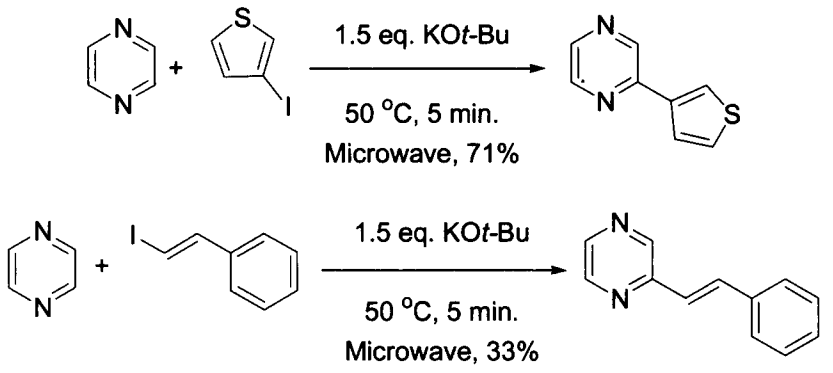

12.4.2 Palladium-catalyzed reactions

Pyrazines and quinoxalines are electron-deficient, 6π-electron heteroaromatic compounds. The inductive effects of the nitrogen atoms induce a partial positive charge on the carbon atoms. The use of palladium-catalyzed cross-coupling reactions in heterobiaryl coupling is linked to, and limited by, the synthetic and commercial availability of heteroaromatic organometallic reagents.[33] Electron-deficient nitrogen heterocycles are expensive, and difficult to prepare and use in cross-coupling reactions.

It is important to note that there are successful examples of biaryl coupling using electron-rich and sterically-hindered phosphine ligands on palladium(0).[55]

Literature research in this area yields few efficient reactions for palladium-catalyzed reactions of pyrazine and the diazine ring of quinoxaline.[56] One of the challenges associated with coupling the pyrazine ring is the free electrons on the nitrogen atoms that could bind and poison the palladium catalyst. The organometallic compounds needed for this coupling are unstable and are rarely isolated, and frequently decompose under cross-coupling reaction conditions.

The formation of the diazinylstannane can be accomplished through two separate pathways. In one pathway the pyrazine can be lithiated followed by quenching with tributyltin chloride.[57] The second pathway provides much higher yields: the chloropyrazine or quinoxaline is treated with a one equivalent of stannyl anion to provide a multifunctional aromatic ring. This equivalent can be manipulated, controlling the number of substitutions on the pyrazine ring.[57a]