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# Copper-catalyzed Cross-Coupling Between Alkyl (Pseudo)Halides and Bicyclopentyl Grignard Reagents

Claire Andersen,<sup>[a]</sup> Vincent Ferey,<sup>[b]</sup> Marc Daumas,<sup>[c]</sup> Patrick Bernardelli,<sup>[d]</sup> Amandine Guérinot,\*<sup>[a]</sup> Janine Cossy\*<sup>[a]</sup>

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Supporting Information Placeholder



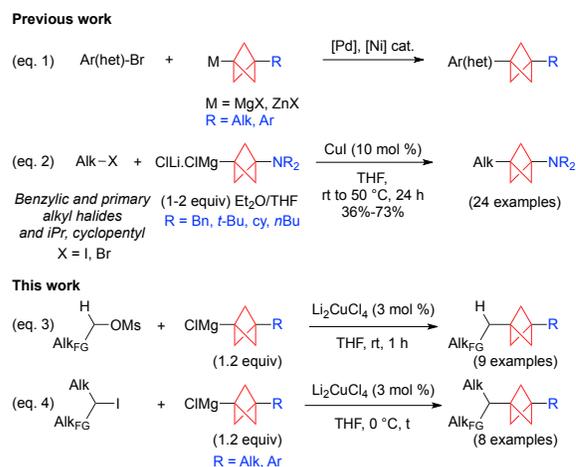
**ABSTRACT:** The development of a copper-catalyzed cross-coupling between primary and secondary (pseudo)halides and bicyclopentyl Grignard reagents is reported. Highly strained bicyclopentanes can be cross-coupled with a large panel of primary alkyl mesylates and secondary alkyl iodides. The catalytic system is simple and cheap, and the reaction is general and chemoselective.

Aryl substituents are ubiquitous in bioactive molecules and represent the most frequently displayed aromatic group in FDA-approved drugs.<sup>1</sup> However, several statistical studies highlighted an existing correlation between the high number of aryl moieties in a molecule and bioavailability and toxicity problems.<sup>2</sup> Indeed, aryl substituents can favor non-specific binding with off-target proteins increasing the risk of side-effects. In addition, they confer to the products poor physico-chemical properties such as high lipophilicity and low aqueous solubility. All these drawbacks brought together reduce the chance for a drug candidate to be launched on the market. In front of these difficulties, some strategies have been considered by medicinal chemists, one of which consisting of the replacement of planar aryl groups by three-dimensional cyclic rings incorporating sp<sup>3</sup> carbons.<sup>3</sup> Among the bioisosteres of phenyl groups, BiCyclo[1.1.1]Pentane (BCP) appeared to be a promising bioisostere to replace 1,4-disubstituted phenyls, allowing to place the substituents in a similar 180° dihedral angle.<sup>4</sup> Several recent studies showed that BCP advantageously replace 1,4-disubstituted phenyl groups improving the physico-chemical profile of bioactive molecules without affecting their activity.<sup>5</sup>

Despite the success of BCP, as bioisosteres of phenyls, their introduction in complex molecular structures remains a synthetic challenge. Most of the syntheses start with the ring-opening of [1.1.1]propellane with concomitant introduction of functional groups on the BCP cycle.<sup>6</sup> The targeted molecules are then constructed in a linear fashion from these building blocks resulting in quite long and non-convergent syntheses. In this context, a method that would be based on a late-stage introduction of the BCP on complex molecular architectures would be highly valuable.<sup>7</sup> Cross-couplings between a (pseudo)halide and an organometallic are considered as a powerful strategy to realize late functionalizations of complex molecules.

In the literature, only few examples of cross-couplings, involving bicyclopentyl organometallics, have been reported. In the early 2000's, Pd- and Ni-catalyzed cross-couplings between aryl halides and bicyclopentyl Grignard or organozinc reagents were described (Scheme 1, eq 1).<sup>8</sup>

## Scheme 1. Cross-couplings with BCP organometallics.

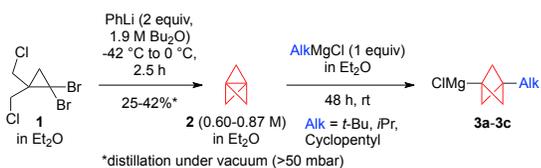


Only very recently, amino-bicyclopentyl Grignard reagents have been used in a copper-catalyzed cross-coupling with activated and non-activated primary alkyl iodides or bromides. However, only two examples with non-functionalized secondary iodides were described (Scheme 1, eq 2).<sup>9,10,11,12</sup> Intrigued by the very few examples of bicyclopentyl organometallic alkylations described in the literature and with the objective of broadening the scope of these reactions, we decided to investigate the coupling between BCP Grignard reagents and alkyl (pseudo)halides. Herein, we would like to disclose an efficient, general and simple copper-catalyzed alkyla-

tion of BCP Grignard reagents by functionalized primary mesylates and secondary iodides (Scheme 1, eq 3-4).

