Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901203

Link to VoR: http://dx.doi.org/10.1002/adsc.201901203

10.1002/adsc.201901203

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Regioselective Iron-Catalyzed Cross-Coupling Reaction of Aryl Propargylic Bromides and Aryl Grignard Reagents

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201

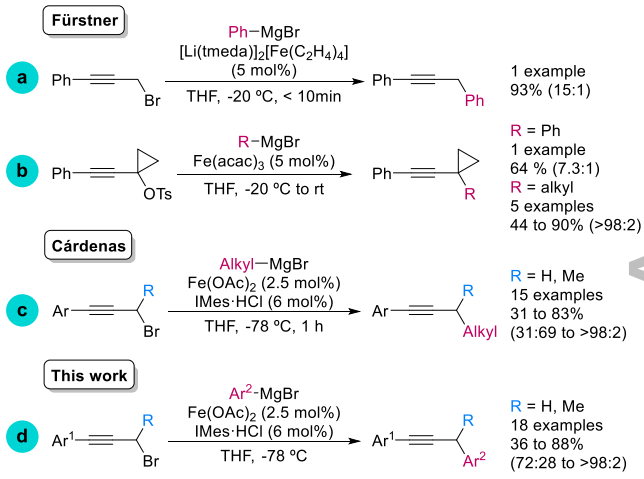
Abstract. An iron-catalysed Kumada-type cross-coupling reaction between aryl substituted propargylic bromides and arylmagnesium reagents has been developed. Propargylic coupling products were the main or only outcome, and propargyl/allene regioselectivity was shown to depend on the electronic nature of the substituents on the triple bond of the substrate and on the arylmagnesium halide. Best selectivities were observed when electron donating substituents were present in either reagent. The process is stereoespecific, occurs with configuration inversion and no carbon-based radicals seem to be involved in the mechanism.

Keywords: cross-coupling; Grignard reagents; Iron; homogeneous catalysis; propargylic bromides

Cross-coupling processes are possibly the most powerful tool in organic synthesis for the generation of new C–C bonds. Among the wide variety of substrates able to undergo this transformation, propargylic derivatives represent a major challenge, due to the difficulty of developing selective methodologies for the formation of propargylic *vs* allenic derivatives. The most thoroughly studied metal catalyst in cross-coupling chemistry is by far palladium. In fact, there are multiple examples of cross-coupling reactions of propargyl derivatives selective to the allenic product catalysed by this metal.[1] However, the need of more sustainable, selective and economic catalysts has shifted the attention of chemists towards other first row transition metals. And indeed, this transformation has been also achieved using a variety of metal catalyst, such as Ni,[2] Cu[3] and Fe.[4]

Regarding the direct cross-coupling of propargylic derivatives in order to form the propargylic coupling products, there are scarce examples in the literature. In 2008, Fu described a Ni-catalyzed Negishi cross-coupling reaction of secondary propargylic bromides with alkyl- and arylzinc reagents.[5] Later that year, they developed the enantioselective version of that reaction,[6] which in 2012 was extended to electrophiles with an oxygen leaving group.[7] Furthermore, in 2017 Tortosa developed a stereospecific Cu-catalyzed reaction of aryl Grignard reagents and propargylic ammonium salts.[8]

Nevertheless, iron catalysis constitutes a more convenient alternative, since this metal is economic, abundant and nontoxic.[9] In 2004, Fürstner published a Fe-catalysed Kumada cross-coupling reaction of alkyl halides with aryl Grignard reagents to obtain alkane derivatives,[10] in which only three examples were reported using propargylic halides as substrates. The iron complex used as catalyst was an ate complex containing Fe(-II) that was previously prepared and was reported to be an air-sensitive crystalline material. Among these examples, the only one with an aryl substituent in the terminal position of the alkyne led to the propargylic coupling product with moderate regioselectivity (Scheme 1a). Racemization was observed when starting from an enantiopure substrate, which was attributed to a radical manifold.



Scheme 1. Fe-catalyzed Kumada-type reactions using aryl-substituted propargylic derivatives.

