

SYNLETT Spotlight 88

MgBr₂·OEt₂ – A Versatile Reagent in Organic Synthesis

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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Introduction

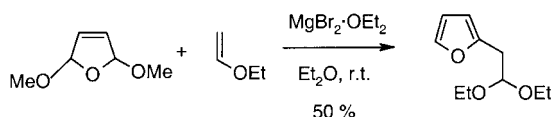
Use of magnesium(II) species as Lewis acid catalysts for various functional group transformations is well documented.¹ Of these, magnesium halides are the most useful. Ready availability and ease of preparation prompted the frequent use of MgBr₂·OEt₂ in various organic transformations. The oxophilic and coordinating nature of MgBr₂·OEt₂ has been demonstrated through its use as a bidentate chelating Lewis acid in a number of chelation-controlled reactions such as cycloadditions,² asymmetric aldol reactions,³ rearrangements,⁴ radical additions,^{5,6}

hydrogen transfer reactions,⁷ stereoselective reductions,⁸ and anomerizations.⁹

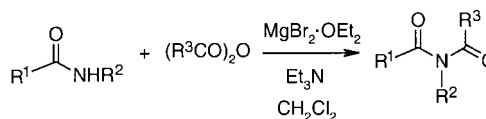
MgBr₂·OEt₂ is commercially available as a grey solid (mp >300 °C, fp 35 °C). It can be readily prepared by reacting a slight excess of magnesium turnings with 1,2-dibromoethane in anhydrous diethyl ether.¹⁰ The solution can be stored at room temperature for several months and the solid can be stored in a vacuum desiccator for indefinite periods without any loss of activity.

Abstracts

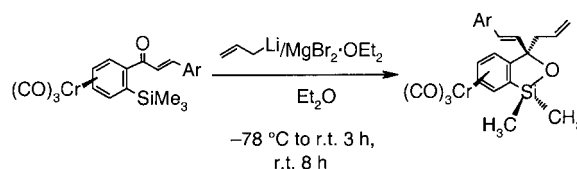
(A) Condensation of 2,5-dimethoxy-2,5-dihydrofuran with ethyl vinyl ether in the presence of a catalytic amount of MgBr₂·OEt₂ resulted in 2-furylacetaldehyde diethyl acetal in 50% yield. The reaction is a formal acetal and ethyl vinyl ether condensation followed by aromatization. The protocol has been employed in the synthesis of various 2-(2-furo)tetrahydrofuranic or -pyranic moieties in good yields.¹¹



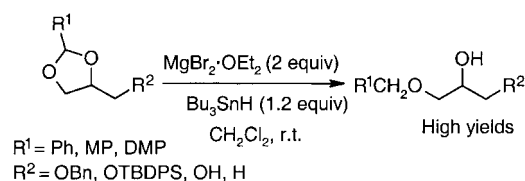
(B) A mild and practical N-acylation of amides was possible by the dual activation of both amides and acid anhydrides with MgBr₂·OEt₂.¹² The method was applicable to amides that can undergo O-acylation and are susceptible to racemization or O,N-acyl migrations.



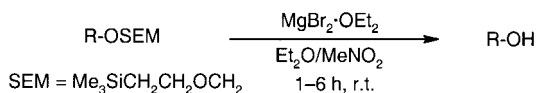
(C) We have recently reported a mild method for the formation of cyclic siloxanes by the exchange of the Li counterion of an intermediate alkoxide with Mg, using excess MgBr₂·OEt₂.¹³ The reaction may formally be considered to be a *semi*-Brook rearrangement.



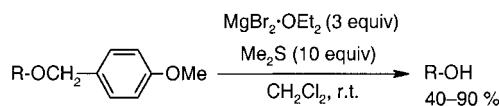
(D) MgBr₂·OEt₂, in combination with Bu₃SnH, was effective in a chelation-controlled reductive opening of methoxybenzylidene acetals.¹⁴ The reaction offers a mild and efficient method for selective mono-MPM ether protection of diols. High conversions, regioselectivity and tolerance to functional groups make this a very useful protocol in natural product synthesis.



