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C–C Coupling

Iron-Catalyzed Sonogashira Reactions[**]

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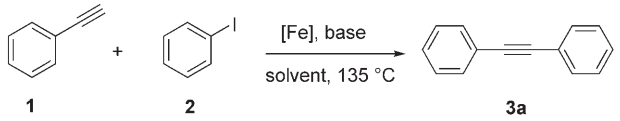
The coupling between an aryl halide and a terminal alkyne, widely known as the Sonogashira reaction, is nowadays the most utilized reaction for the construction of C(sp^2)–C(sp) bonds.[1] It allows the straightforward and facile synthesis of aryl alkynes and conjugated enynes, which are prevalent intermediates in the synthesis of a broad array of naturally occurring products.[2] The vast majority of the existing protocols for performing such transformations involve the use of palladium catalysts, often assisted by a copper co-catalyst.[3] The development of improved procedures in which less expensive and more sustainable catalysts are used has remained an elusive goal. In this respect, iron catalysts stand out as valuable alternatives to those transition metals used in Sonogashira coupling reactions.[4]

The use of iron salts to perform established transition-metal-catalyzed arylation reactions has recently gained significant attention because of their numerous advantages, namely, their low cost, nontoxicity, or interesting chemical properties. In this context, iron-catalyzed cross-coupling reactions that lead to the formation of C–C linkages through the use of Grignard reagents are well known in the field, and have been intensively investigated in the last decade.[4c,5] Likewise, we have recently demonstrated the ability of iron catalysts to effect the formation of carbon–heteroatom bonds by means of arylations with aryl halides.[6–8] However, an iron-catalyzed C–C coupling reaction involving a terminal alkyne and an arylating counterpart has not so far been reported.

In our previous research on iron-catalyzed arylations we observed that the combination of $FeCl_3$ and appropriately chosen ligands delivered remarkably versatile catalysts for the coupling of nitrogen[6] oxygen,[7] and sulfur nucleophiles[8] with aryl halides. Inspired by these findings, we decided to test the efficacy of this key $FeCl_3$/ligand association in Sonogashira reactions, and the most relevant results are reported herein.

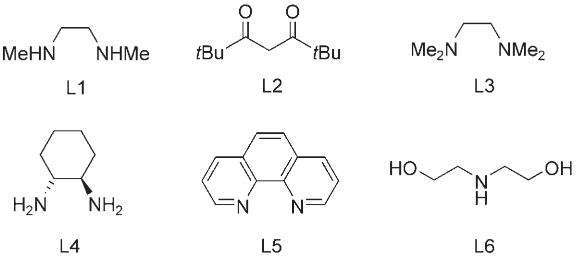
Initially, the coupling of phenylacetylene (**1**) with phenyl iodide (**2**) was selected as a model system. To our delight, preliminary experiments, in which those substrates were submitted to the standard conditions used for the iron-catalyzed arylation of nitrogen[6a] and sulfur atoms,[8] revealed that the target transformation was indeed possible, and afforded diphenylacetylene (**3a**), although in only moderate yields (Table 1, entries 1 and 3, respectively). Conversely, under the optimized conditions for the arylation of oxygen atoms[7] (Table 1, entry 2) the Sonogashira coupling product was not detected. The use of K_2CO_3 and Cs_2CO_3 (instead of K_3PO_4 or NaO*t*Bu) in combination with $FeCl_3$ and *N,N'*-dimethlethylenediamine (dmeda) led to improved results (Table 1, entries 4 and 5). In particular, the use of Cs_2CO_3 was considered superior, since it delivered the target compound in a similar yield as obtained under the previously tested conditions, but in a significantly shorter reaction time

Table 1: Reagent screening for the iron-catalyzed coupling of phenylacetylene (**1**) with phenyl iodide (**2**).[a]



