COMMUNICATION

Copper-catalyzed coupling reaction of unactivated secondary alkyl iodides with alkyl Grignard reagents in the presence of 1,3-butadiene as an effective additive[†]

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Cu-catalyzed cross-coupling of unactivated secondary alkyl iodides with alkyl Grignard reagents in the presence of 1,3-butadiene as a ligand precursor was developed. The use of 1,3-butadiene resulted in improved yields of alkyl–alkyl products with improved selectivities.

Transition-metal catalyzed cross-coupling reactions of organic halides with organometallic reagents are some of the most important C–C bond-forming reactions in organic synthesis.¹ Among the most challenging of these reactions is the use of unactivated alkyl halides as coupling electrophiles to form alkyl–alkyl coupled products, due in part to the fact that alkylmetal intermediates generated *in situ* in the catalytic cycle can undergo β -hydride elimination, as well as participate in other undesired reactions.² In the past decade, many new protocols have been developed to overcome these inherent difficulties in sp³–sp³ cross-coupling *via* the use of transition metal catalysts (such as Pd,³ Ni,⁴ Fe⁵), and a wide range of primary alkyl halides can now be successfully used, when suitable conditions are employed.²

Compared to primary alkyl halides, the utilization of secondary alkyl halides as coupling electrophiles is more interesting⁶ since these reactions could result in the formation of some useful synthetic precursors having tertiary carbon centers and stereogenic centers.⁷ This has been demonstrated by the pioneering work of Fu *et al.* in which the asymmetric catalysis of racemic activated and unactivated secondary alkyl halides was achieved.⁸ However, the coupling of unactivated secondary halides remains a difficult task and is less developed. Thus, only a few methods for the alkyl–alkyl coupling of unactivated secondary alkyl halides have been reported.^{6,9,10}

We previously reported on the development of efficient catalytic systems for cross-coupling reactions of alkyl halides with Grignard or organozinc reagents using Ni, Pd as well as Cu catalysts in the presence of π -carbon ligands, such as

1,3-butadiene,^{11c} tetraenes^{11e} or an alkyne.^{12d} These reactions proceed efficiently for a variety of primary alkyl halides, even alkyl chlorides and fluorides,¹² providing a convenient tool for the construction of carbon–carbon bonds. However, unactivated secondary alkyl halides continue to be impregnable targets for coupling by these methods.

In this communication, we wish to report on the copper(1) iodide catalyzed cross-coupling reaction of unactivated secondary alkyl iodides with alkyl Grignard reagents using 1,3-butadiene as an additive. We found that 1,3-butadiene showed remarkable effects in improving both the efficiency and selectivity of the reaction, resulting in the production of alkyl–alkyl coupled products in good to high yields.^{11,12} The copper-catalyzed coupling of unactivated primary alkyl halides with alkyl Grignards was developed by us^{11b,12a,b,d} and others.¹³ However, regarding unactivated secondary alkyl halides,¹⁴ only one report has been published concerning the coupling of unactivated secondary alkyl sulfonates and halides with alkyl Grignards catalyzed by a copper thiolate catalyst.^{14a} Quite recently, Liu *et al.* reported that a combination of TMEDA and LiOMe with CuI was effective for cross-coupling between secondary alkyl derivatives.^{14b}

When a catalytic amount of CuI was added to a solution of 4-phenylbutan-2-yl iodide (1a), n-BuMgCl (1.5 equiv.) and 1,3-butadiene (1 equiv.) in THF at -78 °C, followed by stirring at 0 °C for 4 h, the cross-coupled product 2a was obtained in 90% yield along with a small amount of the elimination product 3 (1%) and the reduction product 4(<1%) (Table 1, entry 1). In contrast, a similar reaction in the absence of 1,3-butadiene gave a mixture of 2a (56%), 3 (15%) and 4 (8%) (entry 2), clearly indicating that the presence of 1,3-butadiene is crucial for improving the yield and selectivity of the reaction. At lower concentration of 1,3butadiene (0.5 equiv.), the yield was slightly reduced (81%). Decreasing the catalyst CuI from 3 mol% to 1 mol% had no effect and a good yield of the product was also obtained (entry 3). We also examined other additives (see ESI⁺ for details). The use of isoprene gave 2a in 85% yield (entry 4), however, other dienes and alkynes^{11c} gave moderate yields of **2a**, accompanied by a significant amount of by-products 3 and 4 (entries 5-7).

We next examined the reactions of the secondary alkyl iodide **1a** with various Grignard reagents in the presence of CuI and 1,3-butadiene. A variety of RMgX reagents were successfully coupled with **1a** to give the corresponding alkyl–alkyl coupled

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Table 1 Cu-catalyzed cross-coupling of 1a with n-BuMgCl^a

Ph	1a + BuMgCl	2a	Ph Bu ⁺ Ph	3 +
Entry	Additive (1 equiv.)	$2a^{b}$ (%)	$3^{b,c}$ (%)	4^{b} (%)
1	1,3-Butadiene	90(82)	1	<1
2	None	56	15	8
3^d	1,3-Butadiene	89	1	<1
4	Isoprene	85	2	<1
5	1,3-Pentadiene	74	3	1
6 ^{<i>e</i>}	2,3-Dimethyl-1,3-butadiene	69	5	2
7	PhMe	69	12	6

^{*a*} See ESI for details. In each case, *ca.* 9–13% yield of *n*-octane resulting from homocoupling of *n*-BuMgCl was detected as the by-product. ^{*b*} GC yield based on **1a**. Isolated yield in parentheses. ^{*c*} Combined GC yields of the olefin by-products from **1a**. ^{*d*} 1 mol% CuI. ^{*e*} *ca*. 10% of **1a** was recovered.

products in good to high yields, as shown in Scheme 1. In addition to *n*-BuMgCl, the methyl Grignard reagent also gave a satisfactory yield of the product **2b**. When the reactions of allyl or pent-4-enyl Grignard reagents with **1a** were carried out, terminal alkenes **2e** and **2f** were formed in high yields, implying the potent usefulness of this method as a convenient tool for introducing an alkene functionality. The use of 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide gave a moderate yield of the corresponding coupling product **2g**. It is noteworthy that the sterically bulky iso-butyl- and neopentyl Grignard reagents also reacted smoothly with **1a**, giving the coupling products **2c** and **2d** in 82% and 79% yields, respectively. However, the isopropyl Grignard reagent gave a complex mixture.

