## Magnesium-Mediated Carbon-Carbon Bond Formation in Aqueous Media: Barbier-Grignard Allylation and Pinacol Coupling of Aldehydes

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Magnesium-mediated Barbier–Grignard type alkylation of aldehydes with alkyl halides was studied in aqueous media. The reaction of aromatic aldehydes with allyl halides is highly effective with either THF or water as the reaction solvent but poor in a mixture of THF/water. It was found that the magnesium-mediated allylation of aldehydes with allyl bromide and iodide proceeds effectively in aqueous 0.1 N HCl or 0.1 N NH<sub>4</sub>Cl. Aromatic aldehydes reacted chemoselectively in the presence of aliphatic aldehydes. An exclusive selectivity was also observed when both aliphatic and aromatic aldehyde functionalities are present in the same molecule. In the absence of allyl halides, aldehydes and ketones reacted with magnesium in aqueous 0.1 N NH<sub>4</sub>Cl to form the corresponding pinacol coupling products in high yields. The effectiveness of the pinacol reaction was strongly influenced by the steric environment surrounding the carbonyl group. Aliphatic aldehydes and simple alkyl halides appear inert under the reaction conditions for either alkylation or the pinacol coupling reaction.

## Introduction

Carbon-carbon bond formation is the essence of organic synthesis. One of the most important steps in the history of modern chemistry was the introduction by Barbier and Grignard about a century ago<sup>1</sup> of magnesium for carbon–carbon bond formations<sup>2</sup> through the addition of an organometallic reagent to a carbonyl group. The further study of magnesium-based reactions also sparked the development of new reagents based on electronically more negative and more positive metals, as well as semimetallic elements for various synthetic purposes to tailor reactivities and selectivities (chemo, regio, and stereo).3 For carbonyl additions based on organomagnesium reagents, it is generally accepted that strict anhydrous reaction conditions are required for a smooth reaction.<sup>4</sup> The presence of moisture delays the initiation and/or inhibits the reaction. Various methods, such as dibromoethane<sup>5</sup> or iodine initiators, mechanical activation,<sup>6</sup> ultrasonic irradiations,<sup>7</sup> and more recently, activated magnesium have been developed to help initiate the reaction.<sup>8</sup> Because of economical and environmental

(4) Wakefield, B. J. Organomagnesium Methods in Organic Synthesis, Best Synthetic Methods series, Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: San Diego, 1995.

concerns, the use of water as a solvent for metal-mediated carbon-carbon bond formations has generated considerable interest. Within the last several years, various metals have been developed to mediate Barbier-Grignard type reactions.9 For a long time, we have been intrigued by the possibility of performing classical Barbier-Grignard reactions by using magnesium in water. The study would possibly extend the scope of the aqueous metal reaction and increase the understanding of the mechanism of both the classical Barbier-Grignard and the aqueous metal reactions. However, in view of the high reactivity of organomagnesium reagents toward water and moisture, it is doubtful that magnesium can be used for such a purpose. Nevertheless, recently we observed that the reaction of benzaldehyde with allyl iodide is also highly effective in both aqueous 0.1 N NH<sub>4</sub>Cl and dry THF as the reaction solvent.<sup>10</sup> This unusual observation led us to examine the aqueous reaction mediated by magnesium in detail. Historically, the allylation of carbonyl compounds with an organomagnesium reagent had not been well-established for decades until Gilman and McGlumphy developed a new procedure to prepare Grignard reagents from allylic halides.<sup>11</sup> Herein, we report the studies of using magnesium for Barbier-Grignard allylation and pinacol coupling of aldehydes in water.

(10) Li, C. J.; Zhang, W. C. J. Am. Chem. Soc. 1998, 120, 9102.
 (11) Gilman, H.; McGlumphy, J. H. Bull. Soc. Chim. Fr. 1928, 43, 1322.

Barbier, P. Compt. Rend. 1898, 128, 110. Barbier, P. J. Chem. Soc. 1899, 76, Pt. 1, 323. Grignard, V. Compt. Rend. 1900, 130, 1322.
 Kharasch, M. S.; Reinmuth, O. Grignard Reactions of Nonmetallic Substances; Prentice-Hall: New York, 1954.

<sup>(3)</sup> For representative monographs and reviews, see: Wakefield, B. J. Organomagnesium Methods in Organic Synthesis, Best Synthetic Methods series; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: San Diego, 1995. Blomberg, C. The Barbier Reaction and Related One-Step Processes; Springer-Verlag: New York, 1993. Lai, Y. H. Synthesis **1981**, 585. Courtois, G.; Miginiac, L. J. Organomet. Chem. **1974**, 69, 1. Normant, H. Adv. Org. Chem. **1960**, 2, 1. Ioffe, S. T.; Nesmeyanov, A. N. The Organic Compounds of Magnesium, Beryllium, Calcium, Strontium and Barium; North-Holland: Amsterdam, 1976.