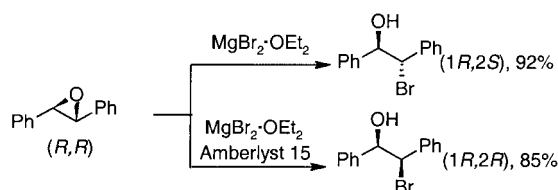
(E) MgBr₂·OEt₂ effected deprotection of aliphatic SEM ethers under extremely mild and high yielding conditions in the presence of other sensitive groups like acetonides, TBS and TIPS ethers and O-silylated cyanohydrins.¹⁵ A variety of functionalities including alcohols, esters, benzyl groups, dithianes, and methoxy acetals are tolerated.



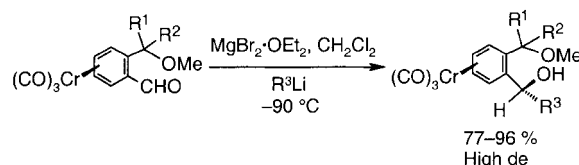
(F) The $\text{MgBr}_2\cdot\text{OEt}_2\text{-Me}_2\text{S}$ system was used for a mild and chemo-selective deprotection of *p*-methoxybenzyl (PMB) ethers in the presence of 1,3-diene, *t*-butyldimethylsilyl (TBDMS) ether, benzoate, benzyl ether, and acetonides.¹⁶ The method is especially effective for 1,3-diene systems that tend to isomerize rapidly when other protocols are employed.¹⁷



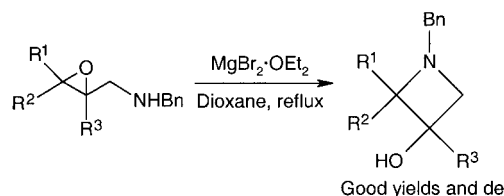
(G) A stereodivergent opening of the oxirane ring with $\text{MgBr}_2\cdot\text{OEt}_2$ was recently described.¹⁸ While $\text{MgBr}_2\cdot\text{OEt}_2$ alone resulted in the *anti*-bromohydrin in high diastereomeric excess, use of $\text{MgBr}_2\cdot\text{OEt}_2/\text{Amberlyst 15}$ gave the *syn*-product in high yields.



(H) The efficacy of $\text{MgBr}_2\cdot\text{OEt}_2$ as a chelating Lewis acid in highly diastereoselective addition of nucleophiles¹⁹ to $\text{Cr}(\text{CO})_3$ -complexed aryl aldehydes was recently demonstrated by us.^{19a} The results indicated that $\text{MgBr}_2\cdot\text{OEt}_2$ can form an effective seven-membered chelate.



(I) $\text{MgBr}_2\cdot\text{OEt}_2$ could afford 3-hydroxyazetidines by a highly regio- and stereoselective cyclization of 2,3-epoxy amines.²⁰



