Priority Communication

Nickel-catalyzed cross-coupling reaction of carbamates with silylmagnesium reagents

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1. Introduction

Over the past few decades, aryl halides emerged as powerful electrophiles in cross-coupling reactions though they generate toxic halide waste [1]. On the other hand, the phenolic derivatives are highly attractive electrophiles since they are more abundant, environmentally benign and affordable [2]. They often utilized in the form of sulfonates that further undergo Pd mediated cross-coupling reactions, less attention has been paid for the development of cross coupling reactions involving esters like carbamates which can be readily obtained. It is due to the inertness of C(aryl)O bond especially in Pd catalysis and the presence of multiple reactive C=O sites [2]. Fortunately, nickel complexes possess an exceptional reactivity towards the cleavage of C(aryl)O bond [3] and the carbamates have been successfully coupled with various nucleophiles [4–6]. In particular, aryl carbamates can be ortho and para functionalized prior to the cross-coupling event via directed ortho metalation (DoM) [7] or C–H activation strategies [8], whereas the ethers and pivalates are reported to be modest [4d,7a].

Organosilanes have widespread application in synthetic organic chemistry [9], medicinal [10] and material science [11]. In recent years, silylboranes (RSiBpin) are regularly employed as nucleophilic coupling partner in order to introduce a silicon functional group and they are synthesized from either silyllithium or silane as shown in Scheme 1a [6c,12,13]. Notably, silylboranones require the use of stoichiometric base or activator for transmetallation [14]. Strategies that are atom-economical and highly efficient for the construction of C–Si bonds are compelling. Inspired by the earlier work [15,16], we wondered if the silylmagnesium reagents can be used to cross-couple the inactive carbamate derivatives [17]. Although the silylmagnesium reagents are known for a long time (Scheme 1b) [18], they have not been explored in cross-coupling reactions [19]. Importantly, the synthesis and cross-coupling of Me3SiMgI is crucial since the coupled product ArSiMe3 has wider scope in synthetic applications than the commonly employed PhMe2Si–Bpin and PhMe2SiMXn nucleophiles [20]. Herein, we report a nickel catalyzed cross-coupling of various silylmagnesium reagents with aryl, alkenyl and benzyl carbamates, their mechanistic studies by kinetics and radical clock experiment. The pivotal role of aryl carbamates in orthogonal reactivity and its synthetic applications are also discussed.

2. Results and discussion

At the outset of our studies, 1-naphthyl diethylcarbamate 1a was treated with PhMe2Si–Li in the presence of 5 mol% of NiBr2(PPh3)2, unfortunately, the cross-coupled product 4a was obtained only in 7% yield (entry 2) along with 61% of hydrolyzed 1-naphthol [21]. The use of PhMe2SiZnCl was ineffective with most of the carbamate recovered (entry 3). As we expected the involvement of Ni(0) in the catalytic cycle, we employed Ni(0) complexes; such as Ni(COD)2 and Ni(PPh3)4 and observed 4a in 16% and 76% yields respectively (entries 4 and 7). Although the use of CH3CN...
inhibited the cross-coupling of 1a (entry 11), the use of toluene and THF offered the cross-coupled products in good yields, (entries 12 and 14) and Et₂O resulted in remarkable improvement in the yield and reproducibility (entry 1). The greener solvent 2-Me-THF gave moderate yield (entry 15). Virtually none of the silylated product 4a was formed in the absence of catalyst (entry 10). Furthermore, employing 2-naphthyl dimethylcarbamate 1ab and 2-naphthyl diisopropylcarbamylate 1ac in place of 1a resulted in slightly diminished yields (entries 16 and 17). Replacing 1-naphthyl pivalate 1ac in place of 1a gave the aryl silane 4a only in 13% yield (see S6 in SI). In order to demonstrate the practicability and to further explore the application of this methodology, the reaction was scaled up to 4.0 mmol with just 1 mol% of the catalyst 1a and furnished moderate yield in the cross-coupling of 2a (entry 4, Table 3) [32].