<sup>(5)</sup> Pearson, D. E.; Cowan, D.; Beckler, J. D. J. Org. Chem. 1959, 24, 504.

<sup>(6)</sup> Shaw, M. C. J. Appl. Mechanics 1948, 15, 37.

<sup>(7)</sup> Sprich, J. D.; Lewandos, G. S. Inorg. Chim. Acta 1983, 76, L241.

<sup>(8)</sup> For reviews, see: Rieke, R. D. *Science* **1989**, *246*, 1260. Bogdanovic, B. *Acc. Chem. Res.* **1988**, *21*, 261. For a review on graphite-metal compounds, see: Csuk, R.; Glanzer, I.; Furstner, A. *Adv. Organomet. Chem.* **1988**, *28*, 85.

<sup>(9)</sup> For reviews, see: Li, C. J.; Chan, T. H. Organic Reactions in Aqueous Media; John Wiley & Sons: New York, 1997. Li, C. J. Tetrahedron 1996, 52, 5643. Chan, T. H.; Isaac, M. B. Pure Appl. Chem. 1996, 68, 919. Lubineau, A.; Auge, J.; Queneau, Y. Synthesis 1994, 741. Lubineau, A.; Auge, J.; Queneau, Y. In Organic Synthesis in Water; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998. Paquette, L. A. In Green Chemistry-Frontiers in Benign Chemical Syntheses and Processes; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: New York, 1998. Li, C. J. *ibid.* Li, C. J. Chem. Rev. 1993, 93, 2023.

Table 1. Magnesium-Mediated Barbier–Grignard Allylation of Benzaldehyde in Various Solvents<sup>a</sup>

| entry | allyl halide  | solvent                        | mediator          | 3/4/benzyl alcohol (%) | conversion (%) of aldehyde |
|-------|---------------|--------------------------------|-------------------|------------------------|----------------------------|
| 1     | allyl bromide | THF/H <sub>2</sub> O (10:0.04) | Mg/I <sub>2</sub> | 100/0/0                | quantitative               |
| 2     | allyl bromide | THF/H <sub>2</sub> O (10:0.2)  | $Mg/I_2$          | 100/0/0                | quantitative               |
| 3     | allyl bromide | THF/H <sub>2</sub> O (10:0.55) | $Mg/I_2$          | 98/0/0                 | 98                         |
| 4     | allyl bromide | THF/H <sub>2</sub> O (10:0.67) | $Mg/I_2$          | 9/43/4                 | 56                         |
| 5     | allyl bromide | THF/H <sub>2</sub> O (10:0.7)  | $Mg/I_2$          | 0/0/0                  | 0                          |
| 6     | allyl bromide | H <sub>2</sub> O               | $Mg/I_2$          | 13/2/1                 | 16                         |
| 7     | allyl bromide | 0.1 N HCl                      | $Mg/I_2$          | 28/66/6                | quantitative               |
| 8     | allyl bromide | 0.1 N NH4Cl                    | Mg                | 41/52/7                | quantitative               |
| 9     | allyl iodide  | 0.1 N NH <sub>4</sub> Cl       | Mg                | 58/34/8                | quantitative               |

<sup>*a*</sup> Entries 1–6, benzaldehyde: allyl halide: magnesium = 1:3:20. Entries 7–9, benzaldehyde: allyl halide: magnesium = 1:3:10 (the use of a stoichiometric amount of magnesium resulted in a low conversion).

## **Results and Discussion**

To start our investigation, we stirred allyl bromide with benzaldehyde and magnesium turnings in aqueous 0.1 N HCl for 3 h at room temperature. TLC measurement of the ether extract clearly showed a spot that corresponded to the desired allylation product. Subsequently, <sup>1</sup>H NMR measurement of the crude reaction mixture showed about 28% of the allylation product (3), together with 66% pinacol coupling product (4)<sup>12</sup> and 6% benzyl alcohol. This promising result prompted us to examine factors that influence the reaction. Subsequently, we have examined in greater detail the effect of the solvent system on the magnesium reaction by using various combinations of water and THF as the reaction solvent, together with a small amount of iodine to initiate the reaction. To reflect the composition of the product mixture, we extracted the reaction mixture with diethyl ether after each reaction, dried the combined organic layers over magnesium sulfate, and carefully removed the low-boiling solvent in vacuo. In the case where no organic cosolvent was involved, the reaction mixture was extracted with CDCl<sub>3</sub> and the extract was examined directly. <sup>1</sup>H NMR measurements of the reaction products under various solvent combinations revealed a very interesting phenomenon. The results are listed in Table 1. In freshly distilled THF dried over sodium/benzophenone, the reaction between benzaldehye, allyl bromide, and magnesium turnings together with a small amount of iodine occurred almost quantitatively, generating the expected allylation product. The addition of a small amount of water to the freshly dried THF did not affect the progress of the reaction. The expected reaction proceeded effectively until about 7% water in THF was used, which suddenly blocked the reaction progress. After repeating this several times, we identified a midpoint at which ca. 56% conversion of the starting benzaldehyde was observed. However, when the composition of the solvent is changed to water alone, a smooth reaction started again, generating the allylation product albeit with a low conversion. The low conversion could be attributed to the formation of magnesium hydroxide on the metal surface, which blocks further reactions. Subsequently, by using aqueous 0.1 N HCl or 0.1 N NH<sub>4</sub>Cl as the reaction solvent, a quantitative conversion was observed that generated a mixture of the allylation and pinacol coupling products. The use of aqueous 0.1 N NH<sub>4</sub>-Cl as the solvent was found to be superior to the use of 0.1 N HCl. Recently, various Lewis acids have been reported to mediate aqueous Barbier-Grignard type





