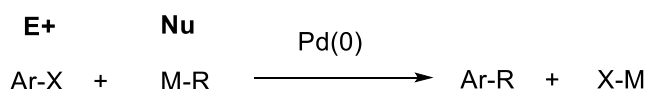


Problem Set #2: Cross-coupling reactions in medicinal chemistry

Besides amide bond synthesis, a second common process used in assembling drug molecules is cross-coupling reactions. These represent a range of reactions and several versions were awarded the Nobel Prize in Chemistry in 2010 (<https://www.nobelprize.org/prizes/chemistry/2010/summary/>). At their most fundamental level, most cross-coupling reactions (eqn. 1) involve the linking of aromatic molecules, acting as electrophiles, with various nucleophilic partners. The nucleophile and electrophile are catalytically coupled by transition metals and the most common metal by far, is palladium. As with the amide bond formation, drug chemists try to assemble two similar size pieces as that's the most efficient and convergent strategy.



Ar= -aromatic and heteroaromatic structures

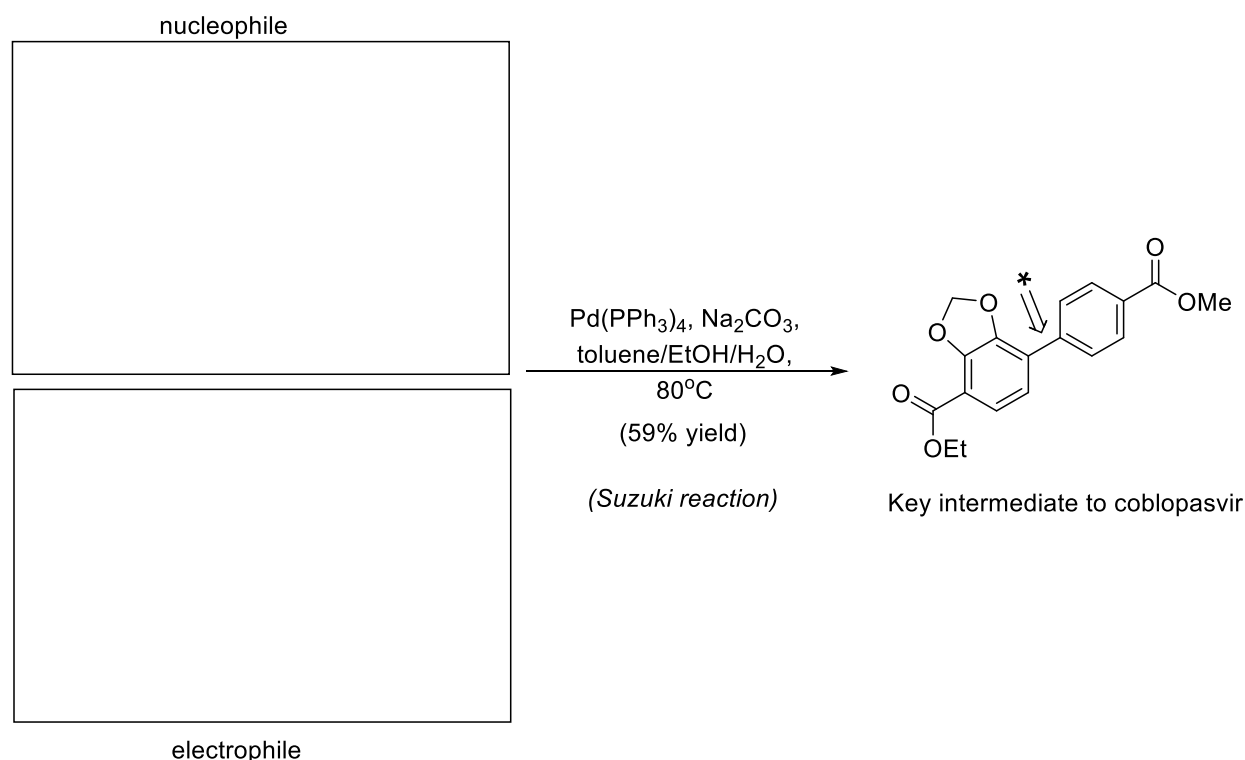
X= -I, -OS(O₂)CF₃ (a.k.a. -OTf), -Br, -Cl

