ORGANIC
LETTERS

2013
Vol. 15, No. 18
4690–4693

Iron-Catalyzed Homocoupling of Aryl Halides and Derivatives in the Presence of Alkyllithiums

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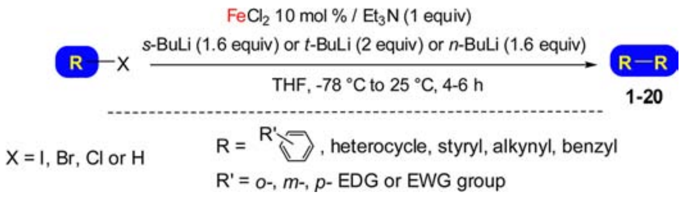
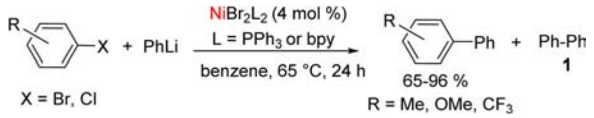
Received July 17, 2013

ABSTRACT



Direct synthesis of biaryl derivatives from aryl halides takes place under very mild temperature conditions by using a ligand-free iron catalytic system. The procedure, which proceeds via an in situ quantitative aryl halide exchange with alkyllithiums, allows for excellent control of the reactivity and is in line with the sustainable development. The method is also applicable to styryl and benzyl halides and to phenylacetylene.

In the last decades, symmetrical and unsymmetrical biaryls have received increased attention as privileged structures for the agrochemical and pharmaceutical industries.[1] Many classes of natural products[2] and optical materials and organic conductors[3] involve the biaryl unit. Ullmann first reported in 1901 the synthesis of biaryl units from the copper-mediated coupling of aryl halides performed under harsh reaction conditions.[4,5] The first evolution in this field occurred 70 years later and consisted of the use of stoichiometric amounts of nickel instead of copper in a traditional Ullmann-like procedure. Then systems based on nickel catalysts appeared, with the works of Kumada[6] and Corriu[7] involving the coupling of aryl halides and aromatic Grignards. The latter were next used with palladium, and the procedure was also extended to zinc, tin, and boron derivatives in the Negishi, Stille, and Suzuki reactions. As far as the synthesis of symmetrical biaryls is concerned, studies recently have been reported. The homocoupling of Grignard reagents has, for example, been described by Hayashi and Cahiez for the preparation of biaryl units. These authors used iron salts ($FeCl_3$) as catalysts and dihalogenoethane[8,9] or dry air[10] as the oxidant. Xu also developed a $Fe(acac)_3$-catalyzed procedure from arylmagnesiums under oxidant-free conditions.[11] The homocoupling of aryllithium derivatives also permits to obtain symmetrical biaryls. While studying the $NiBr_2(bpy)_2$ catalyzed cross-coupling of phenyllithium with aryl chlorides, we observed the formation of biphenyl **1** resulting from the nickel-catalyzed homocoupling of PhLi.[12]



[†] Institut Charles Gerhardt Montpellier.

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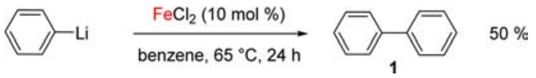
10.1021/ol401987s

Later, the same $NiCl_2(bpy)_2$ precatalyst and strategy were reported[13] for the synthesis of symmetrical biaryl units, and more recently, a similar route was applied from vanadium catalysts.[14] A procedure for homocoupling from aryllithium reagents was also described by Iyoda using stoichiometric amounts of the Lipshutz cuprate[15] in combination with 1,4-benzoquinone as the electron acceptor.[16] Stoichiometric amounts of copper[17] or palladium[18] catalysts were also employed for the synthesis of symmetrical biaryls from arylboronic acids. In addition, during the redaction of this paper, Severin et al. presented an original development of the magnesium route by using nitrous oxide as oxidant in the iron catalyzed homocoupling of Grignard reagents.[19]

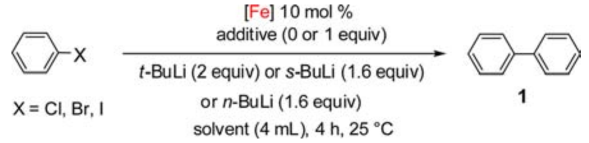
Here, we report a new method allowing for the synthesis of various symmetrical biaryl units via an homocoupling of aryl lithium derivatives, in situ generated from aryl halides. We used a very simple iron-based catalytic system ($FeCl_2$), in which this less toxic and inexpensive metal is used in mild temperature (25 °C) and under ligand-free conditions, in the absence of any additional oxidant.

