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Synthesis of 1,1-Diarylethylenes via Efficient Iron/Copper Co-Catalyzed Coupling of 1-Arylvinyl Halides with Grignard Reagents

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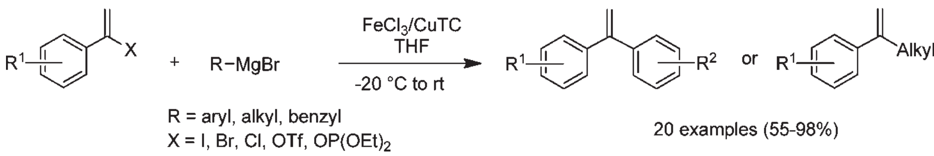
ABSTRACT



An efficient access to 1,1-diarylethylenes of biological interest by coupling functionalized aryl Grignard reagents and 1-arylvinyl halides in the presence of $FeCl_3$/CuTC is described. This bimetallic system proved to be superior to the use of Fe or Cu catalyst alone. The synthetic utility of this protocol is illustrated in the field of steroid chemistry.

The 1,1-diarylethylenes are part of the *gem*-disubstituted olefin family, known either as a common pharmacophore of biological interest or as synthetic intermediates in organic synthesis.[1] Examples of biologically active agents containing this structural motif are depicted in Figure 1.[2] Recently, our efforts to discover novel vascular disrupting agents (VDA),[3] led us to identify isocombretastatin A-4 (isoCA-4), isoNH_2CA-4, and *iso*FCA-4 as lead compounds that exhibit potent antineoplastic and antivascular properties.[4]

Classical protocols for the synthesis of 1,1-diarylethylene rely on the use of Wittig reactions with benzophen ones or addition of Grignard reagents to either aceto- or benzophenones followed by dehydration.[4b] An attractive transition-metal-catalyzed process to 1,1-diarylethylenes consists of alkenylation of arenes with alkynes.[5] However, this transformation suffers from issues of poor regioselectivity when unsymmetrical arenes were used. Another efficient way for making 1,1-diarylethylenes, recently reported by Barluenga and by us, is the coupling of aryl halides with *N*-tosylhydraoznes derived from acetophenones under

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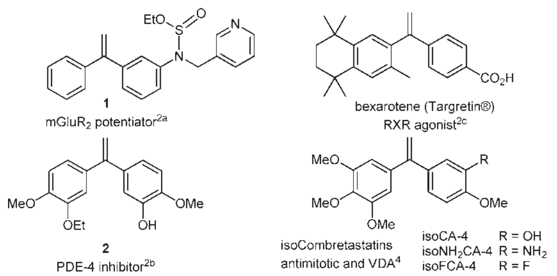


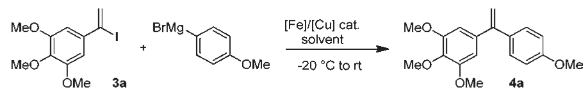
Figure 1. Structures of some bioactive 1,1-diarylethylenes.

Pd catalysis.[4a,6] Traditional cross-coupling reactions of vinyl or aryl halides with aryl- or vinylmetal derivatives (Sn,[7] Si,[8] B,[9] Mg,[10] Zn[11]) have also been reported. To be successful, these transformations require the presence of palladium or nickel as catalysts. These metals are costly or toxic and often necessitate sophisticated and expensive ligands of high molecular weight. There is a great need for cheap and environmentally friendly catalysts that do not require complicated ligands.

In recent years, iron salts have emerged as a promising alternative as a catalyst for C–C bond-forming reactions because of their low cost and toxicity and offer attractive industrial possibilities in terms of sustainable chemistry.[12]

Since the pioneering works of Kochi in the 1970s,[13] alkenylation of alkyl Grignard reagents has been extensively studied.[14] However, alkenylation of aryl Grignard reagents under iron salt catalysis has received much less attention.[15] In these instances, this transformation has often been devoted to aliphatic vinyl halides and very rarely to β-styryl halides. To the best of our knowledge, only one example is reported for the coupling with a simple α-bromostyrene ($Fe(dbm)_3$ in DME),[15a] probably because of the more difficult oxidative addition step and, hence, higher requirements to the catalytic system. From a synthetic viewpoint, the development of cross-coupling reactions with α-styryl halides as viable coupling partners would be of great interest for the synthesis of 1,1-diarylethylenes in the context of medicinal chemistry programs.[3,4] Herein we disclose a general and very efficient coupling of polyoxygenated α-styryl halides with functionalized aryl Grignard reagents. We found that the coupling occurred in the presence of the new catalytic system combining $FeCl_3$ and copper(I) thiophene-2-carboxylate (CuTC) under mild conditions to give the corresponding cross-coupling products in good to excellent yields. This bimetallic combination catalytic system[16] is clearly more efficient than the corresponding Fe-catalyzed Grignard procedure mentioned above[15a] and offers an efficient alternative to the Pd- and Ni-catalyzed procedures used until now.