References

- (1) For some lead references see: (a) Li, W.-D. Z.; Zhang, X.-X. *Org. Lett.* **2002**, *4*, 3485. (b) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.
- (2) (a) Tamura, O.; Kuroki, T.; Sakai, Y.; Takizawa, J.; Yoshino, J.; Morita, Y.; Mita, N.; Gotanda, K.; Sakamoto, M. *Tetrahedron Lett.* **1999**, *40*, 895; and ref. 8 therein. (b) Kashima, C.; Fukusaka, K.; Takahashi, K.; Yokoyama, Y. *J. Org. Chem.* **1999**, *64*, 1108. (c) Oblin, M.; Pons, J.-M.; Parrain, J.-L.; Rajzmann, M. *Chem. Commun.* **1998**, 1619. (d) Zemribo, R.; Romo, D. *Tetrahedron Lett.* **1995**, *36*, 4159.
- (3) (a) Fujisawa, H.; Sasaki, Y.; Mukaiyama, T. *Chem. Lett.* **2001**, 190. (b) Kiyooka, S.; Shahid, K. A.; Hena, M. A. *Tetrahedron Lett.* **1999**, *40*, 6447. (c) Swiss, K. A.; Choi, W. B.; Liotta, D. C.; Abdel-Magid, A. F.; Maryanoff, C. A. *J. Org. Chem.* **1991**, *56*, 5978.
- (4) Black, T. H.; McDermott, T. S.; Brown, G. A. *Tetrahedron Lett.* **1991**, *32*, 6501; and ref. 4 and 7 therein.
- (5) (a) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984. (b) Hayen, A.; Koch, R.; Saak, W.; Haase, D.; Metzger, J. O. *J. Am. Chem. Soc.* **2000**, *122*, 12458.
- (6) (a) Enholm, E. J.; Lavieri, S.; Cordóva, T.; Ghiviriga, I. *Tetrahedron Lett.* **2003**, *44*, 531; and ref. 3 therein. (b) Nagano, H.; Toi, S.; Matsuda, M.; Hirasawa, T.; Hirasawa, S.; Yajima, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2525; and ref. 4 therein.
- (7) Guindon, Y.; Liu, Z.; Jung, G. *J. Am. Chem. Soc.* **1997**, *119*, 9289.
- (8) (a) Guanti, G.; Banfi, L.; Riva, R.; Zannetti, M. T. *Tetrahedron Lett.* **1993**, *34*, 5483. (b) Kawate, T.; Nakagawa, M.; Kakikawa, T.; Hino, T. *Tetrahedron: Asymmetry* **1992**, *3*, 227.
- (9) Mukaiyama, T.; Takeuchi, K.; Uchiro, H. *Chem. Lett.* **1997**, 625.
- (10) For crystal structure and other details see: Ecker, A.; Ueffing, C.; Schnoekel, H. *Chem.-Eur. J.* **1996**, *2*, 1112.
- (11) Malanga, C.; Mannucci, S. *Tetrahedron Lett.* **2001**, *42*, 2023.
- (12) Yamada, S.; Yaguchi, S.; Matsuda, K. *Tetrahedron Lett.* **2002**, *43*, 647.
- (13) Tipparaju, S. K.; Mandal, S. K.; Sur, S.; Puranik, V. G.; Sarkar, A. *Chem. Commun.* **2002**, 1924.
- (14) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Kusaka, S.; Matsui, K.; Yonemitsu, O. *Tetrahedron Lett.* **2000**, *41*, 6441.
- (15) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 1447.
- (16) Onoda, T.; Shirai, R.; Iwasaki, S. *Tetrahedron Lett.* **1997**, *38*, 1443.
- (17) For use of $\text{MgBr}_2\cdot\text{OEt}_2$ in deprotection of MOM, MTM, and SEM ethers see: Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett* **1991**, 183.
- (18) Lupattelli, P.; Bonini, C.; Caruso, L.; Gambacorta, A. *J. Org. Chem.* **2003**, *68*, 3360; and references cited therein.
- (19) (a) Tipparaju, S. K.; Puranik, V. G.; Sarkar, A. *Org. Biomol. Chem.* **2003**, *1*, 1720. (b) Ward, D. E.; Hrapchak, M. J.; Sales, M. *Org. Lett.* **2000**, *2*, 57. (c) Minassian, F.; Pelloux-Leon, N.; Vallee, Y. *Synlett* **2000**, 242. (d) Kornienko, A.; d'Alarcao, M. *Tetrahedron Lett.* **1997**, *37*, 6497. (e) Banfi, L.; Guanti, G.; Zannetti, M. T. *J. Org. Chem.* **1995**, *60*, 7870. (f) Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 999.
- (20) Karikomi, M.; Arai, K.; Toda, T. *Tetrahedron Lett.* **1997**, *34*, 6059.