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Copper-Catalyzed Oxidative Homo- and Cross-Coupling of Grignard Reagents Using Diaziridinone

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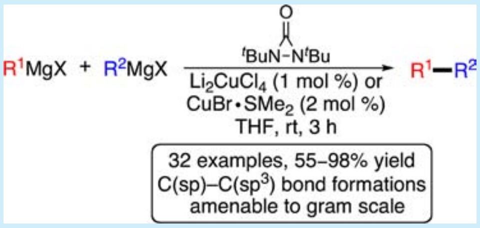
Supporting Information

ABSTRACT: Transition-metal-catalyzed cross-coupling reactions are among the most powerful synthetic transformations. This paper describes an efficient copper-catalyzed homo- and cross-coupling of Grignard reagents with di-*tert*-butyldiaziridinone as oxidant under mild conditions, giving the coupling products in good to excellent yields. The reaction process has a broad substrate scope and is also effective for the C(sp)−C(sp^3) coupling.



Transition-metal-catalyzed cross-coupling reactions between organometallic reagents and organic electrophiles have become indispensable tools in organic synthesis.[1] Oxidative coupling reactions of various organometallic reagents present new strategies for C−C bond formations and have received intense attention in recent years.[2] Grignard reagents, a class of readily available organometallic reagents, have also been actively investigated for oxidative coupling. A number of metal-mediated[3] and -catalyzed[4,5] as well as metal-free[6] oxidative homocouplings of Grignard reagents have been developed. Fewer examples of the oxidative cross-coupling of Grignard reagents have been reported.[7−9] There are still some unsolved problems. For example, the oxidative cross-coupling between alkynyl and alkyl Grignard reagents for C(sp)−C(sp^3) bond formation has remained challenging. The development of new, efficient, mild, and operationally simple cross-coupling reactions of Grignard reagents is highly desirable and valuable.

Previously, we have shown that di-*tert*-butyldiaziridinone (**1**)[10] is a highly effective nitrogen source for the Pd(0)-[11] and Cu(I)-catalyzed[12] diamination of olefins. In our subsequent studies, diaziridinone **1** has also been found to be a versatile oxidant for the oxidation of alcohols to aldehydes and ketones,[13] homocoupling of anilines to azo compounds and hydrazines,[14] and homocoupling of terminal alkynes to symmetrical 1,3-diynes.[15] In our continuing efforts, we have discovered that various Grignard reagents can be efficiently coupled to give the corresponding coupling products using di-*tert*-butyldiaziridinone (**1**) in the presence of a metal catalyst (Scheme 1). In particular, this coupling process is also effective for C(sp)−C(sp^3) bond formations.[16−21] Herein we wish to report our preliminary studies on this subject.

Scheme 1. Metal-Catalyzed Coupling of Grignard Reagents Using Diaziridinone

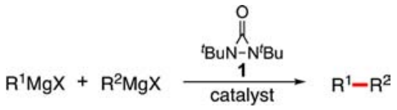
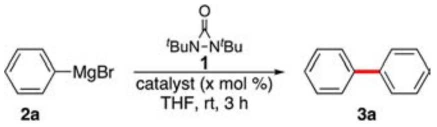


Table 1. Studies on Reaction Conditions[a]



entry	catalyst	x (mol %)	yield[b] (%)
1	$FeCl_2$	5	85
2	$CoCl_2$	5	94
3	$NiBr_2$	5	90
4	$Pd(OAc)_2$	5	96
5	$Pd(PPh_3)_4$	5	76
6	CuCl	5	95
7	CuBr	5	94
8	$CuBr\cdot SMe_2$	5	95
9	CuI	5	95
10	$CuCl_2$	5	94
11	$CuBr_2$	5	93
12	$CuSO_4$	5	46
13	Li_2CuCl_4	5	97
14	$\mathbf{Li_2CuCl_4}$	**1**	**97**
15[c]	Li_2CuCl_4	0.1	83
16[d]	Li_2CuCl_4	1	11
17	none		8

[a]All reactions were carried out with phenylmagnesium bromide (**2a**) (0.60 mmol), di-*tert*-butyldiaziridinone (**1**) (0.45 mmol), and catalyst (0.1−5 mol %) in THF (0.60 mL) at rt under Ar for 3 h unless otherwise stated. [b]Isolated yield. [c]Reaction time, 24 h. [d]The reaction was carried out in the absence of di-*tert*-butyldiaziridinone (**1**).

Our studies began with the homocoupling of Grignard reagents. Phenylmagnesium bromide (**2a**) was used as test substrate and was treated with di-*tert*-butyldiaziridinone (**1**) and various transition-metal catalysts in THF at room temperature.

