



## Copper(II) bromide as an efficient catalyst for the selective protection and deprotection of alcohols as bis(4-methoxyphenyl)methyl ethers

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### ABSTRACT

In a cheap and eco-friendly process, primary and secondary alcohols were easily protected as bis(methoxyphenyl)methyl (BMPM) ethers in good yields using CuBr<sub>2</sub> as a catalyst in acetonitrile at room temperature. Deprotection could easily be achieved using the same catalyst but in ethanol. Both Cu-catalyzed protection and deprotection were orthogonal to other methods and fully compatible with other functional groups.

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### 1. Introduction

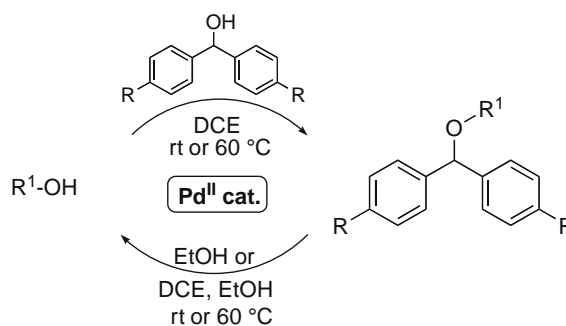
Tuning the reactivity of functional groups is often a key task in multi-step synthesis and to do so, organic chemists used a full arsenal of protecting groups.<sup>1,2</sup> Compatibility with other functions, chemoselective removal, and high yields in protection and deprotection steps are key elements for the use and development of new protecting groups.

These aspects are especially important for alcohol groups due to their dual nucleophilic and acidic properties. Alcohols are thus usually converted to less reactive and non-acidic functional groups such as ethers, esters, and acetals. Among the panel of alcohol protecting groups already developed, benzyl-type ethers are the most commonly used in organic synthesis, due to their deprotection conditions orthogonal to other protecting and functional groups, despite troubles often arising due to the basic or acid conditions required for their introduction.<sup>1,2</sup> Benzyl and triphenylmethyl groups, substituted or not with *para*-methoxy groups,<sup>3</sup> are the most popular in this family, whereas diphenylmethyl groups, substituted or not, are still scarcely used in total synthesis.

In this context, aiming at developing new and milder solutions for such benzyl-type protecting groups, we are currently exploring

the behavior of diphenylmethyl derivatives. We recently described new chemoselective conditions for the protection and deprotection of alcohols as diphenylmethyl (DPM; Scheme 1; R = H) and bis(methoxyphenyl)methyl (BMPM; Scheme 1; R = OMe) ethers using PdCl<sub>2</sub> or PdCl<sub>2</sub>(MeCN)<sub>2</sub> as a catalyst.<sup>4,5</sup>

The use of palladium even as a catalyst could nevertheless be a drawback for therapeutic applications,<sup>6</sup> as well as from more general environmental concerns<sup>7</sup> and of course, from an economical point of view.<sup>8</sup> In order to perform these Lewis acid-mediated transformations in a more eco-friendly way and to decrease the



**Scheme 1.** Pd-catalyzed protection of alcohols as DPM (R = H) or BMPM (R = OMe) ethers and their deprotection.

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catalyst cost, we envisaged replacing palladium salts or complexes by copper salts. Indeed, our preliminary investigation revealed that  $\text{CuCl}_2$  or  $\text{CuSO}_4$  was able to protect alcohols as DPM ethers, although very long reaction times were needed.<sup>4</sup> Moreover,  $\text{CuCl}_2$  associated with water in acetonitrile has been reported for deprotection of trityl ethers.<sup>9</sup> It was thus clear to us that the scope and the limitation of the use of copper salts as catalyst for the protection of alcohols with benzhydryl derivatives and deprotection of substituted benzhydryl ethers are still underestimated.

We present here a very simple, cheap, and environmentally friendly procedure for the protection and deprotection of alcohols as BMPM ethers, offering smooth reaction conditions. Chemoselectivity and orthogonality with other protecting groups are also described in this Letter.

## 2. Results

In order to find the best catalyst, various copper salts were screened in the transformation of bis(*para*-methoxyphenyl)methanol, the most reactive of the benzhydryl derivatives, in ethanol as a reagent and a solvent at room temperature (Table 1).

