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Copper(II) bromide as efficient catalyst for silyl- to bisarylmethyl ethers interconversion (transprotection)

Simon Specklin [a], Florian Gallier [a], Rofia Mezaache [b], Hassina Harkat [b], Yénimégué Albert Dembelé [c], Jean-Marc Weibel [a,*], Aurélien Blanc [a], Patrick Pale [a,*]

[a] Laboratoire de Synthèse et Réactivité Organiques, Associé au CNRS, Institut de Chimie de Strasbourg UMR 7177, Université de Strasbourg, 67000 Strasbourg, France
[b] Laboratoire de Chimie et Chimie de l'Environnement, Département de Chimie, Faculté des Sciences, Université de Batna, Batna 05000, Algeria
[c] Laboratoire de chimie, FMPOS, Université de Bamako, Mali

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ABSTRACT

Primary and secondary silylated alcohols are easily converted to bis(methoxyphenyl)methyl (BMPM) ethers in good yields using $CuBr_2$ as catalyst in acetonitrile at room temperature. Various other protecting groups are compatible with this mild and convenient process.

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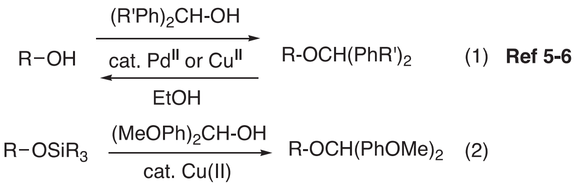
Organic synthesis of complex molecular structures is still heavily relying on selective protection and deprotection of functional groups.[1,2] Selectivity and compatibility in these critical steps are often at the heart of a successful synthesis,[2,3] and it is not so rare in total syntheses that a protecting group has to be changed for another one, more compatible with the next steps of the synthesis.[3] This is usually performed by deprotection and reprotection. Transprotection, converting one protecting group to another, usually from a different orthogonal set, in a single step would be a better choice.[2] However, straightforward methods for such transprotection are surprisingly scarce.[2,4]

Developing new conditions for the protection and deprotection of alcohols recently led us to introduce diarylmethyl ethers as protecting groups using palladium(II) salts[5] and more recently copper(II) bromide[6] as catalysts (Scheme 1, Eq. 1). During our investigations, we demonstrated that copper(II) bromide induced the formation of diarylmethyl cations. We thus wondered if copper(II) could also catalyze the interconversion of silyl ethers to bis(methoxyphenyl)methyl (BMPM) ethers (Scheme 1, Eq. 2).

Copper(II) salts are cheap, nontoxic, soft and mild Lewis acids, widely used in organic synthesis.[7] Among other things, copper(II) salts have already been applied in a few protection or deprotection reactions. Trityl,[8] *tert*-butyldimethysilyl[9] ethers and acetals,[10] such as tetrahydropyranyl or ethoxyethyl can be cleaved in the presence of copper(II) salts (Scheme 2, Eq. 1). So far, only two examples of transprotection, both to acetate, has been reported with copper(II) salts (Scheme 2, Eqs. 2 and 3).[11] So, the transprotection of silyl to BMPM ethers would offer a new, mild, and interesting method for organic synthesis. We now report here our results in this area.

As for our protection and deprotection of alcohols as diarylmethyl ethers,[6] copper bromide(II) proved to be the most efficient copper catalyst for the interconversion of silyl ethers to diarylmethyl ethers.[12] To examine the importance of the nature of the silyl group in the outcome of this transformation, hexanol was protected with silyl groups of various bulkiness and electronic properties and the corresponding derivatives were submitted to copper(II) bromide



Scheme 1. Palladium and copper-promoted protection/deprotection of alcohols (Eq. 1) and copper-promoted transprotections of silylethers (Eq. 2).

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* Corresponding authors. Tel./fax: +33 390 24 15 17.
E-mail addresses: jmweibel@unistra.fr (J.-M. Weibel), ppale@unistra.fr, ppale@chimie.u-strasbg.fr (P. Pale).

