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Iron-Catalyzed Cross-Coupling between 1-Bromoalkynes and Grignard-Derived Organocuprate Reagents

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Keywords: Alkynes / Cross-coupling / Iron / Grignard reagents / Homogeneous catalysis

An efficient iron-catalyzed cross-coupling reaction between alkynyl bromides and Grignard-derived organocuprates has been developed. A series of alkynylarenes were successfully synthesised by starting from different 1-bromoalkynes and Grignard reagents. The methodology was successfully used for the two-step stereoselective synthesis of combretastatins and represents a valid alternative to the classical syntheses of alkynylarenes.

Introduction

Transition-metal-catalyzed cross-coupling reactions are very powerful in forming new C–C bonds, and constitute the basis of many contemporary syntheses.[1] The search for novel electrophiles and efficient catalysts continues to capture significant interest. Iron catalysts, first reported by Kochi and co-workers,[2] have been very actively investigated in the last decade for their performance in C–C bond-forming cross-coupling reactions.[3] A variety of iron-catalyzed cross-couplings between alkyl/alkenyl/aryl halides and Grignard reagents have been reported.[4] However, although iron-catalyzed cross-coupling at C(sp^3) (alkyl halides) and C(sp^2) (alkenyl and aryl halides) centers have been widely documented, to the best of our knowledge, successful applications of iron-catalyzed cross-couplings between Grignard reagents and alkynyl halides [C(sp) center] as substrates have not been yet reported. Due to our previous studies in the field of acetylene chemistry,[5] we were tempted to explore the reactivity of haloalkynes in iron-catalyzed cross-coupling reactions. Herein, we report the first example of iron-catalyzed reactions between 1-haloalkynes and aryl Grignard-derived organocuprates for the preparation of alkynylarenes. The use of magnesium-derived organocuprates as nucleophilic species instead of simple Grignard reagents represents the key factor that allows the cross-coupling to occur.

The most frequently utilized method for the preparation of alkynylarenes is the Sonogashira–Hagihara reaction, in which C(aryl)–C(sp) bonds are constructed by the palladium/copper-catalyzed cross-coupling of aryl halides and terminal alkynes.[6] On the other hand, the Corey–Fuchs approach together with its modification,[7] the Seyferth–Gilbert homologation,[8] represent an alternative method for the synthesis of alkynylarenes. However, both of these synthetic approaches present several limitations such as the availability of substrates, namely aryl iodides and arenecarbaldehydes, the need of strong reaction conditions and in some cases poor yields. Hence, the synthesis of alkynylarenes through cross-coupling reaction between 1-haloalkynes and Grignard-derived organocuprates could represent a valid and versatile alternative to the well-known methodologies. Finally, the use of iron instead of palladium catalysts provides obvious economical and environmental merits.

Results and Discussion

The reaction of TIPS-bromoacetylene (**1**) with PhMgBr in the presence of catalytic amounts of $Fe(acac)_3$, was first explored (Scheme 1; Table 1, Entries 1–3). The reaction was carried out at different temperatures and with different amounts of PhMgBr. In all the cases phenylalkyne **2** was not obtained, but biphenyl (**3**), due to the homocoupling reaction of the Grignard reagent, and 1,3-diyne **4**, due to the homocoupling of the alkyne **1**, were isolated from the reaction mixtures. Alkyne **2** was obtained in small amounts only when an excess of Grignard reagent was used. It has been well documented that the extensive homo-couplings of the arylmagnesium species remain a big issue in iron-catalyzed cross-coupling reactions.[4d,9] It has been assumed that the homo-coupling side-reaction may arise from the formation of ferrate complexes with the highly reactive organomagnesium compounds.[10] Knochel et al. recently reported a partial remedy to homocoupling side-reactions in iron-catalyzed biaryl syntheses by the use of arylmagnesium cup-

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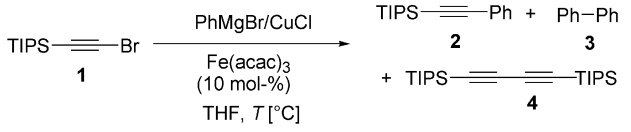
rates, prepared from arylmagnesium halides and Cu^I sources.[4f] Hence, we decided to investigate the reaction of 1-haloalkynes with phenylmagnesium cuprate reagents, prepared in situ from PhMgBr and CuCl and in the presence of $Fe(acac)_3$. The reaction of stoichiometric amounts of PhMgBr/CuCl complex and alkyne **1** at 25 °C led to the formation of the desired compound **2** and biphenyl (**3**) in an almost 1:1 ratio (Entry 5).



Scheme 1. Cross-coupling between **1** and PhMgBr/CuCl leading to product **2** and side-products **3** and **4**.