Entry	Fe source	Ligand	Base	Solvent	*t* [h]	**3a** [%][b]
1	$FeCl_3$	L1	K_3PO_4	PhMe	72	37
2	$FeCl_3$	L2	Cs_2CO_3	DMF	24	0
3	$FeCl_3$	L1	NaO*t*Bu	PhMe	72	20
4	$FeCl_3$	L1	K_2CO_3	PhMe	72	43
5	$FeCl_3$	L1	Cs_2CO_3	PhMe	18	31
6	**$FeCl_3$**	**L1**	**Cs_2CO_3**	**PhMe**	**120**	**95**
7	$FeCl_3$	L3	Cs_2CO_3	PhMe	120	33
8	$FeCl_3$	L4	Cs_2CO_3	PhMe	24	traces
9	$FeCl_3$	L5	Cs_2CO_3	PhMe	24	6
10	$FeCl_3$	L6	Cs_2CO_3	PhMe	24	0
11	[Fe(acac)$_3$]	L1	Cs_2CO_3	PhMe	24	0
12	$FeCl_3\cdot 6\,H_2O$	L1	Cs_2CO_3	PhMe	24	traces
13	[Fe(bzac)$_3$]	L1	Cs_2CO_3	PhMe	48	6
14	$Fe(ClO_4)_2$	L1	Cs_2CO_3	PhMe	24	traces
15[c]	**$FeCl_3$**	**L1**	**Cs_2CO_3**	**PhMe**	**72**	**68**

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.5 equiv), Fe source (0.1 equiv), ligand (0.2 equiv), base (2.0 equiv), solvent (1 mL mmol^{-1}), 135 °C, under argon. [b] Yield of isolated product after flash chromatography. [c] Use of 15 mol % $FeCl_3$ and 30 mol % L1. acac = acetylacetonate, bzac = benzoylacetonate.



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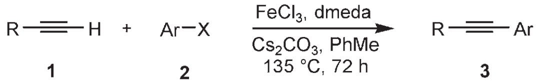
(Table 1, entry 5 versus entries 1, 3, and 4). Therefore, Cs_2CO_3 was selected as the base of choice for further screening reactions.

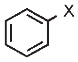
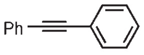
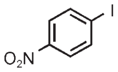
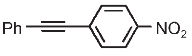
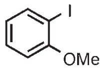
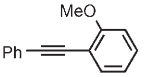
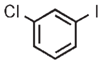
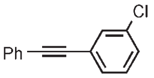
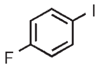
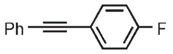
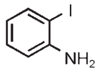
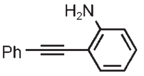
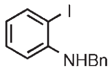
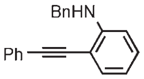
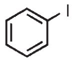
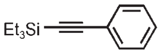
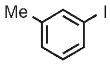
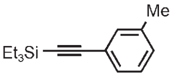
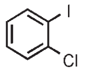
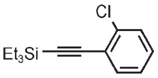
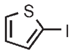
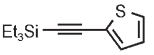
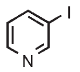
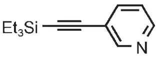
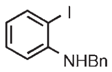
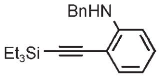
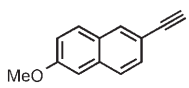
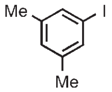
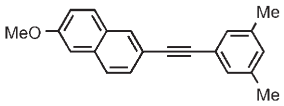
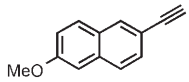
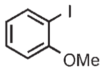
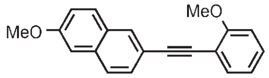
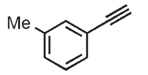
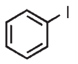
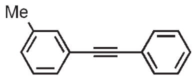
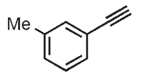
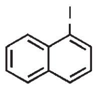
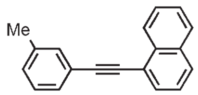
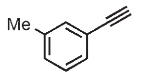
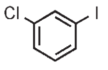
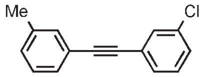
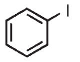
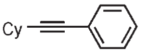
It is noteworthy that the reaction time was a key parameter of the process, and when the coupling reaction between **1** and **2** was allowed to proceed for prolonged times, the target acetylene **3a** was obtained in 95 % yield (Table 1, entry 6). Unfortunately, initial attempts to decrease the reaction time without a significant loss in the yield failed. The use of different nitrogen- and/or oxygen-based chelating ligands in combination with $FeCl_3$ resulted in either low yields of **3a** or recovered starting material (Table 1, entries 7–10). Likewise, iron sources other than $FeCl_3$ failed to accomplish the target arylation of **1** (Table 1, entries 11–14). Moreover, the use of different solvents such as acetonitrile, *o*-xylene, or dioxane had a detrimental effect on the outcome of the reaction. Eventually, by raising the catalyst loading from 10 to 15 mol %, **3a** was obtained in lower, but still good, yield after a more reasonable reaction time (Table 1, entry 15). Test experiments carried out in the absence of the $FeCl_3$/ligand system led to recovered starting materials, which illustrated the key role of the iron catalyst in this transformation. Likewise, the use of an isolated preformed catalyst, obtained by combining $FeCl_3$ and dmeda,[9] led to very low conversion of the starting materials. Hence, it was concluded on the basis of the reaction times and yields that the best conditions involved 15 mol % $FeCl_3$, 30 mol % dmeda, and 2 equivalents of Cs_2CO_3 in toluene at 135 °C for 72 h.

