Pr_2NH	Dioxane	5.5	45
11	CuI (80)	i-Pr_2NH	THF	5.5	nd[c]
12	CuI (80)	i-Pr_2NH	DMSO	5.5	nd[c]
13	CuI (80)	i-Pr_2NH	Toluene	5.5	85
14	CuI (80)	Cy_2NH	Toluene	5.5	57
15	CuI (80)	Morpholine	Toluene	5.5	Trace
16	CuI (80)	Pyrrolidine	Toluene	5.5	Trace
17	CuI (80)	Cy_2NH	Dioxane	6	80
18[d]	CuI (80)	i-Pr_2NH	Toluene	5.5	90
19[d]	CuBr (80)	i-Pr_2NH	Toluene	5.5	69
20[d]	CuCl (80)	i-Pr_2NH	Toluene	5.5	61

[a] All the reactions were carried out with **1a** (0.24 mmol), paraformaldehyde (0.60 mmol) and base (0.48 mmol) in 3.0 mL of solvent if not otherwise indicated. [b] Yield of isolated product after chromatography. [c] **2a** was not detected. [d] Ratio of **1a**/$(CH_2O)_n$/i-Pr_2NH was 1.0 : 1.8 : 1.7; in 3.0 mL of toluene.

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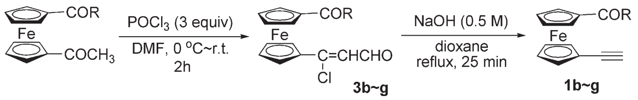
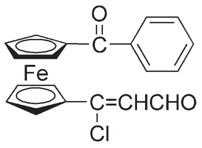
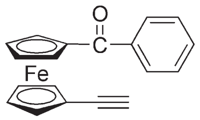
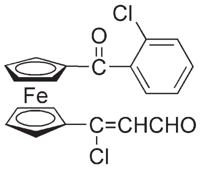
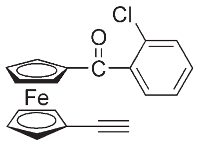
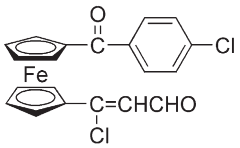
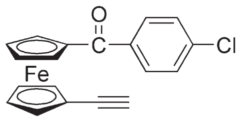
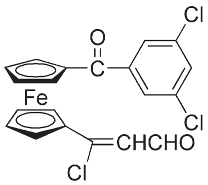
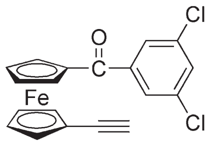
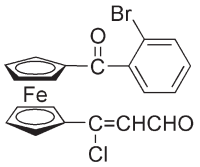
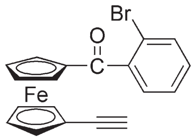
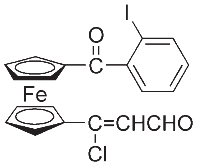
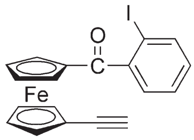
Moreover, the incorporation of ferrocenyl groups to the frameworks of allenes would offer effective modification of their original properties. However, to the best of our knowledge, there are very few examples in the literature that report this type of ferrocene-containing allene.[11] In continuation of our work on the synthesis of ferrocene derivatives,[12] we herein report an efficient method for the synthesis of bifunctional allenyl ferrocene derivatives based on the modified Crabbé homologation reaction of ferrocenylacetylenes with paraformaldehyde promoted by CuI (Scheme 1).