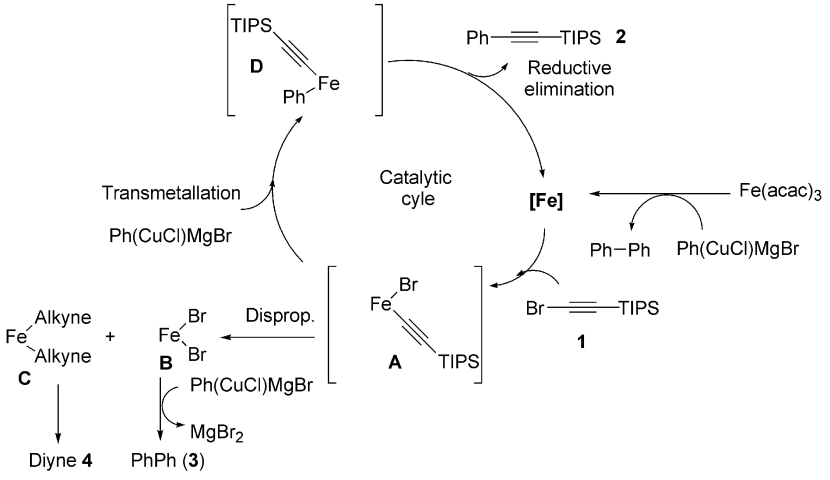
Table 1. $Fe(acac)_3$-catalyzed cross-coupling between PhMgBr or PhMgBr/CuCl and alkyne **1**.[a]

Entry	PhMgBr [equiv.]	CuCl [equiv.]	*T* [°C]	**2** [%][b]	**3** [%]	**4** [%]
1	1.1		0/25		98	98
2	2.2		–20	6	82	88
3	2.2		0/25	4	88	91
4	1.1	1.1	–20	35	39	35
5	1.1	1.1	25	32	41	37
6	2.2	2.2	0	63[c]	30[c,d]	
7	2.2	2.2	25	65[c]	28[c,d]	
8[e]	1.1		25		98[f]	

[a] All the reactions were carried out in the presence of $Fe(acac)_3$ (10 mol-%). [b] Ratios were determined by GC–MS and ^{1}H-NMR analysis of the crude mixtures. [c] Isolated yields. [d] Based on PhMgBr total amount. [e] The reaction was performed without $Fe(acac)_3$. [f] Bromoalkyne **1** was recovered.

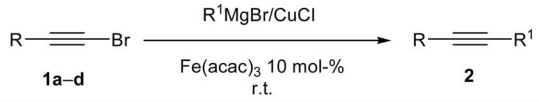
A considerable amount of **4** was also obtained. The same reaction was performed at –20 °C, but also in this case compounds **2**, **3** and **4** were obtained in a 1:1:1 ratio (Entry 4). The use of an excess of PhMgBr/CuCl reagent (2.2 equiv.) led the reaction to completion after 3 h, and **2** was obtained in 65% yield, together with a smaller amount of **3** (28% yield, based on PhMgBr total amount; Entry 7). When the reaction was performed at lower temperature, compounds **2** and **3** were obtained in almost the same ratio (Entry 6). Finally, the reaction of PhMgBr/CuCl with **1** in the absence of $Fe(acac)_3$ did not result in the formation of **2**, whereas **3** and starting material **1** were recovered from the reaction mixture (Entry 8). It seems clear that the presence of $Fe(acac)_3$ is fundamental to achieve the cross-coupling product **2**. On the basis of this latter result, the plausible mechanisms, based on the mechanism generally accepted for the cross-coupling reactions catalyzed by iron, is proposed in Scheme 2. The oxidative addition of bromoalkyne **1** to the low-valent iron intermediate $\mathbf{Fe^I}$, which is generated by the reaction of $Fe(acac)_3$ with the Grignard reagent, gives alkynyliron species **A**. At this stage two pathways would be possible: (a) transmetallation of the phenyl group from magnesium to iron followed by reductive elimination of cross-coupling product **2**; (b) disproportionation, leading to the formation of intermediates **B** and **C**, which in turn give homocouplig products **3** and **4** by reductive elimination regenerating catalyst $\mathbf{Fe^I}$. Experimental results suggest that when aryl Grignard species are used, the intermediate **A** follows pathway (b). On the other hand, when the reaction was carried out between **1** and the PhMgBr/CuCl complex (Entries 4–7), pathway (a) seems to be preferred. It might be assumed that organocuprates interact with intermediate **A** leading to transmetallation intermediate **D** faster than Grignard reagents. This hypothesis might be confirmed by the well-known affinity of Cu^I toward triple bonds;[11] in this case, copper would accelerate the transmetallation step reducing the tendency of **A** to give disproportionation side-reactions. Finally, when the cross-coupling reactions are carried out with 2.2 equiv. of the PhMgBr/CuCl reagent, smaller amounts of homocoupling side products were obtained. The excess of organocuprate reagent would interact with **A** rapidly leading to the formation of **D** and reducing the amount of homocoupling side products.

