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Synthesis of Substituted Naphtho-Ferrocenes via a Gold(I)-Catalyzed Intramolecular 6-*endo*-Dig Cyclization

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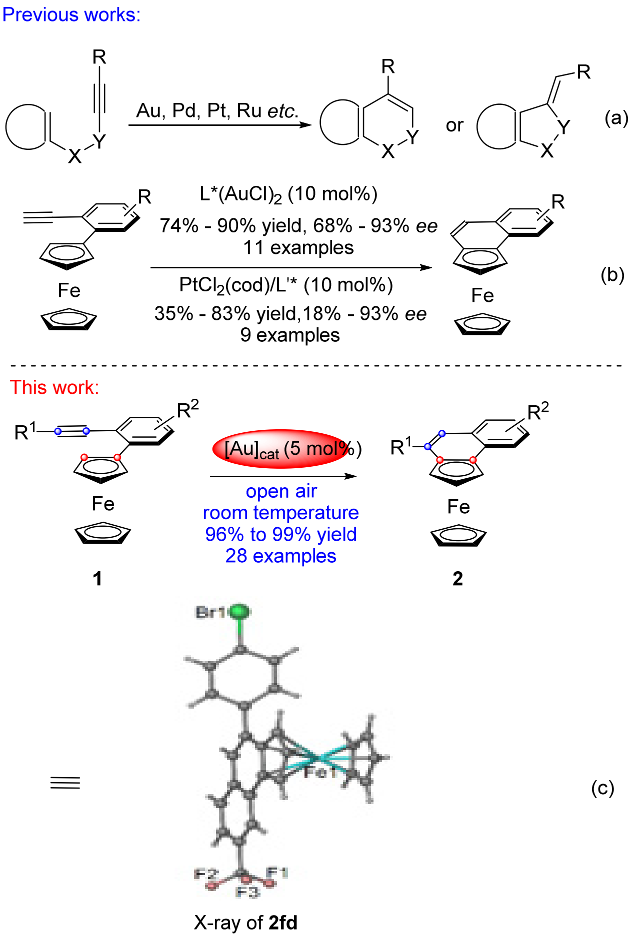
A novel series of naphtho-ferrocene derivatives were synthesized in high yields by an efficient gold-catalyzed intramolecular 6-*endo*-dig cyclization strategy. The salient features of this reaction include easy operation, broad substrate scope, high yields, mild conditions and it works well in wet solvent under air at room temperature.

Keywords gold(I)-catalysis, cyclization, hydroarylation, PAHs-metallocenes, naphtho-ferrocenes

Introduction

Because most of the ‘low-hanging polycyclic aromatic hydrocarbons (PAHs) fruits’ have already been harvested,[1] some researchers have now started paying more attention to other multi-dimensional organic molecules, such as fullerene[2] and metallocene.[3] The PAHs-metallocenes based two-dimensional core, because of π-systems’ unique electrochemical and photochemical properties, could be suitable for luminescent materials and organic semiconductors directed toward electronic devices, such as thin-film transistors and organic light-emitting diodes.[4] So the development of efficient strategies for the synthesis of structurally diverse PAHs-metallocenes based two-dimensional core in an atom-economical manner is of great importance. Traditionally, transition-metal-catalyzed transformations, represent one of the most effective approaches for synthesis of cyclic compounds, and significant progress has been achieved with the cyclization approach in recent years (Scheme 1a).[5] Against this background, the efficient intramolecular hydroarylation of alkynes is believed to be the key issue for construction of the fused ferrocene derivatives.[6] More recently, the group of Urbano and Carreño[7a] reported the first gold-catalyzed cyclization of terminal-alkynylaryl ferrocenes, leading to enantioenriched chiral PAHs-metallocenes (Scheme 1b). Later, Kanyiva[7b] achieved the same transformation by the use of chiral platinum-catalysis. However, relatively high catalyst loading or high temperature is often required and the scope of ferrocene derivatives with a substituted alkyne moiety is limited in this process.

Scheme 1 Previous and this work



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In Memory of Professor Enze Min.