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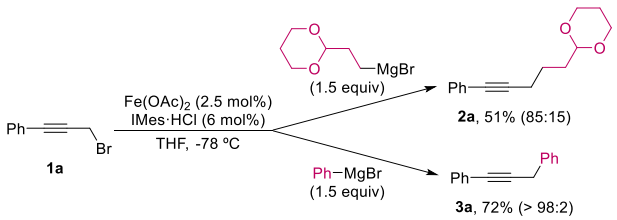
In 2016, the same group extended the reaction to 1-alkynylcyclopropyl tosylates using aryl- and alkylmagnesium reagents,[11] obtaining excellent propargyl:allene ratios, except in the case of phenyl- and benzyl-magnesium reagents, in which a decrease of the regioselectivity was observed (Scheme 1b). Lastly, in 2018, our group described a new method using aryl and alkyl propargylic bromides together with alkyl Grignard reagents (Scheme 1c).[12] The factors governing the regioselectivity were studied and it was concluded that it mainly depends on the electronic nature of the substituent on the triple bond, and better ratios were obtained when primary propargylic substrates were used.

In view of the limited number of examples found in the literature dealing with cross-coupling processes of propargylic bromides with aryl Grignard reagents, in this work, we report a new study on the regioselectivity of the reaction using aryl substituted propargylic derivatives as electrophiles and arylmagnesium halides as nucleophiles in a Fe-catalysed process (Scheme 1d).

Firstly, we decided to test if the reaction conditions previuosly optimized in our group for alkyl Grignard reagents [2.5 mol% of $Fe(OAc)_2$ as catalyst, 6 mol% of IMes (formed by deprotonation of 1,3-bis(2,4,6-trimethylphenyl)-imidazolium) as ligand, in THF at –78 °C],[12] led to good results when using PhMgBr. To our delight, the reaction of propargylic bromide **1a** under these conditions furnished product **3a** with an excellent regioselectivity and a good yield that we did not manage to beat by tuning the reaction conditions (Scheme 2).[13] The use of different NHC ligands to try to improve the yields provided worse results in terms of conversion, yield and regioselectivity. Only the SIPr (1,3-bis(2,6-diisopropylphenyl)imidazolidene) gave a slightly better yield (78%), but showed a decrease in the regioselectivity from > 98:2 to 92:8, which made us decide to continue with IMes (*see SI for details*). Worth of mentioning is that the best result obtained for the alkyl Grignard reagent was a 85:15 mixture of propargylic **2a** and allenic regioisomers with a 51% yield.



Scheme 2. Fe-catalyzed Kumada-type reactions of **1a** with alkyl- and aryl-Grignard reagents.

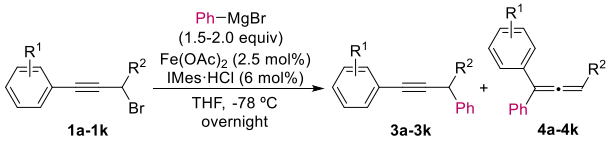
Biphenyl derived from the homocoupling of the Grignard reagent was isolated from the reaction mixture (~ 40% yield), which could indicate that reduction of Fe catalyst may be taking place under the reaction conditions. However, the formation of biaryl species does not necesarily infer the formation of low valent iron species, since it can be caused by the quenching of arylated iron species.[14] The relatively high amount of this compound suggests that a non-desired secondary reaction is taking place, which accounts for the need of more than one equivalent of the Grignard reagent.

Control experiments were carried out to ensure the need of ligand and iron source. The absence of IMes·HCl led to worse yields and incomplete transformation of **1a**. Besides, the reaction did not occur without $Fe(OAc)_2$, and propargylic derivative **1a** was recovered unaltered (*see SI for details*).

With an iron catalytic system in hand, able to promote the formation of propargylic products with excellent regioselectivity, we sought to explore the reaction scope using different aryl-substituted propargylic bromides (Table 1).