Having identified the optimal reaction condition, we moved further to explore the scope of aryl and alkyl carbamates. The results are summarized in Table 2. As expected, 1 and 2-naphthyl diethylcarbamates gave the silanes 4a and 4b in 84% and 80% isolated yields, bisilylation with excess of silylmagnesium bromide 4a resulted in 81% of 4c. While the fluoride is compatible (product 4q) under the reaction condition, bromide, chloride and iodo substituents were not compatible and traces of the expected product was observed. We next turned our attention to explore the functional group tolerance, ether substituted carbamates 1d, 1g and 1j offered the cross-coupled product 4d, 4g and 4j in excellent yields (Table 2). Notably, the sterically congested 2-methoxy substituted carbamate 1d, trimethylsilyl (TMS) substituent (substrate 1e), terminal alkenes 1f, 1i-1k, boronic ester 1r and morpholine substituent 1w were well tolerated. Substrates with carbonyl or nitrile functional group are not compatible under the reaction condition [22]. Carbamates derived from enol ethers were also examined, gratifyingly, substrates 1i, 1j and 1k were cross-coupled in 40% (4i), 85% (4j) and 88% (4k) isolated yields. The CF₃ substituted carbamate 1i was also compatible [23]. It is worth to note that both electron-rich and electron-deficient groups on carbamates were compatible under the optimized condition. As heterocycles are highly attractive in the field of medicinal chemistry [24], we subjected β-deficient quinoline 1o, pyridines (1m and 1n), and π-rich pyrazole 1l derivatives in the cross-coupling of silylmagnesium bromide 2a and observed good to excellent yields of the corresponding ipso-silylated products. It has been observed that aryl carbamates with no extended π-system were reluctant to undergo cross-coupling reactions (see SI) [25], but pyridyl-carbamate 1m underwent cross-coupling reaction smoothly. This may due to the requirement of deaeromatization during oxidative addition, similar observations were reported by the other research groups [6d,25].

Further studies were carried out to uncover the scope of silylmagnesium reagents [26]. It has been described in the literature that the Ar₃SiMgBr can be prepared by the cation exchange of Ar₃Si–I, with either in-situ prepared MgBr₂ from dibromoethane and Mg [26a] or commercial MgBr₂·Et₂O [26b,26c]. As described above in Scheme 1, we initially prepared PhMe₃SiMgBr from PhMe₃SiI which in turn was synthesized from PhMe₃SiCl via lithium/halogen exchange [15a,26a,26b,27]. This protocol was extended further for the synthesis of silylmagnesium reagents 2b and 2c [26a]. Although the reagents 2a–c offered the cross-coupling product 4c in excellent yields (entries 1–3, Table 3), the synthetic application of 4a is very limited due to (i) the presence of multiple arenés on silicon center which may cause selectivity issues, (ii) synthetic transformations of biaryl-substituted silanes are rare [28]. This forced us to turn our attention to the synthesis of trimethylsilyl substituted arenés (Ar-TMS) since substrates of this type can readily undergo various transformations [29]. Unlike PhMe₃SiCl, the direct lithiation of Me₃SiCl cannot be carried out [30], hence we prepared Me₃SiI from hexamethyldisilane (Me₂Si–SiMe₃) as described in the literature [27d,31], subsequent cation exchange with MgBr₂·Et₂O offered Me₃SiMgBr, which furnished moderate yield in the cross-coupling of 1a [21]. Fortunately, we came across a protocol [26i] that uses Me₃Si–I, magnesium and TMEDA to prepare Me₃SiMgI and with a little modification we prepared Me₃SiMgI that gave us excellent yield in the cross-coupling of 1a (entry 4, Table 3) [32].

Concurrent with the above studies, benzylic carbamates 1v and 1x underwent cross-coupling reaction with PhMe₂SiMgBr to offer

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**Scheme 1.** Synthesis of organosilanes via C–O bond cleavage.