Representative examples of various combinations of secondary alkyl iodides with Grignard reagents are shown in Table 2. Reactions of 2-iodooctane and 4-iodoheptane with *n*-BuMgCl both gave the expected coupling products in high yields (entries 2 and 3). A homoallyl iodide was also applicable to the reaction (entries 5 and 7). The iodocyclohexane reacted with the bulky neopentyl Grignard to give the coupled product in moderate yield (entry 4). The reaction also proceeded efficiently to give **2m** in 80% yield when a branched alkyl iodide was employed (entry 6). However, more sterically hindered 2,4-dimethylpentan-3-yl iodide gave poor yields of the coupled products (entries 9 and 10). The corresponding bromides, though more reactive than chlorides or tosylates,^{12d} resulted in no reaction.

As proposed earlier, this reaction appears to proceed by ionic mechanisms *via* the formation of magnesiocuprates from the Grignard reagent and copper catalyst, which then react with the alkyl iodide to give the cross-coupling product.¹⁵



Scheme 1 Cross-coupling of 1a with various RMgX.

 Table 2
 Cu-catalyzed cross-coupling of secondary alkyl iodides with alkyl Grignard reagents in the presence of 1,3-butadiene^a

$\stackrel{R^1}{>}_{R^2}$		1 mo ,3-butadi THF, 0	ol% Cul ene (1 equiv) <u></u> ⁰C, 4-6 h	$ \begin{array}{c} R^1 \\ $	
Entry	R ¹	\mathbf{R}^2	R ³ MgX	$\operatorname{Yield}^{b}(\%)$	
1	PhCH ₂ CH ₂	<i>n</i> -Pr	n-BuMgCl	2h , 85	
2	$n-C_6H_{13}$	Me	n-BuMgCl	2i , 87 ^c	
3	<i>n</i> -Pr	<i>n</i> -Pr	n-BuMgCl	2j , 81 ^c	
4	Cyclohexyl iodide		Neopentyl MgCl	2k , 65^c	
5	PhCH ₂ CH ₂	Allyl	EtMgBr	21 , 70	
6^d	PhCH ₂ CH ₂	<i>i</i> -Pr	n-BuMgCl	2m , 80	
7	PhCH ₂ CH ₂	Allyl	n-BuMgCl	2n , 89	
8	$n-C_6H_{13}$	Me	Allyl MgCl	20 , 93 ^c	
9	<i>i</i> -Pr	<i>i</i> -Pr	n-BuMgCl	2p , 42^c	
10^{d}	<i>i</i> -Pr	<i>i</i> -Pr	Neopentyl MgCl	2q , 17^c	
^{<i>i</i>} See ESI for details. ^{<i>b</i>} Isolated yield. ^{<i>c</i>} GC yield. ^{<i>d</i>} 3 mol% CuI.					

The function of 1,3-butadiene may be to stabilize the cuprate intermediates, thus preventing β-hydride elimination and reduction (hydrodehalogenation) reactions that could occur during the catalytic cycle.¹⁶ It has been proposed that cross-coupling reactions involving an alkyl iodide and an organometallic reagent may follow a radical pathway. For example, Oshima *et al.*^{9*j*,k,17} and Hu *et al.*^{9*g*} reported that the Co and Ni catalyzed coupling of alkyl iodides that contain an olefin functionality often produced cyclic products. They suggested that free alkyl radicals are readily formed from alkyl iodides, leading to the subsequent cyclization. However, in our case, the reaction of 1-phenyloct-7-en-3-yl iodide (1b) with MeMgCl gave the coupling product 2f exclusively in high yield and formation of a cyclopentane ring from a possible intramolecular radical cyclization was not detected (eqn (1)).¹⁷ This is in sharp contrast to the lithium cuprate mediated methylation of the haloalkyl olefins, where cyclization was the exclusive reaction.¹⁸ These data suggest that free radical species are not involved in our Cu-butadiene catalytic system.17-20



In a synthetic application of the present reaction, we attempted to prepare dienes and an enyne and the results are summarized in Scheme 2. Terminal dienes such as 1,6-, 1,8-, 1,10-, and 1,11-dienes were produced in high yields using the current method without any by-products arising from radical cyclization.²¹ In addition, an alkynylalkyl iodide was also coupled with allylmagnesium chloride to give the 1,6-enyne **2v** in moderate yield. When the formed dienes **2r** and **2s** were subjected to Ru-catalyzed metathesis, the corresponding 5- and 7-membered cycloalkenes were obtained in good yields (eqn (2)).



Scheme 2 Cross-coupling reaction for the synthesis of enynes and dienes.



In conclusion, the findings reported herein demonstrate that CuI, aided by 1,3-butadiene, catalyzes the cross-coupling of unactivated secondary alkyl iodides with a variety of alkyl Grignard reagents giving rise to alkyl–alkyl coupled products in good to high yields under mild conditions. The reaction is convenient and practical, and expensive noble metals or ligands are not required. The present catalytic system provides a useful method for the synthesis of 1,*n*-dienes or enynes.

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