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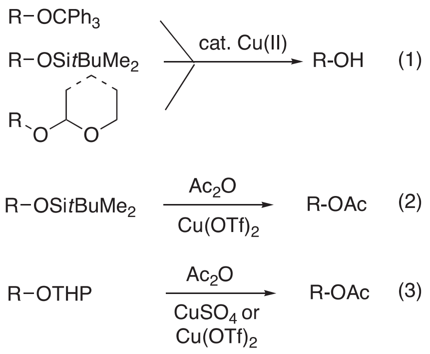


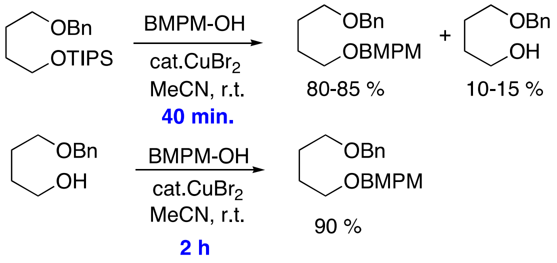
Scheme 2. Known copper-promoted deprotections and transprotection of alcohols.

and bis(methoxyphenyl)methanol (BMPM-OH) in acetonitrile at room temperature (Table 1).

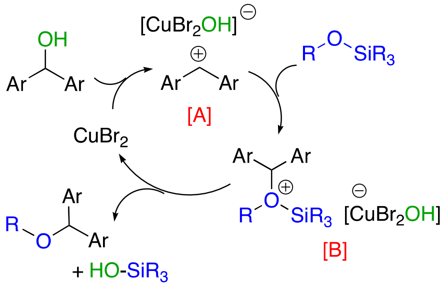
The bis(methoxyphenyl)methyl (BMPM) ether derived from hexanol was produced in every case investigated, but at different rates. Monitoring the reaction revealed that TES, TPS, and TBS ethers exhibited a higher kinetic interconversion at the beginning of the transformation compared to TIPS and TBDPS ethers, the latter being by far the slowest to interconvert (entry 5 vs 4 vs 1–3). The reaction rates were thus mostly dependent on the size of the substituents at the core Si atom. Interestingly, they approximately followed the rate order of acid-catalyzed hydrolysis of silyl ethers, known to be due to increasing substituent size and electronic effects around the Si atom. [2]

It is worth noting that in all these transformations, except for that with a TPBDS group, we did not see the formation of hexanol. Such observations suggested a direct transprotection and not a stepwise process, including deprotection and re-protection.

To clarify this mechanistic aspect, 4-benzyloxybutanol was protected using classical conditions into its TIPS ether. The latter was submitted to copper dibromide and BMPM-OH. As expected, transprotection rapidly occurred in high yield but the concomitant formation of the deprotected 4-benzyloxybutanol was observed with a nonnegligible yield (Scheme 3). However, the protection of 4-benzyloxybutanol in the presence of copper dibromide and BMPM-OH required a longer reaction time (at least 2 h vs 40 min). These results also suggest a direct transprotection rather than a stepwise process, although the latter cannot entirely be ruled out.



Scheme 3. Copper-promoted transprotection of an alcohol compared to its protection.



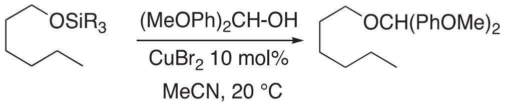
Scheme 4. Proposed mechanism for the Cu(II)-catalyzed interconversion of silyl ethers into BMPM ethers.

From these results, we can infer the following mechanism (Scheme 4). As shown earlier,[6] copper(II) bromide probably acts as Lewis acid. Reacting with BMPM-OH, it would provide the dimethoxybenzhydryl carbocation and a hydroxycuprate (A in Scheme 4). In close analogy to reactions promoted by the trityl carbocation,[13] the dimethoxybenzhydryl carbocation could then be trapped by the oxygen atom of the silyl ether, providing a silyl diarylmethyl oxonium intermediate (B in Scheme 4) while weakening the Si–O bond. Hydroxide ion transfer to the silyl atom would then give the corresponding silanol, generating the transprotected product while regenerating the copper catalyst.