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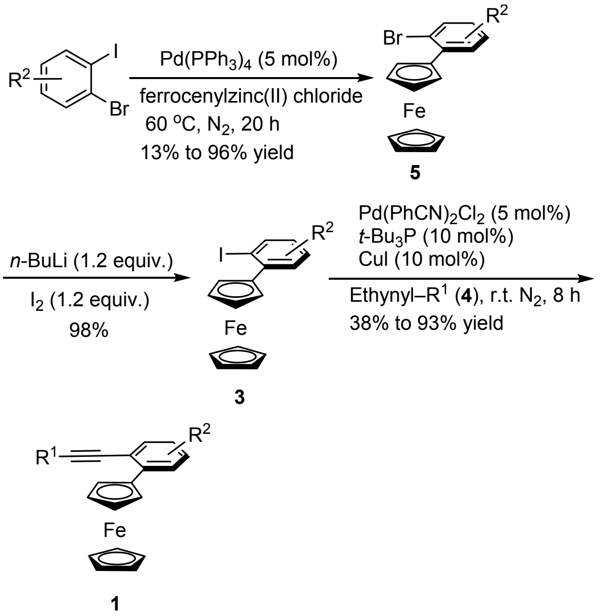
Therefore, the efficient construction of the π-conjugated PAHs-metallocene still remains a valuable work by transition metal-catalyzed cyclization of internal alkynylaryl ferrocenes. Herein, we reported an efficient gold-catalyzed[5,8] intramolecular 6-*endo*-dig cyclization of 1-ferrocenyl-2-(1-alkynyl)benzenes which were easily prepared via palladium-catalyzed Negishi coupling[9] and Sonogashira coupling[10,11] reaction (Scheme 2), to give structurally diverse naphtho-ferrocenes derivatives under very mild reaction conditions (Scheme 1c).

Scheme 2 Synthesis of **1** via Negishi coupling and Sonogashira coupling reaction



Experimental

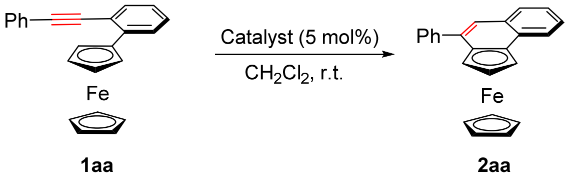
$Pd(PhCN)_2Cl_2$ (5 mol%) and the substituted 2-ferrocenyl-1-iodobenzene **3** were transferred to a Schlenk tube under a N_2 atmosphere. In a separate flask, Et_3N (0.3 mol/L) was sparged with N_2 for 30 min, after which it was transferred into the Schlenk tube. *t*-Bu_3P (10 mol%, 1 mol/L in toluene) was then added to the solution, stirred at room temperature for 10 min, then the substituted acetylene **4** (1.2 equiv.) and CuI (10 mol%) were added respectively, the reaction mixture was stirred at room temperature for 8 h, during which the reaction progress was monitored by TLC. After **3** was completely consumed, the solvent was evaporated under vacuum, the residue was purified by flash column chromatography on silica gel (Hexane-EtOAc as eluent) to give product **1**.

In a Schlenk tube, a mixture of **1** (0.2 mmol) and $IPrAuSbF_6$ (5 mol%) was stirred in DCM (2 mL) at room temperature. After the reaction was completed, the organic solvent was evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (Hexane-EtOAc as eluent) to afford the desired product **2**.

Results and Discussion

We initiated our studies by investigating the cyclization of 2-phenylethynyl-1-ferrocenylbenzene **1aa** in the presence of cationic Au(I) complexes (Table 1, Entries 1—3). To our delight, the desired product **2aa** was obtained in 99% yield (Table 1, Entries 2, 3). Subsequently, the effect of the counterion was investigated (Table 1, Entries 3—5): hexafluoroantimonate (SbF_6^-) was the best counterion, and the desired product **2aa** was obtained in 99% yield at room temperature for 2 h. IPrAuCl or $AgSbF_6$ did not catalyze the reaction at all, indicating that $IPrAuSbF_6$ was the real active catalyst (Table 1, Entries 8, 9). Other metal catalysts such as $AuCl_3$, $Pd(PPh_3)_4$ and $Cu(OTf)_2$ could not catalyze the reaction either (Table 1, Entries 10—12). It should be noted that the reaction works well in wet DCM under air without any detriment to the reaction rate or yield (Table 1, Entries 6 and 7).