reactions, but in the present study, the use of a catalytic amount of various Lewis acids, such as  $InCl_3$  or  $Sc(OTf)_3$ , did not significantly affect the reaction.<sup>13</sup> However, changing the allyl bromide to allyl iodide further increased the formation of the allylation product (58%). Only a minute amount of the allylation product was observed with allyl chloride. In the absence of 0.1 N HCl, 0.1 N NH<sub>4</sub>Cl, or iodine, virtually no reaction was observed with allyl bromide. Subsequent experiments also revealed that in water alone and with iodine as the initiator, the reaction of allyl bromide proceeded through an allyl iodide intermediate (Scheme 1). The formation of such an allyl iodide intermediate, however, is not necessary in aqueous 0.1 N NH<sub>4</sub>Cl or 0.1 N HCl.

To explain the unusual phenomenon of the solvent change, we postulate that in freshly dried THF, the normal reaction occurs between the organic halide and magnesium, generating the magnesium reagent. Subsequent reaction with carbonyl compounds generates the allylation product. However, in a homogeneous mixture of THF and water, the water molecules would be evenly distributed throughout the solution; hence, the contact between water and the metal surface would prohibit the formation of the organomagnesium reagent. The solvent with ca. 7% water may correspond to the point where the surface is completely covered by water molecules. With water alone, allyl bromide might be squeezed onto the metal surface as a result of hydrophobic effect.<sup>14</sup> Locally and microscopically, magnesium would not be in direct contact with water but would be in contact with allyl bromide. The formation of allylmagnesium can thus occur as in dry organic solvents, which leads to the generation of allylation products.

Subsequently, a variety of aldehydes were tested with this allylation method (eq 1), and the results are listed in Table 2.



(13) For representing examples of using InCl<sub>3</sub> in aqueous Barbiertype reactions, see: Li, X. R.; Loh, T. P. *Tetrahedron: Asymmetry* **1996**, *7*, 1535. For examples of using other Lewis acids for aqueous Barbiertype reactions, see: Kobayashi, S. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998. (14) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and* 

<sup>(14)</sup> Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*, 2nd ed.; John Wiley & Sons: New York, 1980. Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.

Table 2. Allylation Reaction Mediated by Magnesium in Aqueous Medium

| entry  | substrate (1)           | yield ( <b>3</b> , %) <sup>a</sup> | ield ( <b>4</b> , %) <sup>ء</sup> | <sup>ı,b</sup> yield ( <b>11</b> , %) <sup>a</sup> | entry | substrate (1)          | yield ( <b>3</b> , %) <sup>a</sup> | yield ( <b>4</b> , %) <sup>a,</sup> | <sup>b</sup> yield ( <b>11</b> , %) <sup>a</sup> |
|--|-------------------------|------------------------------------|-----------------------------------|--|-------|------------------------|------------------------------------|-------------------------------------|--|
|  | СНО                     |                                    |                                   |  |       | сно                    |                                    |                                     |  |
| 1  | (1a)                    | 58(50)                             | 34                                | 8  | 10    | (1)                    | 47(40)                             | 38                                  | 5  |
| 2  | (1b)<br>F               | 57(50)                             | 36                                | 7  | 11    |                        | )<br>30(21)                        | 54                                  | 16   |
| 3  | FCHO<br>(1c)            | 52(45)                             | 36                                | 12   | 12    |                        | )<br>45(40)                        | 37                                  | 18   |
| 4  | E CHO                   | 53(43)                             | 35                                | 12   | 10    |                        | )                                  |                                     |  |
| 5  | CHO<br>(1e)             | 42(35)                             | 53                                | 5  | 13    | H <sub>3</sub> CO (1m) | 27(10)                             | 52                                  | 21   |
| 6  | CI<br>CI<br>CHO<br>(1f) | 42(34)                             | 37                                | 21   | 14    | NC (1n)                | 3                                  | 2                                   | 95(90)   |
| 7  | CHO<br>(1g)             | 40(32)                             | 47                                | 13   | 15    | OHC CHC                | 0                                  | 0                                   | 0  |
|  | Cl                      |                                    |                                   |  | 16    | CHC<br>(1p)            | 0 0                                | 0                                   | 0  |
| 8  | (1h)                    | 39(30)                             | 54                                | 7  | 17    |                        | ) 0                                | 0                                   | 0  |
| <sup>9</sup> но  | (1i)                    | 53(45)                             | 33                                | 14   | 18 _  | CHC<br>(1r)            | 0 0                                | 0                                   | 0  |
| Reactions were carried out by using aldehyde: allyl iodide: magnesium turning(1: 3: 10) in 0.1 N aqueous NH <sub>4</sub> Cl. <sup>a</sup> Measured by <sup>1</sup> H NMR (isolated yields in parentheses). <sup>b</sup> The total yields of threo and erythro isomers. For entry 15, a polymeric product was obtained. |                         |                                    |                                   |  |       |                        |                                    |                                     |  |