Results and discussion

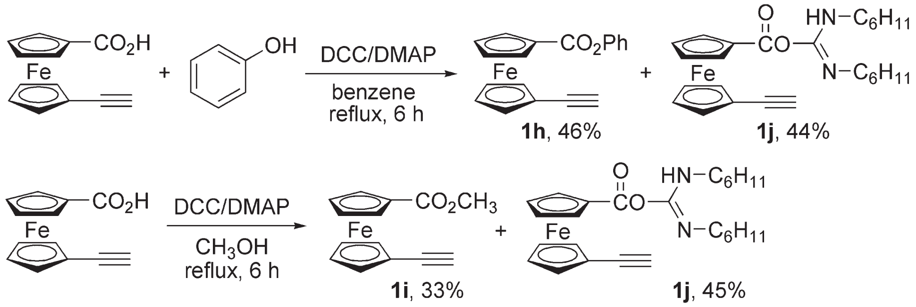
Our initial study was performed with commercially available ferrocenylacetylene **1a** as a model substrate in the presence of paraformaldehyde. The results are summarized in Table 1. Under the reported conditions,[9] the reaction of ferrocenylacetylene with paraformaldehyde and *i*-Pr$_2$NH mediated by CuBr in dioxane afforded the desired ferrocenyl allene **2a** in 56% yield (entry 1, Table 1). Further experiments led to the observation that CuCl may play the same role affording **2a** in a slightly higher yield (entry 2). Moreover, we were delighted to find that the isolated yield of **2a**

Table 2 Preparation of 1′-ethynyl-1-acylferrocenes



Entry	Product **3**		Yield (%)[a]	Product **1**		Yield (%)[a]
1		**3b**	68		**1b**	73
2		**3c**	45		**1c**	77
3		**3d**	76		**1d**	79
4		**3e**	72		**1e**	71
5		**3f**	65		**1f**	63
6		**3g**	70		**1g**	57

[a] Yield of isolated product after chromatography.



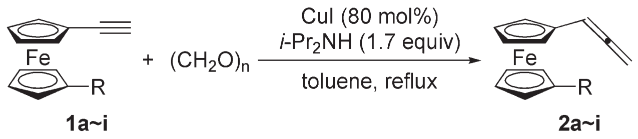
Scheme 2 Synthesis of 1′-ethynylferrocene-1-carboxylic esters.

was increased to 78% when CuI was used as the catalyst (entry 3).[9g] Other catalysts, such as $CuCl_2$, $Cu(OAc)_2$ and ZnI_2, were confirmed to be ineffective for this transformation (entries 4–6). Encouraged by these results, we next carefully examined the effect of the catalyst loading on this homologation reaction (entries 7–10). The results indicated that 80 mol% of CuI could give the best yield of the product under the same conditions (entry 9). After CuI (80 mol%) was identified as the most efficient catalyst, the effect of the solvent on this reaction was next examined (entries 11–13).[10a] No product was formed in THF and DMSO; toluene turned out to be the best. Next, we went on to screen the effect of different amines, because previous investigations showed that the amine may be crucial for the Crabbé homologation reaction.[9g] It was found that Cy_2NH also led to the formation of ferrocenyl allene **2a** in moderate yield (entry 14). However, only a trace of **2a** was detected when morpholine or pyrrolidine was used in this reaction (entries 15 and 16). It was noted that when the reaction was carried out in dioxane using Cy_2NH as base and CuI as catalyst, 80% yield of product **2a** was obtained (entry 17). Therefore, by comparing to Ma's report,[9g] we observed that the most appropriate amine for this ferrocene-containing allene forming reaction is i-Pr_2NH. Furthermore, the ratio of substrates was examined, and it was found that a **1a**/$(CH_2O)_n$/i-Pr_2NH ratio of 1.0 : 1.8 : 1.7 led to the highest yield of **2a** (entry 18). Once again, the reactivities of other Cu(I) salts were checked carefully under optimal conditions and the results indicated that CuI was still the most effective for this transformation (entries 19 and 20).