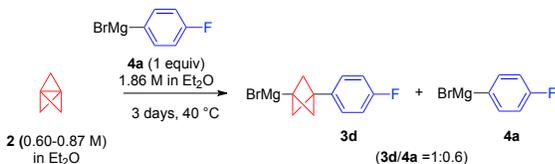
BCP Grignard reagents substituted by an alkyl substituent (*t*-Bu, *i*Pr, cyclopentyl) at C3 were prepared in two steps from the commercially available tetrahalogeno-cyclopropane **1**.<sup>13</sup> Alkyl Grignard reagents were reacting smoothly with the intermediate [1.1.1]propellane **2** under mild conditions (rt, 48 h) to give the corresponding BCP Grignard reagents (Scheme 2).

### Scheme 2. Synthesis of BCP Grignard reagents substituted by an alkyl group at C3.



By contrast, the addition of aryl Grignard reagents on **2** was sluggish and longer reaction times (3 days) as well as higher temperature (40 °C) were required. For instance, when [1.1.1]propellane **2** was reacted with *p*-fluorophenylmagnesium bromide, the desired BCP Grignard reagent was obtained as a mixture with the unreacted aryl Grignard reagent in a 1:0.6 ratio (Scheme 3).<sup>14,15</sup>

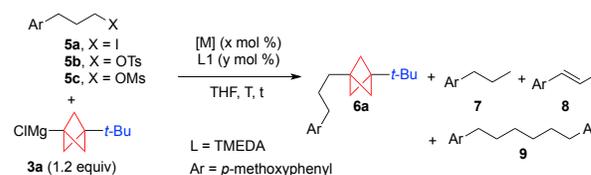
### Scheme 3. Synthesis of BCP Grignard reagents substituted by an aryl group at C3.



To identify a catalytic system able to promote the alkylation of a BCP Grignard reagent, the reaction between the primary alkyl iodide **5a** and the BCP Grignard reagent, substituted by a *t*-Bu group at C3, **3a**, was first examined. Based on our previous results on the cross-coupling between alkyl iodides and cyclopropyl Grignard reagents, the use of a cobalt catalyst, Co(acac)<sub>2</sub>, associated to *N,N,N',N'*-tetramethylethylenediamine (L = TMEDA), was first selected.<sup>16</sup> Unfortunately, under these conditions, no conversion of the alkyl iodide **5a** was observed after 1 h at 0 °C (Table 1, entry 1). To ensure full conversion of **5a**, the reaction time was increased to 16 h and the temperature was raised to 50 °C. However, the coupling product **6a** was not detected and the dehalogenated product **7** was predominantly formed alongside some elimination and homo-coupling products **8** and **9** (Table 1, entry 2). Since the use of Co(acac)<sub>2</sub> seemed to be non-productive to form the desired coupling product, a test on iodide **5a** was performed with another abundant, sustainable and eco-friendly metal salt, CuCl. Pleasingly, with 6 mol % of CuCl, in the absence of any ligands or additives, the coupling product **6a** was exclusively formed and isolated with a yield of 88% after only 30 min at rt (Table 1, entry 3). Starting from the more accessible tosylate **5b** resulted in the formation of **6a** with an excellent yield of 99% (Table 1, entry 4). As CuCl is insoluble in most organic solvents, the use of a commercially available Li<sub>2</sub>CuCl<sub>4</sub> solution (1 M in THF) was considered advantageous from a practical point of view. Using Li<sub>2</sub>CuCl<sub>4</sub> (6 mol %), an excellent yield of 93% in the coupling product **6a** was obtained (Table 1, entry 5). As mesylates are more atom economical than tosylates

and easily synthesized from alcohols, mesylate **5c** was synthesized and involved in the coupling reaction with the BCP Grignard reagent in the presence of Li<sub>2</sub>CuCl<sub>4</sub> (6 mol %). The coupling product **6a** was then isolated with a similar yield than the one obtained with the tosylate (94%) (Table 1, entry 6). The catalytic charge of Li<sub>2</sub>CuCl<sub>4</sub> can be decreased to 3 mol % without affecting the yield of **6a** (93%) (Table 1, entry 7) and the reaction was successfully carried out on a 2 mmol scale of mesylate **5c**. However, using only 1 mol % of Li<sub>2</sub>CuCl<sub>4</sub> afforded the coupling product **6a** with a slight decrease in the yield (87%) (Table 1, entry 8). To explore the scope of the reaction, the conditions previously developed were thus selected (3 mol % of Li<sub>2</sub>CuCl<sub>4</sub>, Table 1, entry 7).<sup>17</sup>