**Table 1**

Optimization of the reaction condition.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard conditions</th>
<th>Time (h)</th>
<th>Yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>1</td>
<td>89 (84)</td>
</tr>
<tr>
<td>2</td>
<td>PhMe₃SiI instead of 2a</td>
<td>2</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>PhMe₃SiZnCl instead of 2a</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>Ni(COD)₂ instead of 3</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>NiBr₂ instead of 3</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>NiBr₂ + diglyme instead of 3</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>Ni(PPh₃)₂ instead of 3</td>
<td>18</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>Ni(acac)₂ instead of 3</td>
<td>18</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>NiCl₂(PPh₃)₂ instead of 3</td>
<td>18</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>without 3</td>
<td>12</td>
<td>ND</td>
</tr>
<tr>
<td>11</td>
<td>CH₂CN instead of Et₂O</td>
<td>18</td>
<td>ND</td>
</tr>
<tr>
<td>12</td>
<td>Toluene instead of Et₂O</td>
<td>18</td>
<td>79</td>
</tr>
<tr>
<td>13</td>
<td>Et₂O 0.1 M instead of 0.15</td>
<td>18</td>
<td>69</td>
</tr>
<tr>
<td>14</td>
<td>THF instead of Et₂O</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>15</td>
<td>2-Me-THF instead of Et₂O</td>
<td>18</td>
<td>59</td>
</tr>
<tr>
<td>16</td>
<td>1ab instead of 1a</td>
<td>1</td>
<td>73 (70)</td>
</tr>
<tr>
<td>17</td>
<td>1ac instead of 1a</td>
<td>1</td>
<td>80 (74)</td>
</tr>
<tr>
<td>18</td>
<td>1 mol% of 3 instead of 5 mol%</td>
<td>4</td>
<td>75-</td>
</tr>
<tr>
<td>19</td>
<td>Fe(acac)₃/dtbpyb instead of 3</td>
<td>18</td>
<td>70</td>
</tr>
</tbody>
</table>

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*a* Reaction condition: 0.2 mmol of 1a, 0.3 mmol of 2a (0.45 M in THF), 5 mol% of NiBr₂(PPh₃)₂, Et₂O, 0.15 M, rt (26–28 °C), 2 h.

*b* Determined by GC analysis using n-decane as internal standard, value in parentheses are isolated yield.

† Repeated a minimum of four times.

‡ Hydrolyzed product 1-naphthol was observed in 61% GC yield.

§ Traces of reduced product naphthalene was seen.

‖ 4 mmol of 1a was used.

& 10 mol% of Fe(acac)₃ was used. Et₂O: diethyl ether. ND: Not detected. 1ab: 2-Naphthyl dimethylcarbamate. 1ac: 2-naphthyl diisopropylcarbamate.
the coupled products 4v and 4x in 89% and 92% isolated yields (Scheme 2).

In order to explore the synthetic application of the cross-coupled product 4, trimethyl(naphthalen-1-yl)silane 4u was subjected to halogenation in the presence of various N-halosuccinimides, and the corresponding 1-chloro, 1-bromo and 1-iodo substituted naphthalenes were isolated in excellent yields (Scheme 3a). Furthermore, 4u was also employed in the palladium catalyzed coupling of 3-methylthiophene via C—H activation, the cross-coupled 3-methyl-4-(naphthalen-1-yl)thiophene 6b was isolated in 60% yield (Scheme 3) [29h].

As discussed earlier, aryl carbamates are excellent directed metalation groups (DMG) [7]. In order to demonstrate the synthetic application of the methodology, we explored the orthogonal reactivity of the carbamate as shown in Scheme 4 [33], where the ortho-lithiation/iodination of 1m afforded the intermediate 7b. A chemoselective palladium catalyzed cross-coupling with phenylboronic acid followed by the nickel mediated cross-coupling with silylmagnesium bromide under the optimized condition afforded the cross-coupled product 4n in 61% yield.

We studied the quantitative kinetics of the reaction between 1a and Me₃SiMgI in order to elucidate the mechanism (Fig. 1) [34]. The order of the reaction with respect to each reagent was determined using initial rates (k in). Plots of initial rate versus the concentration of each reagent are shown in Fig. 1. As expected, a...
zero-order (−0.0475 ± 0.166; Fig. 1b) dependence on the concentration of the Me3SiMgI over a range of 150–375 mM was observed, the reaction showed first-order (1.116 ± 0.22; Fig. 1c) dependence on the concentration of the carbamate 1a over a range of 30–150 mM. Notably, a half-order (0.521 ± 0.050; Fig. 1d) dependence on the concentration of NiBr2(PPh3)2 over a range of 3–7.5 mM was observed and this may be attributed to the dissociation of ligands from NiBr2(PPh3)2 or the dimerization of nickel complex [3,34d]. The kinetic data obtained here reveals that the oxidative addition of carbamate to the nickel complex must be the rate-limiting step.

