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Synthesis of Functionalized Diarylmethanes via a Copper-Catalyzed Cross-Coupling of Arylmagnesium Reagents with Benzylic Phosphates

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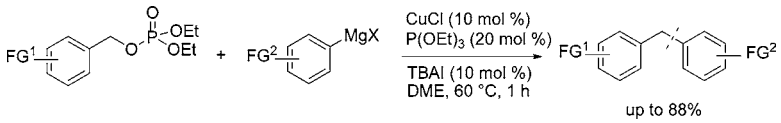
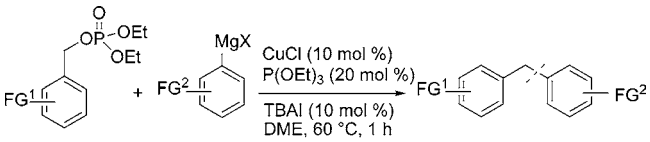
ABSTRACT



A combination of copper chloride, triethyl phosphite, and tetrabutylammonium iodide is a very efficient catalytic system for the synthesis of polyfunctionalized diarylmethanes, using the cross-coupling reaction of arylmagnesium halides with benzylic phosphates. The antibiotic Trimethoprim has been prepared using this Cu(I)-catalyzed cross-coupling in 52% overall yield (four steps).

Transition-metal-catalyzed cross-coupling reactions provide powerful tools for the formation of carbon−carbon bonds.[1] The cross-coupling between benzylic electrophiles and aryl organometallics is a useful approach to diarylmethanes, which play an important role in several biologically active compounds[2] and drugs[3] such as Trimethoprim **1**, a synthetic antibiotic; Papaverin, a muscle relaxing agent; or Piritrexim, a dihydrofolate reductase inhibitor for the potential treatment of cancer. Herein, we wish to report a new Cu(I)-mediated cross-coupling reaction, using functionalized aromatic magnesium reagents with various functionalized benzylic phosphates (Scheme 1). Several Cu(I)-catalyzed cross-coupling reactions between Grignard reagents and alkyl or benzyl halides have been reported.[4] The Suzuki−Miyaura cross-coupling can be used to prepare diarylmethane derivatives,

Scheme 1. Cross-Coupling between Benzylic Phosphates of Type **4** and Arylmagnesium Reagents of Type **3** Leading to Diarylmethanes of Type **2**



4 **3** **2**

but this reaction requires an expensive palladium catalyst and often sophisticated ligands.[5]

We envisioned that benzylic phosphates,[6] which are easily available from the corresponding alcohols and are highly

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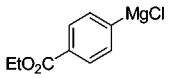
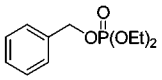
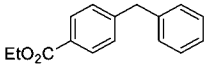
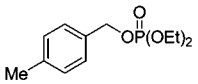
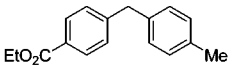
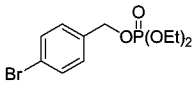
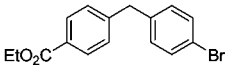
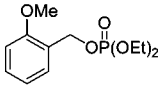
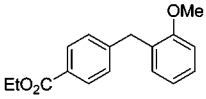
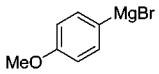
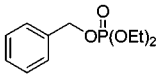
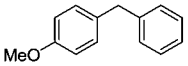
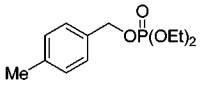
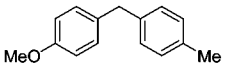
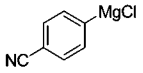
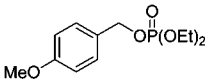
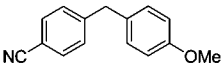
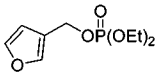
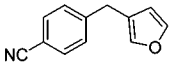
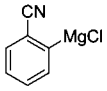
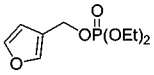
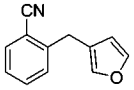
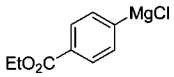
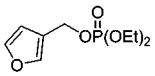
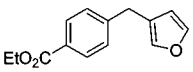
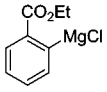
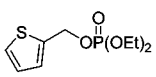
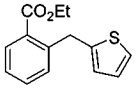
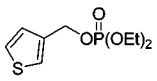
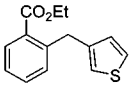
Table 1. Cu(I)-Mediated Cross-Coupling between Functionalized Arylmagnesium Reagents of Type **3** and Benzylic Phosphates of Type **4**, Leading to Polyfunctionalized Diarylmethanes of Type **2**

entry	arylmagnesium reagent **3**	benzylic phosphate **4**	product	yield [%][a]
1	 **3a**	 **4a**	 **2a**	80
2	**3a**	 **4b**	 **2b**	88
3	**3a**	 **4c**	 **2c**	72
4	**3a**	 **4d**	 **2d**	81
5	 **3b**	 **4a**	 **2e**	73
6	**3b**	 **4b**	 **2f**	80
7	 **3c**	 **4e**	 **2g**	72
8	**3c**	 **4f**	 **2h**	63
9	 **3d**	 **4f**	 **2i**	88
10	 **3a**	 **4f**	 **2j**	71
11	 **3e**	 **4g**	 **2k**	61
12	**3e**	 **4h**	 **2l**	82