With such a mechanism, it was tempting to check whether other protecting groups known for their cation stabilizing properties would react or not. We thus screened several other groups in the transprotection from silyl ethers to other alcohol protecting groups (Table 2). Compared to BMPM-OH, the less cation-stabilizing diphenylmethanol (DPM-OH) cleanly reacted but at a slower rate, giving within the same duration the corresponding DPM ether with a lower yield (entry 2 vs 1). The same trend was observed for trityl (entries 3 and 4) and benzyl derivatives (entries 5 and 6). Triphenylmethanol (Tr-OH) was able to achieve the transprotection from silyl to trityl ethers, but very slowly, while the monomethoxytrityl analog reacted more rapidly, giving the corresponding ether in reasonable yield (entry 4 vs 3). The reactivity difference between di- vs triarylmethyl derivatives could be ascribed to the bulkiness of the latter, as one could expect with the intermediate

Table 1

Screening of silyl groups proned to interconversion[a]



Entry	Silyl group	Time (h)	Yield[b] (%)
1	$SiEt_3$	2	90
2	$SiPh_3$	2	86[c]
3	Si*t*BuMe$_2$	2	81
4	Si*i*Pr$_3$	2	78
5	Si*t*BuPh$_2$	18	43[d]

[a] [BMPM-OH] = 1 M, [R-OSiR$_3$] = 0.9 M, [Cu^{2+}] = 0.1 M.

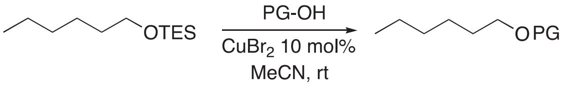
[b] Isolated yield after complete conversion.

[c] Estimated yield; due to contamination by bis(methoxyphenyl)methane.

[d] Hexanol was detected as well as some starting material.

Table 2

Screening of other related protecting groups[a]



Entry	PG-OH	Time (h)	Yield[a] (%)
1	BMPM-OH	2	90
2	DPM-OH	2	45[b]
3	Tr-OH	22	42
4	MeOTr-OH	2	56[b]
5	Bn-OH	24	–[c]
6	PMB-OH	12	30

[a] Isolated yields of pure product; the starting material accounted for the mass balance unless otherwise stated.

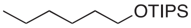
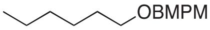
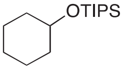
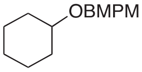
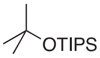
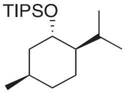
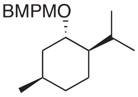
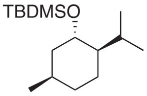
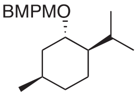
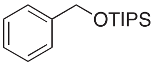
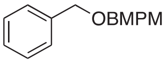
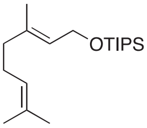
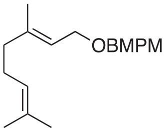
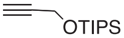
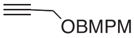
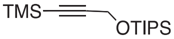
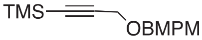
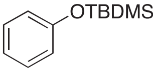
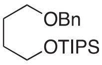
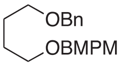
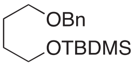
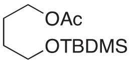
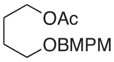
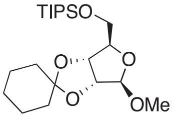
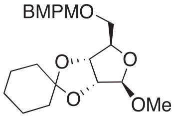
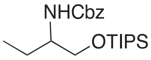
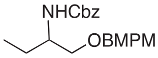
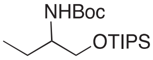
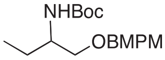
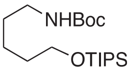
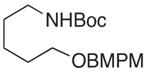
[b] Degradation also occurred.

[c] No reaction.

formation of a silyl arylmethyl oxonium species (cf. Scheme 4). As expected, the less cation-stabilizing benzyl derivatives compared to the two preceding series proved less reactive. The simplest benzyl alcohol did not react, while the *para*-methoxybenzyl analog did, but again very slowly, inducing a low yield of the transprotected product (entry 6 vs 5).

