

### Nickel-Catalyzed Kumada Coupling of Benzyl Chlorides and Vinylogous Derivatives

Rita Soler-Yanes,<sup>[a]</sup> Manuel Guisán-Ceinos,<sup>[a]</sup> Elena Buñuel,<sup>[a]</sup> and Diego J. Cárdenas\*<sup>[a]</sup>

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Conditions for the fast Ni-catalyzed Kumada-type cross-coupling of functionalized benzyl and allyl chlorides with alkylmagnesium reagents were discovered. The use of Ni(acac)<sub>2</sub>– TMEDA (acac = acetylacetonate, TMEDA = N, N, N', N'-tetramethyl-1,2-ethylenediamine) allows the presence of reac-

Introduction

The success of cross-coupling reactions as synthetic tools has been based on the use of reagents with low basicity and nucleophilicity, such as organozinc, boron, tin, or silicon compounds, which allows the formation of C-C bonds in the presence of functional groups.<sup>[1]</sup> Preparation of maingroup organometallic reagents usually employs Mg (or Li) derivatives as starting materials. Therefore, it is desirable to find novel catalytic systems able to promote the fast coupling of Grignard reagents so that functional groups may be present, as this would avoid additional steps for the preparation of the nucleophilic partners. A major challenge is to be able to use functionalized halides for the direct preparation of the corresponding coupling compounds, that is, to provide conditions for the catalyzed cross-coupling of functionalized reagents. Ni catalysis has demonstrated its utility in the field of alkyl-alkyl cross-coupling reactions.<sup>[2]</sup> In addition, the use of Ni catalysts in Suzuki,<sup>[3]</sup> Negishi,<sup>[4]</sup> and Kumada-type<sup>[5,6]</sup> couplings has uncovered novel mechanisms.<sup>[4i,7]</sup> Most cases involve radical pathways, in contrast to the well-established mechanism for Pd-catalyzed processes. Kumada-type couplings have experienced a renaissance owing to the discovery of methods for the preparation of functionalized Grignard reagents<sup>[8]</sup> and to the discovery of active catalytic systems able to perform fast reactions of functionalized reagents at low temperatures. We planned to develop conditions for the efficient cross-coupling of benzyl chlorides with alkylmagnesium reagents. Benzyl bromides have been previously used in Ni-catalyzed stereoconvergent Negishi couplings.<sup>[9]</sup> The use of more con-

E-mail: diego.cardenas@uam.es http://www.uam.es/organometalica tive functional groups on the electrophile. On the other hand, the use of diallyl ether was shown to provide fast coupling at low temperature with a low catalyst loading. The reaction seems to follow a radical pathway.

venient chlorides,<sup>[10]</sup> as well as avoiding the preparation of organozinc nucleophiles from Grignard reagents, would have some advantages.

### **Results and Discussion**

We started our research by studying the coupling of p-(methoxycarbonyl)benzyl chloride (1a) with Mg reagent 2a with a variety of Ni salts, ligands, and reaction conditions (Table 1). The goal was to obtain high yields of coupled product in the presence of the ester group. This study was based on our recently reported general Ni-catalyzed Kumada coupling of alkyl halides.<sup>[6]</sup> Thus, the model reaction was run in THF in the presence of the Ni source (10 mol-%) by using 1.5 equiv. of the organomagnesium reagent, which was slowly added over 30 min. Nitrogen-based ligands and the N-heterocyclic carbene 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) were effective, whereas 1,2-bis(diphenylphosphino)ethane (dppe) gave no product at all (Table 1, entry 4). Bidentate 2,2'-bipyridine (bpy; Table 1, entry 1) and tridentate 2,6-bis(4-sec-butyl-4,5-dihydrooxazol-2-yl)pyridine (sBuPybox; Table 1, entry 2) gave low yields. The best results were obtained with N, N, N', N'tetramethyl-1,2-ethylenediamine (TMEDA) as the ligand (Table 1, entries 5-10). Among the different Ni salts and complex precursors,  $Ni(acac)_2$  (acac = acetylacetonate) afforded the most satisfactory result (76% yield; Table 1, entry 5). By using this optimized catalytic system, we observed that the yields were lower if the reaction was performed at either 60 °C (43%, as determined by <sup>1</sup>H NMR spectroscopy) or 0 °C (39%, as determined by <sup>1</sup>H NMR spectroscopy, along with 19% unreacted 1a). The use of either 2 or 1.2 equiv. of nucleophile provided slightly lower yields (63%, as determined by <sup>1</sup>H NMR spectroscopy, and isolated in 71% yield, respectively). Fast addition of the nucleophile also gave poorer results (70% yield).

<sup>[</sup>a] Department of Organic Chemistry, Facultad de Ciencias, Universidad Autónoma de Madrid, Campus de Cantoblanco, 28049 Madrid, Spain

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Table 1. Optimization of ligand and Ni source.[a]



[a] Nucleophile was slowly added over 30 min. py = pyridine. [b] Determined by <sup>1</sup>H NMR spectroscopy by using (E,E)-1,4-diphenyl-1,3-butadiene as an internal standard. [c] Product was isolated in 76% yield.