It was found that various aromatic aldehydes are allylated efficiently by allyl halides and magnesium in aqueous 0.1 N NH<sub>4</sub>Cl. It is noteworthy to mention that aromatic aldehydes bearing various halogens were allylated without any problem (entries 2-8). The allylations of hydroxylated aldehydes also gave the allylation products in good yields (entries 9 and 11). Reaction of 4-hydroxybenzaldehyde under the standard conditions led to the formation of the allylation product. The high electron density of hydroxylated benzene led to formation of some ether product (entry 11), which was reflected by the decreased isolated yield. It is interesting to note that although the allylation of 3-methoxybenzaldehyde was equally successful (entry 12) in this reaction, the allylation of a similar substrate, 4-methoxybenzaldehyde, gave the desired product in a much lower yield (entry 13). This could be attributed to the difference in the reduction potential of these two aldehydes. However, the reaction of a cyano-substituted aldehyde gave rise to the formation of a benzyl alcohol product almost in quantitative yield (entry 14). This indicates that a delicate tuning of the reduction potential of the aldehyde is needed in the magnesium reaction. Instead of forming the corresponding allylation product, a dark powder was generated in the reaction of phthalic dicarboxaldehyde with ally iodide and magnesium in 0.1 N NH<sub>4</sub>Cl, which appears to be a polymer as it is insoluble in any organic or inorganic solvent (entry 15). In contrast, aliphatic aldehydes are inert under the reaction conditions (entries 16-18). The result could be attributed to the difference in reduction

potentials between aliphatic and aromatic aldehydes.<sup>15</sup> Such a reactivity difference between an aromatic aldehyde and an aliphatic aldehyde suggests a useful chemoselectivity of the aqueous magnesium reaction.

To further investigate this, competitive studies were carried out between an aliphatic and an aromatic aldehyde (eq 2). Under the standard reaction conditions, a



single allylation product was generated when a mixture of different aliphatic aldehydes (e.g., hexaldehyde, hept-

<sup>(15)</sup> The reduction potentials of aldehydes are affected by many factors. Under similar conditions, the half wave reduction potentials of aliphatic aldehydes are more negative than those of aromatic aldehydes; for example, CH<sub>3</sub>CHO (EtOH, pH = 8,  $E_{1/2} = -1.7$  eV), PhCHO (EtOH, pH = 8,  $E_{1/2} = -1.4$  eV), see: Meites, L.; Zuman, P. *CRC Handbook Series in Organic Electrochemistry*, Vol I–V; CRC Press: Boca Raton, FL, 1977–1982.

aldehyde, or octaldehyde) and benzaldehyde was reacted with allyl iodide. Such a selectivity appears similar to our recently reported manganese-copper method.<sup>16</sup> Aqueous methodologies mediated by other metals (Zn,<sup>17</sup> Sn,<sup>18</sup> and In<sup>19</sup>) all generated a 1:1 mixture of allylation products of both aldehydes. As a comparison, a 1:1 mixture of products was also generated when the allylation was performed with allylmagnesium bromide in ether.

An intramolecular discrimination study was also carried out on a compound bearing both aromatic and aliphatic carbonyl groups. Allylation of dialdehyde 5<sup>16</sup> under the identical conditions mediated by magnesium resulted in 50% yield of the allylation product  $6^{16}$  (eq 3).



A complete chemoselectivity<sup>20</sup> was observed in which the allylation only occurred on the aromatic carbonyl. This result again resembles the manganese-copper method.

The use of terminally substituted ally halides, e.g., 1-chloro-2-butene, 3-methyl-1-chloro-2-butene, cinnamyl chloride, and ethyl 4-bromocrotonate, generated a complicated mixture of products which again resembled the Mn-Cu reaction.<sup>16</sup> In addition, the possibility of reactions between aldehydes and alkyl halides, e.g., CH<sub>3</sub>I and C<sub>2</sub>H<sub>5</sub>I, was also examined by using magnesium as a mediator in water. The reactions did not generate the alkylation product but gave mainly the pinacol products.