With these results in hand, we then determined the scope and limitation(s) of this copper-catalyzed transprotection from silyl- to BMPM ethers (Table 3). As expected, primary and secondary alcohols were easily transprotected whereas tertiary alcohols were unreactive (entries 1–2 vs 3). The latter result is in agreement with the proposed mechanism, especially with the strain occurring in the silyl arylmethyl oxonium intermediate (B in Scheme 4). As suspected on these bases, hindered secondary silylated alcohols proved sensitive to the bulkiness of the silyl group, and they could be more or less easily transprotected depending on the silyl group nature, as shown in the reactions of TBS- and TIPS-isomenthol (entry 4 vs 5). It is nevertheless worth noting that during these reactions, the transprotected product was obtained without isomerization, ruling out other cationic mechanisms. Allylic and benzylic silylated alcohols readily react, cleanly giving the corresponding BMPM ethers (entries 6 and 7). Particularly noteworthy in the latter series is the geranyl derivative, which did not rearrange under such conditions, in agreement with the proposed mechanism (entry 7). We were also glad to notice that even propargyl silyl ethers gave the transprotected product in a very rapid and clean reaction, with or without protection of the terminal acetylenic moiety (entries 8 and 9). In the latter, the selectivity is noteworthy, since only the *O*-silyl group reacted and not the *C*-silyl group (entry 9). In contrast, silylated phenols led to complex

Table 3
Scope and limitation for BMPM ether transprotection[a]

Entry	Substrates	Products	Time (h)	Yield[b] (%)
1			2	78
2			4	74
3		–	24	–[e]
4			4	10[c,d]
5			4	82
6			4	84
7			5	77
8			1	86
9			1.5	89
10		–	4	–[e]
11			3	92
12		“	2	100
13			1	86
14			24	58
15			1.5	73
16			12	48[c,d]
17			12	40[c,d]

[a] [BMPMOH] = 1 M, [ROSiR$_3$] = 0.9 M, CuBr$_2$ 10 mol%.

[b] Isolated yields of pure product after complete conversion unless otherwise stated.

[c] The starting material was also recovered.

[d] Estimated yield; due to some contamination by bis(methoxyphenyl)methane.

[e] No transprotection and degradation occurred.

reaction mixtures, in which the expected transprotected product can hardly be detected (entry 10).

Having surveyed the scope of this transprotection with various alcohols, we then briefly investigated the orthogonality of this method with other protecting groups. Benzyl, ester, acetal, and carbobenzyloxy (CBz) groups proved compatible with this transprotection procedure (entries 11–15). However, Boc-protecting groups gave less satisfactory results, surprisingly inducing a very slow reaction but without BOC deprotection[14] (entries 16 and 17).

In summary, we have further expanded the scope of synthetic applications of copper salts in organic chemistry, demonstrating that transprotection from silyl to diarylmethyl ethers can be achieved in good to high yields with $CuBr_2$ as catalyst at room temperature. With very mild conditions, with a wide tolerance to other protecting groups, this new interconversion of silyl to diarylmethyl protecting groups will find applications in organic synthesis, especially in the total synthesis of natural products.

Further works are now in progress to further explore the scope of this reaction and to apply them in total synthesis.

Typical procedure for the transprotection of silyl alcohols with BMPM-OH

To a solution of the silylated substrate (0.9 mmol) in dry CH_3CN (1 mL) at room temperature under argon, was added bis(4-methoxyphenyl)methanol (244 mg, 1 mmol) and copper(II) bromide (22 mg, 0.1 mmol). The reaction was monitored by TLC. After completion, the reaction mixture was concentrated under vacuum and then diluted with Et_2O (20 mL) and water (20 mL). After partitioning, the aqueous layer was extracted three times with Et_2O and the combined organic layers were dried over Na_2SO_4. The crude product was then purified by flash chromatography over silica gel.

