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Copper catalyzed magnesium-Barbier reaction for γ-selective alkyl–allyl coupling

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Abstract—CuCN catalyzed alkyl–allyl coupling under magnesium-Barbier conditions occurs regioselectively and affords predominantly the γ-products in good to high yields. This one-pot CuCN catalyzed reaction utilising Mg, an alkyl halide and an allylic substrate in THF at room temperature provides an easy alternative to the classical CuCN catalyzed γ-allylation of alkyl Grignard reagents.

Transition metal catalyzed coupling of organometallic reagents with allylic electrophiles is a potentially useful method for the synthesis of new olefinic compounds.[1] Among various organometallic reagents and catalysts, copper catalyzed allylic substitution of Grignard reagents[2] and organozincs[3] constitute an important class of C–C coupling. Numerous important procedures have been reported for controlling the regiochemistry of the copper catalyzed allylation of alkyl Grignard reagents.[4] The process depends on the Grignard reagent, the allylic partner, the copper catalyst and additives as well as on the reaction conditions, that is, the rate of addition of the Grignard reagent, the solvent and the temperature. Recently, various catalytic procedures employing chiral ligands on copper have been developed for the enantioselective γ-substitution of Grignard reagents[5] and diorganozincs[6] with allylic substrates.

During the course of our studies on the copper catalyzed allylation of alkyl zinc reagents,[7] we also investigated the copper catalyzed magnesium-Barbier-type allylic coupling of alkyl Grignard reagents in order to compare it with classical coupling. In classical reactions, organometallic reagents are first prepared and then reacted with an electrophile. In the reactions run under Barbier conditions,[8,9] organometallic reagents are prepared in situ, that is, the metal is allowed to react with organyl halide and electrophile in one pot. Grignard[2c] and organozinc reagents[3b] generated in situ, reacted with various electrophiles such as carbonyl compounds, imines, sulphonyl halides and epoxides to form C–C bonds and also with electrophilic aminating reagents to form C–N bonds.[10] Magnesium and zinc have also been commonly used in Barbier reactions under aqueous conditions.

However, to the best of our knowledge, there are no reports on C–C coupling reactions carried out under non-aqueous magnesium-Barbier or zinc-Barbier conditions. In our initial studies, we observed that[7] the reaction of *n*-butyl bromide and *E*-crotyl chloride in the presence of magnesium and CuCN catalyst in THF gave the same regioselectivity as that obtained in the classical CuCN catalyzed coupling of *n*-butylmagnesium bromide with *E*-crotyl chloride (Scheme 1). We used CuCN as the Cu(I) catalyst since allylic chlorides have been reported to show a preference for γ-substitution in THF in the presence of CuCN.[4h,5a,c]

In the classical coupling (i), α- and γ-products, **4a** and **5a** were formed in a ratio of 13:87 and with a total yield of 93% in the presence of 20 mol % (optimized) CuCN. The one-pot Mg-mediated coupling of *n*-butyl bromide and *E*-crotyl chloride (ii) gave 86% total yield with an α:γ ratio of 10:90.[7] We also presented evidence for the in situ formation of *n*-butyl magnesium bromide as a Grignard reagent in the Mg-mediated *n*-butyl bromide–*E*-crotyl chloride coupling.[7] The only side product was found to be the corresponding alkyl–alkyl homocoupling product, that is, *n*-octane.

Keywords: Allylic coupling; Magnesium-Barbier coupling; In situ Grignard reagents; Barbier-type reaction; Copper catalysis.

