SYNLETT
Spotlight 279

Activated Zinc Dust

Compiled by Craig R. Smith

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

Craig R. Smith received his B.S. in Chemistry (2003) and M.S. in Chemistry (2005) from Youngstown State University under the direction of Professor Peter Norris. The same year, he began his Ph.D. studies at The Ohio State University under the supervision of Professor T. V. RajanBabu. Craig has recently received an ACS Organic Division Fellowship (2009). His current interests are the development of new asymmetric transformations and the synthesis of biologically active natural products.

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Introduction

Traditionally, zinc dust[1] has been employed as a reducing agent in organic synthesis. Notably, zinc dust or an amalgam thereof has been used to reduce carbonyls[2] (Clemmensen reduction), carbon–oxygen bonds,[3] carbon–halide bonds,[4] alkynes,[5] heteroatom bonds (N–N and N–O bonds),[6] and to prepare numerous organozinc reagents. In addition to various reduction reactions, zinc has been employed in several named reactions including the Reformatsky reaction,[7] Serini reaction,[8] the Knorr pyrrole synthesis,[9] and the Simmons–Smith cyclopropanation.[10] Other notable reactions that are dependent upon zinc for the preparation of the active species are the Oshima–Lombardo olefination,[11] the Corey–Fuchs alkynylation,[12] and the Negishi cross-coupling.[13]

Organozinc reagents have also proven highly amenable to asymmetric variants of a number of reactions, as zinc species are mild in comparison to either organolithium or organomagnesium reagents. These reactions include the copper-mediated conjugate addition of dialkylzinc reagents to enones,[14] asymmetric Simmons–Smith cyclopropanations,[15] and enantioselective Reformatsky reactions,[16] amongst others.

Activated zinc dust is commercially available from a number of sources. Alternatively it can be activated by stirring with dilute HCl, then washing with distilled water, ethanol, and absolute diethyl ether before rigorous drying. This procedure removes oxides from the surface of zinc, which form slowly upon standing in air. There are no known toxic properties associated with zinc or organometallics thereof.

Abstracts

(A) Recently, Hou[17] has demonstrated the synthesis of alkylzinc bromides from the direct insertion of zinc into unactivated alkyl halide precursors via activation with 1–5 mol% iodine in polar aprotic solvents. The alkylzinc bromides then underwent Pd- and Ni-mediated coupling reactions with arylhalides to afford functionalized alkylarenes in excellent yields.

1) Zn, cat. I$_2$, DMA, 80 °C
2) NiCl$_2$(PPh$_3$)$_2$, 23 °C

10 examples
71–97%
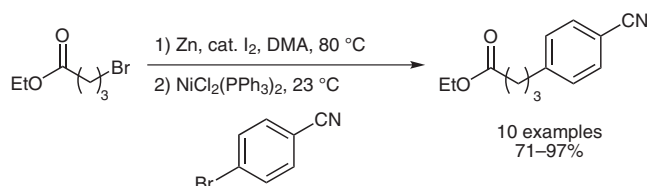
(B) Knochel has outlined the preparation of organozinc reagents via direct insertion of zinc into the carbon–halogen bond in the presence of LiCl in THF at ambient temperature[18] and the subsequent reactions of these organozinc intermediates. These reagents react readily with acid chlorides, allyl halides, and tetramethylthiuram disulfide.

1) Zn, LiCl, THF
2)

91%
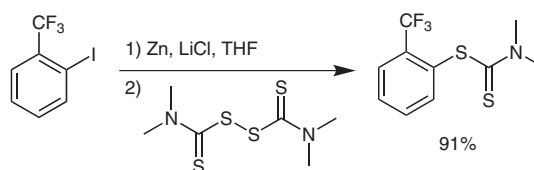
(C) Knochel and co-workers[19] have also utilized zinc reagents in the preparation of homoallylic alcohols containing adjacent tertiary and quaternary stereocenters with high diastereoselectivity from allylzinc chlorides.

ZnCl·LiCl

THF, –30 °C

11 examples
>90% yield, >90% de
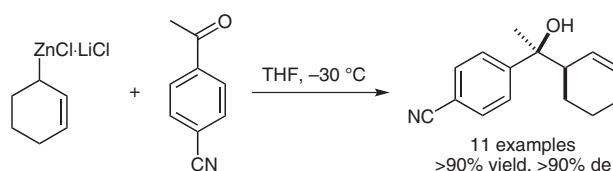
(D) Among new reactions that have been disclosed, two zinc-mediated syntheses of *E*-alkenes have been reported. First, Wang and co-workers[20] reported the Co(I)-catalyzed synthesis of aryl and alkyl *E*-olefins from aldehydes and alkylhalides when treated with zinc and trimethylsilyl chloride. No *Z*-alkenes were reported.
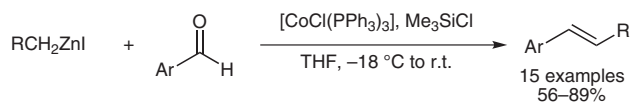

(E) More recently, Kaufman[21] disclosed the stereocontrolled dissolving metal reduction of alkynes with activated zinc metal in which product outcome is controlled by the proton source in the reaction.