Table 1. Fe/Cu Co-catalyzed Cross-Coupling of 1-Arylvinyl Iodide **3a** with 4-Methoxyphenylmagnesium Bromide[a]



entry	[Fe] cat. (0.1 equiv)	[Cu] cat. (0.1 equiv)	solvent	yield[b] (%)
1	$Fe(dbm)_3$		DME	31[c]
2	$Fe(dbm)_3$		THF	34
3	$Fe(acac)_3$		THF	40
4	$Fe(acac)_3$		THF/NMP[d]	36
5	$Fe(acac)_3$	CuI	THF	50
6	$Fe(acac)_3$	CuCl	THF	52
7	$Fe(acac)_3$	CuCN·2LiCl	THF	43
8	$Fe(acac)_3$	$Cu(acac)_2$	THF	50
9	$Fe(acac)_3$	CuTC	THF	55
10	Fe(0)	CuTC	THF	8
11	$Fe(dbm)_3$	CuTC	THF	50
12	$Fe(OAc)_2$	CuTC	THF	57
13	$FeCl_3$	CuTC	THF	82[e,f,g]
14	$FeCl_3$		THF	54
15		CuTC	THF	10

[a] ArMgBr (2.0 equiv) was slowly added at −20 °C to a solution of **3a** (1 equiv), [Fe] (10 mol %), and [Cu] (10 mol %) in the solvent mentioned above (2.0 mL, 0.25 M). [b] Yield of isolated product. [c] Reaction carried out at 20 °C gave **4a** in 30% yield. [d] NMP (22 equiv). [e] The use of ArMgBr (1.5 equiv) gave **4a** in 57% yield. [f] A similar yield (80%) was obtained using 5 mol % of $FeCl_3$ and 5 mol % of CuTC. [g] With 1 mol % of $FeCl_3$ and 1 mol % of CuTC, **4a** was obtained in 60% yield.

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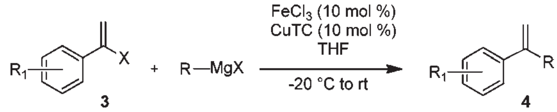
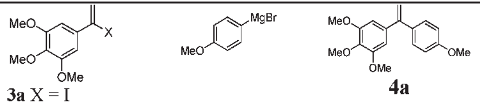
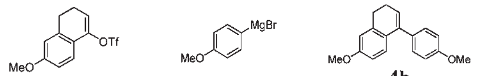
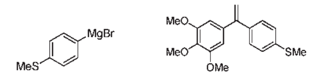
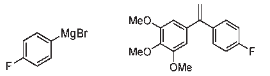
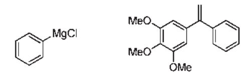
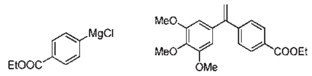
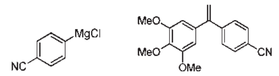
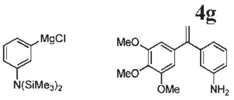
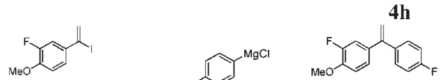
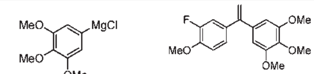
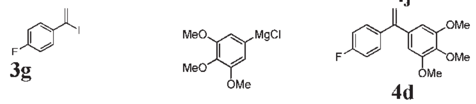
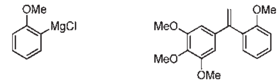
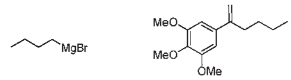
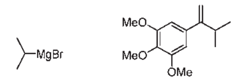
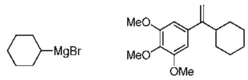
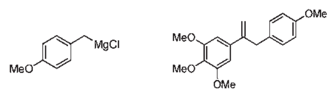
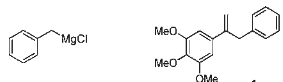
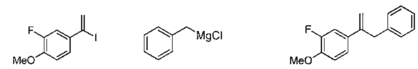
Table 2. Scope of $FeCl_3$/CuTC Co-catalyzed Cross-Couplings of **3** with Functionalized Grignard Reagents