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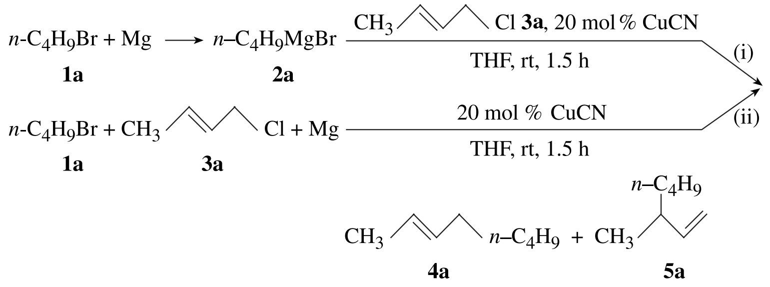


Total yield, %		4a : 5a	
(i)	(ii)	(i)	(ii)
93	86	13:87	10:90

Scheme 1. (i) CuCN catalyzed allylic substitution of *n*-butyl magnesium bromide with *E*-crotyl chloride and (ii) magnesium-Barbier-type CuCN catalyzed *n*-butyl bromide–*E*-crotyl chloride coupling.

It is remarkable that the regiochemical outcome of the copper catalyzed alkyl–allyl coupling can be controlled by preparing alkyl Grignard reagents under Barbier conditions. We therefore decided to study the synthetic potential of this reaction in more detail. In this Letter, we report our successful applications of magnesium-Barbier conditions for γ-selective allylic coupling of alkyl Grignard reagents.

For copper catalyzed allylic coupling of alkyl Grignard reagents, it is believed that the reaction conditions that favour the formation of an intermediate dialkylcuprate (fast addition of Grignard reagent, low temperature, low concentration of catalyst) give nonselective but mainly α-substitution, whereas the reaction conditions favouring the formation of an intermediate mono alkylcopper (slow addition of Grignard reagent, increased temperature and increased concentration of catalyst) lead to γ-substitution.[4h,5c] Hence, we first performed optimization experiments and studied the effect of the following parameters in detail:

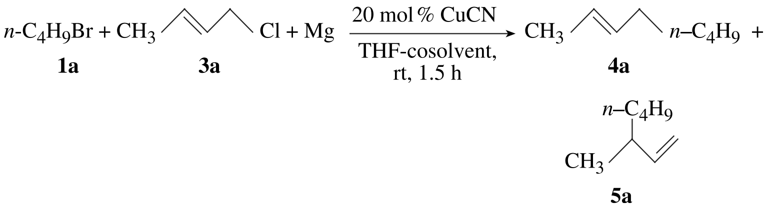
(i) The type of addition of the coupling partners: two different addition methods were investigated. (a) Solutions of *n*-butyl bromide and *E*-crotyl chloride in THF were added separately to Mg and then the copper catalyst was added, or (b) THF solutions of the coupling partners were added to Mg and the copper catalyst. The addition methods gave similar results, however, the second method was used for the one-pot coupling.

(ii) The type and amount of catalyst: a detailed investigation of the copper source on the outcome of the reaction was not carried out. The amount of CuCN catalyst was already optimized at 20 mol % for the highest γ-regioselectivity in THF.[7] The use of 10 mol % CuCN did not change the yield, but decreased the regioselectivity slightly. The use of 20 mol % CuI as catalyst resulted in a lower yield and regioselectivity.

(iii) The addition rate of the coupling partners: this was optimized at 0.3–0.5 mL min^{-1} to afford the highest yield and regioselectivity and suppress alkyl–alkyl coupling.

(iv) The type of solvent: a short screen of coordinating solvents as co-solvents in THF showed that THF alone was the best solvent (Table 1). NMP has previously been successfully used in the copper

Table 1. Effect of the co-solvent on the CuCN catalyzed magnesium-Barbier coupling of *n*-butyl bromide with *E*-crotyl chloride in THF



Entry	Co-solvent[a]	Total yield[b] (%)	**4a**:**5a**[c]
1	—	86	10:90
2	NMP[d]	72	8:92
3	NMP[e]	35	7:93
4	DMPU[d]	71	4:96
5	DMPU[e]	26	11:89
6	TMEDA[e]	75	5:95
7	HMPA[e]	63	6:94

[a] Molar ratio of **1a**:**3a**: Mg was 20 mmol:10 mmol:24 mmol in 10 mL of THF—co-solvent.