We first tried to perform iron-catalyzed homocoupling of phenyllithium itself. We observed that a simple salt such as $FeCl_2$ was able to afford the corresponding biphenyl **1** under mild and ligand-free conditions in an interesting although fair yield (50%).



We then tested the possibility of applying this reaction starting directly from phenyl halides via an in situ generation of phenyllithium (Table 1). The preliminary survey, carried out with various solvents and iron sources, allowed us to identify an efficient catalytic system for the synthesis of biphenyl **1**. The first reaction was performed with bromobenzene (1 equiv), *t*-BuLi (2 equiv added at −78 °C), and $FeCl_2$ (10 mol %) in benzene at 25 °C for 4 h. A low yield was obtained, as it was also the case starting from iodo- or chlorobenzene (Table 1, entries 1−3). The other iron sources tested (Fe, $FeCl_3$ or $Fe(acac)_3$) only permitted to slightly improve the system with a maximum of 50% yield in biphenyl **1** (Table 1, entries 4−6). The presence of additive (1 equiv) such as phenanthroline, 1,4-diazabicyclo-[2.2.2]octane (DABCO), or tributylamine (Bu_3N) was unsuccessful at enhancing the yield. The first significant improvement was observed when tetramethylethylenediamine (TMEDA) was added in the medium, thus affording 70% of biphenyl (Table 1, entries 7−10). Eventually, we were pleased to find that the use of the simple triethylamine (Et_3N) as additive led quantitatively to **1** (Table 1, entry 11). Transposing these conditions in the more environmentally friendly THF also exclusively afforded biphenyl while using a smaller amount of Et_3N (0.5 equiv) lowered the yield (Table 1, entries 12 and 13). Note that excellent and good yields in **1** were obtained with commercial solutions of linear *s*-BuLi (2-Li-butane) or *n*-BuLi at lower concentrations (1.6 equiv; entries 14 and 15). Finally, quantitative and fair yields in biphenyl **1** were obtained from iodobenzene and challenging chlorobenzene respectively (entries 19 and 20).

Table 1. Fe-Catalyzed Synthesis of Biphenyl **1** from Bromo-, Iodo-, or Chlorobenzene in the Presence of *t*-BuLi or of Linear *n*- or *s*-BuLi[a]



entry	X	[Fe]	additive	solvent	yield[b] (%)
1	Br	$FeCl_2$		benzene	32
2	I	$FeCl_2$		benzene	45
3	Cl	$FeCl_2$		benzene	22
4	Br	Fe		benzene	31
5	Br	$FeCl_3$		benzene	50
6	Br	$Fe(acac)_3$		benzene	46
7	Br	$FeCl_2$	1,10-phen	benzene	8
8	Br	$FeCl_2$	DABCO	benzene	13
9	Br	$FeCl_2$	Bu_3N	benzene	54
10	Br	$FeCl_2$	TMEDA	benzene	70
11	Br	$FeCl_2$	Et_3N	benzene	96
12	Br	$FeCl_2$	Et_3N	THF	100, 100[c]
13	Br	$FeCl_2$	Et_3N	THF	58[d]
14	Br	$FeCl_2$	Et_3N	THF	96
15	Br	$FeCl_2$	Et_3N	THF	68
16	Br	$FeCl_2$		THF	37
17	Br		Et_3N	THF	0
18	Br	$FeCl_3$	Et_3N	THF	67
19	I	$FeCl_2$	Et_3N	THF	100
20	Cl	$FeCl_2$	Et_3N	THF	55

[a] Reaction performed with 1 mmol of PhX, 2 equiv of *t*-BuLi (general case), or 1.6 equiv of *s*-BuLi or *n*-BuLi (entries 14 and 15). [b] GCMS yield calculated with undecane as standard. [c] PhBr was added 1 h after *t*-BuLi. [d] Reaction with 0.5 mmol of Et_3N.