The reaction could be extended to simple benzyl chloride (1b) and to *p*-cyano (1c), *m*-methoxy (1d), and *p*-methoxy (1e) derivatives in fair to good yields (Scheme 1). Higher yields could not be obtained, as homocoupling of the electrophile was observed to some extent. Thus, for example, in the case of 1e, 1,2-bis(*p*-methoxyphenyl)ethane was isolated in 16% yield. The reaction scope suggests that good results can be obtained for compounds containing both electronrich (1c: *m*-MeO; 1e: *p*-MeO) and electron-deficient (1a: *p*-CO<sub>2</sub>Me, 1d: *p*-CN) rings. Regarding the nucleophile, the presence of the acetal is not necessary for the reaction to



Scheme 1. Reaction scope for the Ni-catalyzed reaction of benzyl chlorides with alkyl Grignard reagents (FG = functional group).

occur. Thus, phenethylmagnesium chloride (2b) and secondary cyclopropylmagnesium bromide (2c) afforded the expected cross-coupling compounds. In our previous work on Kumada alkyl-alkyl Ni-catalyzed cross-coupling,<sup>[6]</sup> we observed a dependence of the reaction outcome on the nature of the nucleophile. Thus, Grignard reagents containing ketal groups were coupled more efficiently than simple alkyl derivatives. This is probably due to coordination of the acetal oxygen atoms to the intermediate Ni complex, which inhibits undesired  $\beta$ -elimination reactions by hampering the formation of the vacant coordination sites necessary for this process. For simpler alkyl nucleophiles, the yields were usually lower, as observed for compound 7. We found a similar behavior in a related Fe-catalyzed alkyl-alkyl coupling reaction, in which the presence of the acetal proved to be indispensable for the success of the reaction.<sup>[11]</sup>

We tried to find specific conditions for the high-yield coupling of model BuMgCl and **1e** to widen the reaction scope in both the electrophile and the nucleophile and to try to diminish the homocoupling products.

After much experimentation, we were delighted to discover that the use of diallyl ether (DAE) as an additive was crucial to promote the efficient coupling of *p*-(methoxy)benzyl chloride (**1e**) with BuMgCl (**2d**) even at -30 °C. Table 2 shows the optimization experiments. In contrast to previous reports,<sup>[12]</sup> the addition of a 1,3-diene (e.g., 2,3dimethyl-1,3-butadiene) did not improve the results over those obtained in the absence of Ni (Table 2, entries 1 and 2). Instead, a mixture of TMEDA (10 mol-%) and DAE (100 mol-%) increased the yield up to 65% if the reaction was performed at room temperature and up to 85% at 0 °C (Table 2, entries 3 and 4). Moreover, the use of only DAE

Table 2. Optimization of the reaction conditions.

MeO´	1e 0.2 mmol	+ BuMgBr 2d additive 0.4 mmol THF 2 M, added dropwise	MeO <sup></sup>	9d
Entry	Ni(acac) <sub>2</sub> [mol-%]	Additive <sup>[b]</sup> (mol-%)	<i>Т</i> [°С]	Yield <sup>[a]</sup> [%]
1	5	none	-30	50
2	5	$DMB^{[c]}$ (100)	0	50
3	5	DAE (100)/TMEDA (10)	23	65
4	5	DAE (100)/TMEDA (10)	0	85
5	5	DAE (100)	0	93
6	5	DAE (100)	-30	99 (90) <sup>[d]</sup>
7	5	DAE (100)	-30	99 <sup>[e]</sup>
8	5	DAE (20)	-30	96
9	5	DAE (10)	-30	90
10	5	DAE (5)	-30	69
11	2.5	DAE (50)	-30	99
12	2.5	DAE (10)	-30	99
13	1	DAE (20)	0	99 (91) <sup>[d]</sup>
14	1	DAE (4)	-30	92

[a] GC–MS yield determined by using dodecane as an internal standard. [b] DAE = diallyl ether. [c] DMB = 2,3-dimethyl-1,3-butadiene. [d] Yield of the isolated product is given in parentheses. [e] For both fast (over about 1 s) and slow (over 30 min) additions of the organomagnesium solution.

without an additional ligand increased the rate of the reaction, which could be performed at -30 °C, and this led to a quantitative yield, regardless of the addition rate of the nucleophile (Table 2, entries 5–7). The amount of both the Ni precursor and DAE could be reduced to 1 and 20 mol-%, respectively, and in that case the product was obtained quantitatively at 0 °C (Table 2, entry 13). With just 4 mol-% DAE, the process delivered the product in 92% yield at -30 °C (Table 2, entry 14). Therefore, this system works perfectly well at low temperature with a low catalyst loading to provide the cross-coupled product without any  $\beta$ -elimination or homocoupling of the electrophile.

The reaction of **1e** also worked for other alkyl Grignard reagents, and the expected products (i.e., **9a**, **9b**) were provided in high yields (Scheme 2).



