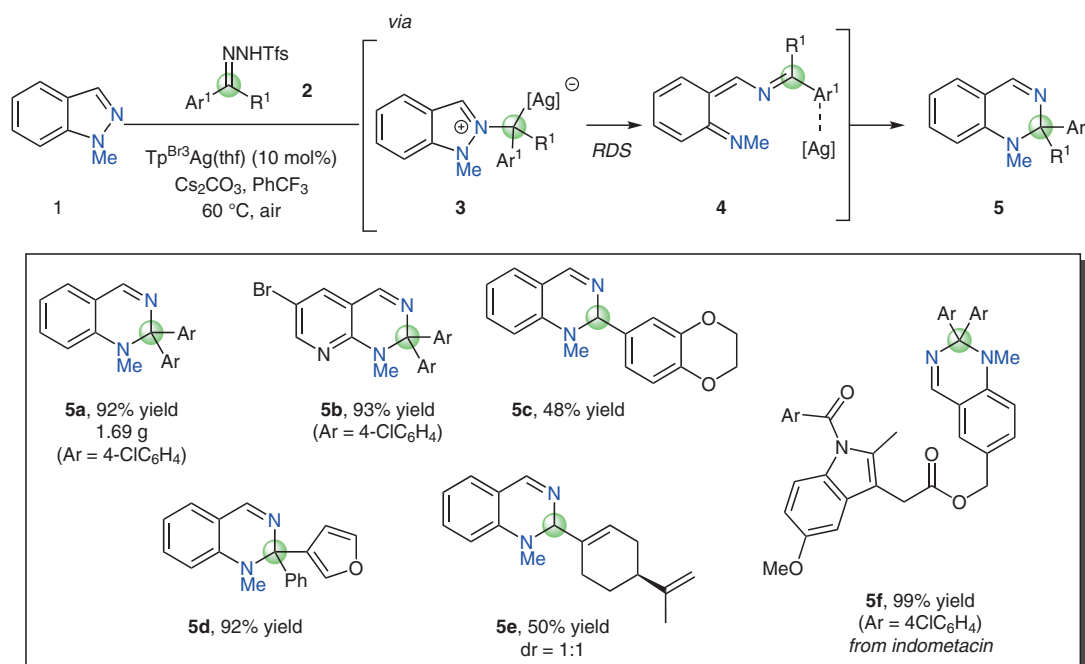


Skeletal Editing of Indazoles via Silver-Catalyzed Carbene Insertion



Significance: Skeletal editing has recently emerged as a powerful synthetic tool for accessing diverse chemical space (J. Jurczyk et al. *Nat. Synth.* 2022, 1, 352). This single-atom logic hinges on the notion of late-stage diversification from simple, stable functional groups which can act as a diversification point. Heterocycle manipulation is one such area which has garnered considerable interest from the medicinal chemistry community. The ability to ‘edit’ a drug-like molecule to modulate its 3D architecture and/or molecular properties can have profound implications on drug-discovery campaigns. Specifically, manipulations of nitrogen-containing rings are particularly powerful as they comprise the main type of aromatic heterocycles found in drugs. Simple and scalable reactions which can lead to the formation of novel heterocyclic, drug-like scaffolds are thus highly beneficial and worthy of pursuit.

Comment: Bi and co-workers recently reported an elegant carbene insertion of indazole derivatives of type 1 to dearomatized 1,2-hydroquinazolines 5. The reaction proceeded via an electrophilic silver carbene which was generated from hydrazone 2. DFT calculations revealed that N–N bond cleavage of indazolium ylide 3 to 4 was the RDS of the reaction. The products 5 were generated in high yield, and the authors found that steric and electronic parameters of the substrates did not have a large effect on the reaction outcome. The reaction could be conducted on gram scale (5a) with no loss of efficiency. Substituted indazoles were tolerated, including azaindazole 5b. Hydrazones 2 derived from ketones (5a,b,d,f), or aldehydes (5c,e) were suitable substrates. The authors also demonstrated that the product 5a could be further derivatized to other valuable molecular scaffolds.