**Table 1. Optimization of the reaction conditions with primary alkyl (pseudo)halides.**



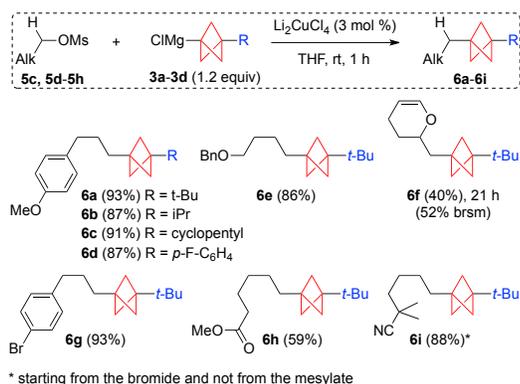
| Entry            | X   | [M] (mol %)                           | L (mol %) | T °C | t      | <b>6a</b> (yield) <sup>[a]</sup> |
|------------------|-----|---------------------------------------|-----------|------|--------|----------------------------------|
| 1 <sup>[b]</sup> | I   | Co(acac) <sub>2</sub> (3.5)           | L (100)   | 0    | 1 h    | — <sup>[c]</sup>                 |
| 2                | I   | Co(acac) <sub>2</sub> (3.5)           | L (100)   | 50   | 16 h   | — <sup>[d]</sup>                 |
| 3                | I   | CuCl (6)                              | —         | rt   | 30 min | 88                               |
| 4                | OTs | CuCl (6)                              | —         | rt   | 30 min | 99                               |
| 5                | OTs | Li <sub>2</sub> CuCl <sub>4</sub> (6) | —         | rt   | 30 min | 93                               |
| 6                | OMs | Li <sub>2</sub> CuCl <sub>4</sub> (6) | —         | rt   | 30 min | 94                               |
| 7 <sup>[e]</sup> | OMs | Li <sub>2</sub> CuCl <sub>4</sub> (3) | —         | rt   | 30 min | 93                               |
| 8                | OMs | Li <sub>2</sub> CuCl <sub>4</sub> (1) | —         | rt   | 30 min | 87                               |

[a] Yields obtained after flash column chromatography. [b] Slow addition of the Grignard reagent (0.52 mmol·h<sup>-1</sup>). [c] Unreactive **5a** was recovered. [d] **7** was the major product, **8** was present as well as traces of **9**. [e] When the reaction was run on 2 mmol scale (489 mg of **5c**) using a similar procedure, **6a** was isolated in 96% yield (525 mg).

With the optimized conditions in hand, the scope of the reaction was examined, and a range of primary mesylates was evaluated with different BCP Grignard reagents substituted at C3. All of the synthesized BCP Grignard reagents reacted smoothly with the primary mesylate **5c** affording the corresponding coupling products with yields around 90%.<sup>18</sup> The presence of a protected alcohol such as the benzyl ether present in **5e** was well tolerated, and the corresponding BCP product **6e** was formed in good yield (86%). The presence of a dihydropyran in the  $\alpha$  position of the mesylate seems to be detrimental to its conversion since, after 21 h, the full conversion of the mesylate was not observed and the coupling product **6f** was isolated with a moderate yield of 40% (52% based on the recovered starting material). It is hypothesized that the oxygen atom

of the dihydropyran, in conjunction with the oxygens of the mesylate, could coordinate the copper salt which would be detrimental to the reaction. When an alkyl mesylate bearing an aryl bromide was involved in the cross-coupling, a selective introduction of the BCP group on the alkyl chain was observed and **6g** was isolated in 93% yield. Pleasingly, electrophilic moieties were compatible with the reaction conditions as **6h**, containing an ester group, was obtained in 59% yield<sup>19</sup> while **6i** possessing a nitrile group was isolated in 88% yield (Scheme 4).<sup>20</sup>

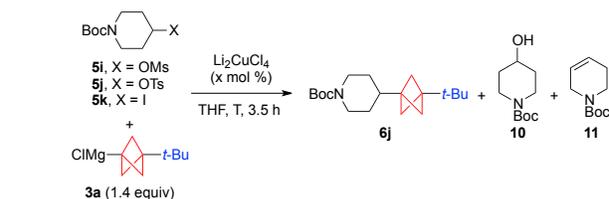
#### Scheme 4. Cross-coupling between BCP Grignard reagents substituted at C3 and primary alkyl mesylates.



