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N,N,N’,N’-Tetramethylethane-1,2-diamine (TMEDA)

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Dedicated to my parents and my esteemed supervisor Professor Dr. Krishna Nand Singh

Introduction

N,N,N’,N’-Tetramethylethane-1,2-diamine (TMEDA) is a colorless, liquid, organic base with a fishy odor. TMEDA serves as an excellent donor of methylene and formyl groups under base switching.1 It functions as an important ligand and additive for a broad spectrum of transition-metal-catalyzed reactions because of its unique ability to enhance the rate of metalation for a variety of compounds.2 Because of its easy solvating and bidentate ligand properties it stabilizes and activates a number of organometallic reagents and metal salts. TMEDA exhibits a special affinity towards lithium ions and this feature allows BuLi/TMEDA to metalate many substrates.3

Abstracts

(A) (Phenylsulfonyl)difluoromethylation
Hu’s group has developed an efficient protocol for vinylic difluoromethylation of α,β-unsaturated carboxylic acids catalyzed by CuF2·2H2O and TMEDA in H2O–DCE.4

(B) Direct ortho Arylation of Electron-Deficient N-Heteroarenes
Da and co-workers reported an efficient metal-free protocol for the direct ortho arylation of electron-deficient N-heteroarenes with aromatic Grignard reagents assisted by TMEDA. Differently substituted quinolines, isoquinolines, pyridines, and quinoxalines have participated well in the addition reactions with Grignard reagents.5

(C) Syntheses of Unsymmetrical Conjugated Diynes
The aerobic oxidative coupling of two different terminal alkynes has been achieved through the cooperative catalysis of NiCl2·6H2O and CuI. The protocol utilizes 20 mol% TMEDA as the ligand and air or O2 as the oxidant.6

(D) Cyanation of Aryl Halides
Shen et al. have discovered an inexpensive and non-toxic cyanation of electron-rich and electron-deficient aryl halides using ethyl cyanacetate as a source of the cyano group. The reaction has been conducted using Pd(OAc)2, as a catalyst and in the presence of 1,2-bis(diphenylphosphino)ethane (DPPE), potassium iodide, and TMEDA in DMF.7
(E) Synthesis of 2H-Indazoles
S. Lee and co-workers have investigated a three-component reaction for the construction of 2H-indazoles through a sequential C–N and N–N bond formation in the presence of CuI and TMEDA.8

(F) Annulation of 2-Bromoalkynylbenzenes with Na2S
The synthesis of 2-substituted benzo[b]thiophenes was achieved from a CuI/TMEDA-catalyzed thiolation-annulation reaction between 2-bromoalkynylbenzenes and Na2S·9H2O. The use of Na2S·9H2O as a cheap and operationally convenient sulfur source makes this protocol simple and environmentally viable.9

(G) Conjugate Addition of Alkyl Halides to Enones
Lipshutz et al. have reported a green protocol for the copper-catalyzed conjugate addition of alkyl halides to enones in water at room temperature without an organometallic precursor.10

(H) Cross-Coupling between Two Tertiary Alkyl Carbons
Liu and co-workers have reported a rare copper-catalyzed cross-coupling between two tertiary alkyl carbons with the key use of TMEDA and LiOMe. The reaction offers the stereocontrolled formation of C–C bonds and involves an S_N2 mechanism with inversion of configuration.11

(I) As a Carbon Source
TMEDA can be served as an excellent donor of methylene and formyl groups. An investigation carried out by Li and co-workers has revealed the base-switched use of TMEDA for methylation and formylation catalyzed by CuCl2 with atmospheric O2 as an oxidant.1

(J) Direct C–H Functionalization
A highly regioselective direct C–H functionalization of benzol[h]quinoline and phenylpyridine derivatives with alkyl or aryl Grignard reagents has been achieved with the use of Co(acac)3 as the catalyst and TMEDA as an additive.12

(K) C–N Bond Cleavage
S.-K. Tian et al. have reported a palladium-catalyzed cross-coupling reaction of aliphatic aliphatic amines and boronic acids. The strategy results in a C–C bond by C–N bond cleavage.13

References