An important feature of organolithium derivatives is the strong relationship between their degree of aggregation and their reactivity.[20] The latter, which evolves in the same manner as their solubility, can be increased by deaggregation in donor solvents (Et_2O, THF) in the presence of Lewis bases, particularly of the nitrogen type. This general feature seems to be supported by the spectacular influence of the NEt_3 additive in THF (Table 1), which could favor the aryl halide exchange or the further reactivity of an in situ formed phenyllithium.

Next, we explored the breadth of application of this method by using the conditions optimized in the model

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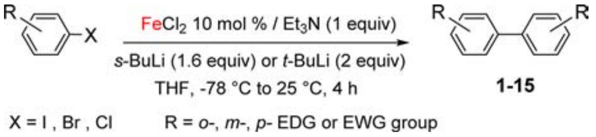
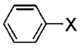
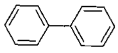
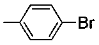
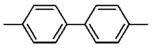
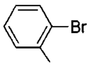
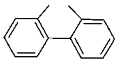
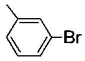
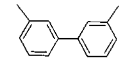
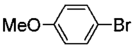
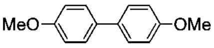
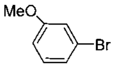
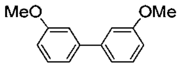
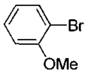
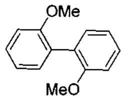
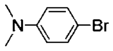
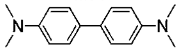
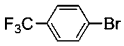
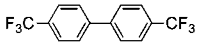
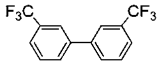
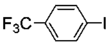
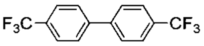
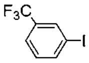
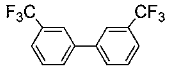
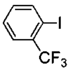
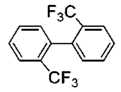
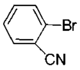
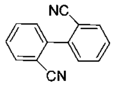
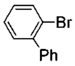
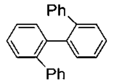
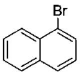
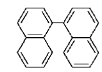
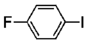
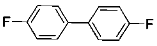
reaction (Table 1, entries 12 and 14). The system FeCl$_2$/Et$_3$N in the presence of *t*-BuLi (2 equiv) or of the more convenient linear *s*-BuLi (1.4−1.6 equiv), efficiently promoted the homocoupling of aryl bromides with electron-donating (EDG) groups, to afford the corresponding biaryls in excellent yields. With bromotolyl derivatives, the reaction was successfully performed whatever the position of the methyl substituent either ortho, meta or para (Table 2, entries 2−4). Similarly, the three possible bromoanisyl regioisomers also led to the corresponding biaryls with very good yields (Table 2, entries 5−7). The dimethylamino substituent (para) was also an excellent candidate for the synthesis of the corresponding homocoupling product **8** (Table 2, entry 8). Subsequently, we performed the coupling with aryl bromides bearing electron-withdrawing groups (EWD) and started with the *p*-bromotrifluoromethylbenzene. We obtained the homocoupling product but the NMR spectra showed the presence of a mixture of the para and meta isomers **9**/**10** (ratio 4/1) (Table 2, entry 9). Interestingly, the synthesis of biaryl ether **9** could be selectively achieved using *p*-iodotrifluoromethylbenzene as the starting halide (entry 10). This result might be related to the lithium-halide interchange rate, known to decrease following the order I > Br > Cl.[21] The meta and the sterically demanding *o*-iodotrifluoromethylbenzenes also allowed for the synthesis of the corresponding *m*-biaryl **10** and of the challenging *o*-biaryl **11** (entries 11 and 12).

Two other *o*-biaryls, *o*,*o*′-dicyanobiphenyl **12** and *o*,*o*′-quaterphenyl **13**, were obtained in good to excellent isolated yields (entries 13 and 14), from *o*-cyanobromobenzene and *o*-bromobiphenyl, respectively. Finally, binaphthyl **14** was obtained from *o*-bromonaphthalene (entry 15), and an interesting regioselectivity was observed with 1-iodo-4-fluorobenzene as the starting substrate. Indeed, the reaction led to the exclusive formation of *p*,*p*′-difluorobiphenyl **15** (entry 16), thus allowing further functionalization of aromatic cycles.