entry	vinyl iodide **3**	RMgX	olefin **4**	yield (%)[a]
			**4a**	
1	**3a** X = I			82
2	**3b** X = Br			80
3	**3c** X = Cl			78
4	**3d** X = OP(OEt)$_2$			56
5	**3e**		**4b**	70
6	**3a**		**4c**	62
7	**3a**		**4d**	96
8	**3a**		**4e**	77
9	**3a**		**4f**	55[b]
10	**3a**		**4g**	60
11	**3a**		**4h**	87[c]
12	**3f**		**4i**	95
13	**3f**		**4j**	65
14	**3g**		**4d**	84
15	**3a**		**4k**	65
16	**3a**		**4l**	86
17	**3a**		**4m**	80
18	**3a**		**4n**	78[d,e]
19	**3a**		**4o**	60[f]
20	**3a**		**4p**	98
21	**3f**		**4q**	93

[a] Yield of isolated product. [b] **3a** was added to the solution of Grignard reagent at −20 °C. [c] After the coupling, the crude was subjected to methanolysis by refluxing for 8 h. [d] Reaction with $FeCl_3$ alone led to **4n** in 55% yield. [e] Reaction with CuTC alone gave **4n** in 46% yield. [f] Reaction with $FeCl_3$ alone gave **4o** in 8% yield.

At the outset of our studies, we first examined the coupling of polyoxygenated α-iodostyrene **3a** with 4-methoxyphenylmagnesium bromide under the conditions described by Molander[15a] using $Fe(dbm)_3$ (5 mol %) as the catalyst in DME as the solvent at room temperature. However, this transformation was inefficient, and the desired product **4a** was isolated in a low 30% yield. Similar results were obtained when the reaction was performed at lower temperature (−20 °C, Table 1, entry 1) or using THF as the solvent[13b] (entry 2). In the light of Cahiez's previous work,[14a] we thought that the use of NMP as the cosolvent in combination with $Fe(acac)_3$ could have a beneficial influence on the coupling reaction. The results shown in entry 4 revealed that no significant improvement of the yield of **4a** was observed. Finally, with $Fe(acac)_3$ as the iron source and THF as the solvent, we examined the efficiency of copper(I) salts as the cocatalyst[16] for this C−C bond-forming reaction (entries 5−9). We were delighted to find that the use of CuCl and CuTC leads to improvement of performance of the coupling reaction with a yield that exceeds the 50% (entries 6 and 9). With CuTC as the cocatalyst, the screening reactions were continued by changing the iron source (entries 9−13). We were pleased to find that $FeCl_3$ seems to be the iron source of choice for

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(16) Su, Y.; Jia, W.; Jiao, N. *Synthesis* **2011**, 1678.

this reaction and to exceed the threshold of 80% of the desired product **4a** (entry 13). A control experiment revealed that the two catalysts $FeCl_3$ and CuTC work cooperatively to promote the coupling reaction that does not efficiently take place with either of the catalysts alone. We observed that without a copper source, catalytic amounts of $FeCl_3$ alone were not able to promote efficiently the reaction (entry 14). The other blank experiments in the absence of $FeCl_3$ but in the presence of CuTC also revealed that this transformation was inefficient providing **4a** in only 10% yield (entry 15).