As already observed with DPM,<sup>4</sup> copper sulfate was able to catalyze the reaction. This protection occurred with higher yield and at lower temperature than the Pd(II)-catalyzed reactions<sup>4,5</sup> but unfortunately with long reaction time (entry 1). Copper(II) chloride, hydrated or not (entries 2 and 3), gave nearly similar results but within only 4 or 5 h. The nature of the Cu(II) counter-ion thus played a critical role, probably through modulation of Cu(II) Lewis acidity. Indeed,  $\text{Cu}(\text{OAc})_2$  did not catalyze the reaction at all, whereas  $\text{Cu}(\text{OTf})_2$  catalyzed well (entry 4 vs entry 5). The latter surprisingly slowed down the reaction rate again and thus behaved as  $\text{CuSO}_4$  in this protection (entry 5 vs entry 1). We were eventually pleased to find that  $\text{CuBr}_2$  was very effective, quantitatively leading to the BMPM ether in only 1.5 h at room temperature (entry 6).

Having these reaction conditions in hand, we checked if all classes of alcohols could be protected by this procedure (Table 1, en-

tries 6–13). As primary alcohols, secondary alcohols were easily protected whereas tertiary alcohols gave a messy reaction mixture (entry 6 vs entry 7 vs entry 8). Interestingly, diols were only protected as mono BMPM ethers in very high to good yields, probably depending on the way chelation occurred (entry 9 vs entry 10). The more sensitive allylic and propargylic alcohols were rewardingly easily protected in nearly quantitative yields under these conditions (entries 11–13). It is worth noting that propargylic alcohol and (*Z*)-but-2-en-1,4-diol could not be protected when using Pd catalysts due to degradation.<sup>4,5</sup> The latter results highlighted the smoothness and effectiveness of this new procedure.

For total synthesis applications, we also set up conditions with solvent. Acetonitrile was first selected as a solvent for solubility reasons and we screened copper salts with 4-benzyloxybutanol as model alcohol (Table 2) again. Except for copper sulfate, the same trends as without solvent were observed (Table 2 vs Table 1, entries 1–6) and the superiority of  $\text{CuBr}_2$  was again observed (entry 6 vs entries 1–5). Interestingly, the protection also occurred in less polar and coordinating solvents such as dioxane and THF with similar rates and yields (entries 7 and 8 vs entry 6).

With these alternative conditions in hand, we again examined the scope of this protection, emphasizing the compatibility of this method with other protecting groups (Table 3).

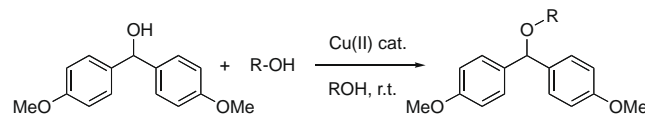
Isomenthol was selected as a secondary alcohol and its protection proved to be very fast at room temperature (Table 3, entry 1). Benzylic and allylic alcohols were also easily protected (entries 2 and 3). As suspected from Cu(II) coordination chemistry<sup>10</sup> and its biological implications,<sup>11</sup> phenol could not be protected under our conditions (entry 5) and even interfered with other protections (entry 4 vs entry 3).


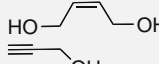

Conventional arylmethyl protecting groups such as benzyl and *p*-methoxybenzyl (entries 6 and 7) proved fully compatible, whereas trityl ether rapidly exchanged with bis(methoxyphenyl)methyl group leading to a mixture of mono- and diprotected BMPM ethers (entry 8).<sup>12</sup>

Ester and acetal groups were also fully compatible with our protection conditions as exemplified with 4-acetoxybutanol (entry 9) and the more sophisticated methyl 2,3-*O*-cyclohexylidene- $\beta$ -D-ribofuranoside (entry 10). It is worth noticing that  $\text{CuCl}_2$  was described as an effective catalyst for the deprotection of acetals.<sup>13</sup> Our conditions are thus clearly milder. Common N-protecting groups such as benzyloxycarbonyl and *tert*-butyloxycarbonyl were also compatible with our conditions (entries 11 and 12).