The mechanism of the classical magnesium-mediated Barbier and Grignard reactions have been studied intensively by several groups.<sup>21,22</sup> It is generally believed that the radicals on the metal surface are involved in the organomagnesium reagent formation.<sup>21</sup> There is still no conclusion as to the freedom of these free radicals.<sup>22</sup> For the Barbier allylation of carbonyl compounds with magnesium in anhydrous solvent, it is believed that the reaction of allyl bromide on the metal surface generates an organometallic intermediate that is in equilibrium with the charge-separated form and the radical form, as proposed by Alexander (Scheme 2).<sup>23</sup> These two forms will also lead to either the protonation of the carbanion (overall reduction of the halide) or Wurtz-type coupling,<sup>24</sup> whereas the intermediate reacts with aldehydes through the usual six-membered ring mechanism, as proposed by





Young and Roberts<sup>25</sup> (represented by the symbol  $S_E2'$ ).<sup>26</sup> The radical intermediate could lead to the formation of 1,6-hexadiene, pinacol product, and benzyl alcohol.<sup>27</sup>

To gain mechanistic information on the present reaction, several experiments were performed, which can be generalized as follows: (1) The allylation process in aqueous 0.1 N NH<sub>4</sub>Cl was interrupted. The reaction mixture was extracted with CDCl<sub>3</sub>, and a <sup>1</sup>H NMR spectrum was taken directly. The measurement shows the formation of the three products (allylation, pinacol, and benzyl alcohol), reflecting our previous experiments. In addition, 1,5-hexadiene was clearly formed. No propene formation was detected with <sup>1</sup>H NMR. However, GC-MS analysis of the gaseous component collected during the reaction did reveal the presence of propene. (2) Aliphatic aldehydes do not react under the present reaction conditions, which implies that the reduction potential of the aldehyde is important. (3) Although the allylation products can also be observed by using allyl chloride in these types of reactions, it is not as reactive as either allyl bromide or allyl iodide. No reaction was observed with nonactivated alkyl halides. For that matter, halogen substituents on the aromatic rings did not complicate the reaction. This implies that the reduction potential of the halide is also critical to the reaction. On the basis of these observations, we propose an alternative mechanism (Scheme 3) for the aqueous magnesium reaction. The transfer of electrons from magnesium to the allyl halide (path a), the aldehyde (path b), or both generates the corresponding radical anions 7 and 8. Then, reaction of either 7 with the aldehyde or 8 with the allyl halide generates the corresponding allylation product 3.

<sup>(16)</sup> Li, C. J.; Meng, Y.; Yi, X. H.; Ma, J. H.; Chan, T. H. J. Org. Chem. **1997**, 62, 8632. Li, C. J.; Meng, Y.; Yi, X. H.; Ma, J. H.; Chan, T. H. J. Org. Chem. 1998, 63, 7498.

<sup>(17)</sup> Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. Orgnometallics 1983, 2, 191

<sup>(18)</sup> Petrier, C.; Luche, J. L. J. Org. Chem. 1985, 50, 910.

<sup>(19)</sup> Li, C. J.; Chan, T. H. Tetrahedron Lett. 1991, 32, 7017.

<sup>(20)</sup> Trost, B. M. Science 1985, 227, 908.

<sup>(21)</sup> Gomberg, M.; Bachmann, W. E. J. Am. Chem. Soc. 1927, 49, 236.

<sup>(22)</sup> Lawrence, L. M.; Whitesides, G. M. J. Am. Chem. Soc. 1980, 102, 2493. Walborsky, H. M.; Zimmermann, C. J. Am. Chem. Soc. 1992, 114, 4996. Walling, C. Acc. Chem. Res. 1991, 24, 255. Garst, J. F. Acc. Chem. Res. 1991, 24, 95. Walborsky, H. M. Acc. Chem. Res. 1990, 23, 286

<sup>(23)</sup> Alexander, E. R. Principles of Ionic Organic Reactions; John Wiley & Sons: New York, 1950; p 188.

<sup>(24)</sup> For a recent review, see: Billington, D. C. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1.

<sup>(25)</sup> Young, W. G.; Roberts, J. D. J. Am. Chem. Soc. 1946, 68, 1472. [26] Felkin, H.; Roussi, G. *Tetrahedron Lett.* **1965**, 4153. Benkeser,
 R. A.; Broxterman, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 5162. Sakurai,

H.; Kudo, Y.; Miyoshi, H. Bull. Chem. Soc. Jpn. 1976, 49, 1433.

<sup>(27)</sup> Ashby, E. C.; Goel, A. B. J. Am. Chem. Soc. 1977, 99, 310.





