Generation and Synthetic Applications of Calcium-Based Heavy Grignard Reagents under Mechanochemical Conditions

([1]*Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University*, [2]*Department of Chemistry, Faculty of Science, Hokkaido University*, [3]*Division of Applied Chemistry, Graduate School of Engineering, Hokkaido University*)
○Pan Gao,[1] Julong Jiang,[2] Satoshi Maeda,[1,2] Koji Kubota,[1,3] and Hajime Ito[1,3]
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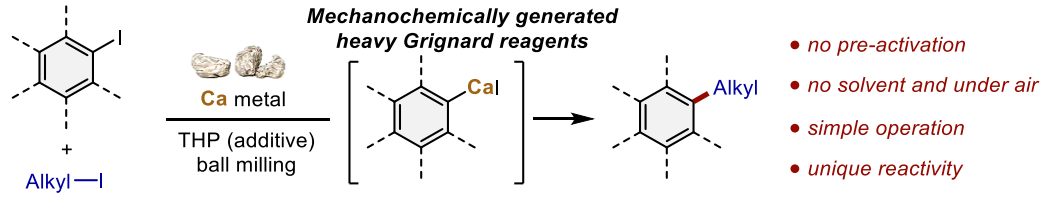
In sharp contrast to the use of conventional magnesium-based Grignard reagents (R−MgX), the application of calcium-based heavy Grignard reagents (R−CaX) remains poorly explored. This is mainly due to the lack of experimentally simple ways to access such organocalcium nucleophiles from readily available starting materials under mild conditions. The direct synthesis from organic halides with calcium metal would be a versatile route to obtain organocalcium reagents. However, due to the relatively high atomization energy of calcium metal, pre-activation of the calcium metal is necessary. One reliable pre-activation method is first dissolving the calcium metal in liquid ammonia and then quickly removing the solvent by distillation at low temperature to provide highly reactive and pyrophoric calcium powder. Rieke calcium metal can also be prepared by reduction of CaX_2 with lithium biphenylide. The requirements for toxic ammonia or harsh reduction conditions, dry organic solvents, and strict control of the reaction temperature greatly impede the widespread use of calcium-based carbon nucleophiles in organic synthesis.

Based on our experiences with mechanochemical organic synthesis using a ball mill,[2] we hypothesized that the mechanical impact could provide sufficient energy to overcome the relatively high atomization energy of calcium metal, which would allow the efficient activation of calcium metal and thus make the direct generation of organocalcium reagents feasible. In this study, using the mechanochemical method, we have achieved for the first time the generation of calcium-based heavy Grignard reagents from commercially available, unactivated calcium metal without applying any pre-activation process. Furthermore, we present the first example of the alkylation of arylcalcium nucleophiles with alkyl electrophiles to form carbon−carbon bonds, which has not been reported using previous pre-activation methods for the direct generation of organocalcium compounds.[3] This operationally simple approach will significantly advance the synthetic organic chemistry of organocalcium compounds.



1) A. Koch, Q. Dufrois, M. Wirgenings, H. Görls, S. Krieck, M. Etienne, G. Pohnert, M. Westerhausen, *Chem. Eur. J.* **2018**, 2*4*, 16840. 2) R. Takahashi, A. Hu, P. Gao, Y. Gao, Y. Pang, T. Seo, J. Jiang, S. Maeda, H. Takaya, K. Kubota, H. Ito, *Nat. Commun.* **2021**, *12*, 6691. 3) P. Gao, J. Jiang, S. Maeda, K. Kubota, H. Ito, *Angew. Chem. Int. Ed.* **2022**, DOI: *10.1002/anie.202207118*.