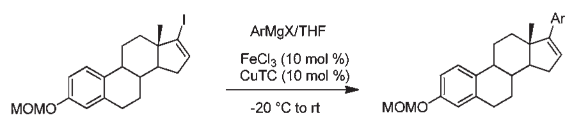
Prompted by these results, we subsequently investigated the substrate scope for the Fe/Cu-catalyzed coupling of structurally diverse Grignard reagents with α-halostyrenes **3** (Table 2). As can be seen from the results of entries 1–5, 1-alkenyl iodide, bromide, chloride or triflate derivatives gave rise to similar yields. Our cross-coupling conditions were also successfully applied to enol phosphate, but the yield was lower than that obtained from alkenyl halides (entry 4). The results summarized in Table 2 show that the conditions described above proved to be general for the coupling with a large variety of functionalized Grignard reagents containing electron-donating or electron-withdrawing groups.[17] 4-Methoxy-, 4-methylthio-, and 4-fluorophenylmagnesium bromide underwent reaction with **3a** to give products **4a**–**d** in 62–96% yields (Table 2, entries 1–7). Interestingly, our protocol successfully revealed an excellent chemical compatibility with a number of sensitive functional groups, such as ester, nitrile, and amino groups (entries 9–11). Compound **4h** was isolated in a 87% yield after treatment of the crude product in refluxing methanol for 8 h to remove the silyl groups. One can note that compound **4f** may be regarded as an analogue of bexarotene.[2c] Variations with respect to the partner **3** were examined next. To our satisfaction, the reaction proceeded well with both 1-arylvinyl iodides **3** bearing an electron-donating or electron-withdrawing group on the aromatic ring, affording 1,1-diarylethylenes **4i,j** and **4d** (65–95%, entries 12–14), including **4j** (isoFCA-4), which is a potent antimitotic and VDA recently identified by us.[4b] Finally, aryl Grignard reagents containing ortho-substituent can be employed successfully (entry 15).

With these successful cross-coupling conditions of the Csp^2–Csp^2 bond in hand, we next proceeded to examine the generality of this reaction to form a Csp^2–Csp^3 bond (Table 2, entries 16–21). It is noteworthy that primary and secondary aliphatic Grignard reagents reacted well with **3a** and gave the coupling products **4l**–**n** in good yields (entries 16–18). Interestingly, the reaction with benzylmagnesium chloride also was successful providing olefins **4o**–**q** in yields ranging from 60 to 98% (entries 19–21). Of note, reaction of 4-methoxybenzylmagnesium chloride with **3a** without CuTC was unsuccessful and gave **4o** in only 8% yield, demonstrating the efficiency of our bimetallic catalytic system.

(17) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701.
(18) Ang, J. E.; Olmos, D.; de Bono, J. S. *Br. J. Cancer* **2009**, *100*, 671.

The synthetic potential of this iron–copper cooperative catalysis was well-illustrated by the preparation of 17-arylestrene derivatives **6** (Figure 2) related to abiraterone acetate (Zytiga, CYP17 inhibitor), a new drug currently used in the treatment of metastatic prostate cancer.[18]

The growth inhibitory activity of 1,1-diarylethylenes (Table 2) against human colon carcinoma cell line (HCT-116) was evaluated and compared to the potent antimitotic isoCA-4 (GI_{50} = 2.0 nM).[4] Except for known compounds **4a** (GI_{50} = 40 nM) and **4j** (GI_{50} = 7 nM),[4b] the best result was obtained with compound **4c** which inhibited the growth of HCT-116 cell line with GI_{50} value of 35 nM. The cytotoxicity of **4c** is comparable to that of **4a** but slightly weaker than that of isoCA-4. Interestingly, the in vitro tubulin assembly assay revealed that **4c** act as a potent inhibitor of tubulin polymerization with an IC_{50} of 2.0 μM which is similar to that of isoCA-4 (IC_{50} = 2 μM) and **4a** (IC_{50} = 2 μM). These results suggest that the 4-OMe substituent in **4a** and 4-SMe group in **4c** are bioequivalent in this series of compounds.



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6a: Ar = 4-FC_6H_4 (60%)
6b: Ar = 4-$MeOC_6H_4$ (64%)

Figure 2. Synthesis of 17-arylestrene derivatives **6**.

In conclusion, we demonstrated a cooperative bimetallic effect of $FeCl_3$/CuTC that allows the formation of Csp^2–Csp^2 and Csp^2–Csp^3 bonds by coupling several 1-arylvinyl halides with functionalized Grignard reagents. To the best of our knowledge, the $FeCl_3$/CuTC combination has never been employed as the catalytic system for cross-couplings of Grignard reagents with alkenyl halides. Our optimized reaction conditions proved to be general and chemoselective and, thus, have been successfully developed for easy access to a variety of 1,1-diarylethylenes of biological interest. The commercial availability and low cost of the catalysts, the mild conditions, experimental simplicity, and environmental friendliness are all features of our catalytic system.

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Supporting Information Available. Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.