Phenyl substituted primary and secondary bromides **1a** and **1e** led to excellent regioselectivities and moderate yields to **3a** and **3e** propargylic products (entries 1 and 5). A similar trend was observed with an electron-donating group in the *para*- position of the aryl substrates **1b** and **1f** (entries 2 and 6). However, substrates with deactivated rings (**1c**, **1g**, **1h** and **1i**) reacted with lower but still useful regioselectivity (entries 3, 7, 8 and 9). Surprisingly, substrate **1d** bearing an electron-withdrawing *p*-CN group (entry 4), gave the propargylic product **3d** with excellent regioselectivity. It is worth noting that substrates with functional groups potentially sensitive to the Grignard reagents, such as esters or nitriles, were well-tolerated (entries 3, 4, 8 and 9).

Table 1. Fe-catalyzed Kumada-type reactions using



different aryl-substituted propargylic bromides.

Entry	Sub. **1**	R^1	R^2	**3**:**4** ratio[a]	Yield (%)
1	**1a**	H	H	> 98:2	72
2	**1b**	*p*-OMe	H	93:7	55
3[b]	**1c**	*p*-CO_2Me	H	88:12	66
4[c]	**1d**	*p*-CN	H	> 98:2	58
5	**1e**	H	Me	> 98:2	55
6	**1f**	*p*-Me	Me	> 98:2	88
7	**1g**	*m*-OMe	Me	84:16	50
8	**1h**	*p*-CO_2Me	Me	82:18	74
9[c]	**1i**	*p*-CN	Me	72:28	68
10[d]	**1j**	H	Cy	65:35	57
11[e]	**1k**	H	^{t}Bu	--	--

[a] **3:4** ratio was determined by ^{1}H NMR of the crude mixture. [b] 84% conversion. [c] Reaction time was 2 days. [d] Nucleophile homocoupling by-product could not be fully separated by column chromatography. [e] Starting material recovered.

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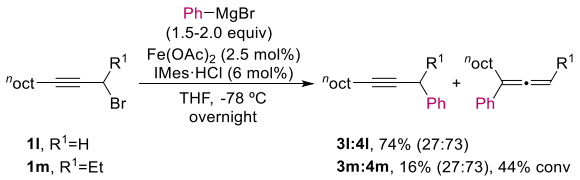
As a general rule, it can be observed that reactivity and regioselectivity seem to depend on the electronic nature of the aromatic ring. Worse yields and selectivities were obtained with electron withdrawing substituents. In addition, substitution in the *ipso*-position of the bromide does not seem to have a major impact on the propargyl *vs* allene selectivity in the case of a methyl group (entries 1 and 5). Bulkier substituents, such as cyclohexyl led to a decrease in the selectivity (entry 10) and no reaction was observed when a ^{t}Bu group was introduced in that position (entry 11).[15]

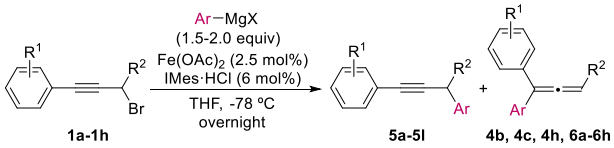
The methodology was also studied for propargylic substrates bearing an alkyl substituent in the alkyne. In the case of **1l**, the reaction proceeds to the formation of the allene **4l** as the major product. Secondary propargylic bromide **1m** led to similar selectivity. However, in that case, conversion and yield dropped off.



Scheme 3. Fe-catalyzed Kumada-type reaction of alkyl substituted propargylic bromides.

In order to elucidate the importance of the substitution in the Grignard reagent, [(4-(methoxycarbonyl)phenyl] magnesium chloride and (4-methoxyphenyl)magnesium bromide were tested with different propargylic derivatives (Table 2. Please, note that the same allene can be obtained in some cases from differently substituted electrophiles and nucleophiles, and that the compound is named as **4** instead of **6** if it already appears in Table 1).

Table 2. Fe-catalysed Kumada-type reactions using



different aryl Grignard reagents.