M= -B(OR)₂, -SNR₃, Zn, -NH₂/NH(-), -SiR₃, -MgBr

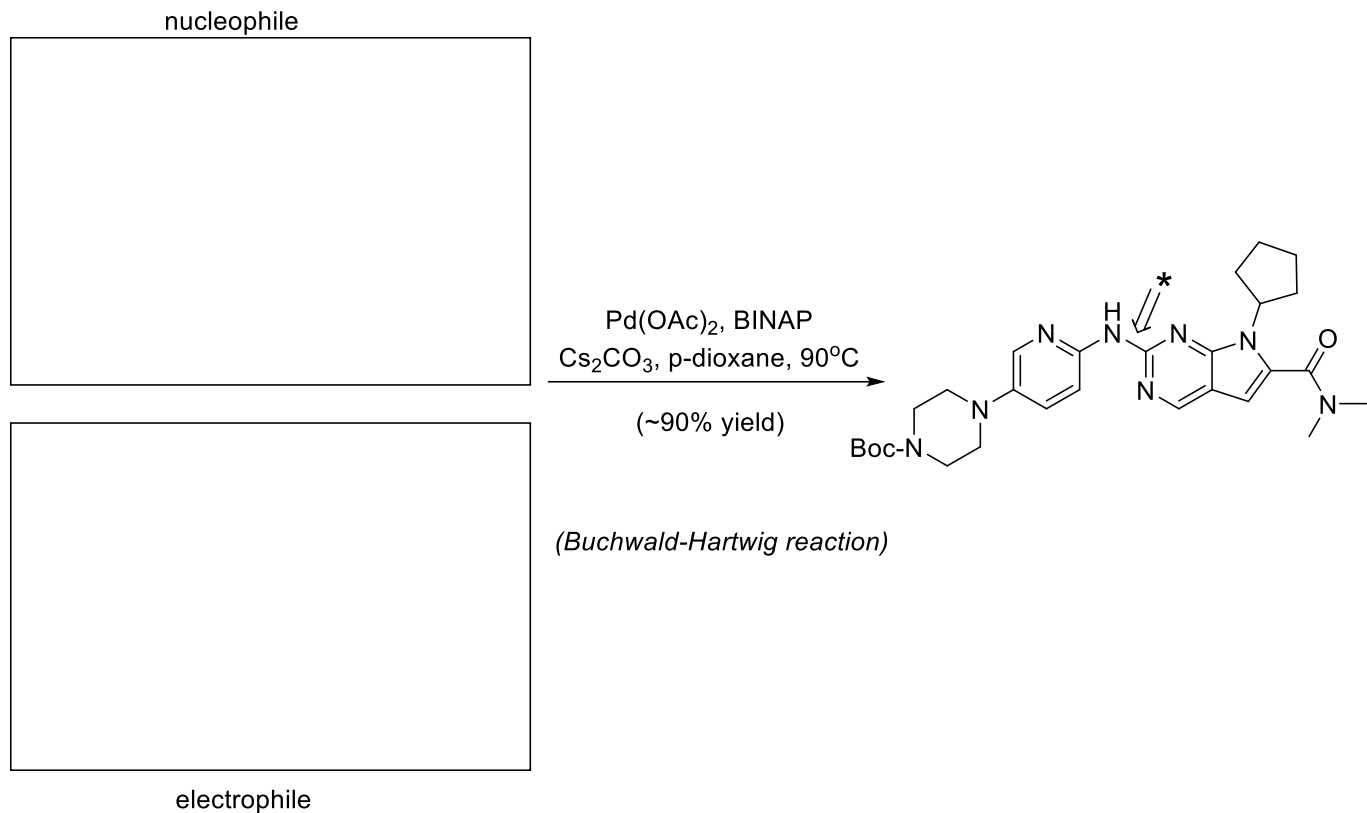
R= -aromatic and heteroaromatic structures, alkynyl, alkenyl or alkyl groups

The following recently reported drug molecules or intermediates were made through cross-coupling reactions. Propose nucleophiles and electrophiles that could be used in the reaction shown to form the highlighted bond. You could also scour the chemical literature for these reactions and provide Ar-X and M-R reagents that might be used to produce the drug molecule or intermediate. There may be more than one acceptable answer and you do NOT need to match the exact structures used in the chemical literature. Note: There are many forms of Pd(0) that are used and the reaction conditions may all be optimized for the particular reaction shown, so there will be small differences. Also note that the "name" reaction used in each case is given below the reaction arrow as a hint to the type of reagent combination to be used. You can search for details of these name reactions in Wikipedia.

a) Coblopassvir Dibromide synthesis. Coblopassvir was an anti-viral developed by Beijing Kawin Technology for the treatment of hepatitis C virus infections and approved in 2020 in China. (5 pts.)



b) Ribociclib synthesis. Ribociclib was developed by Novartis for advanced or metastatic breast cancer and approved in 2017. (5 pts.)



c) Enarodustat synthesis. Enarodustat was developed by Japan Pharmaceuticals and Medical Devices Agency for the treatment of anemia. (5 pts.)