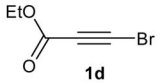
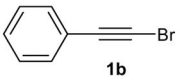
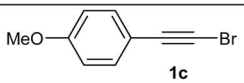
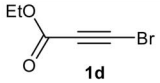
A variety of haloalkynes **1a**–**d** were then coupled with different Grignard-derived organocuprates. Haloalkynes **1a**–**d** were prepared from corresponding terminal alkynes through NBS bromination[12] and treated with different RMgBr/CuCl reagents under the same conditions set up



Scheme 2. Plausible catalytic cycle.

Table 2. Cross-coupling between PhMgBr/CuCl and different alkynyl bromides **1a**–**d**.

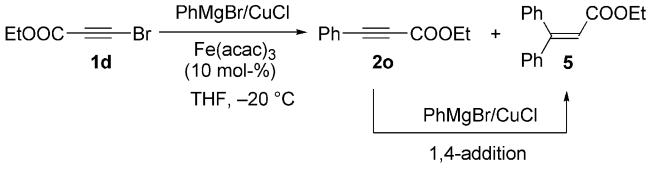


Entry	Alkyne **1**	$R^1MgBr/CuCl$[a]	Compound **2**	Yield (%)[b]
1		Ph	**2a**	65
2		4-$MeOC_6H_4$	**2b**	80
3		4-FC_6H_4	**2c**	52
4		4-MeC_6H_4	**2d**	69
5		3-PhC_6H_4	**2e**	74
6		4-$MeSC_6H_4$	**2f**	82
7		thienyl	**2g**	38
8		$PhCH_2CH_2$	**2h**	78
9		Ph	**2i**	41
10		3,4-$(OCH_2O)C_6H_3$	**2j**	49
11		thienyl	**2k**	52
12		$PhCH_2CH_2$	**2l**	55
13		3,4-$(OCH_2O)C_6H_3$	**2m**	46
14		3,4,5-$(MeO)_3C_6H_2$	**2n**	57
15[c]		Ph	**2o**	18
16		thienyl	**2p**	54

[a] Prepared in situ from RMgBr and CuCl, THF, 25 °C, 20 min. [b] Isolated yields. [c] Reaction was performed at –20 °C.

before (Table 2). The reaction of TIPS-bromoalkyne **1a** with arylMgBr/CuCl reagents led to the desired arylalkynes **2a**–**f** in high yields after 3 h (Entries 1–6). High yields were obtained with aryl compounds containing electron-donating groups (OMe, SMe) (Entries 2, 6), whereas the presence of an electron-attracting moiety on the aromatic ring led to the desired product in lower yield (Entry 3). The reaction of thienylmagnesiumcuprate with **1a** led to alkyne **2g** in lower yield (Entry 7). The reactivity of an aliphatic Grignard/Cu reagent was also tested. Phenethylmagnesium chloride was converted into its copper derivative and then cross-coupled with **1a** to yield alkyne **2h** in excellent yield (Entry 8). This latter result proved the versatility of the present methodology and its utility also in the synthesis of alkylalkynes through the cross-coupling of C(sp^3) and C(sp) centres. Phenylbromoalkyne **1b** was then treated with arylmagnesiumcuprates leading to desired compounds **2i**–**j** in good yields (Entries 9–10). Also the reaction of thienyl and phenethyl Grignard-derived cuprates led to the desired products **2k**–**l** in high yield (Entries 11–12). Alkyne **1c** was then treated with arylmagnesiumcuprates leading to compounds **2m**–**n** in good yield (Entries 13–14).

The presence of an MeO group on the aromatic ring of substrate **1c** did not seem to change its reactivity in cross-couplings compared to **1b**. On the other hand, the electron-rich alkyne **1a** seemed to be the best substrate for cross-coupling reactions with arylmagnesium cuprates. Finally, the reactivity of electron-deficient bromoalkyne **1d** was explored. The reaction of **1d** with the PhMgBr/CuCl complex at room temp. gave alkene **5** as the main product (78% yield).[13] Only traces of the desired alkyne **2o** were observed by ^1H NMR analysis. When the same reaction was performed at –20 °C, alkyne **2o** was obtained in 18% yield together with **5** (56%) (Entry 15) (Scheme 3).