Next, the scope of this iron-catalyzed Sonogashira reaction was explored by treating different acetylene derivatives with an array of aryl halides under the aforementioned optimized conditions. As shown in Table 2, all reactions afforded the desired arylated alkynes **3** in good to excellent yields, as long as aryl iodides were used as the arylating agents. Indeed,

Table 2: Iron-catalyzed Sonogashira coupling of terminal alkynes with aryl iodides.[a]



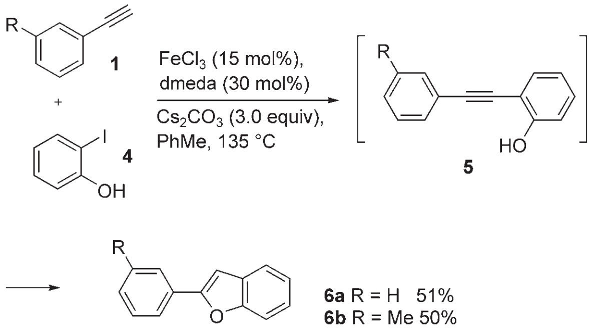
$$\underset{\mathbf{1}}{R{-}{\equiv}{-}H} + \underset{\mathbf{2}}{Ar{-}X} \xrightarrow[\text{Cs}_2\text{CO}_3,\ \text{PhMe},\ 135\ ^\circ\text{C},\ 72\ \text{h}]{\text{FeCl}_3,\ \text{dmeda}} \underset{\mathbf{3}}{R{-}{\equiv}{-}Ar}$$

Entry	1	2	3		Yield [%][b]
1	$Ph{-}{\equiv}$			**3a**	X = I, 68 (95)[c] X = Br, traces X = OTs, 0
2	$Ph{-}{\equiv}$			**3b**	74
3	$Ph{-}{\equiv}$			**3c**	60
4	$Ph{-}{\equiv}$			**3d**	89
5	$Ph{-}{\equiv}$			**3e**	69
6	$Ph{-}{\equiv}$			**3f**	89
7	$Ph{-}{\equiv}$			**3g**	86
8	$Et_3Si{-}{\equiv}$			**3h**	80
9	$Et_3Si{-}{\equiv}$			**3i**	90
10	$Et_3Si{-}{\equiv}$			**3j**	73
11	$Et_3Si{-}{\equiv}$			**3k**	40
12	$Et_3Si{-}{\equiv}$			**3l**	58
13	$Et_3Si{-}{\equiv}$			**3m**	85
14				**3n**	99.9
15				**3o**	54
16				**3p**	51
17				**3q**	55
18				**3r**	77
19	$Cy{-}{\equiv}$			**3s**	15

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.5 equiv), $FeCl_3$ (0.15 equiv), dmeda (0.30 equiv), Cs_2CO_3 (2.0 equiv), toluene (1 mL mmol^{-1}), 135 °C, 72 h, under argon. [b] Yield of isolated product after flash chromatography. [c] The value in brackets refers to the yield after 5 days using 10 mol % $FeCl_3$ and 20 mol % dmeda. Bn = benzyl, Cy = cyclohexyl.

