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

**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. 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. 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.

### 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.

(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.

(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.

(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 cyanoacetate 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.
(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[h]quinolin-8(9H)-ones has been achieved with the use of Co(acac)₃ as the catalyst and TMEDA as an additive.12

(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 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 S₂N₂ 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 methylenation 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 benzo[h]quinoline and phenylpyridine derivatives with alkyl or aryl Grignard reagents has been achieved with the use of Co(acac)₂ 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 allylic amines and boronic acids. The strategy results in a C–C bond by C–N bond cleavage.13

References