The method (with *s*-BuLi or *t*-BuLi) was then successfully applied to the synthesis of heteroaromatic molecules such as bipyridine **16** (table 3, entry 1). The same procedure also allowed the coupling of alkenes and alkynes. Therefore, the reaction performed from the *β*-bromostyrene (commercial mixture of *E*/*Z* = 50/50) selectively led to the *E*,*E*-1,4-diphenylbutadiene **17** (Table 3, entry 2). Remarkably, none of the other possible isomers were observed in the course of the reaction likely attesting to Fe-catalyzed isomerization steps. In this case, the sole byproduct observed was 1,4-diphenylbut-2-ene (4 mol %). From phenylacetylene, the resulting homocoupling product **18** (1,4-diphenylbutadiyne) was also obtained in good yield (Table 3, entry 3); the lithiation was directly performed without requiring the presence of a halide derivative as starting partner.[22] By this method, we could also readily obtain 9,10-dihydrophenanthrene **20**, from which phenanthrene is obtained by a well-described oxidative dehydrogenation.[23] The molecule results from the double intramolecular and concomitant homocoupling of the commercial 2-bromobenzylbromide, performed in only one step

Table 2. Fe-Catalyzed Synthesis of Biaryls from Aryllithiums, Generated in Situ from Aryl Halides and *s*-BuLi or *t*-BuLi[a]



entry	Ar-X	Ar-Ar		yield[b]	
				s-BuLi	*t*-BuLi
1		 X = Br	**1**	94	98
		X = Cl			55
		X = I		97	95
2			**2**	68	68
3			**3**	84	90
4			**4**	85	95
5			**5**	75	80
6			**6**	72	82
7			**7**	69	75
8			**8**	83	91
9			**9**		70[c]
			**10**		15[c]
10			**9**	72	78
11			**10**	70	68
12			**11**	58	60
13			**12**	51	56
14			**13**	81	83
15			**14**	67	78
16			**15**	65	70

[a] Reaction performed on 1 mmol scale: FeCl$_2$ 99.998% (Aldrich) and FeCl$_2$ 99.5% (Alfa Aesar). [b] Isolated yields. [c] The para/meta isomers **9**/**10** are obtained in a 4/1 ratio.

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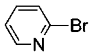
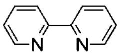
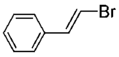
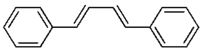
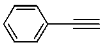
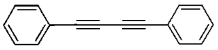
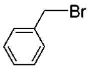
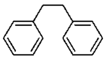
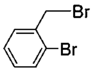
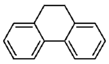
Table 3. Fe-Catalyzed Coupling of Heteroaryl Halides, Styryl Halides, Alkynes, Benzyl Bromide, or 2-Bromomethylbromobenzene[a]

$$\text{R-X} \xrightarrow[\text{THF, -78 °C to 25 °C, 4 h}]{\text{FeCl}_2\text{ 10 mol \% / Et}_3\text{N (1 equiv)}} \text{R-R}$$

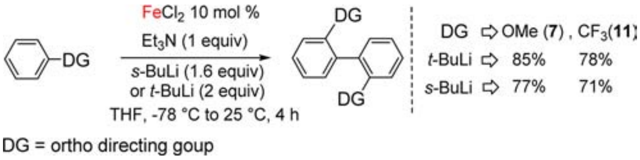
s-Buli (1.6 equiv) or *t*-BuLi (2 equiv)

X = Br or H R = heterocycle, styryl, alkynyl, benzyl

entry	R-X	R-R[b]		yield[b]	
				s-BuLi	*t*-BuLi
1			**16**	68	67
2			**17**	66	65[c]
3			**18**	67	72
4			**19**		89, 65[d]
5			**20**		70

[a] Reaction performed on 1 mmol scale: $FeCl_2$ 99.998% (Aldrich) and $FeCl_2$ 99.5% (Alfa Aesar). [b] Isolated yields. [c] 4 mol % of 1,4-diphenylbut-2-ene was also obtained. [d] Yield in the absence of iron salt.