Entry	Sub. **1**	Ar–MgX	**5**:**4** or **5**:**6** ratio[a]	Yield (%)
1	**1a**	MgCl, CO_2Me	53:47 (**5a:4c**)	26
2	**1b**		55:45 (**5b:6a**)	55
3	**1c**		> 2:98 (**5c:6b**)	33
4	**1e**		> 98:2 (**5d:4h**)	40
5	**1g**		87:13 (**5e:6c**)	36
6	**1h**		88:12 (**5f:6d**)	40
7	**1a**	MgCl, OMe	80:20 (**5g:4b**)	60
8	**1b**		85:15 (**5h:6e**)	48[b]
9	**1c**		87:13 (**5i:6b**)	52
10	**1e**		90:10 (**5j:6f**)	47
11	**1g**		> 98:2 (**5k:6g**)	38[b]
12	**1h**		> 98:2 (**5l:6h**)	66

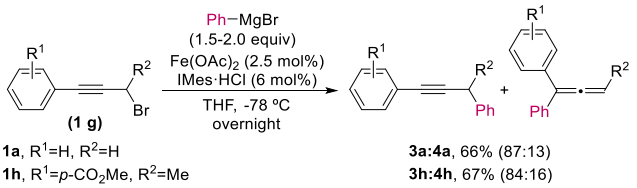
[a] **5:4** and **5:6** ratios were determined by ^{1}H NMR of the crude mixtures. [b] Nucleophile homocoupling by-product could not be fully separated by column chromatography.

p-CO_2Me aryl substituted Grignard reagent led to worse yields and regioselectivities when compared to phenylmagnesium bromide. The selectivity is completely lost with primary bromides **1a** and **1b** (entries 1 and 2) and a total inversion of the regioselectivity was obtained using the *p*-CO_2Me aryl substituted primary propargylic bromide **1c** (entry 3), which led to allenic product **4c**. In contrast, secondary bromides **1e-1h** provided better propargyl *vs* allene ratios (entries 4-6), with phenyl derivative **1e** showing an excellent regioselectivity towards the propargylic product **5e** (> 98:2 ratio).

These results are similar to those obtained using phenylmagnesium bromide, suggesting that the secondary bromides are less affected by the electronic richness of the aryl Grignard reagent.

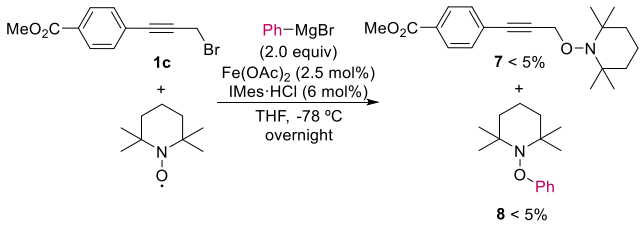
Contrarily, the (4-methoxyphenyl)magnesium bromide provided higher regioselectivities and yields than *p*-CO_2Me aryl substituted Grignard reagent, and the same trend was observed regarding the substitution at the *ipso* position of the bromide with a methyl group. Using primary derivatives **1a-1c**, propargylic compounds **5a-5c** were obtained as the major products with moderate yields and ratios between 80:20 and 90:10 (entries 7-9). Secondary propargylic bromide **1e** led to products **5e**:**6c** with a 90:10 ratio and a 47% yield (entry 10). The regioselectivity towards the propargylic product was excellent when secondary bromides **1g** and **1h** were used (entries 11 and 12). Although similar regioselectivities were expected using the methoxyphenyl Grignard derivative when compared with phenylmagnesium bromide, the reaction of this Grignard reagent with phenyl-substituted substrates **1a** and **1e** (entries 7 and 10) provided worse results.

To assess the feasibility of the methodology in a preparative scale, the reaction was performed starting from a gram of substrates **1a** and **1h** with phenyl magnesium bromide. Coupling products **3:4** were obtained with no significant reduction of the yields. However, in the case of products **3a:4a** a decrease in the regioselectivity from 98:2 to 87:13 was observed (Scheme 4).



Scheme 4. Gram-scale Fe-catalyzed Kumada-type reaction of selected substrates.