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References and notes

1. Greene, T. W.; Wuts, P. G. M. *Protective groups in Organic Synthesis*, 3rd ed.; J. Wiley & Sons: New York, 1999.
2. Kocienski, P. J. *Protecting groups*, 3rd ed.; G. Thieme: Stuttgart: New York, 2004.
3. (a) Nicolaou, K. C.; Sorensen, E. *Classics in Total Synthesis*; Wiley-VCH: Weinheim, 1996; (b) Nicolaou, K. C.; Snyder, S. *A. Classics in Total Synthesis II*; Wiley-VCH: Weinheim, 2003; (c) Nicolaou, K. C.; Chen, J. *S. Classics in Total Synthesis III*; Wiley-VCH: Weinheim, 2011.
4. For selected exemples of transprotection: (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030–3031; (b) Roos, E. C.; Bernabé, P.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J. *J. Org. Chem.* **1995**, *60*, 1733–1740; (c) Furlán, R. L. E.; Mata, E. G. *ARKIVOC* **2003**, *x*, 32–40; through organocatalysis, see: (d) Poisson, T.; Dalla, V.; Papamicael, C.; Dupas, G.; Marsais, F.; Levacher, V. *Synlett* **2007**, 381–386; through Cu-catalysis,see: (e) Chandra, K. L.; Saranavan, P.; Singh, V. K. *Tetrahedron Lett.* **2001**, *42*, 5309–5311; through Fe-catalysis, see: (f) Asadolah, K.; Heravi, M. M. *Monatsh. Chem.* **2007**, *138*, 867–869; (g) Ganem, B.; Small, V. R. *J. Org. Chem.* **1974**, *39*, 3728–3730; (h) Harjani, J. R.; Nara, S. J.; Salunkhe, M. M. *Nucleosides, Nucleotides & Nucleic Acids* **2005**, *24*, 819–822; (i) Bourdreux, Y.; Lemétais, A.; Urban, D.; Beau, J.-M. *Chem. Commun.* **2011**, *47*, 2146–2148; through other catalysis, see: (j) Oriyama, T.; Oda, M.; Gono, J.; Koga, G. *Tetrahedron Lett.* **1994**, *35*, 2027–2030; (k) Norsikian, S.; Holmes, I.; Lagasse, F.; Kagan, H. *Tetrahedron Lett.* **2002**, *43*, 5715–5717.
5. (a) Bikard, Y.; Weibel, J.-M.; Sirlin, C.; Dupuis, L.; Loeffler, J.-P.; Pale, P. *Tetrahedron Lett.* **2007**, *48*, 8895–8899; (b) Bikard, Y.; Mezaache, R.; Weibel, J.-M.; Benkouider, A.; Sirlin, C.; Pale, P. *Tetrahedron* **2008**, *64*, 10224–10232.
6. Mezaache, R.; Dembélé, Y. A.; Bikard, Y.; Weibel, J.-M.; Blanc, A.; Pale, P. *Tetrahedron Lett.* **2009**, *50*, 7322–7326.
7. *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley: New-York, 2002.
8. Pathak, A. K.; Pathak, V.; Seitz, L. E.; Tiwari, K. N.; Akhtar, M. S.; Reynolds, R. C. *Tetrahedron Lett.* **2001**, *42*, 7755–7757.
9. (a) Tan, Z. P.; Wang, L.; Wang, J. B. *Chin. Chem. Lett.* **2000**, *11*, 753–756; (b) Bhatt, S.; Nayak, S. K. *Tetrahedron Lett.* **2006**, *47*, 8395–8399.
10. Wang, J.; Zhang, C.; Qu, Z.; Hou, Y.; Chen, B.; Wu, P. *J. Chem. Research (S)* **1999**, 294–295; (b) Saravanan, P.; Chandrasekhar, M.; Anand, R. V.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 3091–3092.
11. For Cu-catalyzed transprotection to acetates, see Refs. 4e,f and Bhatt, S.; Nayak, S. K. *Lett. Org. Chem.* **2008**, *5*, 435–443. For a specific Cu-catalyzed transprotection and reaction in glycochemistry, see: Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662–8665.
12. Copper sulfate, chloride, acetate and triflate were examined as in Ref. 6.
13. (a) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759–1762; (b) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1985**, 447–450; (c) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1535–1538; (d) Ohshima, M.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1871–1874.
14. *N*-Boc derivatives are known to undergo deprotection with active silylation reagent (see Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543–5546 and *J. Org. Chem.* **1990**, *55*, 870–876) and the silyl oxonium intermediate (B in Scheme 4) could have acted as such.