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Time/h	Yield[b]/%
1	$PPh_3AuCl/AgSbF_6$	24	NR
2[c]	$LAuCl/AgSbF_6$	48	99
3[d]	$IPrAuCl/AgSbF_6$	2	99
4[d]	IPrAuCl/AgOTf	4	99
5[d]	$IPrAuCl/AgNTf_2$	24	NR
6[d,f]	$IPrAuCl/AgSbF_6$	2	99
7[d,e,f]	$IPrAuSbF_6$	2	99
8[d]	IPrAuCl	24	NR
9	$AgSbF_6$	24	NR
10	$AuCl_3$	24	NR
11	$Pd(PPh_3)_4$	24	NR
12	$Cu(OTf)_2$	24	NR

[a] Unless specified, the reaction was carried out with **1aa** (0.1 mmol), catalyst (5 mol%) in anhydrous DCM (2 mL) at room temperature under N_2. [b] Isolated yields. NR: no reaction. [c] LAuCl: $(2,4\text{-}t\text{-}Bu_2C_6H_3O)_3PAuCl$. [d] IPr=1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene. [e] $IPrAuSbF_6$ is prepared from IPrAuCl and $AgSbF_6$. [f] Wet DCM under air.

With the optimized reaction conditions in hand, we investigated the substrate scope of this gold-catalyzed intramolecular 6-*endo*-dig cyclization reaction (Table 2). Firstly, a series of internal aryl (R^1)-alkynes were prepared and tested to this cyclization process. Various substituents on different positions of the phenyl ring (R^1), regardless of their electronic nature, were well tolerated to afford naphtho-ferrocenes **2aa**—**2ia** in 96%

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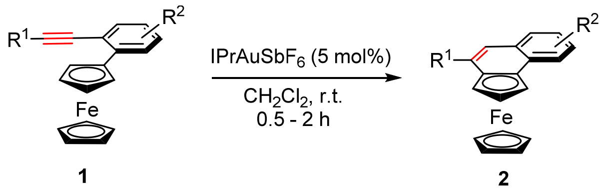
to 99% yields (Table 2, Entries 1—9). It is worth noting that, electron donating and steric hindrance groups were well tolerated, such as methyl, methoxyl and *tert*-butyl, and the desired products were achieved in 96% to 99% yields (Table 2, Entries 10—15). Secondly, $IPrAuSbF_6$ also displayed super performance in the reactions of internal alkyl-alkynes, conjugated enynes and aromatic heterocycle-alkynes (**1pa**—**1ta**), furnishing the corresponding products **2pa**—**2ta** in 98% to 99% yields (Table 2, Entries 16—20). In particular, intramolecular cyclization of trimethylsilane (R^1)-alkynes **1ua** along with desilylation[12] provided the same product **2va** as well as terminal alkyne **1va** (Table 2, Entries 21, 22). Finally, the reaction scope of this cyclization reaction was explored with the phenyl ring (R^2) bearing electron-donating and electron-withdrawing groups at the *para*- or *meta*-position, delivering the desired products **2fb**—**2mb** in 97% to 99% yield as well (Table 2, Entries 23—28). Single-crystal X-ray study of **2fd**[13] further confirmed the regioselectivity of cyclization strategy, as expected a selective intramolecular 6-*endo*-dig cyclization sequence.