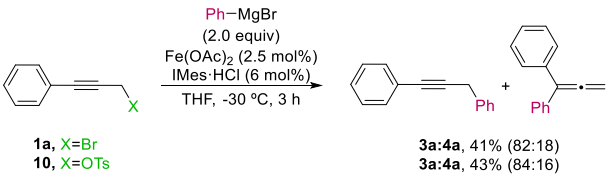
Previous works on this type of iron catalysed Kumada cross-couplings suggest the participation of radical species in the reaction mechanism.[16] To test whether carbon-based radicals were formed in our reaction conditions, we performed the reaction of the propargylic bromide **1b** in the presence of TEMPO (Scheme 5).



Scheme 5. Influence of TEMPO in Fe-catalyzed Kumada-type reaction of propargylic bromides.

The reaction was completely inhibited and no coupling products, neither propargylic nor allenic, were obtained. Substrate **1b** was recovered mostly unaltered. However, traces of compounds **7** and **8**, resulting from the coupling of the TEMPO with C-centred radicals coming from nucleophile and electrophile, were detected by ^{1}H-NMR and GC-MS. Although the formation of these C-centred radicals in the reaction media could not be fully ruled out, the low amounts of **7** and **8** encountered suggest that this is not the main manifold of the process. The inhibition of the reaction could be due to the formation of radical metal complexes from the catalyst.

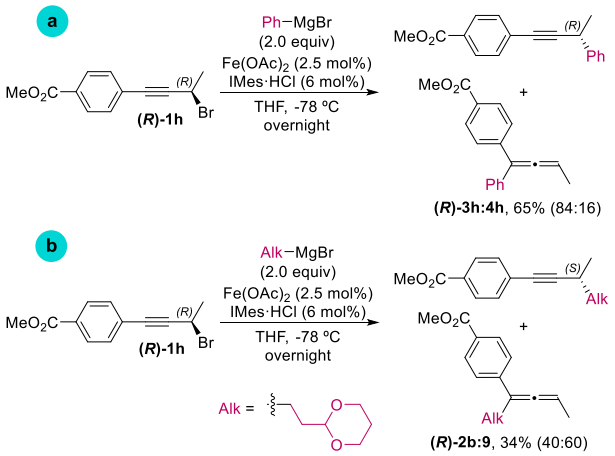
To further explore the idea of a non-radical mechanism,[17] the reaction was performed with a propargylic tosylate, which cannot be activated though homolytic cleavage. At a temperature of -78 ºC, this substrate was unreactive. However, at -30 ºC, both bromide and tosylate gave similar reactivity in the presence of the iron catalyst (Scheme 6), providing worse yield and regioselectivity when compared to the reaction at -78 ºC (*See SI for further details*).



Scheme 6. Comparison of the reactivity of propargylic bromides vs propargylic tosylates.

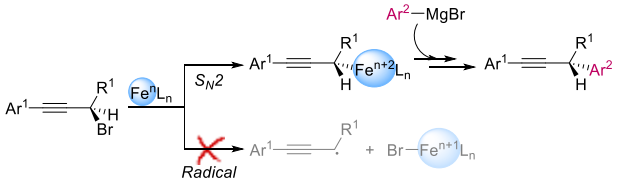
As the final test to ensure the absence of C-based radicals, the reaction was carried out using an enantiomerically pure propargylic bromide **(*R*)-1h** (Scheme 7). The corresponding product was obtained as an enantiopure mixture of propargyl:allene **(*R*)-3h:4h** 84:16, in which racemization was not observed by chiral HPLC (Scheme 7a).