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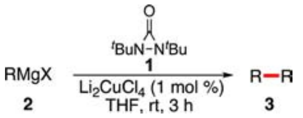
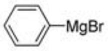
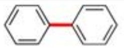
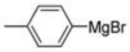
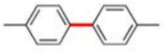
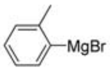
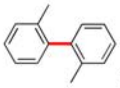
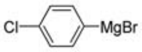
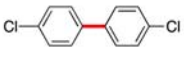
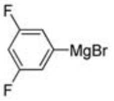
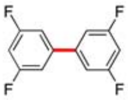
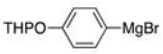
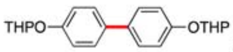
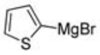
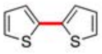
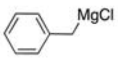
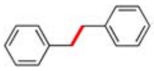
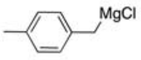
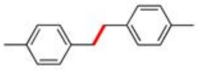
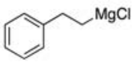
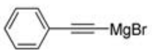
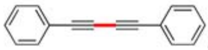
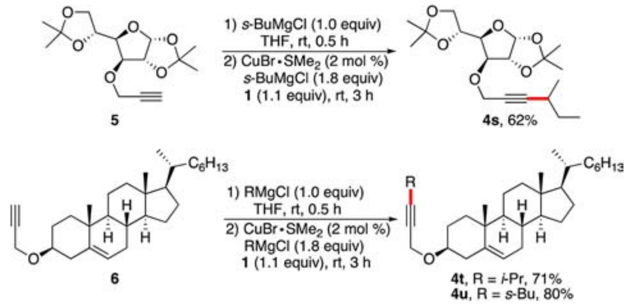
Table 2. Copper-Catalyzed Oxidative Homocoupling of Grignard Reagents[a]



entry	substrate **2**	product **3**	yield (%)[b]
1		 **3a**	97
2		 **3b**	96
3		 **3c**	84
4		 **3d**	96
5		 **3e**	73
6		 **3f**	95
7		 **3g**	98
8		 **3h**	98
9		 **3i**	96
10		 **3j**	93
11		 **3k**	96

[a] All reactions were carried out with RMgX (**2**) (0.60 mmol), di-*tert*-butyldiaziridinone (**1**) (0.45 mmol), and Li$_2$CuCl$_4$ (0.0060 mmol) in THF (0.60 mL) at rt under Ar for 3 h. [b] Isolated yield.

Scheme 2. Copper-Catalyzed Oxidative Cross-Coupling of Grignard Reagents



As shown in Table 1, the homocoupling was readily achieved with 5 mol % of metal catalyst such as FeCl$_2$, CoCl$_2$, NiBr$_2$, Pd(OAc)$_2$, Pd(PPh$_3$)$_4$, CuCl, CuBr, CuBr·SMe$_2$, CuI, CuCl$_2$, CuBr$_2$, and Li$_2$CuCl$_4$, giving biphenyl (**3a**) in 76–97% yield (Table 1, entries 1–11 and entry 13). The reaction yield did not decrease as the amount of Li$_2$CuCl$_4$ was reduced from 5 to 1 mol % (Table 1, entries 13 and 14). A good yield (83%) was still obtained when the reaction was carried out with 0.1 mol % of Li$_2$CuCl$_4$ over 24 h (Table 1, entry 15). Only small amounts of biphenyl (**3a**) were isolated when the reaction was carried out in the absence of di-*tert*-butyldiaziridinone (**1**) (Table 1, entry 16) or metal catalyst (Table 1, entry 17), suggesting that both di-*tert*-butyldiaziridinone (**1**) and metal catalyst are important for the coupling under the reaction conditions.

The generality of the oxidative homocoupling was subsequently investigated. As shown in Table 2, various aryl Grignard reagents were smoothly coupled to give the corresponding biaryls in 73–98% yield (Table 2, entries 1–7). Alkyl Grignard reagents were also effective substrates for this reaction, giving the corresponding coupling products in 93–98% yield (Table 2, entries 8–10). In the case of phenethylmagnesium chloride, no β-hydride elimination product styrene was observed (Table 2, entry 10). The coupling of phenylethynylmagnesium bromide afforded 1,4-diphenylbutadiyne (**3k**) in 96% yield (Table 2, entry 11).

Having established the feasibility of copper-catalyzed homocoupling reactions of Grignard reagents with diaziridinone **1**, we next turned our attention to more challenging cross-coupling. As shown in Table 3, the oxidative cross-coupling reaction can be applied to C(sp^2)–C(sp^2) (Table 3, entry 1), C(sp)–C(sp^2) (Table 3, entries 2–5), and C(sp)–C(sp^3) (Table 3, entries 6–18) bond formations, affording the coupling products in 55–83% yield with 2 mol % CuBr·SMe$_2$ and 1.1 equiv of di-*tert*-butyldiaziridinone (**1**) in THF at rt for 3 h.[22] The reaction is amenable to gram scale as illustrated in the preparation of product **4m** (Table 3, entry 13). For the C(sp)–C(sp^3) coupling, both primary (Table 3, entries 6–11) and secondary (Table 3, entries 12–18) alkyl Grignard reagents were effective coupling partners. The current catalytic system well tolerates β-hydrogen-containing alkyl Grignard reagents. In most cases, the desired cross-coupling product was formed with high selectivity. Little C(sp)–C(sp) homocoupling product was detected by GC–MS. As shown in Scheme 2, the present coupling process also proceeded smoothly with functionalized and complex substrates such as D-glucose- and cholesterol-derived propargyl ethers **5** and **6**, giving products **4s–u** in 62–80% yield.

