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Tetrahedron Letters

Tetrahedron Letters 49 (2008) 610–613

Efficient Fe-catalyzed homo-coupling of aryl Grignard reagents using O_2 as the oxidant

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Received 26 October 2007; revised 22 November 2007; accepted 23 November 2007

Abstract

$FeCl_3$/Bipy catalyst system was found to be a good combination in the oxidative homo-coupling of aryl Grignard reagents directly using molecular oxygen as the oxidant. Moderate to good yields of desired corresponding symmetrical biaryls were obtained at room temperature in 10 min.

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Keywords: Iron; Homo-coupling; Grignard reagents; Biaryls; Dioxygen

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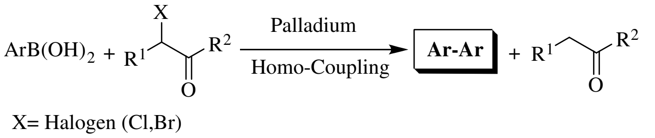
Biaryls as a central part of organic framework have been found in a large number of natural products and widely applied in many useful man-made materials.[1–3] Transition metal catalyzed oxidative homo-coupling reaction is one of the efficient methods to construct symmetrical biaryls. Palladium-catalyzed carbon–carbon coupling reactions have been extensively studied and well established in the past several decades.[4] Our group have used α-halocarbonyl compounds as oxidants in palladium-catalyzed oxidative homo-coupling reactions and several important results were achieved (Scheme 1).[5–8] Although an excellent chemo-selectivity in the reactions was given, we reconsidered the applications and limitations of oxidative homo-coupling reaction protocol. Palladium, a kind of expensive noble metal, has a toxic effect on human and environment. Moreover, using a stoichiometric amount of organic oxidant is considered to be neither 'green' (environmentally friendly) nor economical. Thus, with the urgent demand for green chemistry process and sustainable development in the chemistry industry, searching for cheap and nontoxic catalysts as well as green and inexpensive oxidants obviously becomes one of the most important topics. And there have been some examples carried out on palladium-catalyzed homo-coupling reactions using molecular oxygen as the oxidant.[1,9–15] In addition, several other kinds of transition metal salts ($CoCl_2$,[16] $TiCl_4$,[17] $VO(OEt)Cl_2$,[18] and $CuCl_2$[19]) were used in stoichiometric amount or catalytical amount in the presence of reoxidant,[9,14,18,20,21] such as oxygen or other organic oxidants, to carry out the oxidative coupling process. Iron is a very common and cheap metal, which has been widely applied as a catalyst in carbon–carbon bond formation reactions[22–33] and other types of reactions.[34–36] Recently, Nagano and Hayashi[37] and Cahiez et al. [38] reported their iron-catalyzed oxidative homo-coupling of aryl Grignard reagents using 1,2-dihalogenoethanes as an oxidant. Undoubtedly, using cheap iron salts as catalysts combined with oxidant in the synthesis of biaryls is of great potential importance. However, 1,2-dihalogenoethanes[37,38] is not an ideal oxidant candidate



Scheme 1. Palladium-catalyzed oxidative homo-coupling reactions involved α-halocarbonyl compounds as organic oxidants.

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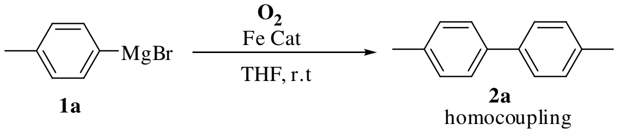
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.144

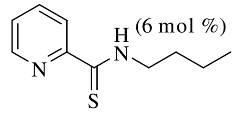
from both the sustainable and green point of view. Obviously, molecular oxygen should be the best choice of green and environment-friendly oxidant for the oxidative homo-coupling reactions and other oxidation processes. To the best of our knowledge, directly using molecular oxygen as an oxidant combined with catalytical amount of commercially available and cheap iron salts was seldom[39] reported in oxidative homo-coupling of aryl Grignard reagents for the preparation of corresponding symmetrical biaryls. Herein, we would like to present our results in this area.

In our initial study on the iron-catalyzed oxidative homo-coupling reactions using 4-methylphenyl magnesium bromide **1a** as a model substrate in the presence of catalytical amount of $FeCl_3$ (5 mol %), at oxygen atmosphere (bubbling by oxygen balloon), the result gave 4,4′-dimethyldiphenyl **2a** as the main product, and 62% isolated yield was obtained (Table 1, entry 3). And meanwhile a little amount of phenol was observed from TLC. As we know, without adding any transition metal salts, aryl Grignard reagents could react directly with oxygen to give ArOH as the oxidation products.[16,40] In this experiment, we found that the reaction proceeded so quickly that only 10 min was needed. Encouraged by the above promising result, a series of experiments were carried out to optimize the reaction conditions.