[a] Isolated yield of analytically pure products.

reactive intermediates, can be used in the copper-catalyzed cross-coupling reaction with arylmagnesium reagents. Because we have recently reported several methods for preparing polyfunctionalized aryl and heteroarylmagnesium species,[7] this approach would allow the preparation of highly functionalized diarylmethanes of type **2**.

Thus, we have found that polyfunctionalized arylmagnesium reagents of type **3**, which were easily prepared via a halogen−magnesium exchange or by direct insertion, smoothly react with benzylic phosphates of type **4** in the presence of a Cu(I) catalyst, leading to highly functionalized diarylmethanes **2** in good to excellent yields. Triethyl phosphite, which is stabilizing the intermediate arylcopper reagent, and tetrabutylammonium iodide proved to be essential additives. The reaction is very fast, and full conversion is observed after 1 h at 60 °C. The scope of this new cross-coupling reaction is summarized in Table 1.

Both electron-poor arylmagnesium reagents, bearing an ester or nitrile function **3a**, **3c**, **3d**, or **3e**, and an electron-rich arylmagnesium reagent, bearing a methoxy group **3b**, undergo the reaction with functionalized benzylic phosphates in good to excellent yields. The benzyl phosphates may bear a bromide **4c**, a methyl group **4b**, or a methoxy group in ortho (**4d**) or para (**4e**) position. Cross-coupling between these reagents leads to the desired diarylmethanes **2a**−**2g** in high yields up to 88% (entries 1−7).

Also, heterocyclic phosphates such as the furan derivative **4f** or the thiophene derivatives **4g** and **4h** are excellent electrophiles in this reaction, yielding 3-substituted functionalized furans **2h**−**2j** (entries 8−10) and 2- or 3-substituted functionalized thiophenes **2k** and **2l** (entries 11 and 12) in yields up to 88%.

Furthermore, using this copper-catalyzed cross-coupling reaction, a broad variety of functionalized indole derivatives can be prepared (Scheme 2).

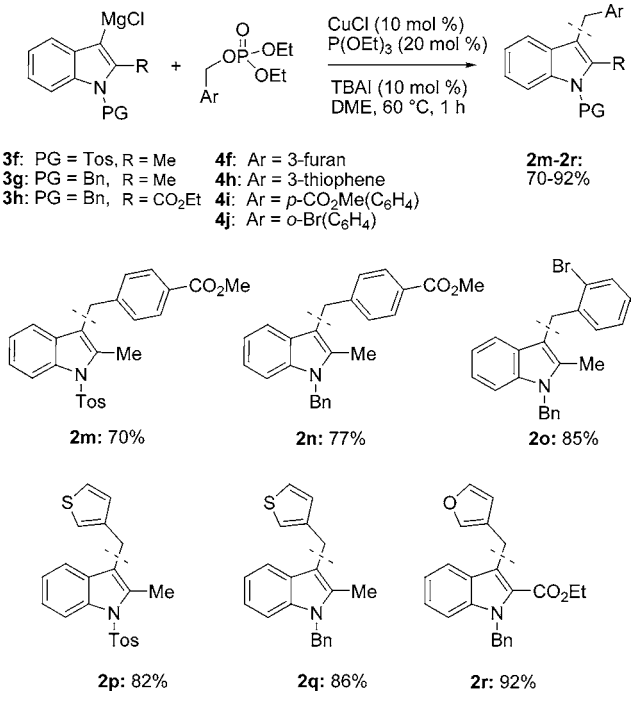
Thus, the readily available magnesiated indoles **3g** and **3f** can be coupled with benzylic phosphates bearing an ester group **4i** or a bromide **4j** leading to the desired products **2m**−**2o** in 70−85% yield, as shown in Scheme 2.

Moreover, two heterocyclic moieties can be linked together. Thus, various magnesiated functionalized indoles **3f**−**3h** were treated with furan **4f** or thiophene **4h** leading to the heterocyclic derivatives **2p**−**2r** in 82−92% yield.