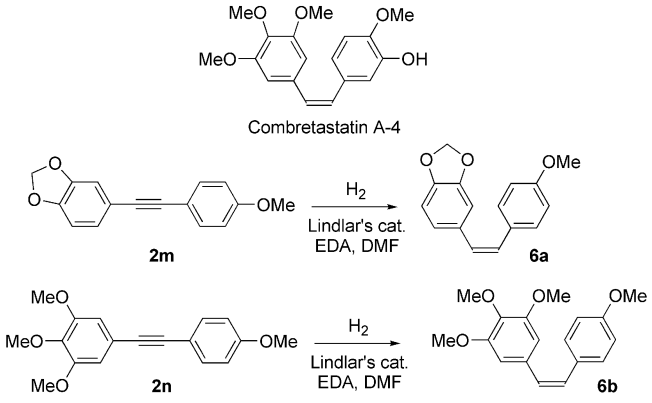


Scheme 3. Michael addition of PhMgBr/CuCl to **2**.

The same reaction was performed by using an equimolar ratio of **1d** and the PhMgBr/CuCl reagent, leading to the formation of **2o**/**5** in 1:5 ratio as revealed by ^1H NMR analysis. The formation of **5** as the main product was due to the Michael 1,4-addition of the organocuprate to **2o**. Nucleophilic organocuprate seems to prefer to react with the elecrophilic **2o** as it forms to give the 1,4-addition product **5**, rather than to react with bromoalkyne(iron) complex **A** in a cross-coupling. On the contrary, when **1d** was treated under standard conditions (25 °C) with thienylMgBr/CuCl, the desired compound **2p** was obtained in good yield (Entry 16), and no traces of the corresponding alkene were detected. Compound **2p**, due to the presence of an electron-rich thienyl ring, could be considered a poor Michael acceptor and poor electrophile in comparison with alkyne **2o**. The organocuprate reacts with the (**1d**)iron complex faster than with **2p**, which consequently does not act as the substarte for the 1,4-addition side-reaction. The present methodology could represent a versatile and stereoselective approach to the synthesis of cytotoxic and antimitotic agents related to Combretastatin A-4 (CA4), one of the most cytotoxic agents tested so far against several cancer cell lines.[14]

Combretastatins are generally prepared by non-stereoselective Wittig reactions between arenecarbaldehydes and phosphonium bromides, which leads to the formation of a mixture of (*Z*)/(*E*)-alkene isomers.[15] Alkynes **2m**–**n** could

be considered as the synthetic precursors of combretastatin analogs. Partial hydrogenation of **2m**–**n** with Lindlar's catalyst led selectively to (*Z*)-alkenes **6a**–**b** in excellent yields (78% and 82%) (Scheme 4).[16] Compound **6b** is known to be one of the most active CA4 analogs possessing antimitotic activity with inhibition of tubuline polymerization IC_{50} values similar to that of natural Combretastatin A-4 (2.5 ± 0.1 of **6b** vs. 2.0 ± 0.3 of CA4).[17]



Scheme 4. Synthesis of Combretastatin analogs.

Conclusions

We report the first example of iron-catalyzed cross-coupling reaction between C(sp) and C(sp^2/sp^3) centres. Haloalkynes were converted into aryl/alkyl-acetylenes through coupling with magnesium-derived organocuprates generated in situ from Grignard reagents and CuCl. The use of organocopper instead of simple Grignard reagents was the key factor to suppress the undesirable side homocoupling and to lead the reaction to completion. The present methodology represents a valid and alternative way to standard methodologies in the synthesis of substituted alkynes. Finally, it could represent a fast and versatile approach for the synthesis of natural and synthetic biologically active combretastatin and stilbenoid analogues that can be obtained in only two steps with a high degree of stereoselectivity.

Experimental Section

A dry 50 mL flask, equipped with a mechanical stirrer and a septum, was charged with THF (4 mL) and CuCl (2.2 mmol), and cooled to 0 °C. Then the arylmagnesium bromide/chloride (2.2 mmol), as a solution in THF, was added dropwise in 5 min. After completion of the addition, the reaction mixture was stirred at room temperature for an additional 20 min. In a separate 10 mL flask, equipped with a mechanical stirrer and a septum, alkynyl bromide (1 mmol) was dissolved in THF (2 mL). To the alkyne solution was added $Fe(acac)_3$ (35 mg, 0.1 mmol), and the resulting solution was stirred at room temperature for 10 min. The alkyne solution was then transferred dropwise into the first solution through a cannula. The reaction mixture was stirred at room temperature for an additional 3 h. An NH_4Cl saturated solution (10 mL) and NH_4OH (2 drops) were then added, and the resulting solution was stirred for 1 h. The organic layer was separated; the aqueous phase was extracted twice with Et_2O. The organic layers were then collected, washed with saturated sodium chloride solution, dried with magnesium sulfate, and concentrated in a rotary evaporator. The crude product was purified by column chromatography (Et_2O/hexanes, 98:2).

Supporting Information (see footnote on the first page of this article): Full characterization of new compounds, NMR spectra.

Acknowledgments

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