As shown in Table 1, with no iron salts added, trace of homo-coupling product was observed (Table 1, entry 1) at oxygen atmosphere, which indicated that iron salts were essential to this reaction. Then, iron salts were also evaluated. When $Fe(acac)_3$ (Table 1, entry 4) was added, only 46% homo-coupling product **2a** was obtained. While $FeCl_3$ was proved to be more efficient than $Fe(acac)_3$ (Table 1, entries 3 and 4). On the basis of our experiments (Table 1, entries 1–4), the homo-coupling results were not satisfying due to the direct oxidation of aryl Grignard reagents with oxygen, which acted as a main side reaction. To facilitate the oxidative homo-coupling reactions, we examined the efficiency of $FeCl_3$ as a catalyst with the aid of various ligands (Table 1, entries 5–7), *N*,*N*,*N*,*N*-tetramethylethane-1,2-diamine (TMEDA), 2,2′-bipyridine (Bipy), and *N*-butylpyridine-2-carbothioamide. TMEDA and Bipy were commonly used as ligands in the iron-catalyzed coupling reactions. The results indicated TMEDA was not efficient in this reaction (Table 1, entry 5), as well as *N*-butylpyridine-2-carbothioamide (Table 1, entry 7). We were glad to find that $FeCl_3$ in the presence of Bipy appeared much more powerful (Table 1, entry 6), with 85% isolated yield given in 10 min. Furthermore, we increased the amount of catalyst used in this reaction and the yield of homo-coupling product **2a** was enhanced to 91% in 10 min when 6 mol % $FeCl_3$ and 12 mol % Bipy were used (Table 1, entry 8). In general, Table 1, entry 8 gave the best condition.

Table 1
Optimizing the reaction conditions for the oxidative homo-coupling of aryl Grignard reagent



Entry	Iron salt	Ligand	Yield (%)
1	No	No	<5[a]
2	$FeCl_3$ (2 mol %)	No	47
3	$FeCl_3$ (5 mol %)	No	62
4	$Fe(acac)_3$ (5 mol %)	No	46
5	$FeCl_3$ (3 mol %)	TMEDA (6 mol %)	35
6	$FeCl_3$ (3 mol %)	Bipy (6 mol %)	85
7	$FeCl_3$ (3 mol %)		57
8	*$FeCl_3$ (6 mol %)*	*Bipy (12 mol %)*	*91*
9	$FeCl_3$ (5 mol %)	Bipy (10 mol %)	87

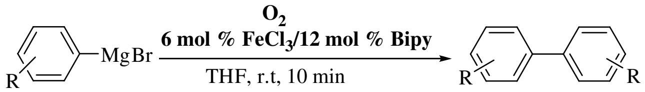
Reactions were carried out with 1.0 mmol of **1a**. All reactions completed in 10 min at room temperature in THF.

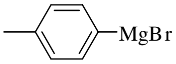
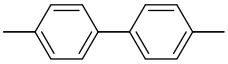
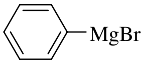
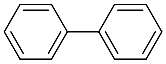
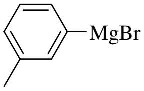
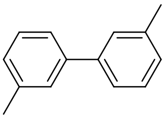
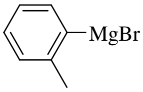
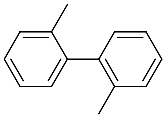
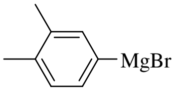
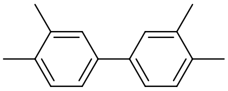
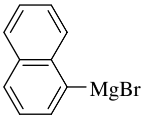
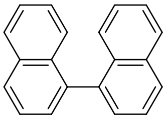
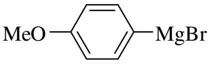
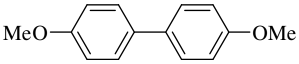
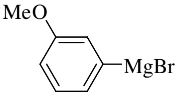
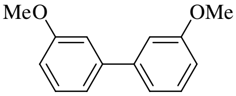
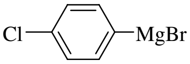
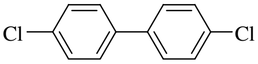
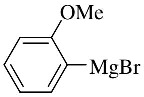
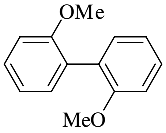
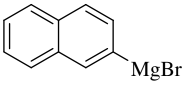
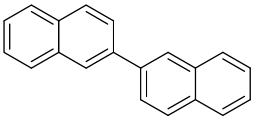
[a] The yield was checked by GC.

