Solvent-less mechanochemical synthesis of magnesium-based carbon nucleophiles and their application to organic synthesis

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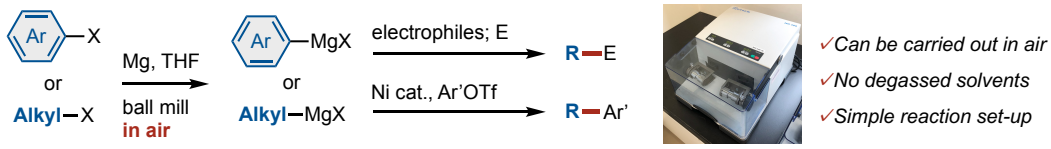
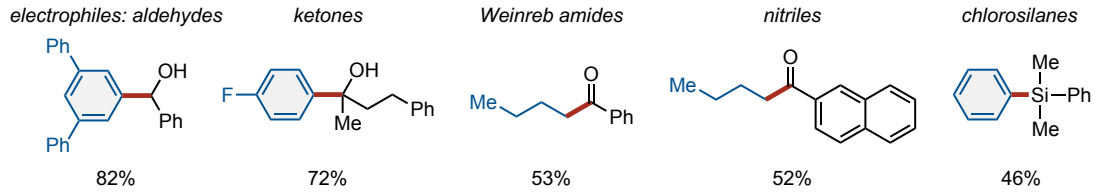
Grignard reagents are magnesium-based carbon nucleophiles that have been used in organic synthesis since their discovery in 1900.[1] One of the preferred methods for the preparation of Grignard reagents is direct insertion of magnesium into organic halides.[2] However, several drawbacks limit the practical application. Large amounts of dry organic solvents and Schlenk-line techniques are needed for preparation of the Grignard reagents because these reagents are often air- and moisture-sensitive. In addition, magnesium metal surface may be covered with an unreactive oxide layer, which sometimes requires a pre-activation process. These requirements are major drawbacks from both an environmental and a cost perspective.

Herein we report a novel method for the synthesis of magnesium-based carbon nucleophiles in air under solvent-less mechanochemical conditions using ball milling machine.[3] This protocol is simple and cost-effective, which does not require synthetic techniques and any special precautions. The key to the success of the developed protocol is the addition of stoichiometric amounts of liquid ethers. We demonstrated that the carbon nucleophiles so formed can be used for direct one-pot nucleophilic addition to various organic electrophiles, nickel-catalyzed Kumada-Tamao-Corriu cross-coupling reactions, and metal-mediated selective addition to conjugated enones under mechanochemical conditions.





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