RSC Advances



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COMMUNICATION



Cite this: RSC Adv., 2016, 6, 86998

Homocoupling of heteroaryl/aryl/alkyl Grignard reagents: I₂-promoted, or Ni- or Pd- or Cu- or nano-Fe-based salt catalyzed⁺

Received 13th July 2016 Accepted 7th September 2016

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DOI: 10.1039/c6ra17859f

www.rsc.org/advances

Five efficient processes for the homo-coupling of various Grignard reagents including aryl, heteroaryl and aliphatic ones in the presence of I_2 , Pd(OAc)₂, Ni(OAc)₂, Cul, and nano-Fe₃O₄ were developed, respectively.

The symmetrical biaryl unit is found in a number of natural products, pharmaceuticals, optical materials and functional molecules.1 Oxidative homo-coupling reactions of Grignard reagents have gained great attention as they provide an easy and efficient access for the construction of such compounds. Several kinds of transition metal promoters including cobalt salts,² TlBr,³ TiCl₄,⁴ vanadium salts,⁵ copper salts,⁶ etc.⁷ have been used in the presence of a reoxidant to carry out the oxidative coupling process in most cases.8 In these reactions, however, a stoichiometric or excess amount of transition metal is used for smooth transformation. Consequently, with the urgent demand for green chemistry process and sustainable development, the exploration of the suitable catalytic systems with efficient catalysts and inexpensive oxidants obviously becomes one of the most important topics. On the other hand, some common and easily available transition metal catalysts have been successfully used in the crosscoupling reactions of Grignard reagents with organic electrophiles and possessed the synthetic advantages such as high selectivity, broad substrate scopes and mild reaction conditions in recent years.9 In contrast, the catalyzed routes to symmetrical biaryls from Grignard reagents about them have not received as much attention although there have been several examples carried out on manganese-,10 iron-,11 cobalt-,12 ruthenium-13 and copper-catalyzed¹⁴ homo-coupling reactions. Therefore, we anticipate that similar Pd- and Ni-catalyzed methods can also be realized under certain conditions, and to the best of our knowledge, there have been no reports on I2-mediated, nano-Fe3O4- and CuI-catalyzed

oxidative homo-coupling so far. Herein, we will report $Pd(OAc)_2$ -, $Ni(OAc)_2$ -, CuI-, and nano-Fe₃O₄-catalyzed, and I₂-promoted routes to symmetrical biaryls from Grignard reagents.

First, when phenylmagnesium bromide was treated with 0.2 equiv. of I_2 in toluene at 110 °C, the desired product was obtained in 37% yield (Table 1, entry 1). The yield was improved greatly by increasing the amount of I_2 and the highest yield was provided when 0.8 equiv. I_2 was used (Table 1, entry 4 ν s. 2, 3 and 5).

With the promising results, the scope of Grignard reagents was next investigated and the results are shown in Table 2. The results indicated that a variety of Grignard reagents could also be quickly transformed into the corresponding products in the presence of I_2 . Grignard reagents having electron-poor or -rich groups on benzene ring underwent smoothly transformation to give products in good to high yields (Table 2, entries 1–7). The benzylmagnesium bromide could afford the corresponding product in 54% yield, although a longer time and higher temperature was required (Table 2, entry 8). Heteroaryl Grignard reagents such as pyridylmagnesium bromide and thienylmagnesium bromide were found be suitable substrates

Table 1 The optimization of the homocoupling of Grignard reagents with ${\rm I_2}^a$

MgBr I2.	, Toluene, 110 °C ►	
		h .

Entry	I_2 (equiv.)	Yield ^b (%)		
1	0.2	37		
2	0.4	65		
3	0.6	80		
4	0.8	96		
5	0.9	92		

 $[^]a$ Reaction conditions: phenylmagnesium bromide (0.3 mmol), I_2, toluene (1.5 mL), temperature (110 $^\circ \rm C)$, time (48 h). b Isolated yield.