Under the aforementioned optimized conditions and promising results, we have examined the substrate scope of this reaction.[41] As shown in Table 2, our experiments indicated that a variety of aryl Grignard reagents could quickly transform to the desired corresponding symmetrical biaryls. Using our new protocol, the oxidative homo-coupling reactions could afford excellent yields (Table 2, entries 1, 2, and 11). And moderate to good yields of biaryls (Table 2, entries 3–10) were also obtained with this new efficient method. In the oxidative homo-coupling reaction of *ortho*-methyl phenyl Grignard reagent **1d** (Table 2, entry 4), because of the presence of *ortho* position, 72% homo-coupling product **2d** was obtained. In Table 2, entry 9, 4,4′-dichlorobiphenyl **2j** was given in 76% yield. Furthermore, when the methoxy group was present at the *ortho* position, the yield of **2k** was not apparently affected (Table 2, entry 10). And considering the catalyst loadings used in our oxidative homo-coupling reactions and to enhance this new method's preparative meaning, we attempted to use 1 mol % catalyst system to carry out the reaction at 10 mmol scale, 86% isolated yield of **2b** (Scheme 2) was given in 15 min by dropping the phenyl Grignard reagent **1b** into the reaction system. In addition, we directly used dry air as the oxidant, a very good result (Scheme 3) was observed after 2 h at room temperature, which made us believe that this new method would be easily applied in the synthesis of symmetrical biaryls under a very mild condition.

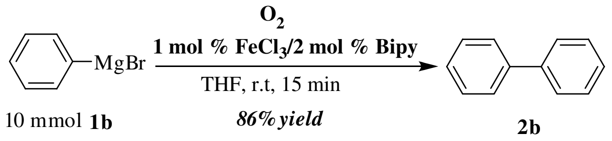
In summary, we have developed a novel and practical reaction system for oxidative homo-coupling reaction of aryl Grignard reagents directly using molecular oxygen as an oxidant and $FeCl_3$ combined with Bipy as catalyst. Moderate to good yields of desired corresponding symmetrical biaryls were obtained at room temperature in 10 min. This reaction system is applicable to the quick preparation

Table 2
$FeCl_3$/Bipy catalyzed homo-coupling of aryl Grignard reagents using oxygen as an oxidant

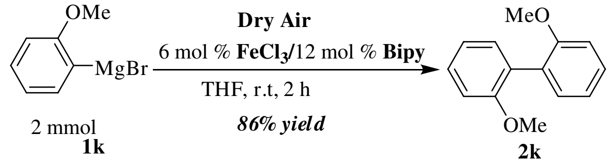


Entry	Aryl Grignard reagents		Product		Yield (%)
1		**1a**		**2a**	91
2		**1b**		**2b**	91
3		**1c**		**2c**	80
4		**1d**		**2d**	74
5		**1f**		**2f**	78
6		**1g**		**2g**	82
7		**1h**		**2h**	80
8		**1i**		**2i**	84
9		**1j**		**2j**	76
10		**1k**		**2k**	80
11		**1m**		**2m**	88

All reactions were performed on a 2 mmol scale at room temperature.



Scheme 2. Iron-catalyzed oxidative homo-coupling reaction using 1 mol % FeCl$_3$/Bipy as catalyst.



86% yield was determined by GC.

Scheme 3. Directly using dry air as the oxidant in the oxidative homo-coupling reaction.

of symmetrical biaryls from the corresponding aryl Grignard reagents under the very mild condition. And further study on the mechanism is in progress.

Acknowledgments

This work was supported by National Natural Science Foundation of China (Grant No. 20502020) and the start-up fund from Wuhan University.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.144.

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39. Before we intended to submit this paper, we noted that Cahiez et al. reported a similar Fe/O$_2$ catalyzed homocoupling of ArMgCl without the addition of ligand: Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**. ASAP.
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41. *General procedure for the oxidative homo-coupling of aryl Grignard reagent catalyzed by iron*. In a Schlenk tube were added anhydrous FeCl$_3$ (0.12 mmol), Bipy (0.24 mmol), and 3 mL dry THF. Under the atmosphere of nitrogen, 2.0 mmol aryl Grignard reagent was added into the above stirred mixture and then the reaction mixture was degassed and refilled with pure oxygen by an oxygen balloon, and the reaction mixture was stirred at room temperature for 10 min. After the reaction was completed, 10 mL of ethyl acetate and a little amount of silica gel were added to the reaction mixture. The solvent was removed under reduced pressure and the residue was purified by column chromatograph to afford the desired product. All the products are known and have been characterized by ^{1}H NMR.