Table 2 Synthesis of naphtho-ferrocenes derivatives[a]

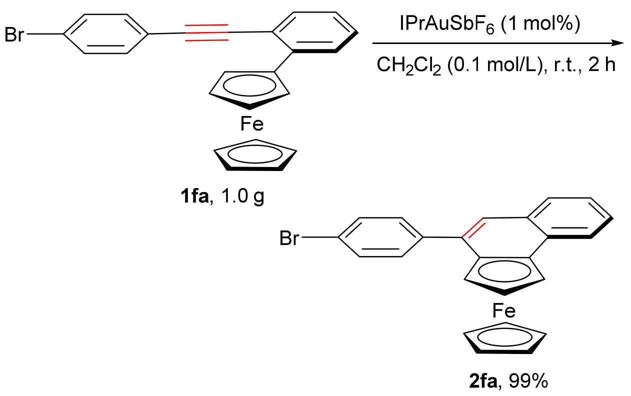


Entry[a]	R^1	R^2	*T*/h	Yield/%
1	C_6H_5	H	2	**2aa**, 99
2	$4\text{-}FC_6H_4$	H	4	**2ba**, 99
3	$4\text{-}ClC_6H_4$	H	0.5	**2ca**, 99
4	$3\text{-}ClC_6H_4$	H	8	**2da**, 98
5	$2\text{-}ClC_6H_4$	H	4	**2ea**, 98
6	$4\text{-}BrC_6H_4$	H	0.5	**2fa**, 99
7	$4\text{-}AcC_6H_4$	H	2	**2ga**, 99
8	$4\text{-}O_2NC_6H_4$	H	0.5	**2ha**, 99
9	$4\text{-}MeCO_2C_6H_4$	H	2	**2ia**, 99
10	$4\text{-}MeC_6H_4$	H	3	**2ja**, 99
11	$3\text{-}MeC_6H_4$	H	8	**2ka**, 96
12	$2\text{-}MeC_6H_4$	H	3	**2la**, 99
13	$4\text{-}MeOC_6H_4$	H	0.5	**2ma**, 99
14	$3,4,5\text{-}(MeO)_3C_6H_2$	H	1	**2na**, 99
15	4-*t*-BuC_6H_4	H	3	**2oa**, 99
16	Cy	H	4	**2pa**, 98
17	1-Cyclohexenyl	H	4	**2qa**, 98
18	1-Naphthyl	H	8	**2ra**, 98
19	2-Thiophene	H	0.5	**2sa**, 99
20	2-Benzofuranyl	H	3	**2ta**, 99
21[b]	TMS	H	5	**2va**, 98
22	H	H	4	**2va**, 99
23	$4\text{-}BrC_6H_4$	4-Cl	1	**2fb**, 99
24	$4\text{-}OMeC_6H_4$	4-Cl	1	**2mb**, 99
25	$4\text{-}BrC_6H_4$	4-Me	1	**2fc**, 99
26	$4\text{-}MeOC_6H_4$	4-Me	1	**2mc**, 99
27	$4\text{-}BrC_6H_4$	$5\text{-}CF_3$	8	**2fd**, 97
28	$4\text{-}MeOC_6H_4$	$5\text{-}CF_3$	8	**2md**, 99

[a] The reaction was carried out with **1aa** (0.2 mmol), $IPrAuSbF_6$ (5 mol%) in DCM (2 mL) at room temperature. [b] The cyclization of **1ua** along with desilylation provided the product **2va**.

To demonstrate the practical utility of our protocol, a gram-scale reaction was carried out. To our delight, the catalyst loading could be reduced to only 1 mol% on a 2.3 mmol scale to furnish **2fa** in 99% yield for 2 h, indicating that this transformation is easy to scale-up to gram scale without a loss of efficiency (Scheme 3).

Scheme 3 Gram-scale synthesis of **2fa**



Conclusions

In summary, a highly efficient and practical gold-catalyzed intramolecular 6-*endo*-dig cyclization reaction has been discovered to prepare a series of novel naphtho-ferrocenes derivatives from 2-arylethynyl-1-ferrocenylbenzene. Various substituted groups can be tolerated on alkynes and ferrocenylbenzenes. Importantly, the starting materials can be prepared easily, providing the corresponding naphthalene fused ferrocene derivatives in excellent yield under very mild conditions. This work would shine some light on researching the luminescence and electrochemical properties of the PAHs-metallocene based two-dimensional core. Further investigations on the enantioselective variant of this protocol and deep study of electrochemical and photochemical properties were underway in our laboratories.

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