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[†] Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra17859f

Table 2 The scope of the homocoupling of Grignard reagents with l_2^{a}

	2 ArMgX	0.8 equiv I ₂ Toluene, 110 °C	Ar—Ar	
Entry	Grignard reagent	Product	<i>t</i> (h)	Yield ^b (%)
1	MgBr	$\bigcirc - \bigcirc$	48	96
2	MgBr	Q.	50	83
3	MgBr	Ń	48	88
4	MgBr	D _Q	48	92
5	H ₃ CO ^{MgBr}	H ₃ CO	48	86
6	FMgBr	F	50	84
7	F MgBr	FF	50	91
8	MgBr		48	54 ^c
9	S MgBr	∫ S→S)	48	82
10	N MgBr		48	76
11	MgBr	N N	48	81
12	MgCl	$\bigcirc - \bigcirc$	48	89
13	MgCl	Ń	50	82
14	MgCl	D _Q	48	87
15	MgBr		48	62
16		2 (<i>(</i> _))	48	N.D. ^d

^{*a*} Reaction conditions: Grignard reagent (0.3 mmol), I_2 (0.8 equiv.), toluene (1.5 mL), temperature (110 °C). ^{*b*} Isolated yield. ^{*c*} 140 °C was used. ^{*d*} N.D. = not detected.

found that through the use of $Pd(OAc)_2$,¹⁵ a wide range of Grignard reagents, including arylmagnesium bromide, heteroarylmagnesium bromide, and arylmagnesium chloride could be effectively transformed in good to excellent yields in the presence of LiClO₄ (Table 3, entries 1–7 and 9–14).¹⁶ Finally, benzylmagnesium bromide also represented a compatible substrate under the reflux conditions (Table 3, entry 8).

To prove the generality of $Ni(OAc)_2$ as a catalyst in the homo-coupling of Grignard reagents, various substrates were investigated. Optimized reaction conditions¹⁷ were next

_	2 ArMgX -	$\frac{\text{Pd(OAc)}_2 (10 \text{ mol }\%)}{\text{LiClO}_4 (1 \text{ equiv})}$ Toluene, 100 °C	Ar-Ar		
Entry	Grignard reagen	t Product	<i>t</i> (h)	Yield ^b (%)	
1	MgBr		15	98	
2	MgBr		17	87	
3	MgBr		15	93	
4	MgBr		15	96	
5	H ₃ CO MgBr	H ₃ CO	15	87	
6	FMgBr	F	17	86	
7	F MgBr	FF	15	98	
8	MgBr		24	61 ^c	
9	∬ ^S → ^{MgBr}	ſ,×,S)	15	86	
10	N MgBr		15	85	
11	N MgBr	N N	15	88	
12	MgCl		15	92	
13	MgCl		16	86	
14	MgCl	D.	15	89	

to give the homo-coupled products in good yields (Table 2, entries 9–11). Homo-couplings of arylmagnesium chloride also proceeded well under similar conditions (Table 2, entries 12–14). Excitedly, 1,4-diphenylbuta-1,3-diyne was provided in 62% yield when (phenylethynyl)magnesium bromide was used as a substrate (Table 2, entry 15). However, no product was detected for styrylmagnesium bromide (Table 2, entry 16).

Subsequently, our studies focused on the Pd-catalyzed homo-coupling of various types of Grignard reagents. It was

^{*a*} Reaction conditions: Grignard reagent (0.3 mmol), Pd(OAc)₂ (10 mol%), LiClO₄ (0.3 mmol, 1.0 equiv.), toluene (2.0 mL), temperature (100 °C). ^{*b*} Isolated yield. ^{*c*} 120 °C was used.

applied to prepare a variety of homo-coupled products. For the aryl Grignard reagents having electron-poor or -rich groups on benzene ring (Table 4, entries 2-7), the coupling reactions provided high yields (85-97%). The steric hindrance also played an important role (Table 4, entries 4 vs. 2 and 7 vs. 6). The longer reaction time was required for the reaction with benzylmagnesium bromide, giving relatively low yields (58%) (Table 4, entry 8). Heteroarylmagnesium

bromide with Ni(OAc)₂ as a catalyst provided somewhat lower vields than that with Pd(OAc)₂ (Table 4, entries 9-11). Similar yields were obtained with arylmagnesium chloride (Table 4, entries 12-14).