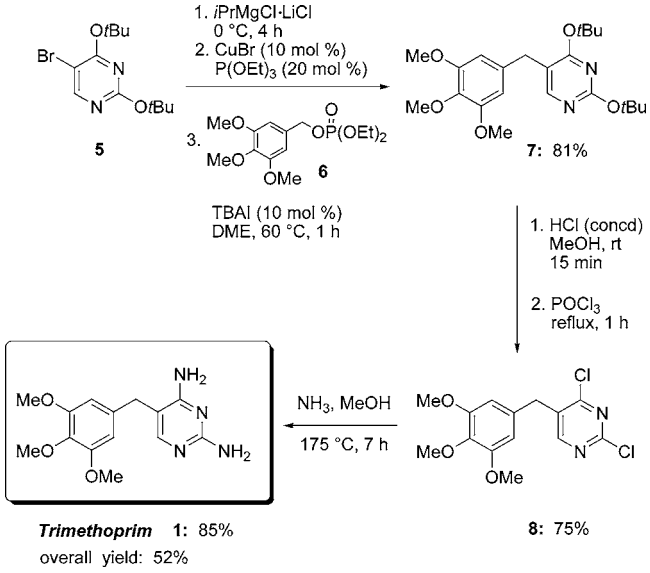
To demonstrate the synthetic potential of this reaction, we have developed a synthetic route, to synthesize Trimethoprim **1** in four steps (Scheme 3). The treatment of 5-bromo-2,4-di-*tert*-butoxypyrimidine (**5**) with *i*PrMgCl·LiCl (0 °C, 4 h) provides the intermediate magnesium reagent in >95% yield.[8] Its cross-coupling with diethyl 3,4,5-trimethoxybenzyl phosphate (**6**) (60 °C, 1 h) led to 2,4-di-*tert*-butoxy-5-(3,4,5-trimethoxybenzyl)-pyrimidine (**7**) in 81% yield.

The pyrimidine derivative **7** was deprotected using concentrated HCl in methanol giving the corresponding uracil derivative, which was converted to the 2,4-dichloro-5-(3,4,5-trimethoxybenzyl)-pyrimidine (**8**) by using $POCl_3$ in 75% yield over two steps.[9] The nucleophilic substitution of the chlorines by two amino functions was performed by heating

Scheme 2. Substituted Indole Derivatives **2m**−**2r**



Scheme 3. Synthesis of Trimethoprim **1**



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(6) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017.

(7) (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (b) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(8) For the preparation of **5**, see: Peters, D.; Hörnfeldt, A. B.; Gronowitz, S. *J. Heterocycl. Chem.* **1990**, *27*, 2165. For the Br−Mg exchange on pyrimidines, see: Boudet, N.; Knochel, P. *Org. Lett.* **2006**, *8*, in press.

pyrimidine derivative **8** with a 7 M solution of methanol with ammonia at 175 °C in the autoclave, providing Trimethoprim **1** in 85% yield.[9]

This reaction sequence leads to 5-(3,4,5-trimethoxybenzyl)-pyrimidine-2,4-diamine (**1**) (Trimethoprim) in an overall yield of 52% and offers an easy access to various analogues of this compound because a broad variety of functionalized and heterocyclic phosphates can be used in this reaction.

In summary, we have developed a new, efficient copper-catalyzed reaction for the formation of highly functionalized carbocyclic and heterocyclic diarylmethanes using catalytic amounts of triethyl phosphite and tetrabutylammonium iodide as additives.[10] This convenient protocol complements the Suzuki−Miyaura cross-coupling reaction and does not require expensive palladium catalysts or sophisticated ligands. Further applications are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0616790

(10) **Typical procedure of ethyl 4-(4-methylbenzyl)benzoate (2b):** In a flame-dried Schlenk tube under nitrogen, ethyl 4-iodobenzoate (207 mg, 0.75 mmol) is dissolved in DME (0.5 mL) and cooled to −20 °C. *i*PrMgCl (0.89 mL, 0.80 mmol, 0.9 M in THF) is added dropwise via syringe. After 20 min at −20 °C, CuCl (5.0 mg, 10 mol %) and $P(OEt)_3$ (17 mg, 20 mol %) are added. This mixture is added over 30 min via cannula to a mixture of diethyl 4-methylbenzyl phosphate (129 mg, 0.50 mmol) and TBAI (19 mg, 10 mol %) at 60 °C. The reaction mixture is heated at 60 °C for 1 h. GC analysis of a reaction aliquot shows completion of the reaction. The reaction mixture is quenched with saturated NH_4Cl solution, extracted with ether, and dried (Na_2SO_4), and the crude product was purified by flash chromatography (pentane/ether 19:1). Compound **2b** was isolated as a colorless liquid (112 mg, 88%).