\* starting from the bromide and not from the mesylate

Incorporating secondary functionalized alkyl moieties onto BCPs is of great importance to access attractive building blocks. As illustrated by the scarce examples reported in the literature, this alkylation is challenging. Since piperidine is an essential scaffold for medicinal chemists, mesylate **5i** was involved in the cross-coupling with the BCP Grignard reagent **3a** using 6 mol % of Li<sub>2</sub>CuCl<sub>4</sub> at 40 °C. The BCP coupling product was obtained albeit with a low yield (18%) and was contaminated by 6% of the elimination product **11**. The low yield in **6j** was due to the demesylation of **5i**, resulting in the formation of alcohol **10** as the major product (Table 2, entry 1). In order to favor the coupling product, several other conditions were screened using either Cu(II) or Cu(I) salts but none of them gave the expected results.<sup>21,22</sup> As detosylation is less favored than demesylation, starting from tosylate **5j** would enhance the selectivity of the reaction in favor of the coupling product by reducing the formation of alcohol **10**. Thus, when **5j** was treated with 6 mol % of Li<sub>2</sub>CuCl<sub>4</sub>, the alcohol **10** was the minor product and the yield in the BCP coupling product **6j** was increased to 50%. However, a significant amount of the elimination product **11** was formed alongside **6j** (16%) (Table 2, entry 2). The addition of several ligands (TMEDA, isoprene, 1-phenyl-1-propyne) to the reaction mixture was attempted to decrease the elimination process but, unfortunately no effect was observed on the outcome of the reaction.<sup>23</sup> It was finally found that for a selective cross-coupling to occur, the use of a secondary iodo derivative, the 4-iodo-*N*-Boc-piperidine **5k**, was necessary. After 1 h at 0 °C, in the presence of 6 mol % of Li<sub>2</sub>CuCl<sub>4</sub> the BCP coupling product **6j** was isolated with a good yield of 78% without any by-products contamination (Table 2, entry 3).<sup>24</sup> The catalytic loading in Li<sub>2</sub>CuCl<sub>4</sub> could be reduced to 3 mol % without any deleterious effect on the yield of **6j** (Table 2, entry 4).

**Table 2. Optimization of the reaction conditions with secondary alkyl (pseudo)halides.**

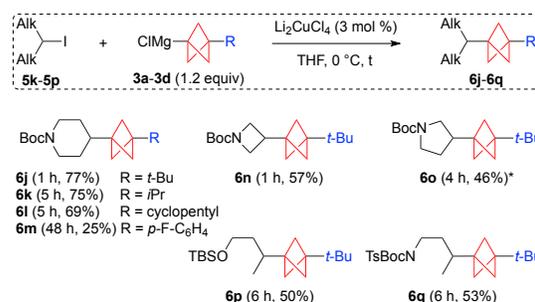


| Entry | X   | Li <sub>2</sub> CuCl <sub>4</sub> (x mol %) | T °C | <b>6j</b> (yield) <sup>[a]</sup> | <b>10</b> (yield) | <b>11</b> (yield) <sup>[a]</sup> |
|-------|-----|---|------|----------------------------------|-------------------|----------------------------------|
| 1     | OMs | 6   | 40   | 18                               | maj               | 6                                |
| 2     | OTs | 6   | 40   | 50                               | min               | 16                               |
| 3     | I   | 6   | 0    | 78                               | -                 | -                                |
| 4     | I   | 3   | 0    | 77                               | -                 | -                                |

[a] Yields obtained after flash column chromatography.

With these established conditions, the coupling of 4-iodo-*N*-Boc-piperidine **5k** was extended to other BCP Grignard reagents substituted with an alkyl group at the C3 position, delivering **6k** and **6l** with yields around 70%. However, the coupling between **5k** and the BCP Grignard reagent **3d**, which bears an aryl substituent at C3, led to the desired coupling product **6m** in only 25% yield after 48 h.<sup>25</sup> It is known that through-space interactions operate in BCP moieties and therefore the BCP Grignard reagents containing an aryl group at C3 might have a reactivity similar to the corresponding aryl Grignard reagent.<sup>26</sup> Pleasingly, the 3-iodoazetidine could be coupled with the BCP **3a** to give the desired product **6n** with a yield of 57%. By contrast, the treatment of 3-iodo-*N*-Boc-pyrrolidine with the BCP Grignard reagent **3a** did not produce the desired coupling product **6o** but exclusively the non-cyclic *N*-Boc-but-3-en-1-amine resulting from the ring-opening of the pyrrolidine. To avoid this side reaction, the tosylate derivative was preferred instead of the iodide and, under slightly harsher conditions (1.4 equiv of the BCP, 6 mol % of Li<sub>2</sub>CuCl<sub>4</sub> at 40 °C), the desired pyrrolidine **6o**, substituted by a BCP group, was isolated with a moderate yield of 46%. In addition, when acyclic secondary alkyl iodides possessing either a silyl ether or a protected amine were involved in the cross-coupling, the corresponding BCP coupling products were obtained with decent yields (around 50%) (Scheme 5).<sup>27</sup>