To demonstrate the efficiency and scope of the method with CuI as a catalyst,¹⁸ we applied the catalytic system to a variety of Grignard reagents (Table 5). Various substrates including arylmagnesium bromide possessing methyl, methoxy and fluro groups, heteroarylmagnesium bromide, and arylmagnesium chloride were smoothly converted to the desired products in good to excellent yields (Table 5, entries

Table 4	The scope	of the I	homocoupling	of Grignard	reagents with
Ni(OAc) ₂	а				

Ni(OAc) ₂ (10 mol %) 2 ArMoX Ag ₂ O (1 equiv.)			Ar-Ar		Table 5 Cul ^a	The scope o	f the homocoupling of Gri	homocoupling of Grignard reagents with		
	DCM, 25 °C		n n			2 ArMgX	CuI (15 mol %), Toluene	Ar-Ar		
Entry	Grignard reagent	Product	<i>t</i> (h)	$\operatorname{Yield}^{b}(\%)$		8	Air, 100 °C			
1	MgBr	$\bigcirc - \bigcirc$	18	95 ^c	Entry	Grignard rea	gent Product	<i>t</i> (h)	Yield ^b (%)	
2	MgBr		20	90	1	MgBr		15	95	
3	MgBr		18	93	2	MgBr		18	95	
4	MgBr		18	97	3	MgBr		15	95	
5	H ₃ CO	H ₃ CO	17	90	4	MgBr		15	96	
6	FMgBr	F F F	20	85	5	H ₃ CO Mg	Har Haco	15	95	
7	F MgBr	F C C	18	92	6	FMgBi	F F	18	86	
8	MgBr		24	58	7	F	r F	18	98	
9	SMgBr	⊂ S→S)	18	82	8	MgBr		24	57 ^c	
10	N MgBr		18	77	9	∬ ^S → ^{MgBr}	Č→Š ⇒	15	88	
11	MgBr		18	81	10	N MgBr		15	82	
12	MgCl	\bigcirc	18	83	11	N MgBr		15	87	
13	MgCl		18	86	12	MgCl		15	89	
14	MgCl		18	90	13	U		16	79	
		~			14	MgCl		16	84	

^a Reaction conditions: Grignard reagent (0.3 mmol), Ni(OAc)₂ (10 mol%), Ag₂O (0.3 mmol, 1.0 equiv.), CH₂Cl₂ (1.5 mL), temperature (25 °C). b Isolated yield. c 13% yield was obtained in the absence of $Ni(OAc)_2$.

 a Reaction conditions: Grignard reagent (0.3 mmol), CuI (15 mol%), toluene (2.0 mL), temperature (100 $^\circ$ C), air. b Isolated yield. c 120 $^\circ$ C was used.

1–7 and 9–14). Treatment of benzylmagnesium bromide also provided 57% yield at 120 $^{\circ}$ C (Table 5, entry 8).

Nano Fe_3O_4 was also found to be a good catalyst.¹⁹ Various Grignard reagents turned out to be suitable substrates and worked well (Table 6, entries 1–5 and 9–14) even though the materials bearing electron-withdrawing groups (Table 6, entries 6 and 7). Benzylmagnesium bromide could afford the corresponding product in 50% yield (Table 6, entry 8).

