Imidazoles and Imidazoliums from Propargylamines and Isonitriles

Significance: Reported is a multicatalytic methodology for the synthesis of 1,4,5-trisubstituted imidazoles 3 from the reaction of isonitriles 1 with propargylamines 2 in the presence of catalytic amounts of Yb(OTf)$_3$ and AgOTf. The same reaction of 2 with the primary, secondary, and aryl isonitriles 1 in the presence of Yb(OTf)$_3$, AgOTf, and KOTf affords 1,3,4,5-tetrasubstituted imidazoliums 4 in good to excellent yields. Compounds 1 and 2, with bulky alkyl groups and with aryl groups with different electronic properties, including heterocycles, were found to be well tolerated and led to various substituted imidazoles and imidazoliums. In addition, chiral propargylamines 2 were converted into enantioenriched imidazoliums without racemization. Imidazole 3a was elaborated into the polycyclic compound 6.

Comment: Imidazoles 3 and imidazolium salts 4 are important classes of heterocycles which are widely used in pharmaceuticals and organic synthesis (see Review below). The reported method involves a one-pot substrate-specific multiple metal salt catalytic route to a wide range of multi-substituted 3 and 4. The synthesis of a bioactive compound, 1-benzyl-5,6-dihydro-imidazo[5,1-a]-isoquinoline (7), by the developed method is reported. A possible mechanism is proposed based on the quantitative isolation and identification of the intermediate 5 and X-ray crystal analysis of 3 ($R^1 = R^2 = Ph$; $R^3 = Bn$) and 6. Intramolecular nucleophilic addition of the amidine nitrogen atom in 5 to the silver-coordinated triple bond through a 5-exo-dig cyclization to 3 is proposed. Further investigation of the reaction mechanism and applications of this methodology are encouraged.