The allylation product can also be formed between the radical anions 7 and 8. Reaction of 7 with the allyl halide gives the Wurtz-coupling product **10**; reaction of **8** with the aldehyde gives pinacol product 4. The reaction of these radical anions with water led to the corresponding reduced products 9 and 11.

The encouraging results obtained from the allylation reaction led us to investigate the pinacol coupling reaction mediated by magnesium under aqueous conditions.<sup>28</sup> Although discovered well over a century ago, the pinacol coupling reaction is still one of the most important reactions for the formation of carbon-carbon bonds.<sup>12</sup> Traditionally, pinacol couplings have been effected by using metals such as sodium,<sup>29</sup> lithium,<sup>30</sup> or magnesium-(I) iodide<sup>21</sup> (and Rieke Mg<sup>31</sup>) under strictly anhydrous conditions. Other reagents used for such a reaction include chromium or vanadium,<sup>32</sup> SmI<sub>2</sub>,<sup>33</sup> Ce-I<sub>2</sub>,<sup>34</sup> Yb,<sup>35</sup> Bu<sub>3</sub>SnH,<sup>36</sup> Al(Hg),<sup>37</sup> and Rieke Mn,<sup>38</sup> as well as the versatile TiCl<sub>3</sub>-based reducing agents (the McMurry pinacol coupling).<sup>39</sup> Recently, pinacol coupling reactions mediated by Ti(III) in aqueous media have been intensively investigated.<sup>40</sup> Other metals such as Zn-Cu<sup>41</sup> or

- (36) Hays, D. S.; Fu, G. C. J. Am. Chem. Soc. 1995, 117, 7283.
  (37) Hulce, M.; LaVaute, T. Tetrahedron Lett. 1988, 29, 525.
  (38) Rieke, R. D.; Kim, S. H. J. Org. Chem. 1998, 63, 5235.

 (39) For reviews, see: Furstner, A.; Bogdanovic, B. Angew. Chem., Int. Ed. Engl. 1996, 35, 2443. McMurry, J. E. Chem. Rev. 1989, 89, 1513. Kahn, B. E.; Rieke, R. D. Chem. Rev. 1988, 88, 733.

(40) Clerici, A.; Porta, O. Tetrahedron Lett. 1982, 23, 3517. Clerici, A.; Porta, O. J. Org. Chem. 1982, 47, 2852. Gansauer, A. Chem. Commun. 1997, 457. Clerici, A.; Porta, O.; Riva, M. Tetrahedron Lett. 1981, 22, 1043 and references cited therein. Barden, M. C.; Schwartz, J. J. Am. Chem. Soc. 1996, 118, 5484.

(41) Delair, P.; Luche, J. L. J. Chem. Soc., Chem. Commun. **1989**, 398. See also: Tsukinoki, T.; Kawaji, T.; Hashimoto, I.; Mataka, S.; Tashiro, M. Chem. Lett. 1997, 235. Tanaka, K.; Kishigmi, S.; Toda, F. J. Org. Chem. 1990, 55, 2981.

In<sup>42</sup> have also been found to promote the aqueous reaction under ultrasonic radiation and manganese in acidic conditions.<sup>15,16</sup> When benzaldehyde was reacted with magnesium in aqueous 0.1 N NH<sub>4</sub>Cl, the corresponding pinacol coupling product was obtained in high yield. The use of water alone as the reaction solvent was also effective; however, it resulted in a low conversion of the starting material. The use of aqueous 0.1 N HCl as solvent also decreased the yield of the desired pinacol coupling products. Other aryl aldehydes (eq 4) were

coupled similarly to obtain the corresponding diols 2 (Table 3). Aromatic aldehydes bearing halogens (bromo, chloro, fluoro) were coupled without any complication in product formation. Furfural coupled equally well under the reaction conditions. The couplings of aryl ketones were also successful (entries 15 and 16). An aliphatic aldehyde, however, was inert under the reaction conditions (entry 11). The magnesium-mediated pinacol coupling in water appears strongly affected by steric effects. The position of the substituents present on the aromatic rings shows a dramatic effect on the course of the reaction. Although no substantial difference was observed between meta- or para-substituted aromatic aldehydes (compare entries 3 and 4, 6 and 7, 9 and 10), the presence of ortho-substituents increased the formation of the benzyl alcohol product (entries 2, 5, and 8). A similar increase in the amount of the benzyl alcohol product was observed with increase in the size of the ortho-substituents. When two substituents were present (entry 13), no pinacol coupling product was obtained; only complete reduction of the aldehyde (to give the benzyl alcohol product) was observed.

In the notable report by Gomberg and Bachmann,<sup>21</sup> the use of a  $Mg/MgI_2$  (1:1) mixture in anhydrous benzene or ether for carbonyl coupling was rationalized through the

<sup>(28)</sup> Zhang, W. C.; Li, C. J. J. Chem. Soc., Perkin Trans. 1 1998, 3131.