In order to identify the nature of the intermediate, we prepared a radical clock substrate 8a and subjected to the optimized reaction condition as shown in scheme 5 [12b]. The uncyclized product 8b was isolated in 55% yield and we have not observed the cyclized product 8c, also the reaction with TEMPO [35] and cyclohexene did not inhibit the reaction that may rule out a carbon-centered radical as the transition state.

When NiBr2(PPh3)2 (1.0 eq.) and PhMe2SiMgBr (10 eq.) were mixed, instant formation of PhMe2Si–SiMe2Ph was observed. However, the concentration of disilane remains constant throughout the course of the reaction, which may be an indication to the formation of Ni(0)Ln (Scheme 6) [34a]. Subjecting PhMe2Si–SiMe2Ph instead of 2a did not offer the expected product that rules out PhMe2Si–SiMe2Ph as the source silicon nucleophile [34h,34i].

Although a detailed mechanistic study has been initiated, we propose a plausible mechanism based on the above-mentioned studies. We hypothesize the formation of an active Ni(0) catalyst A upon mixing NiBr2(PPh3)2 and R3SiMgBr. Subsequent oxidative addition (RDS) of the R–OCb to Ni(0)Ln (Scheme 6) [34a]. Subjecting PhMe2Si–SiMe2Ph instead of 2a did not offer the expected product that rules out PhMe2Si–SiMe2Ph as the source silicon nucleophile [34h,34i].

3. Conclusions

In summary, we have developed an unprecedented cross-coupling reaction that utilizes inexpensive, bench-stable catalyst NiBr2(PPh3)2. This methodology has a wide scope with respect to relatively inert C(sp2)–O carbamates and silylmagnesium reagents. The C(sp3)–O carbamates have also been successfully employed in the cross-coupling reactions. The synthetic application of this methodology was shown in the orthogonal reactivity of the carbamate in combination with directed ortho metalation (DoM). Studies aimed at expanding the scope of silylmagnesium reagents in asymmetric cross-coupling reactions are currently advancing in our laboratory.

Declaration of Competing Interest

There are no conflicts to declare.

Acknowledgments

We thank the Science and Engineering Research Board, EMR: EMR/2015/001103/OC and Ramanujan research grand: SB/S2/RJN059/2015 for financial support. VM and VB acknowledge IISER, Trivandrum for their financial support. We thank Dr. Paul Gates (Mass spec, University of Bristol), Dr. Thirumurugan, Dr. Muthukrishnan and Dr. Subrata Kundu for kinetics discussions.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2019.07.026.

References


[6] The two most commonly used groups are PhMe2Si–Bpin, PhMe2SiZnX and PhMe2SiB(pin) (Scheme 1c) that includes the oxidative addition of Mg to iodoalkanesilanes, cationic exchange of silylboranes with MgBr2.

[7] [26] The most commonly used reagents are PhMe2Si–Bpin, PhMe2SiZnX and PhMe2SiB(pin) obtained from these reagents are stenuous to explore in the synthetic application due to the presence any or more impurities on silane (see following discussion on page 3).
The generated highly reactive Me3SiLi attacks the solvent THF and generates the corresponding irreversible by-product, the use of other solvents instead of THF was not successful. We believe that the aryl group on silicon center (e.g., PhMe2SiLi) helps to stabilize the generated silyl lithium (see SI for more details).

Presence of TMEDA did not affect the efficiency of the reaction, crystal structure of Me3SiMgBr/TMEDA complex has been reported in reference 26i and we have also obtained the crystals.

We obtained 61% of 4b in presence of TEMPO, the remaining mass accounts the unreacted carbamate 1b.

The oxidatively added aryl pivalates to Ni(0) has been isolated earlier: K. Muto, J. Yamaguchi, A. Lei, K. Itami J. Am. Chem. Soc. 135 (2013) 16384.