neither phenylbromide nor phenyl tosylate furnished the coupling product **3a** in more than trace amounts when treated with phenylacetylene (Table 2, entry 1). The coupling reactions of various terminal alkynes with both electron-rich and electron-deficient aryl iodides provided products in good yields. 2-Thiophenyl iodide and 3-pyridinyl iodide led to the corresponding arylated alkynes in moderate yields (Table 2, entries 11 and 12). In general, the presence of *ortho* substituents in the electrophilic reagent did not hamper the reaction, which proceeded smoothly in those cases, and afforded the corresponding products **3** in good yields (Table 2, entries 3, 6, 7, 10, 13, and 15). In regard to the alkynes, both aryl acetylenes (Table 2, entries 1–7 and 14–18) as well as triethylsilylacetylene (Table 2, entries 8–13) underwent efficient arylation with a number of aryl iodides (Table 2, entries 8–13). Conversely, alkyl-substituted acetylenes proved less reactive (Table 2, entry 19). It is noteworthy that alkyne homocoupling products were not detected in any reaction, despite the oxidative character of $FeCl_3$.

Interestingly, the coupling reactions with both *N*-benzyl-substituted and non-substituted 2-iodoaniline as the arylating agents were very clean, and selectively delivered the projected Sonogashira coupling products in high yields, without competitive side reactions on the amine moiety (Table 2, entries 6, 7, and 13). In contrast, when 2-iodophenol (**4**) was employed, benzofurans **6** resulting from domino Sonogashira coupling reactions followed by intramolecular hydroalkoxylations were isolated in moderate yields along with recovered aryl acetylenes **1** (Scheme 1). Although the use of iron catalysts assisted by silver additives for the addition of a hydroxy moiety to olefins is known,[10] to the best of our knowledge these results represent the first reported exclusively iron-catalyzed hydroalkoxylations of alkynes. Further experiments to improve the conversions and to expand the substrate scope of this unprecedented transformation are currently under study.



Scheme 1. Iron-catalyzed domino Sonogashira coupling and hydroalkoxylation.

Theoretical and mechanistic studies are currently underway to reveal possible reaction pathways, but we hypothesize that the Lewis acidity of $FeCl_3$ plays a determinant role by increasing the electrophilic character of the starting aryl iodide. Clearly, further experiments are required to gain a deeper understanding of the reaction mechanism.

In summary, we have developed a novel iron-catalyzed arylation of terminal alkynes by utilizing catalytic amounts of $FeCl_3$ in conjunction with dmeda. The use of an iron catalyst instead of the commonly used palladium or copper ones renders the reported methodology comparatively more economical, experimentally simple, and, therefore, appealing for industry. Furthermore, a novel iron-catalyzed domino Sonogashira/hydroalkoxylation of alkynes has been reported, which increases the significance of the iron catalyst system as a versatile tool in organic synthesis. The extension of the herein presented Sonogashira coupling to other arylating agents as well as attempts to improve the catalyst performance are currently being targeted.

Experimental Section

General procedure for the iron-catalyzed Sonogashira coupling: A sealable tube equipped with a magnetic stir bar was charged with Cs_2CO_3 (2.0 equiv) and $FeCl_3$ (0.15 equiv). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. Phenyl iodide (**2**, 1.5 equiv), *N,N'*-dimethylethylenediamine (0.30 equiv), phenylacetylene (**1**, 1.0 equiv), and toluene (1 $mL\,mmol^{-1}$ of **1**) were added by syringe. The septum was then replaced by a teflon-coated screw cap, and the reaction vessel was placed in an oil bath at 135 °C. After stirring the heterogeneous mixture at this temperature for 72 h, it was cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of silica gel and concentrated to afford the product, which was purified by chromatography on silica gel (pentane) to yield diphenylacetylene **3a**. The identity and purity of known products was confirmed by ^1H and ^{13}C NMR spectroscopic analysis, and new products were fully characterized. See the Supporting Information for full details.

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