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# Deoxygenative Cross-Electrophile Coupling of Benzyl Chloroformates with Aryl Iodides

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Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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This work describes Ni-catalyzed cross-electrophile of benzyl chloroformate derivatives with aryl iodides that generates a wide range of diaryl methane products. The mild reaction conditions merit C–O bond radical fragmentation of benzyl chloroformates via halide abstraction or a single electron reduction by Ni catalyst. This work offers a new substrate type for cross-electrophile couplings.

Use of benzyl alcohol and its derivatives as the coupling partners has spurred considerable interests in the field of C-C bond forming chemistry.1 Among various transition metal catalyzed benzyl C-O bond couplings, the earth abundant nickel has been widely adopted. Notable protocols include Jarvo's benzyl ether coupling with organometallic reagents,<sup>2</sup> Shi's Kumada and Suzuki process (Scheme 1).<sup>3</sup> These elegant methods are compatible with naphathyl-, benzofuanyl-, benzo[b]thiophenyl-, and furylmethylenyl C-O bonds.<sup>2-3</sup> The reactions appear to take advantages of arene-assisted C–O bond oxidative addition to low valent Ni.<sup>2-3</sup> On the other hand, benzyl C-O bonds has been intensively used in Ni-catalyzed crosselectrophile couplings.<sup>4-11</sup> In this context, generation of benzyl radicals are often involved. Whereas Weix utilized Co,<sup>4</sup> Ukaji employed Ti as the reducing reagent to unlock the C-O bond homolytically to create benzyl radical.<sup>5</sup> The benefits of using benzyl alcohol and its derivatives over benzyl halides is obvious,<sup>12</sup> as the latter are generally reactive on benchtop, and need to store with care. This is even true for benzyl tosylates and mesylates.<sup>4</sup> However, the concurrent benzyl C-O bond activation/coupling methods are generally limited to primary alcohols or diaryl methanols,<sup>4-11</sup> unlike their halide counterparts which are suitable for alkyl-substituted secondary benzyl substrates. More recently, Shu has developed a Nicatalyzed cross-electrophile coupling of primary benzyl oxalates with



We envisaged that activation of benzyl alcohols with chlorocarbonyl may allow C–O bond scission via halide abstraction or one electron reduction followed by decarboxylation. Further reaction of the resultant benzyl radicals with Ar–Ni(II) intermediates under the Ni-catalyzed reductive coupling conditions may enable the formation of benzyl C(sp<sup>3</sup>)–C(sp<sup>2</sup>) products. Herein, we report our discovery of Ni-catalyzed reductive coupling of benzyl chloroformates with aryl iodides that generates diaryl methane products. The mild reaction conditions are compatible with secondary benzylic derivatives and tolerate a wide range of functional groups such as aldehydes.



Scheme 1. Ni-catalyzed cross-electrophile arylation of benzyl C–O bonds.

We commenced our studies with the reaction of chlorobenzylformate with 4-iodoanisole, by setting the latter as the

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limiting reagent.<sup>15</sup> After extensive investigations, we identified that a combination of Ni(acac)<sub>2</sub> (10 mol%) with L4 in the presence of MgBr<sub>2</sub> (1.0 equiv) at 40 °C, gave 1a with an excellent yield 96%, wherein DMA was used as the solvent and Zn as the reductant (Table 1, entry1). Variation of the temperatures did not result in a better yield (entries 2-3). Reducing the amount of chloroformates to 1.2 equiv did not lead to appreciable reduction of yield, whereas use of 1 equiv of chloroformate only generated 1a in 74% yield (entries 4-5). Exploration of other ligands (entries 6-11), salt additives (e.g., MgCl<sub>2</sub> and LiCl, entries 12-13) and solvents (14-15) were not satisfactory. Control experiments indicated that only Ni was indispensable; without MgBr<sub>2</sub>, 1a was obtained in 53% yield (entries 16-18). Finally, use of 4-chloro and 4-boromo anisoles to replace the 4-iodo counterpart was not effective (entries 19-20). We reason that MgBr<sub>2</sub> may serve to activate Zn surface. In addition, a possible halide exchange between Cl and Br may take place, as MgCl<sub>2</sub> appears to be less important (Table 1, entry 12 vs 18). This may accelerate the reduction of chloroformates since bromide is a better leaving group.

