

# 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

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

### Introduction

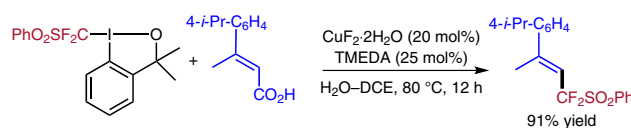
*N,N,N',N'*-Tetramethylethane-1,2-diamine (TMEDA) is a colorless, liquid, organic base with a fishy odor. TMEDA serves as an excellent donor of methylene and formyl groups under base switching.<sup>1</sup> It functions as an important ligand and additive for a broad spectrum of transition-metal-catalyzed reactions because of its unique ability to

enhance the rate of metalation for a variety of compounds.<sup>2</sup> 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.<sup>3</sup>

### Abstracts

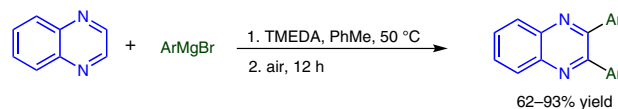
#### (A) *(Phenylsulfonyl)difluoromethylation*

Hu's group has developed an efficient protocol for vinylic difluoromethylation of  $\alpha,\beta$ -unsaturated carboxylic acids catalyzed by  $\text{CuF}_2 \cdot 2\text{H}_2\text{O}$  and TMEDA in  $\text{H}_2\text{O}$ –DCE.<sup>4</sup>



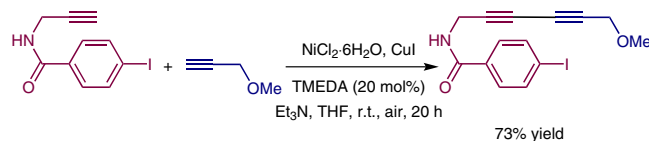
#### (B) *Direct ortho Arylation of Electron-Deficient N-Heteroarenes*

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.<sup>5</sup>



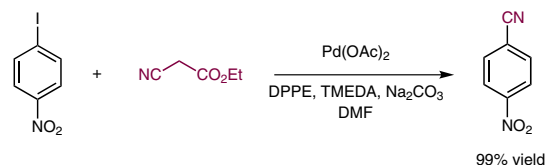
#### (C) *Syntheses of Unsymmetrical Conjugated Diynes*

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  $\text{O}_2$  as the oxidant.<sup>6</sup>



#### (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.<sup>7</sup>



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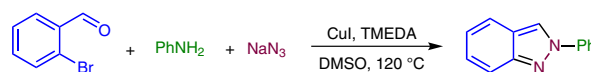
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DOI: 10.1055/s-0033-1339856; Art ID: ST-2013-V0456-V

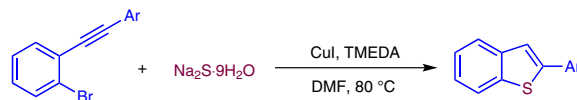
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## (E) Synthesis of 2H-Indazoles

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.<sup>8</sup>

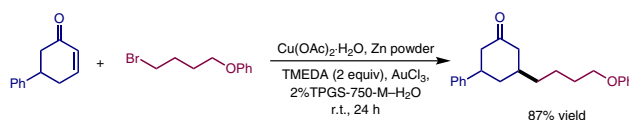
(F) Annulation of 2-Bromoalkynylbenzenes with Na<sub>2</sub>S

The synthesis of 2-substituted benzo[*b*]thiophenes was achieved from a CuI/TMEDA-catalyzed thiolation–annulation reaction between 2-bromoalkynylbenzenes and Na<sub>2</sub>S·9H<sub>2</sub>O. The use of Na<sub>2</sub>S·9H<sub>2</sub>O as a cheap and operationally convenient sulfur source makes this protocol simple and environmentally viable.<sup>9</sup>



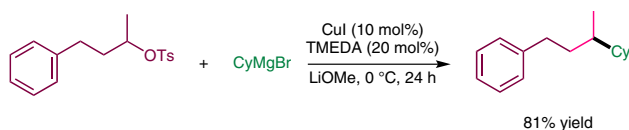
## (G) Conjugate Addition of Alkyl Halides to Enones

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.<sup>10</sup>



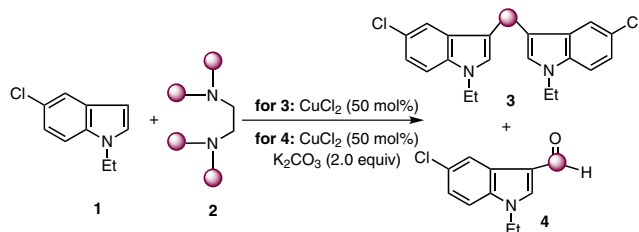
## (H) Cross-Coupling between Two Tertiary Alkyl Carbons

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<sub>N</sub>2 mechanism with inversion of configuration.<sup>11</sup>



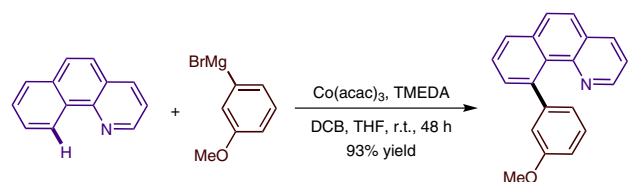
## (I) As a Carbon Source

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 CuCl<sub>2</sub> with atmospheric O<sub>2</sub> as an oxidant.<sup>1</sup>



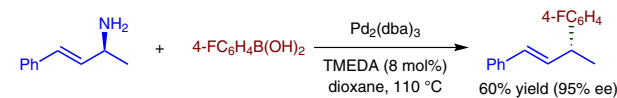
## (J) Direct C–H Functionalization

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)<sub>3</sub> as the catalyst and TMEDA as an additive.<sup>12</sup>



## (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.<sup>13</sup>



## References

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