 <sup>(29)</sup> Nelsen, S. F.; Kapp, D. C. J. Am. Chem. Soc. 1986, 108, 1265.
 (30) Pradhan, S. K.; Thakker, K. R. Tetrahedron Lett. 1987, 28, 1813. (31) Furstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. J. Chem. Soc.,

Perkin Trans. 1 1988, 1729. (32) Conant, J. B.; Cutter, H. B. J. Am. Chem. Soc. 1926, 48, 1016.

<sup>(33)</sup> Namy, J. L.; Souppe, J.; Kagan, H. B. Tetrahedron Lett. 1983, 24, 765.

<sup>(34)</sup> Imamoto, T.; Kusumoto, T.; Hatanaka, Y.; Yokoyama, M. Tetrahedron Lett. 1982, 23, 1353 (35) Hou, Z.; Takamine, K.; Fujiwara, Y.; Taniguchi, H. Chem. Lett.

<sup>1987, 2061.</sup> 

<sup>(42)</sup> Lim, H. J.; Keum, G.; Kang, S. B.; Chung, B. Y.; Kim, Y. Tetrahedron Lett. 1998, 39, 4367.

Table 3. Pinacol Coupling Mediated by Magnesium in Aqueous Medium

| entry            | substrate (1)  | yield ( <b>4</b> , %) <sup>a</sup> | yield ( <b>11</b> , %) <sup>a</sup> | threo:erythro <sup>b</sup> | entry | substrate (1)                         | yield ( <b>4</b> , %) <sup>a</sup> | yield ( <b>11</b> , %) <sup>a</sup> | threo:erythro <sup>b</sup> |
|------------------|--|------------------------------------|-------------------------------------|----------------------------|-------|---------------------------------------|------------------------------------|-------------------------------------|----------------------------|
| 1                | CHO<br>(1a)  | 88(80)                             | 1                                   | 59:41                      | 10    | H <sub>3</sub> CO <sup>CHO</sup> (1m) | 96(89)                             | 0                                   | 61:39                      |
| 2                | CHO<br>(1b)  | 73(67)                             | 10                                  | 51:49                      | 11    | CHO<br>(1q)                           | 0                                  | 0                                   | na                         |
| 3                | F CHO<br>(1c)  | 90(83)                             | 6                                   | 54:46                      | 12    | CHO<br>(1s)                           | (65)                               | (8)                                 | 61:39                      |
| 4                | F CHO (1d)   | 93(87)                             | 0                                   | 80:20                      | 13    | CI<br>CHO<br>(1s)                     | 0                                  | (74)                                | na                         |
| 5                | CHO<br>(1e)<br>CI  | 61(50)                             | 27                                  | 52:46                      |       |                                       | quant (00                          |                                     |                            |
| 6                | CI CHO<br>(1f)   | 56(42)                             | 11                                  | 54:46                      | 14    | O CHO<br>(1u)                         | quant.(92                          | :) 0                                | 64:36                      |
| 7                | CHO<br>CI<br>CI  | (90)                               | (7)                                 | 50:50                      | 15    |                                       | H <sub>3</sub> 66(59)              | 8                                   | 53:47                      |
| 8                | (1j)   | (62)                               | (30)                                | 30:79                      | 16    |                                       | H <sub>3</sub> (41)                | na                                  | 53:47                      |
| 9 H              | l <sub>3</sub> CO CHO (1I)   | (78)                               | 0                                   | 54:46                      | 17    | CH<br>(1w)                            | H <sub>3</sub> 0                   | 0                                   | na                         |
| <sup>a</sup> Me: | <sup>a</sup> Measured by <sup>1</sup> H NMR (isolated yields in parentheses). <sup>b</sup> Three:ervthre ratios were measured by <sup>1</sup> H NMR based on the intensities of benzylic |                                    |                                     |                            |       |                                       |                                    |                                     |                            |

<sup>a</sup>Measured by <sup>I</sup> H NMR (isolated yields in parentheses). <sup>b</sup>*Threo:erythro* ratios were measured by <sup>I</sup> H NMR based on the intensities of benzylic hydrogens. For entry 15, 26% of the starting material was recovered.





formation of magnesium(I) iodide (MgI) and the coupling of radical intermediates. In the present investigation, no magnesium salt was present, thus indicating the apparent occurrence of the reaction through a different mechanism. We tentatively rationalize the experimental results in the aqueous conditions by Scheme 4. During the reaction, there are two potential pathways competing with each other generating either the pinacol coupling product (path a) or the benzyl alcohol product (path b). The increase in steric hindrance around the carbonyl would destabilize the transition state in the formation of the pinacol product (route a), which results in an increase in the formation of the benzyl alcohol product.