Table 6 The scope of the homocoupling of Grignard reagents with ${\rm Fe_3O_4}^a$

) 2 A-M-X	Nano Fe_3O_4 (10 mol%) AgNO ₃ (1.2 equiv.)			
	2 Arwiga –	Toluene, 100 °C	Ar-Ar		
Entry	Grignard reage	nt Product	t (h)	Yield ^b (%)	
1	MgBr		20	93 ^c	
2	MgBr		24	87	
3	MgBr		20	89	
4	MgBr		20	94	
5	H ₃ CO ^{MgBr}	H ₃ CO	20	90	
6	FMgBr	F	18	76	
7	F MgBr	FF	18	83	
8	MgBr		24	50^d	
9	⟨S MgBr	rs→s)	18	80	
10	N MgBr		20	77	
11	MgBr	N	20	83	
12	MgCl		20	86	
13	MgCl		20	82	
14	MgCl		20	87	

^{*a*} Reaction conditions: Grignard reagent (0.3 mmol), nano-sized Fe_3O_4 (10 mol%), AgNO₃ (0.36 mmol, 1.2 equiv.), toluene (2.0 mL), temperature (100 °C). ^{*b*} Isolated yield. ^{*c*} 9% yield was obtained in the absence of Nano-Fe₃O₄. ^{*d*} 120 °C was used.

To clarify the possible reaction mechanism I₂-promoted, the homocoupling of iodobenzene with the I₂/toluene system, cross coupling of iodobenzene with phenyl magnesium bromide in the presence of I2, and phenyl magnesium bromide with PhI(OAc)₂/toluene system were carried out (Scheme 1). The experimental results showed that the reaction process may not involve the generation of an iodobenzene (eqn (1) and (2)). The fact that biphenyl was observed in 57% yield when PhI(OAc)₂ was used instead of I2 indicated that hypervalent iodine may play an important role in this process, which suggested that iodine serves not only as the promoter but also as the oxidant (eqn (3)). On the basis of the observations and reported literatures,²⁰ a possible mechanism is postulated as follows (Scheme 2): partial iodine may be first transformed into some hypervalent iodine A in the reaction system. Then a low-valent iodine species B is formed through reduction of A using the Grignard reagent as a strong reducing agent. Subsequently, the species **B** reacts with the Grignard reagent in the presence of I_2 as an oxidant to generate intermediate C, which gives the homocoupling product D by reductive elimination and releases A.

In conclusion, we have described the homo-coupling reactions of various Grignard reagents in the presence of $Pd(OAc)_2$, Ni(OAC)₂, CuI, nano-Fe₃O₄, and I₂, respectively. The five synthetic methods worked very well and were applicable to the



Scheme 1 Controlled experiments.



 $\mbox{Scheme}~2$ A proposed mechanism for the $\mbox{I}_2\mbox{-}p\mbox{romoted}$ homocoupling.

homo-coupling of various aryl and heteroaryl Grignard reagents. Similar good yields were obtained regarding nano- Fe_3O_4 , and I_2 . Pd-, Ni-, and Cu-based catalyst systems provided higher yields than them. Notably, the first two systems are more green.

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- 16 LiClO₄ served as an oxidant.
- 17 The optimal reaction conditions screened were 0.3 mmol Grignard reagent, 10 mol% $Ni(OAc)_2$ and 1.0 equiv. of Ag₂O which was used as an oxidant in 1.5 mL CH₂Cl₂ under N₂ atmosphere at 25 °C. (See Table 2 in ESI[†]).
- 18 The optimized reaction conditions were 0.3 mmol Grignard reagent and 15 mol% CuI in 2.0 mL toluene under air atmosphere at 100 °C. (See Table 3 in ESI[†]).
- 19 The optimal reaction conditions were 0.3 mmol Grignard reagent, 10 mol% nano-Fe₃O₄ and 1.2 equiv. of AgNO₃ utilized as an oxidant in 2.0 mL toluene under N₂ atmosphere at 100 °C. (See Table 4 in ESI†).
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