Scheme 2. Ni-catalyzed couplings of benzyl chloride (1e) with different alkylmagnesium reagents in the presence of diallyl ether (yields of the isolated products are given).

These reaction conditions could also be applied to cinnamyl chlorides.<sup>[13]</sup> Thus, reaction of **10a** and **12a** afforded the corresponding coupling products in good yields by reaction with **2a** and **2b**, respectively (Scheme 3). Products from secondary allyl chlorides **10b** and **12b** could not be obtained. Another limitation of these reactions conditions is that coupling derivatives from **1a** and **1c** with **2a** could also not be obtained.<sup>[14]</sup>

In our previous studies on Ni-catalyzed Negishi alkylalkyl couplings, we discovered that the addition of 2,2,6,6tetramethylpiperidin-1-oxyl (TEMPO) promoted C–O coupling of the nucleophile with this radical species as the major product, which inhibited the desired reaction. In con-



trast, if the reaction of **1e** with **2a** was performed with the Ni/DAE system in the presence of TEMPO, we observed a somewhat lower but still high yield of **9a** (84%, Scheme 4), along with a small amount of product resulting from homocoupling of the electrophile (i.e., product **15**, 16%).



Scheme 4. Ni-catalyzed coupling reaction in the presence of TEMPO.

The corresponding C–O coupling product involving the fragment coming from the Grignard reagent (i.e., product 14, Scheme 4) was obtained in 39% yield (based on the amount of TEMPO). This product is proposed to form from reaction of an alkyl-Ni<sup>1</sup> intermediate with TEMPO, which suggests the involvement of radical Ni complexes in the reaction pathway.<sup>[4h]</sup> Ni-catalyzed cross-coupling reactions of alkyl halides have been proposed to occur by initial formation of Ni<sup>I</sup> complexes from the precursors.<sup>[7]</sup> A plausible catalytic cycle that may be operating also in this case is shown in Scheme 5. After formation of Ni<sup>I</sup> halide A,<sup>[7b]</sup> fast transmetalation with the Grignard reagent leads to key Ni<sup>I</sup>alkyl complex B. This kind of complex has been demonstrated to promote homolytic cleavage of carbon-halogen bonds to give Ni<sup>II</sup>-X complex C and a carbon radical. Subsequent coordination of this radical affords intermediate diorgano-Ni<sup>III</sup> D, which evolves through C-C reductive elimination to the final product. Given that coordination of the radical to Ni<sup>II</sup> has been calculated to proceed with a moderate activation energy, homocoupling of radicals may be competitive, provided that they leave the solvent cage.<sup>[6]</sup>

To reinforce to this hypothesis, we subjected benzyl mesylate to the reaction conditions. The reaction failed, which is in accord with homolytic activation of the electrophile, as this is hampered for mesylates. Formation of both **9a** and



Scheme 3. Ni-catalyzed coupling of cinnamyl chlorides in the presence of diallyl ether as an additive.

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Scheme 5. Plausible reaction pathway.

14 (Scheme 4) indicates that they are formed in competitive pathways that do not have very different reaction rates. This may be a consequence of the fact that the reactivity of benzyl halides is higher than that of simple alkyl derivatives, for which addition of TEMPO may inhibit the C–C cross-coupling, as shown in our previous studies.<sup>[4h]</sup> The absence of coupling of TEMPO with the electrophile points to the fast formation of a Ni<sup>III</sup> intermediate by ready coordination of the radical to **C**.

#### Conclusions

In conclusion, we found conditions for the fast Ni-catalyzed cross-coupling reactions of benzyl chlorides with alkylmagnesium reagents. In the presence of TMEDA, the reaction tolerates several functional groups. Diallyl ether was proven to confer special properties on the Ni complexes that boosted the reaction rate and led to quantitative transformations by using a low catalyst loading at -30 °C for substrates containing donating groups. This system did, however, fail for electron-deficient substrates. These transformations avoid the use of bromides and iodides and show great potential applicability.

#### **Experimental Section**

Representative Procedure for the Cross-Coupling Reaction in the Presence of Diallyl Ether: A vial was charged with Ni(acac)<sub>2</sub> (5.2 mg, 0.02 mmol), the corresponding benzyl chloride (0.41 mmol), and a stir bar in air. The vial was sealed with a septum and dried under vacuum and backfilled with Ar. Then, dry THF (2 mL) and diallyl ether (50  $\mu$ L, 0.406 mmol) were added. The resulting mixture was stirred at 23 °C for 5 min and then cooled in an ice bath. A solution of alkylmagnesium halide in THF (0.81 mmol) was added dropwise at 0 °C. During the addition the solution turned orange. After the addition of the Grignard reagent, the mixture was stirred for 10 min. The resulting yellow solution was quenched with a saturated aqueous NH<sub>4</sub>Cl solution. The aqueous layer was extracted several times with ethyl acetate, and the combined organic layer was dried with MgSO<sub>4</sub>. The solvent was

evaporated under vacuum, and the product was purified by column chromatography.

**Supporting Information** (see footnote on the first page of this article): Full experimental details characterization data, and copies of the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of all key intermediates and final products.

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