In conclusion, we found magnesium to be effective for mediating both carbonyl allylation and pinacol coupling reactions in aqueous 0.1 N NH<sub>4</sub>Cl. The product formation of the aqueous magnesium-mediated reactions strongly depends on the reduction potential of the substrates and the steric environment of the reaction site. Nonactivated organic halides and aliphatic aldehydes are not reactive under the present conditions. Thus, in aqueous medium, magnesium offers a high chemoselectivity toward aromatic aldehydes in the allylation of carbonyl compounds and in the pinacol coupling reaction. The product formation of the pinacol coupling was strongly influenced by the presence of substituents around the carbonyl group. Increased congestion around the carbonyl inhibits the carbon–carbon bond formation. We are presently exploring this new reactivity and selectivity in synthetic application.

## **Experimental Section**

Anhydrous reactions were performed under an atmosphere of nitrogen. THF was distilled from sodium/benzophenone ketyl when used as reaction solvent. Water was deionized before use. Magnesium turnings were purchased from Fisher and used directly as received. All other chemicals were also used without additional purification. Flash chromatography employed E. Merck silica gel (Kiesegel 60, 230–400 mesh) purchased from Scientific Adsorbents. <sup>1</sup>H NMR measurements were conducted at 400 MHz in CDCl<sub>3</sub>. Mass spectra were obtained at the Center of Instrumental Facility of Tulane University. All compounds involved in the studies are known ones.

**General Procedure for Allylation of Aldehydes.** To a mixture of benzaldehyde (200 mg, 1.89 mmol) and allyl iodide (950 mg, 5.67 mmol) in aqueous 0.1 N NH<sub>4</sub>Cl (10 mL) were

added magnesium turnings (1 g, 41.6 mmol). The mixture was stirred at room temperature for 12 h. The reaction was quenched by aqueous 1 N HCl and extracted with CDCl<sub>3</sub>. The extract was dried briefly over magnesium sulfate and the <sup>1</sup>H NMR spectrum of the extract was taken. The measurement shows benzaldehyde (0), the allylation product (58%), the pinacol coupling product (34%), and benzyl alcohol (8%). The crude product was purified through flash column chromatography on silica gel (hexanes-ethyl acetate) to give the desired allylation product (139 mg, 50%).

General Procedure for Pinacol Coupling of Aldehydes. A suspension of benzaldehyde (20 mg, 1.89 mmol) and magnesium turning (1 g, 41.67 mmol) in aqueous 0.1 N NH<sub>4</sub>-Cl (10 mL) was stoppered and stirred overnight (vigorously) under an atmosphere of air and at room temperature. The reaction was quenched with 3 N aqueous HCl and extracted with ethyl acetate ( $3 \times 20$  mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated in vacuo to give a crude material, which was purified by flash chromatography on silica gel to afford the pinacol product (162 mg, 80%) as a white crystalline solid.

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Registry Numbers (supplied by author). 1-phenyl-3-buten-1-ol, 936-58-3; 1-(2-furanyl)-3-buten-1-ol, 6398-51-2; 1-(4-chlorophenyl)-3-buten-1-ol, 14506-33-3; 1-(2chlorophenyl)-3-buten-1-ol, 24165-66-0; 1-(3-chlorophenyl)-3-buten-1-ol, 67472-21-3; 1-(1-naphthyl)-3-buten-1-ol, 72551-06-5; 1-(4-methoxyphenyl)-3-buten-1-ol, 24165-60-4; 1-(3-methoxyphenyl)-3-buten-1-ol, 156091-01-9; 1-(3bromophenyl)-3-buten-1-ol, 114095-73-7; 4-hydroxymethylbenzaldehyde, 52010-97-6; 1-(4-hydroxyphenyl)-3-buten-1-ol, 109272-34-6; 1-(4-cyanophenyl)-3-buten-1-ol, 71787-53-6; 1,2-bis(4-methoxyphenyl)-1,2-ethanediol, 4464-76-0; 1,2-bis(2-fluorophenyl)-1,2-ethanediol, 165677-46-3; 1,2-bis(3-fluorophenyl)-1,2-ethanediol, 177981-31-6; 1,2bis(4-fluorophenyl)-1,2-ethanediol, 119441-86-0; 1,2-bisphenyl-1,2-ethanediol, 492-70-6; 1,2-bis(2-chlorophenyl)-1,2-ethanediol, 71776-59-5; 1,2-bis(3-chlorophenyl)-1,2-37580-83-9; 1,2-bis(4-chlorophenyl)-1,2ethanediol, ethanediol, 38152-44-2; 1,2-bis(p-tolyl)-1,2-ethanediol, 24133-59-3; 1,2-bis(1-naphthenyl)-1,2-ethanediol, 116204-39-8; 1,2-bis(2-furanyl)-1,2-ethanediol, 4464-77-1; 2,3diphenyl-2,3-butanediol, 1636-34-6; 2,3-bis[4-methoxyphenyl]-2,3-butanediol, 21985-99-9.

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