Alkyl and aryl Grignard reagents sometimes show different reactivity features.[18] In fact, Neidig isolated an Fe(II) complex with two alkyl ligands coming from the (1,3-dioxan-2-ylethyl)magnesium bromide, under our same conditions.[19] This complex has one the oxygens of both dioxane rings coordinated to the Fe-centre, which gives an additional stability. But that is not possible when aryl Grignard derivatives are used. In order to explore whether the nature of the nucleophile could affect the stereoselectivity of the process, the reaction of the enantiomerically pure electrophile was also performed with (1,3-dioxan-2-ylethyl)magnesium bromide, and similar results were obtained (Scheme 7b). These experiments allow to discard the possibility of a radical oxidative addition. Besides, analysis of the stereochemistry of the product revealed that the process takes place with configuration inversion,[8,20] meaning that a S_N2 type oxidative addition is a more feasible pathway. Allenic product was also obtained in its enantiopure form, but absolute configuration was not determined.



Scheme 7. Use of enantiomerically pure substrate **(*R*)-1f** in the Fe-catalyzed Kumada-type reaction.

Multiple articles deal with the mechanism of Fe-catalysed cross-coupling reactions and the oxidation state of the active species.[21] Thus, Fe(I),[18b, 22] Fe(II),[19, 23] or even Fe(-II)[18a, 24] complexes have been proposed, detected or isolated. In the present case, the experimental evidence suggests the formation of radical iron species, which is compatible with an Fe(I/III) catalytic cycle (Scheme 8). Even so, a Fe(0/II)[25] cycle cannot be discarded, since high spin Fe(II) species could be also formed.[26] More studies would be necessary in order to ascertain the nature of the catalytically-active Fe species.



Scheme 8. Simplified mechanistic proposal for Fe-catalyzed Kumada-type reaction.

In conclusion, we have developed a Fe-catalysed Kumada-type cross-coupling reaction of aryl substituted propargylic bromides and aryl Grignard reagents with substrates underexplored in this kind of chemistry. The reaction shows high regioselectivities towards the propargylic coupling product in most of the cases and tolerates the presence of nitrile and ester groups in both propargylic and Grignard reagents. The formation of the allenic product depends on the electronic properties of the substituents on the aromatic rings of both reagents. Besides, experiments confirming the chirality transfer from reagent to product have been performed, suggesting that no carbon-based radicals are formed in the proccess and opening the posibility of new reactivities under Fe catalysis. However, further studies are necessary to propose a detailed mechanism.

Experimental Section

General procedure: *Formation of the active iron catalyst*: To a solution of iron (II) acetate (2.5 mol%) and 1,3-dimesityl-1H-imidazol-3-ium chloride (6 mol%) in dry and Ar-degassed THF (1 mL/mmol) at 50 °C under argon atmosphere, 0.3 equivalents of arylmagnesium bromide were added dropwise. The mixture was stirred for 5 min. *Reaction procedure*: After cooling at -78 °C, a solution of the corresponding propargylic bromide (1.0 equiv) in dry and Ar-degassed THF (4 mL/mmol) was added, followed by the dropwise addition of arylmagnesium bromide (1.5 - 2.0 equiv). The reaction was stirred at -78 °C and monitored by TLC until completion (16 h to 2 d). Saturated aqueous NH_4Cl solution was added (2 mL) and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The product was purified by column chromatography in silica gel.

Acknowledgements

We thank Spanish MINECO for funding (grant CTQ2016-79826-R and a Juan de la Cierva contract to M. T. Q.) and the CAM for a contract to I. M.-M.

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[13] The reaction was also tried with an aromatic organozinc reagent (*p*-methoxyphenylzinc bromide), but a complex reaction mixture was obtained, where none of the coupling products could be identified (*see SI for details*).

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[15] The introduction of a phenyl substituent in the *ipso*-position of the propargylic bromide led to a drastic change in reactivity, and the product arising from the homocoupling of the electrophile was the only outcome of the reaction (*see SI for details*).

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10.1002/adsc.201901203

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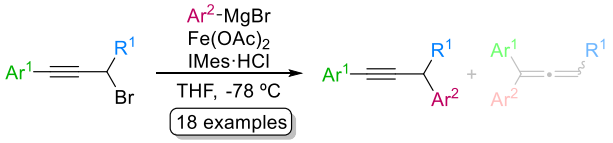
Regioselective Iron-Catalyzed Cross-Coupling Reaction of Aryl Propargylic Bromides and Aryl Grignard Reagents



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