Scheme 1. Fe-Catalyzed Synthesis of the Biaryls from Aryllithium Derivatives via *o*-Metalation



via an in situ lithiation of the benzylic and the phenyl positions (global yield: 76%, entry 5). Note that with the magnesium route, three successive steps are required for the same transformation.[24] The related benzylbromide itself led in our conditions to the corresponding homocoupling molecule **19** with an excellent yield (Table 3, entry 4). Surprisingly,[25] this reaction performed without iron also afforded the product, although in lower yield (Table 3, entry 4).

For the synthesis of *o*,*o*′-biaryls, we also developed a complementary strategy. In a one-pot procedure, both the ortho lithiation of aromatic compounds (with *s*-BuLi or *t*-BuLi) and their iron-catalyzed homocoupling were obtained (Scheme 1). The method was successfully applied in preliminary tests to anisole and trifluoromethylbenzene but failed with benzonitrile for which the homocoupling from the *o*-cyanobromobenzene is possible by the former method (see Table 2, entry 13).

The in situ aryl halide exchange with alkyllithiums, the starting point of our method, displays interesting features compared to the classical insertion reaction with Li or Mg metals. It is characterized by mild reaction conditions and few byproducts especially in the case of substrates involving functional groups sensitive to harsher conditions.[26] Additionally, the use of alkyllithiums (commercially available solution) for the synthesis of aryllithiums limits the risks at the industrial level, compared with for example the corresponding preparation of arylmagnesium derivatives. The latter can indeed be prevented by traces of water or solvent (alcohol or ketone) present in multistep syntheses. This generates a risk for the process, as magnesium may accumulate in the reactor and the reaction thereafter may run out of control, if it finally starts. With the use of alkyllithiums, the first liters added in the reactor vessel neutralize these potentially interfering products and the aryllithium expected is then immediately formed in mild conditions.[26] At the laboratory scale we used *t*-BuLi or the linear *s*-BuLi. For industrial applications, it is clear that the latter or *n*-BuLi would be chosen for pilot plant implementation.

In conclusion, we have discovered an efficient method in which the direct synthesis of symmetrical biaryl derivatives from aryl halides is possible in very mild temperature conditions by using a ligand-free iron catalytic system. The procedure, which proceeds via an in situ quantitative aryl halide exchange with alkyllithiums, allows for an excellent control of the reactivity for the further synthesis of the products. The method is also applicable to styryl and benzyl halides and to phenylacetylene. Iron is one of the most abundant metals on earth and one of the most inexpensive and environmentally friendly ones. For all these reasons this procedure is in line with sustainable development. Work is in progress to generalize its application field to dissymmetric biaryls[12,27] and to understand the mechanism.[28]

Acknowledgment. We thank the CNRST and the ANR for a Ph.D. grant for D.T.

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

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(24) From the same starting 2-bomobenzyl bromide, **20** was also obtained by the magnesium way in three steps via the following: (i) homocoupling of an in situ formed benzyl Grignard; (ii) iodination of two aromatic bromide positions and iron catalyzed homocoupling of an in situ formed aryl magnesium (global yield: 19%): Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943.

(25) In the recent literature, homocoupling of the benzyl bromide takes place via an in situ formation of the benzyl Grignard and the intervention of manganese and iron catalysts: (a) Xu, X.; Cheng, D.; Pei, W. *J. Org. Chem.* **2006**, *71*, 6637. (b) Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788. (c) Yuan, Y.; Bian, Y. *Appl. Organometal. Chem.* **2008**, *22*, 15.

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(27) During the preparation of this manuscript the Pd-catalyzed cross-coupling of aryl halides with organolithium derivatives was published. This Palladium variant of the nickel system we described in ref 12 involves a strategy based on preformed aryllithiums, on halogen—lithium exchanges, and on direct metalations (as in the Fe-catalytic system descibed in this paper for the homocoupling): Giannerini, M.; Fananas-Mastal, M.; Feringa Ben, L. *Nat. Chem.* **2013**, *5*, 667.

(28) We identified two possible catalytic cycles including Fe(0)- and Fe(II)-catalytic species for this reaction. They are presented together with some mechanistic tests and the corresponding discussion in the-Supporting Information.

The authors declare no competing financial interest.