[b] GC yield of product mixture **4a** and **5a**.

[c] Determined by GC.

[d] Molar ratio of co-solvent:**1a** was 1:2.

[e] Molar ratio of co-solvent:**1a** was 2:1.

catalyzed alkylation of alkyl Grignard reagents in THF.[11] However, in the Barbier-type alkylation of alkyl Grignard reagents, the use of 0.5 equiv of NMP based on *n*-butyl bromide did not change the regioselectivity, but decreased the yield (entry 2); in the presence of 2 equiv of NMP, the yield was further decreased (entry 3). Similar results were observed for the reactions in the presence of 0.5 equiv and 2 equiv of DMPU (entries 3 and 4). TMEDA and HMPA, which are commonly used solvents for C–C coupling reactions of Grignard reagents, did not significantly improve the regioselectivity of the magnesium-Barbier alkyl–allyl coupling, but they did lead to a decrease in the yield.

Having confirmed the optimized conditions, we screened several alkyl bromides, benzyl bromide and homobenzyl bromide in the coupling reaction with various allylic substrates under magnesium-Barbier conditions. The results are summarized in Table 2. The data are averages of at least two independent experiments. The products were fully characterized by ^{1}H NMR analysis and the α:γ ratios of the product mixtures were determined by ^{1}H NMR analysis and also by GC analysis. From these results, we can draw the following conclusions:

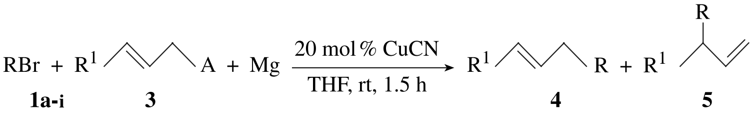
(i) In situ allylation of primary and *sec*-alkyl Grignard reagents occurs regioselectively and affords γ-allylation exclusively or predominantly. The regioselectivities in the alkyl-*E*-crotyl couplings (entries 1–7) were significantly higher compared to those observed for alkyl–*E*-cinnamyl couplings (entries 10–13). Benzyl-*E*-crotyl coupling gave acceptable regioselectivity (entry 8); however homobenzyl–*E*-crotyl coupling gave only the γ-product (entry 9).

(ii) Good to high yields of cross coupling products were obtained in all cases, except with in situ prepared ethyl Grignard and *t*-butyl Grignard reagents (data not included in Table 2), which gave lower yields due to losses of volatile products during isolation and purification. The yields obtained with *E*-cinnamyl substrates (entries 10–13) were somewhat higher than those obtained with *E*-crotyl chloride (entries 1–9). The nature of the leaving group on the cinnamyl substrate, that is, chloride or acetate (entries 10 and 11) did not influence the yield significantly, however, the presence of chloride led to decreased regioselectivity.

(iii) Alkenes could be prepared in good yields by the CuCN catalyzed one-pot, three-component coupling of Mg, a primary or *sec*-alkyl halide and an allylic halide in THF at room temperature. The reactions were clean and complete within 1.5 h.[12]

In conclusion, we have demonstrated that CuCN catalyzed alkyl–allyl coupling can be carried out under magnesium-Barbier conditions with comparable yields and regioselectivies to classical CuCN catalyzed γ-allylation of alkyl Grignard reagents. This work is the first successful magnesium-Barbier reaction for C–C coupling under non-radical conditions. Further studies will focus on detailed screening of organyl halides, copper salts and solvents as well as additives to develop new copper catalyzed magnesium-Barbier and also zinc-Barbier C–C coupling reactions.