To define the generality of the present method, we firstly synthesized a series of 1′-ethynyl-1-acylferrocenes from the corresponding 1′-acetyl-1-acylferrocenes by a two-step procedure.[13] The overall yields for the two-step procedure ranged from 35–51% (Table 2). Moreover, three 1′-ethynylferrocene-1-carboxylic esters were easily prepared by the reaction of 1′-ethynylferrocene-1-carboxylic acid with methanol or phenol using *N*,*N*′-dicyclohexylcarbodiimide/4-dimethylaminopyridine (DCC/DMAP) as dehydrating agents (Scheme 2).[14] The 1′-ethynyl-1-carbonylferrocenes were sufficiently stable to withstand purification by column chromatography and could also be stored at room temperature.

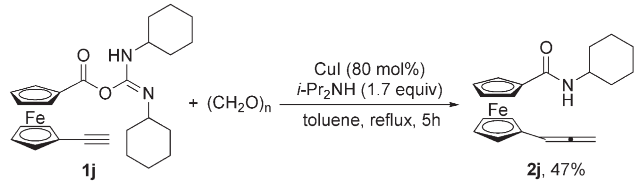
Having prepared a variety of 1′-ethynyl-1-carbonylferrocenes, we next turned our attentions to the homologation reaction for the synthesis of allene ferrocenes using these compounds as the substrates and the results are summarized in Table 3. Various substitutions on the cyclopentadiene ring could be tolerated, and the reaction gave moderate to high yields of the ferrocenyl allene products **2a–i**. For aroyl-substituted ferrocenylacetylenes, the reaction afforded the corresponding allenes **2b–g** in 70–86% isolated yields (entries 2–7). We were curious to know if a ferrocenylacetylene containing ester group such as **1h** (entry 8) would behave similarly to aroyl-substituted ferrocenylacetylenes under our reaction conditions. We were pleased to discover that the reaction proceeded readily to give the corresponding allene product **2h** in 83% yield. However, when methyl 1′-ethynyl-1-ferrocenecarboxylate **1i** was used as the substrate in this reaction,

Table 3 CuI promoted Crabbé homologation reaction of various ferrocenylacetylenes **1a–i** with paraformaldehyde[a]

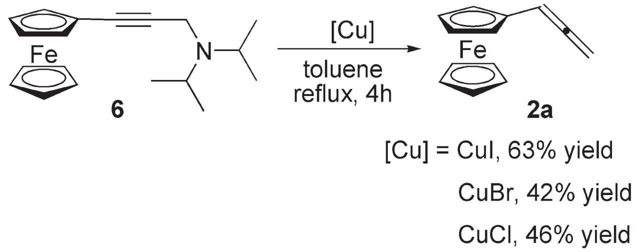


Entry	**1**, R	Reaction time (h)	**2**, yield (%)[b]
1	**1a**, H	4	**2a**, 90
2	**1b**, PhCO	3.5	**2b**, 74
3	**1c**, o-ClC_6H_4CO	2	**2c**, 74
4	**1d**, p-ClC_6H_4CO	5.5	**2d**, 86
5	**1e**, 3,5-Cl,ClC_6H_3CO	1.5	**2e**, 82
6	**1f**, o-BrC_6H_4CO	2.5	**2f**, 70
7	**1g**, o-IC_6H_4CO	5	**2g**, 73
8	**1h**, CO_2Ph	6	**2h**, 83
9	**1i**, CO_2CH_3	5	**2i**, 61

[a] Reactions were carried out with **1a–i** (0.24 mmol), paraformaldehyde (0.43 mmol) and i-Pr_2NH (0.41 mmol) in 3.0 mL of toluene. [b] Yield of isolated product after chromatography.



Scheme 3 Reaction of **1j**.



Scheme 4 Reaction of propargylic amine intermediate **6**.

only a moderate yield of product **2i** was obtained after workup (entry 9).