**Table1**. Optimization of the reaction conditions for the coupling of benzyl chloroformate with 4-iodoanisole.

OMe

100

"standard method" Ni(acac)<sub>2</sub> (10 mol%) Zn (200 mol%) L4 (15 mol%)

MgBr<sub>2</sub> (100 mol%)

126

| 1.5 equi           | 7 1.0 equit DMA (1 m2), 40 c, 12m   | Id                  |
|--------------------|---|---------------------|
|                    | $\begin{array}{c c} R \\ R \\ N \end{array} \end{array} \begin{array}{c} R \\ R \\ N \end{array} \begin{array}{c} R \\ R \\ N \end{array} \begin{array}{c} R \\ R \\ R \\ N \end{array} \begin{array}{c} R \\ R \\ R \\ R \\ R \\ R \end{array} \begin{array}{c} R \\ R $ | N<br>N<br>L6        |
| entry <sup>a</sup> | variation from the "standard  | yield% <sup>b</sup> |
|                    | conditions"   |                     |
| 1                  | none  | 96 (95)⁰            |
| 2                  | 50 °C   | 89                  |
| 3                  | 25 °C   | 86                  |
| 4                  | 1.2 equiv of benzyl chloroformate   | 92                  |
| 5                  | 1.0 equiv of benzyl chloroformate   | 74                  |
| 6                  | L5 instead of L4  | 75                  |
| 7                  | L2 instead of L4  | 72                  |
| 8                  | pyridine instead of L4  | 70                  |
| 9                  | L1 instead of L4  | 42                  |
| 10                 | L3 instead of L4  | 94                  |
| 11                 | L6 instead of L4  | 23                  |
| 12                 | MgCl <sub>2</sub> instead of MgBr <sub>2</sub> , 50 °C  | 60                  |
| 13                 | LiBr instead of MgBr <sub>2</sub> , 50 °C   | trace               |
| 14                 | CH <sub>3</sub> CN instead of DMA   | 60                  |
| 15                 | THF instead of DMA  | 43                  |
| 16                 | w/o Ni(acac) <sub>2</sub>   | nd                  |
| 17                 | w/o <b>L4</b>   | 18                  |
| 18                 | w/o MgBr <sub>2</sub>   | 53                  |
| 19                 | 4-chloroanisole instead of 4-iodoanisole  | nd                  |
| 20                 | 4-bromoanisole instead of 4-  | <10                 |
|                    | iodoanisole   |                     |

<sup>*a*</sup> Reaction conditions: benzyl chloroformate (1.5 equiv), aryl iodide (0.3 mmol, 1.0 equiv), Zn (2.0 equiv), **L4** (15 mol%), Ni(acac)<sub>2</sub> (10 mol%), and MgBr<sub>2</sub> (1.0 equiv) in DMA (1 mL) at 40  $^{\circ}$ C for 12h. <sup>*b*</sup> NMR yield using 2,5-dimethylfuran as the internal

reference. <sup>c</sup> Isolated yield. <sup>d</sup> Not detected by <sup>1</sup>H NMR<sub>ev</sub>DMA N,N-dimethylacetamide, acac = acetylacetonate. detected.

With the optimized reaction conditions in hand, we examined the sc ope and limitations of primary benzyl chloroformates and aryl iodid es (Figure 1). The reaction was effective for aryl iodide substituted w ith electron-withdrawing groups as exemplified by **1b–1e**. The use o f methyl 4-bromobenzoate delivered **1b** in 83% yield, whereas prep aration of **1b** on a 1 mmol scale was obtained in 76% yield. The subs titution patterns of the aryl iodides were not important for the coup ling efficiency (e.g., **1f** and **1g** vs **1a**). Other aryl iodides including 1-n aphthyl, 1-pyrenyl, benzo[b]thiophenyl and benzofuryl were all suita ble, as evident in **1h–1n**. Chloroformates bearing electron-withdraw ing and electron-donating groups at the benzene rings all gave excel lent coupling yields for **2a–7a**.



**Figure 1**. Coupling of primary chloroformates and aryl iodides using the standard method as in Table 1, entry 1.

We next turned out attention to the secondary benzyl chloroformates (Figure 2). Under the standard reaction conditions (Table 1, entry 1), the coupling of chloroformate derived from phenyl-1-ethanol with methyl 4-iodobenzoate only resulted in **8a** in 63% yield. Gratifyingly, the yield was boosted to 86% by replacement of Ni(acac)<sub>2</sub> with NiCl<sub>2</sub>(DME). With these modified conditions, the substrate compatibility was investigated as exemplified by **8a–19a**. Whereas 3-iodobenzoate was inferior to the 4-iodo counterpart, 2-iodobenzoate only resulted in **8c** in a trace amount. The reaction was also effective for electron-rich arenes, as manifested by **8d**. The mild reaction conditions were tolerant of a wide range of functional groups. These comprised aldehyde, fluoro, chloro and cyano groups. Installation of different substituents into the benzene rings of the

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chloroformates were generally effective, as evidenced by examples of **9a–17a**. Increase the size of the alkyl groups at the benzylic carbon with respect to methyl reduced the coupling efficiency, wherein **18a– 18b** were obtained in moderate yields. Finally, chloroformate derived from 2,3-dihydro-1H-inden-1-ol also afforded **19a** in 78% yield.



