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## Cross-couplings between benzylic and aryl halides “on water”: synthesis of diarylmethanes†,‡

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### Abstract

A remarkably simple entry to unsymmetrical diarylmethanes has been developed that relies on an *in situ* organozinc-mediated, palladium-catalyzed cross-coupling. Thus, by mixing a benzyl and aryl halide together in the presence of Zn metal and a Pd catalyst, diarylmethanes are formed at room temperature without assistance by a surfactant; hence, “on water”.

Diarylmethanes have recently come into focus given the presence of this subunit in a substantial number of biologically active molecules.<sup>1</sup> The majority of approaches to this functional group array rely on cross-couplings; *e.g.*, reactions using organoboron derivatives, catalyzed by palladium,<sup>2</sup> or Grignards catalyzed by copper,<sup>3</sup> nickel,<sup>4</sup> or iron<sup>5</sup> salts. Organozinc reagents are very attractive for this purpose given their low cost of preparation, high functional tolerance, and their low toxicity. Surprisingly, since the original work of Negishi *et al.*,<sup>6</sup> few studies have been reported on the synthesis of diarylmethanes based on organozinc reagents with catalysis by palladium,<sup>7</sup> rhodium,<sup>8</sup> nickel,<sup>9</sup> or cobalt.<sup>10</sup> Nonetheless, organozinc reagents are routinely used stoichiometrically and hence, need to be prepared in a separate step.<sup>11</sup> Recently, we have described a new process for effecting cross-coupling reactions that avoid entirely the prior preparation of organo-zinc reagents.<sup>12</sup> Thus, zinc-mediated, palladium-catalyzed couplings are now possible between two organic halides, all of which takes place selectively (including insertion by zinc metal and Pd catalysis) using nanomicelles in water at room temperature.<sup>13</sup> In this report, we describe an alternative approach: that is, an “on water” phenomenon (and hence, in the absence of a surfactant) that leads directly to unsymmetrical diarylmethanes.

This investigation was initiated by treatment of 3-methoxybenzyl chloride (2 equiv.) and ethyl 4-bromobenzoate in pure water (Table 1) with zinc dust and a Pd catalyst (0.5 mol% PdCl<sub>2</sub>(Amphos)<sub>2</sub>).<sup>14</sup> In the presence of TMEDA as the additive of choice,<sup>12</sup> product **1** (R = OMe) is formed in high yields (entries 1–3) compared to that obtained in its absence (entry 4). Interestingly, the use of a surfactant for micellar catalysis in this reaction type does not enhance the reaction rate, or improve the yield of the coupling. Using the more reactive 3-chlorobenzyl chloride, even less TMEDA (*e.g.*, 25 mol%) is required to realize a high yield

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of **2** (entry 3). In fact, if too much TMEDA is present, zinc insertion is uncontrollable and the product from protio-quenching, rather than **2**, is formed (entries 1 and 2).<sup>15</sup>

It is assumed that TMEDA is stabilizing the organozinc species by chelation, in water, rather than solely acting as a surface-cleaning and/or activating agent. Without TMEDA (entries 4 and 8), lower yields are obtained notwithstanding complete consumption of the starting benzyl chloride. Thus, the empirically-determined, optimized amount of TMEDA shown reflects a balance between stabilization and activation. In changing to zinc powder, the same trend was observed for both starting benzyl chlorides that ultimately led to products **1** and **2**. These were obtained in excellent isolated yields (94% and 96%, respectively) employing only 25 mol% of TMEDA. However, in the case of electron-poor benzylic chlorides, zinc powder (rather than zinc dust) is the preferred precursor of this coupling partner.

The reaction appears to be quite general, as reflected by the examples illustrated in Table 2. Simple benzyl bromide and benzyl chloride afford product **3** in high yields within a reaction time of three hours (entries 1 and 2). Both electron-rich or electron-poor benzyl bromides react very quickly with zinc metal; hence, competitive quenching and/or homo-coupling limit yields of desired cross-coupling products (entries 7 and 9). Otherwise, high yields are routinely obtained in all cases with relatively less reactive benzylic chlorides (entries 8 and 10–16). Moreover, only small amounts of homocoupling products are detected in these reaction mixtures. With respect to the aryl halide partner, it is worthy of note that aryl iodides also lead to high isolated yields of diarylmethanes; *i.e.*, they do not compete for zinc insertion (entries 3 and 5). Steric effects do not appear to limit these reactions (entries 4, 13 and 15). A vast array of functionalities on both coupling partners are tolerated, including vinyl, trifluoromethyl, ester, aldehyde, chloride, and nitrile (entries 11–15). Finally 4-(1-chloroethyl)benzene leads to product **13** in excellent isolated yield (98%), whereas no product was detected using benzhydrylchloride.

In summary, a remarkably straightforward method for preparing functionalized diarylmethanes, as described herein, has been uncovered. An aryl and benzylic halide, in the presence of inexpensive Zn and a Pd catalyst, combine in water alone at room temperature to afford the targeted products in high yields.