#### Scheme 5. Cross-coupling between BCP Grignard reagents substituted at C3 and secondary alkyl iodides.



\* Starting from -OTs and not -I with change in conditions: Li<sub>2</sub>CuCl<sub>4</sub> (6 mol %), 40 °C

In summary, we have developed a flexible, efficient, easy-to-handle and cost-effective cross-coupling of both primary and secondary alkyl (pseudo)halides with bicyclopentyl Grignard reagents

allowing the bicyclopentenylolation of sp<sup>3</sup> carbon by (pseudo)halides. The reaction tolerated an array of functional groups and was applied to the functionalization of *N*-heterocycles, which are valuable scaffolds in pharmaceutical industry. To the best of our knowledge, this is the first general cross-coupling of various BCP Grignard reagents with primary alkyl mesylates and secondary alkyl iodides. This sp<sup>3</sup>-sp<sup>3</sup> cross-coupling appears to be a promising method for late-stage introduction of BCP substituents and could thus become an attractive tool for medicinal chemists for the design and synthesis of bioactive molecules.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectral data for all new compounds.

The Supporting Information is available free of charge on the ACS Publications website.

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### Notes

The authors declare no conflict of interests.

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- 13 In order to obtain [1.1.1]propellane **2** in Et<sub>2</sub>O after the addition of phenyllithium on **1**, a distillation under vacuum was necessary. During this step, some of the formed [1.1.1]propellane was lost to avoid contamination with significant amounts of Bu<sub>2</sub>O or phenylbromide (>50 mbar), resulting in moderate yields around 40% in **2**. See SI for details.
- 14 Recently, a flexible and fast access to aryl BCP zinc reagents through a sequence encompassing a ring opening of [1.1.1]-propellane with aryl Grignard reagents and a transmetalation using ZnCl<sub>2</sub> was developed (see ref 4c). The use of high temperature (100 °C) using Et<sub>2</sub>O as sole solvent, seemed to be a high risk profile synthesis. We therefore tried to optimize the conditions without the need of high temperature. See SI for details.
- 15 An addition of the *p*-methoxyphenylmagnesium bromide as well as the *p*-tolylmagnesium bromide on **2** was also attempted resulting in comparable mixtures of BCP and aryl Grignard reagents, see the SI for details.
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- 17 In the absence of copper salt and after 24 h reaction time, **6a** was formed but only in small quantity (**5a/6a** = 1:0.3), showing the essential role of the external catalyst.
- 18 BCP Grignard reagent **3d** was contaminated with residual aryl Grignard reagent **4a** but no coupling product between **5c** and **4a** was detected. It is therefore not necessary to have pure BCP Grignard reagents, as long as 1.2 equiv of the BCP Grignard reagent is added to the mixture (see SI for more details).
- 19 Coupling product **6h** was isolated together with a by-product displaying a *t*-Bu group instead of the BCP cycle, see SI for details.
- 20 The commercially available bromide was used instead of the mesylate.

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<sup>22</sup> See SI for details.

<sup>23</sup> See SI for details.

<sup>24</sup> For other conditions tested, see SI.

<sup>25</sup> The low yield was due to the formation of the dehalogenated product well as the homo- and hetero-coupling products between the two Grignard reagents (**3d** and **4a**).

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<sup>26</sup> Gleiter, R.; Pfeifer, K.-H.; Szeimies, G.; Bunz, U. *Angew. Chem. Int. Ed.* **1990**, *29*, 413–415.

<sup>27</sup> In order to investigate the mechanism, the reaction was performed between Grignard reagent **3a** and a radical clock. Unfortunately, a complex mixture of products was formed avoiding any conclusion. However, based on literature reports a S<sub>N</sub>2-type mechanism without any radical intermediate can be hypothesized, see for example: Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124.

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