More interestingly, when *N,N*′-dicyclohexylcarbamimidoyl 1′-ethynylferrocene-1-carboxylate **1j** was employed in this modified Crabbé homologation reaction, we surprisingly found that the ferrocenyl allene product **2j** was formed in moderate yield under identical reaction conditions (Scheme 3). The formation of **2j** suggested that the reaction proceeded accompanied by the rearrangement of the ester group under these conditions. To examine whether CuI catalyses the displacement of $CyNH_2$ in this transformation, we carried out control experiments by treating **1j** with *i*-Pr_2NH in the absence of formaldehyde, and in the absence of both formaldehyde and copper. However, no new product could be identified in these reactions and the starting material was recovered after refluxing in toluene for 10 h. Therefore, the mechanism for the formation of the corresponding product **2j** remains not completely clear.

Besides, it is noted that we have isolated the propargylic amine **6** which was formed in the reaction of ferrocenylacetylene, paraformaldehyde and *i*-Pr_2NH at 130 °C in toluene for 15 min. Treatment of compound **6** with CuI, CuBr or CuCl in toluene resulted in the formation of the allene product **2a** in 63%, 42% and 46% isolated yields, respectively (Scheme 4). Moreover, no reaction was observed in the absence of a copper catalyst.

On the basis of the results presented above and the previous understanding of this type of reaction,[9,10,15] we propose the following possible mechanism for this homologation reaction, as shown in Scheme 5. In the presence of base and copper(I) salt, copper acetylide **4** is formed from ferrocenylacetylene **1a**. The reaction of copper acetylide **4** with the iminium ion **5**, which is generated *in situ* from paraformaldehyde and *i*-Pr_2NH, leads to the formation of the corresponding propargylic amine intermediate **6** and regenerated CuI. CuI coordinates to the carbon–carbon triple bonds in **6** to give intermediate **7**, which undergoes an intramolecular hydride transfer and β-elimination to afford the ferrocenyl allene product **2a**. It is noted that the formation of **2a** could also be attributed to the S_N2' reaction of intermediate **7** instead of intermediate **8**.

Conclusions

In conclusion, we have developed a concise and efficient method for the synthesis of bifunctional allene ferrocenes based on the modified Crabbé homologation reaction of ferrocenylacetylenes with paraformaldehyde in the presence of *i*-Pr_2NH using CuI as the catalyst. Due to the increasing importance of allenes and ferrocenes in organic chemistry, this method will be a valuable choice for organic synthesis and it may open up new possibilities to incorporate ferrocene chemistry with allenes. Further studies on the applications as well as the transformations of these novel allene ferrocenes are being actively pursued in our laboratory.

Acknowledgements

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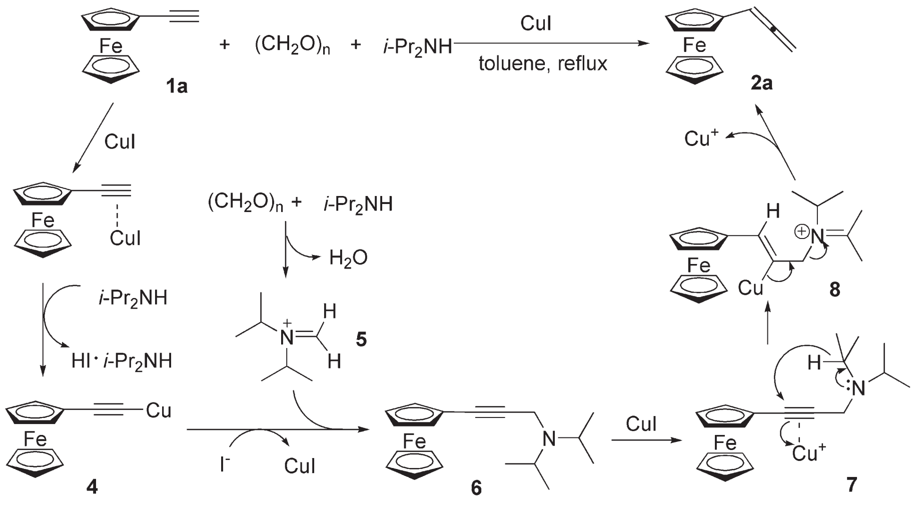

Scheme 5 Possible reaction pathway.

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