## Supplementary Material

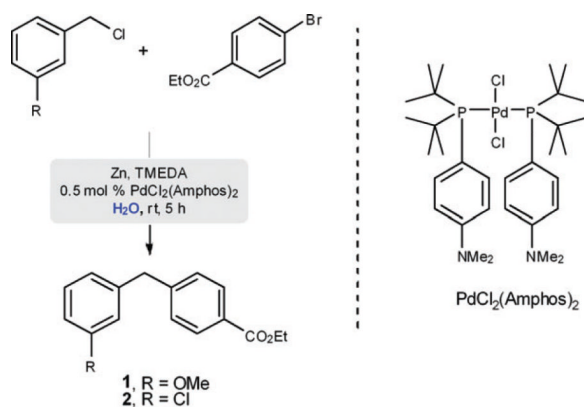
Refer to Web version on PubMed Central for supplementary material.

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Table 1

Optimization of the reaction between substituted benzyl chlorides and ethyl 4-bromobenzoate<sup>a</sup>

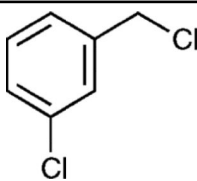
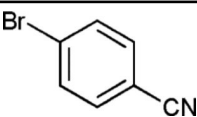
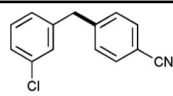
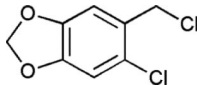
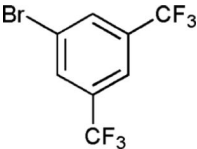
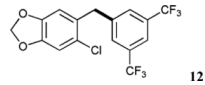
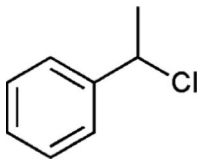
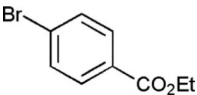
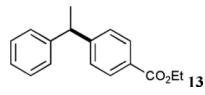
| Entry | Type of zinc | TMEDA ( <i>n</i> equiv.) | Isolated yield of 1 (%) | Isolated yield of 2 (%) |
|-------|--------------|--------------------------|-------------------------|-------------------------|
| 1     | Dust         | 1                        | 92                      | 52                      |
| 2     | Dust         | 0.5                      | 96                      | 66                      |
| 3     | Dust         | 0.25                     | 95                      | 92                      |
| 4     | Dust         | 0                        | 53                      | 65                      |
| 5     | Powder       | 1                        | 84                      | 62                      |
| 6     | Powder       | 0.5                      | 82                      | 86                      |
| 7     | Powder       | 0.25                     | 94                      | 96                      |
| 8     | Powder       | 0                        | 76                      | 74                      |

<sup>a</sup> Conditions: benzyl chloride (4 mmol), ethyl 4-bromobenzoate (2 mmol), zinc (6 mmol), PdCl<sub>2</sub>(Amphos)<sub>2</sub> (0.01 mmol), degassed water (5 mL).

Table 2

Representative benzyl–aryl cross-couplings<sup>a</sup>

| Entry | Benzyl halide     | Aryl halide       | Product | Yield <sup>b</sup> (%) |
|-------|-------------------|-------------------|---------|------------------------|
|       |                   |                   |         |                        |
| 1     | X = Br            | X = Br            |         | 94 <sup>c</sup>        |
| 2     | X = Cl            | X = Br            |         | 95 <sup>d</sup>        |
| 3     | X = Cl            | X = I             |         | 96 <sup>d</sup>        |
| 4     | X = Cl            |                   |         | 92                     |
|       |                   |                   |         |                        |
| 5     | X = Cl            | X = I             |         | 97 <sup>d</sup>        |
| 6     | <b>X = Cl</b><br> | <b>X = Br</b><br> |         | 98 <sup>d</sup>        |
| 7     | X = Br            |                   |         | 70                     |
| 8     | <b>X = Cl</b><br> |                   |         | 95                     |
| 9     | X = Br            |                   |         | 57 <sup>e</sup>        |
| 10    | X = Cl            |                   |         | 96 <sup>e</sup>        |
| 11    | <b>X = Cl</b><br> |                   |         | 74                     |
| 12    |                   |                   |         | 79 <sup>e</sup>        |
| 13    |                   |                   |         | 78                     |

| Entry | Benzyl halide   | Aryl halide   | Product   | Yield <sup>b</sup> (%) |
|-------|---|---|---|------------------------|
| 14    |  |  |  <b>11</b> | 80 <sup>e</sup>        |
| 15    |  |  |  <b>12</b> | 70                     |
| 16    |  |  |  <b>13</b> | 98 <sup>f</sup>        |

<sup>a</sup> Conditions: benzyl halide (5 mmol), aryl bromide (2 mmol), zinc dust (6 mmol), PdCl<sub>2</sub>(Amphos)<sub>2</sub> (0.01 mmol), TMEDA (0.5 mmol), degassed water (5 mL), rt, 8 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> 10 mol % TMEDA.

<sup>d</sup> 2 equiv. BnCl.

<sup>e</sup> Zinc powder was used.

<sup>f</sup> 50 mol % TMEDA.