Table 2. CuCN catalyzed magnesium-Barbier coupling of alkyl bromides with allylic substrates in THF[a]



3a R^1: CH_3, A:Cl
3b R^1: C_6H_5, A:Cl
3c R^1: C_6H_5, A:OAc

Entry	Allylic substrate	R	Total yield[c] (%)	**4**:**5** [d]
1	**3a**	C_2H_5 **a**	33	0:100
2	**3a**	*n*-C_4H_9 **b**	86	10:90 (13:87)
3	**3a**	*sec*-C_4H_9 **c**	60	14:86 (14:86)
4	**3a**	*neo*-C_5H_{11} **d**	61	(27:73)
5	**3a**	*n*-C_6H_{13} **e**	75	12:88 (14:86)
6	**3a**	*n*-C_7H_{15} **f**	67	9:91 (8:92)
7	**3a**	*cyclo*-C_6H_{11} **g**	62	5:95 (6:94)
8	**3a**	$C_6H_5CH_2$ **h**[b]	73	32:68 (21:79)
9	**3a**	$C_6H_5CH_2CH_2$ **i**	95	0:100 (0:100)
10	**3b**	*n*-C_4H_9 **b**	91	33:67 (32:68)
11	**3c**	*n*-C_4H_9 **b**	90	27:73 (19:81)
12	**3c**	*n*-C_7H_{15} **f**	86	20:80 (21:79)
13	**3c**	*cyclo*-C_6H_{11} **g**	80	24:76 (25:75)

[a] Molar ratio of **1**:**3a** (**3b** or **3c**):Mg was 2:1:2.4.

[b] Isolated yield of product mixture **4** and **5**.

[c] Prepared in Et_2O.

[d] Determined by GC. Ratios determined by 500 MHz ^{1}H NMR analysis are given in parentheses.

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12. *Typical procedure for magnesium-Barbier alkyl–allyl coupling*: All reactions were carried out under a positive pressure of nitrogen,[13] using freshly distilled THF over sodium benzophenone dianion under anhydrous conditions. Alkyl halides **1a**–**i** and allylic compounds **3a**–**c** were obtained commercially and purified using literature procedures. Mg turnings were used without further purification. CuCN was purified according to the published procedure.[14] A three-necked flame-dried flask equipped with a reflux condenser, two dropping funnels and a magnetic stirrer was charged with Mg (24 mmol, 0.580 g) and CuCN (2 mmol, 0.180 g) at room temperature. Solutions of an alkyl bromide (20 mmol) in THF (5 mL) and an allylic halide (10 mmol) in THF (5 mL) were added separately to the stirred mixture at room temperature. The reaction was started by adding a few drops of alkyl bromide. The addition rate of the solutions was maintained at 0.3–0.5 mL min^{-1} and the reaction mixture was stirred at room temperature for 1.5 h. The aqueous layer was extracted with ether. The combined organic solutions were concentrated by rotary evaporation and subjected to silica gel column chromatography with petroleum ether as eluent to give a colourless liquid as a mixture of α- and γ-products. The α:γ ratio was determined by 500 MHz ^{1}H NMR analysis and also by GC analysis on a DB-1 glass capillary column packed with dimethylpolysiloxane. ^{1}H NMR spectroscopic data for the coupling products of a selected reaction (**1f**–**3a** coupling, Table 2, entry 6): (CDCl$_3$), δ: Compound **4**: 0.90 (t, 3H, $J = 7$ Hz), 1.29 (m, 12H), 1.64 (d, 3H, $J = 7$ Hz), 1.86 (q, 2H, $J = 7$ Hz), 5.40 (m, 2H). Compound **5**: 0.88 (t, 3H, $J = 7$ Hz), 0.98 (d, 3H, $J = 7$ Hz), 1.29 (m, 12H), 2.10 (m, 1H) 4.90 (dd, 1H, $J = 8$ Hz, 2 Hz), 4.95 (dd, 1H, $J = 17$ Hz, 2 Hz), 5.70 (ddd, 1H, $J = 17$ Hz, 8 Hz, 6 Hz).
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