Since diols were easily protected without a solvent, we examined the protection of hexane-1,5-diol looking for some selectivity for the primary alcohol vs the secondary one in this molecule (en-

**Table 1**  
Effect of copper salts on BMPM ether formation and solvent-free alcohol protection<sup>a</sup>



Entry	Catalyst	R-OH	Time (h)	Yield <sup>b</sup> (%)
1	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	EtOH	24	100
2	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	EtOH	5	100
3	$\text{CuCl}_2$	EtOH	4	99
4	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	EtOH	6	n.r. <sup>c</sup>
5	$\text{Cu}(\text{OTf})_2$	EtOH	21	99
6	$\text{CuBr}_2$	EtOH	1.5	100
7	$\text{CuBr}_2$	<i>i</i> PrOH	2	94 <sup>d</sup>
8	$\text{CuBr}_2$	<i>t</i> BuOH	18	n.d. <sup>e,f</sup>
9	$\text{CuBr}_2$	$(\text{CH}_2-\text{OH})_2$	2	93 <sup>g</sup>
10	$\text{CuBr}_2$	$\text{HO}-(\text{CH}_2)_4-\text{OH}$	6	98 <sup>g</sup>
11	$\text{CuBr}_2$		2	100
12	$\text{CuBr}_2$		2	94
13	$\text{CuBr}_2$		2	100

<sup>a</sup> [BMPM-OH] = 1 M,  $[\text{Cu}^{2+}] = 0.1$  M.

<sup>b</sup> Isolated yield.

<sup>c</sup> No reaction, starting material recovered.

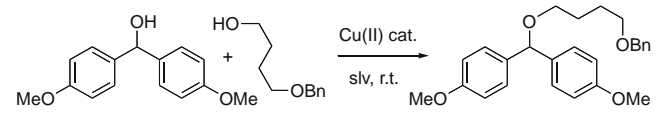
<sup>d</sup> BMPM-OH poorly soluble.

<sup>e</sup>  $\text{CuBr}_2$  partially soluble, reaction temperature 30 °C.

<sup>f</sup> Not determined.

<sup>g</sup> Only the monoprotected diol was observed.

**Table 2**  
Effect of copper salts on BMPM ether formation (condition with solvent)<sup>a</sup>



Entry	Catalyst	Solvent	Time (h)	Yield <sup>b</sup> (%)
1	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	$\text{CH}_3\text{CN}$	30	n.r. <sup>c</sup>
2	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	$\text{CH}_3\text{CN}$	7	70
3	$\text{CuCl}_2$	$\text{CH}_3\text{CN}$	6	73
4	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	$\text{CH}_3\text{CN}$	8	n.r. <sup>c</sup>
5	$\text{Cu}(\text{OTf})_2$	$\text{CH}_3\text{CN}$	24	59
6	$\text{CuBr}_2$	$\text{CH}_3\text{CN}$	2	90
7	$\text{CuBr}_2$	THF	2	86
8	$\text{CuBr}_2$	Dioxane	2	86

<sup>a</sup> [BMPM-OH] = 1 M, [alcohol] = 0.9 M, and  $[\text{Cu}^{2+}] = 0.1$  M.

<sup>b</sup> Isolated yield.

<sup>c</sup> No reaction, starting material recovered.

**Table 3**  
Effect of copper salts on BMPM ether formation (condition with solvent)<sup>a</sup>

Entry	Alcohols	Products	Time (h)	Yield <sup>b</sup> (%)
1			0.5	85
2			3	97
3			1.5	88
4			24	n.d. <sup>c</sup>
5		—	24	n.d. <sup>c</sup>
6			15	95
7			48	92
8			2	86 <sup>d</sup>
				13
9			1	92
10			12	78
11			0.5	94
12			3.5	86
13			48	45 <sup>e</sup>

<sup>a</sup> [BMPM–OH] = 1 M, [alcohol] = 0.9 M, and [Cu<sup>2+</sup>] = 0.1 M.

<sup>b</sup> Isolated yield.

<sup>c</sup> Not determined, complex mixtures were produced in which the product was detected by NMR.

<sup>d</sup> Yield based on BMPM–OH.

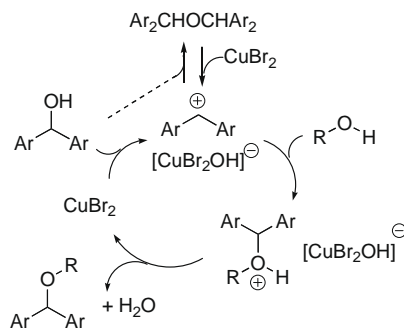
<sup>e</sup> See text, starting material being recovered.

try 13). Despite the low reactivity, only monoprotected derivatives were observed, but as a 5/1 inseparable mixture, the primary alcohol being preferentially protected.