**Figure 2.** Coupling of secondary chloroformates and aryl iodides. The reaction was conducted using the standard method in Table 1, entry 1, except that NiCl<sub>2</sub>(glyme) was used in place of Ni(acac)<sub>2</sub>.

We also briefly investigated whether unactivated alcohol decorated with chloroformate would be adapted to the reaction conditions. As shown in equation 1, cyclopentyl substrate performed best; both electron-rich and deficient aryl iodides were suitable. However cyclohexyl and isopropyl substrates were not effective, suggesting that the nature of unactivated alkyl groups differs from that of benzyl one.

$$R_{alkyl} \xrightarrow{O} Cl + R \qquad (1)$$

$$R_{alkyl} = cyclopentyl, R = CO_2Me: 80\%$$

$$R_{alkyl} = cyclopentyl, R = CO_2Me: 50\%$$

$$R_{alkyl} = cyclohexyl, R = CO_2Me: not detected$$

$$R_{alkyl} = Pr, R = CO_2Me: 30\%$$

To gain insight into the reaction details, we performed the coupling reaction of methyl 4-iodobenzoate with the chloroformate **20** that contains benzylic cyclopropane. The ring-open product **21** was obtained in 70% yield (eq 2). Additionally, the reaction was inhibited by addition of 1 equiv. of TEMPO. These results suggested chloroformates participated in the reactions via benzyl radicals. Thus, we reasoned that the reaction may proceed through a halide abstraction by Ni catalyst, or a single electron reduction of the chloroformate to result in a radical anion.<sup>16</sup> The reduction potential of chloroformate derived from 1-phenylethan-1-ol was determined to be -1.35 V (vs Ag/Ag<sup>+</sup> in CH<sub>3</sub>CN). Thus, the reductive C–O bond scission by Ni(I) or by Zn/MgBr<sub>2</sub> is possible.<sup>13,15-16</sup> Subsequent release

one molecule of carbon dioxide produced a benzyl radical, which can be intercepted by an in situ formed aryl–Ni( $\Omega$ ): \$pecies/fo@RV@3rpA Ni(III)-Bn intermediate. Reductive elimination of the putative Ni(III) species gave the coupling product.<sup>17</sup> This hypothesis was verified by an equimolar reaction of benzyl chloroformate with an aryl-Ni(II) intermediate **22** obtained by oxidative addition of methyl 4iodobenzoate with L3–Ni(0) (eq 3).<sup>18</sup> We obtained **1b** in 38% and 30% yields with or without MgBr<sub>2</sub> (eq 2), suggesting that Ni(II) may abstract the chlorine, and result in benzyl radical by release of CO<sub>2</sub>. Addition of Zn in Eq 3 improved the yield to 58%, suggesting that Zn promotes the reaction. In addition, the reaction of **20** and **22** gave **21** in 33% yield, conforming that alkyl radical is involved.



In summary, we have disclosed that benzyl chloroformates were suitable for radical C–O bond fragmentation and subsequent coupling with aryl–Ni intermediates under Ni-catalyzed reductive coupling conditions. The reaction conditions tolerate a wide arrange of substrates and functional groups. The mild and easy-to-operate method adds a new entry to the construction of diaryl methane products, which is complementary to the concurrent cross-electrophile coupling of benzyl C–O bonds.

## Acknowledgement

Financial support was provided by the Chinese NSF (Nos. 21871173 and 21572127).

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View Article Online DOI: 10.1039/C9OB00628A

## Deoxygenative Cross-Electrophile Coupling of Benzyl Chloroformates with Aryl Iodides

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We disclose herein a Ni-catalyzed benzyl C-O bond radical fragmentation/crosselectrophile coupling of benzyl chloroformates with aryl iodides to generate diaryl methane derivatives.

TOC:

Ar O CI R'-Ni (cat.)/Bipy Zn, DMA

- C-O bond radical fragmentation - mild reaction conditions