SYNLETT Spotlight 448

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

Compiled by Bharat Kumar Allam

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

Bharat Kumar Allam was born in Andhra Pradesh, India, in 1986. He obtained his B.Sc. (2007) and M.Sc. (2009) in organic chemistry from Andhra University, India. Currently, he is pursuing his Ph.D. in synthetic organic chemistry at Banaras Hindu University, India, under the supervision of Professor Dr. Krishna Nand Singh. His research focuses on transition-metal-catalyzed cross-coupling reactions, C–H activation, and C–H oxidation.

Department of Chemistry (Centre of Advanced Study), Faculty of Science, Banaras Hindu University, Varanasi–221005, India
E-mail: allambharatkumar@gmail.com

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 $\text{CuF}_2 \cdot 2\text{H}_2\text{O}$ and TMEDA in H_2O –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 quinoxaline 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 $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and CuI . The protocol utilizes 20 mol% TMEDA as the ligand and air or O_2 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 cyanoacetate as a source of the cyano group. The reaction has been conducted using $\text{Pd}(\text{OAc})_2$ 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 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)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 allylic amines and boronic acids. The strategy results in a C–C bond by C–N bond cleavage.¹³

References

- (1) Zhang, L.; Peng, C.; Zhao, D.; Wang, Y.; Fu, H.-J.; Shen, Q.; Li, J.-X. *Chem. Commun.* **2012**, 48, 5928.
- (2) (a) Krasovskiy, A.; Lipshutz, B. H. *Org. Lett.* **2011**, 13, 3818. (b) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *Org. Lett.* **2010**, 12, 4742.
- (3) Nguyen, T.-H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Org. Lett.* **2005**, 7, 2445.
- (4) He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2012**, 51, 3944.
- (5) Zhuo, F.-F.; Xie, W.-W.; Yang, Y.-X.; Zhang, L.; Wang, P.; Yuan, R.; Da, C.-S. *J. Org. Chem.* **2013**, 78, 3243.
- (6) Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, 11, 709.
- (7) Zheng, S.; Yu, C.; Shen, Z. *Org. Lett.* **2012**, 14, 3644.
- (8) Kumar, M. R.; Park, A.; Park, N.; Lee, S. *Org. Lett.* **2011**, 13, 3542.
- (9) Sun, L.-L.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G. *J. Org. Chem.* **2011**, 76, 7546.
- (10) Lipshutz, B. H.; Huang, S.; Yi Leong, W. W.; Zhong, G.; Isley, N. A. *J. Am. Chem. Soc.* **2012**, 134, 19985.
- (11) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, 134, 11124.
- (12) Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2011**, 50, 1109.
- (13) Li, M.-B.; Wang, Y.; Tian, S.-K. *Angew. Chem. Int. Ed.* **2012**, 51, 2968.