From a mechanistic point of view, copper salts probably act similarly to the palladium(II)-catalyzed reactions we already described (Scheme 2). Coordination of copper salt to the hydroxy group of substituted benzyl alcohol might lead to a benzhydryl carbocation or an intimate ion pair. This intermediate could then be trapped by alcohols, leading to BMPM ethers after formation of water and regeneration of catalyst. Dimerization of BMPM–OH rapidly occurred in this reaction, but the so-formed ether

(BMPM)<sub>2</sub>O disappeared during the course of this transformation, supporting the proposed mechanism.

Due to this probable mechanism and as for the Pd(II)-catalyzed DPM and BMPM deprotection,<sup>4,5</sup> it was tempting to check the reversibility of this process. BMPM ethers were thus mixed with catalytic amounts of copper bromine in a nucleophilic solvent such as ethanol (Table 4). Under these conditions, all examined substrates gave the desired alcohols in very high yields, without heating and in a short reaction time. Interestingly, benzyl and *para*-methoxybenzyl protecting groups proved fully compatible with this deprotection. These results clearly expanded the scope of



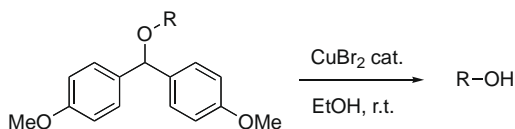
**Scheme 2.** Proposed mechanism for the Cu(II)-catalyzed BMPM ether formation.

BMPM and revealed its orthogonality to other protecting groups, and especially the related benzyl-type groups.

### 3. Conclusion

In conclusion, we have developed a cheap, green, and efficient method for the protection of alcohols as BMPM ethers and for the deprotection of these ethers. This reaction shows a broad compatibility with numerous functional groups and offers orthogonal conditions relative to other O- or N-common protecting groups. The mildness and the originality of the processes described here will certainly find applications in total synthesis.

**Table 4**  
CuBr<sub>2</sub> catalyzed DMPM ether deprotections<sup>a</sup>



Entry	R	Time	Yield <sup>b</sup> (%)
1		0.75 h	90
2		2 h	95
3		8.5 h	90
4		2.5 h	99
5		4.5 h	92
6		3 h	98
7		4 h	95
8		0.5 h	98

<sup>a</sup> [DMPMOR] = 0.5 M, 10 mol % CuBr<sub>2</sub>.

<sup>b</sup> Isolated yields of pure product after complete conversion unless otherwise stated.

## 4. Typical procedures for the protection and deprotection of BMPM ethers

### 4.1. Protection without solvent (Table 1)

To a solution (or a suspension in some cases) of BMPM–OH (244 mg, 1 mmol) in 1 mL of alcohol was added CuBr<sub>2</sub> (10 mol %). After disappearance of the starting material (TLC monitoring), the brown solution was diluted with dichloromethane (15 mL) and transferred to a separating funnel. The organic layer was washed with water (15 mL) and the aqueous layers were extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel, using cyclohexane and ethyl acetate as eluents, when necessary.

### 4.2. Protection with solvent (Tables 2 and 3)

To a solution of BMPM–OH (244 mg, 1 mmol) and alcohol (0.9 mmol) in 1 mL of acetonitrile was added CuBr<sub>2</sub> (10 mol %). After disappearance of the starting material (TLC monitoring), acetonitrile was removed under vacuum and the black residue was diluted in ethyl acetate (15 mL) and transferred to a separating funnel. The organic layer was washed with water (15 mL) and the aqueous layers were extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel, using cyclohexane and ethyl acetate as eluents, when necessary.

### 4.3. Deprotection (Table 4)

To a solution of BMPM ether (0.5 mmol) in 1 mL of ethanol was added CuBr<sub>2</sub> (10 mol %). After disappearance of the starting material (TLC monitoring), ethanol was removed under vacuum and the black residue was diluted in ethyl acetate (15 mL) and transferred in a separating funnel. The organic layer was washed with water (15 mL) and the aqueous layers were extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel, using cyclohexane and ethyl acetate as eluents.

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