Entry	Acid	*E*-olefin (%)	Conv. (%)	pK_a
1	MeOH	n.d.	0	15.5
2	AcOH	9	47	4.8
3	HCl	90	80	−7
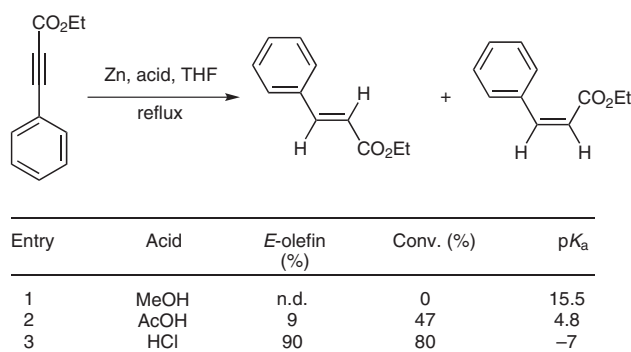
(F) In 2005, Wang et al.[22] published a rapid, solvent-free synthesis of homoallylic and homopropargylic alcohols via a zinc-mediated Barbier-type reaction of carbonyl compounds at ambient temperatures.

25 examples
71–91%
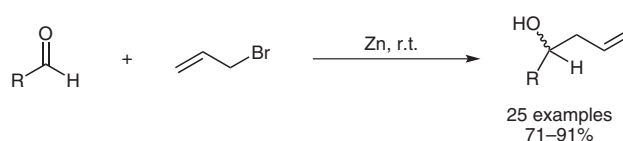
(G) Cheng and co-workers[23] have recently disclosed the novel nickel-catalyzed cyclization of 2-iodoanilines with alkynyl aryl ketones to afford 2,4-disubstituted quinolines. It is likely that the catalytic cycle is initiated by the reduction of Ni(II) to Ni(0) by activated zinc dust.

10 examples
56–91%
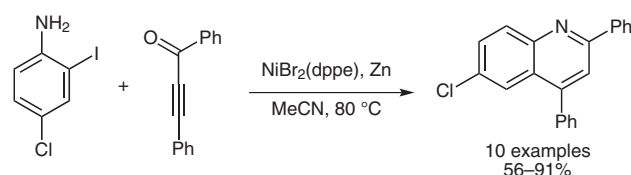
(H) Soon after publishing the quinoline synthesis, Cheng and co-workers[24] published a cobalt-catalyzed reductive [3+2] cycloaddition of allenes with enones to afford cyclopentanols with good diastereoselectivity. The reaction is likely initiated via the reduction of Co(II) to Co(I) by zinc dust. Zinc iodide along with water proved crucial to the success of the reaction.

12 examples,
56–91%

References

(1) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*, Vol. 1; John Wiley and Sons: New York, **1967**, 1276.

(2) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931.

(3) Neo, A. G.; Delgado, J.; Polo, C.; Marcaccini, S.; Marcos, C. F. *Tetrahedron Lett.* **2005**, *46*, 23.

(4) Astudillo, L.; González, A. G.; Galindo, A.; Mansilla, H. *Tetrahedron Lett.* **1997**, *38*, 6737.

(5) Solladié, G.; Stone, G. B.; Andrès, J.-M.; Urbano, A. *Tetrahedron Lett.* **1993**, *34*, 2835.

(6) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515.

(7) Ocampo, R.; Doblier, W. R. Jr *Tetrahedron* **2004**, *60*, 9325.

(8) Fieser, L. F.; Huang-Minlon *J. Am. Chem. Soc.* **1949**, *71*, 1840.

(9) Bellingham, R. K.; Carey, J. S.; Hussain, N.; Morgan, D. O.; Oxley, P.; Powling, L. C. *Org. Proc. Res. Dev.* **2004**, *8*, 279.

(10) Shitama, H.; Katsuki, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 2450.

(11) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *19*, 2417. (b) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293.

(12) Riveiros, R.; Rumbo, A.; Sarandeses, L. A.; Mouriño, A. *J. Org. Chem.* **2007**, *72*, 5477.

(13) Xi, Z.; Zhou, Y.; Chen, W. *J. Org. Chem.* **2008**, *73*, 8497.

(14) Rathgeb, X.; March, S.; Alexakis, A. *J. Org. Chem.* **2006**, *71*, 5737.

(15) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.

(16) Tanaka, T.; Hayashi, M. *Chem. Lett.* **2008**, *37*, 1298.

(17) Huo, S. *Org. Lett.* **2003**, *5*, 423.

(18) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

(19) Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 5376.

(20) Wang, J.-X.; Fu, Y.; Hu, Y.; Wang, K. *Synthesis* **2003**, 1506.

(21) Kaufman, D.; Johnson, E.; Mosher, M. D. *Tetrahedron Lett.* **2005**, *46*, 5613.

(22) Wang, J.-X.; Jia, X.; Meng, T.; Xin, L. *Synthesis* **2005**, 2838.

(23) Korivi, R. P.; Cheng, C.-H. *J. Org. Chem.* **2006**, *71*, 7079.

(24) Chang, H.-T.; Jayanth, T. T.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 4166.