While a precise understanding of the reaction mechanism awaits further study, a plausible catalytic pathway is proposed in Scheme 3. The coupling process may begin with the insertion of CuX into the N–N bond of di-*tert*-butyldiaziridinone

Scheme 3. Proposed Catalytic Cycle

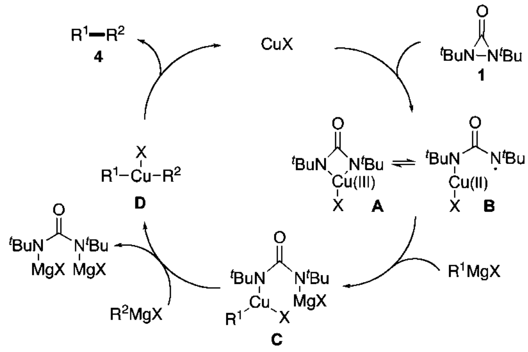
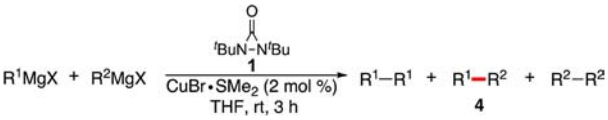
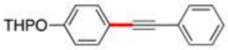
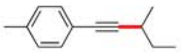
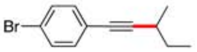
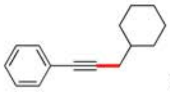
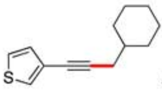


Table 3. Copper-Catalyzed Oxidative Cross-Coupling of Grignard Reagents[a]



entry	R^1–R^2 4	yield (%)[b]	selectivity[c] R^1R^1:**4**:R^2R^2	entry	R^1–R^2 4	yield (%)[b]	selectivity[c] R^1R^1:**4**:R^2R^2
1	 **4a**	58	14:63:23	10[f]	 **4j**	69	0:92:8
2	 **4b**	70	nd[d]	11[e]	 **4k**	55	0:97:3
3[e]	 **4c**	81	0:92:8	12[f]	 **4l**	70	0:82:18
4[e]	 **4d**	75	0:96:4	13[f,g]	 **4m**	71	0:88:12
5[e]	 **4e**	83	0:90:10	14[f]	 **4n**	80	0:90:10
6	 **4f**	58	5:90:5	15[f]	 **4o**	74	0:80:20
7	 **4g**	81	0:95:5	16[f]	 **4p**	76	0:92:8
8[f]	 **4h**	80	5:88:7	17[f]	 **4q**	73	0:93:7
9[f]	 **4i**	80	0:91:9	18[f]	 **4r**	74	0:86:14

[a] All reactions were carried out with R^1 MgX (0.30 mmol), R^2 MgX (0.54 mmol), di-*tert*-butyldiaziridinone (**1**) (0.33 mmol), and CuBr·SMe_2 (0.0060 mmol) in THF (0.60 mL) at rt under Ar for 3 h unless otherwise stated. The left part of the newly formed C–C bond is from R^1 MgX, and the corresponding right part is from R^2 MgX. [b] Isolated yield of product **4** based on R^1 MgX. [c] The selectivity was determined by GC–MS analysis of the crude reaction mixture using hexadecane as internal standard. [d] Compound **4b** is not volatile enough to be detected by GC even at 300 °C. [e] The alkynylmagnesium halide (R^1 MgX) was prepared in situ from the corresponding alkyne (0.30 mmol) and R^2 MgX (0.30 mmol), and additional R^2 MgX (0.36 mmol) was used for the subsequent cross-coupling reaction. [f] The alkynylmagnesium halide (R^1 MgX) was prepared in situ from the corresponding alkyne (0.30 mmol) and R^2 MgX (0.30 mmol), and additional R^2 MgX (0.54 mmol) was used for the subsequent cross-coupling reaction. [g] The reaction was carried out on 10.0 mmol scale.

(**1**) to form four-membered Cu(III) species **A** and/or Cu(II) nitrogen radical **B**,[12b,c,15] which then undergoes transmetalations to give Cu(III) intermediate **D**. Upon reductive elimination, intermediate **D** is converted into coupling product **4** with the regeneration of the CuX catalyst. A radical mechanism for the coupling process cannot be ruled out at this moment.

In summary, we have developed a novel oxidative coupling reaction of Grignard reagents with copper catalysts using di-*tert*-butyldiaziridinone (**1**) as oxidant. A variety of aryl, alkynyl, and alkyl Grignard reagents can be efficiently coupled to give the corresponding homo- and cross-coupling products in good yields. The reaction proceeds at room temperature in short reaction time with low-loading cheap catalysts and is amenable to gram scale synthesis. In particular, this method is also effective for C(sp)–C(sp^3) bond formations. In addition, the current work provides new perspectives and mechanistic insights for the development of other reaction processes with diaziridinones.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, GC–MS data, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

†These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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