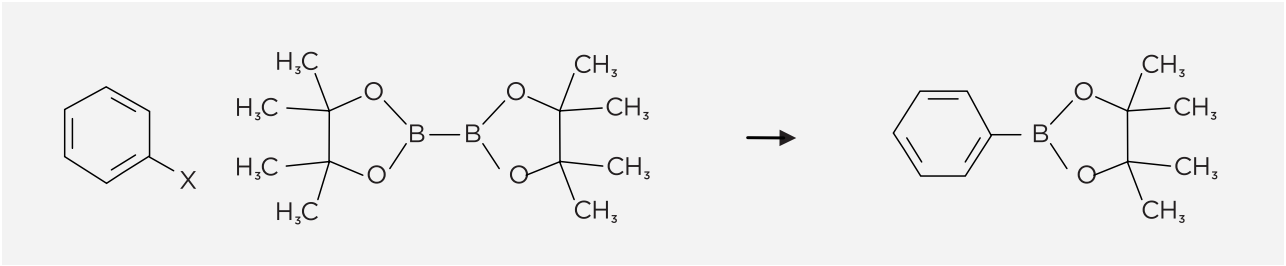
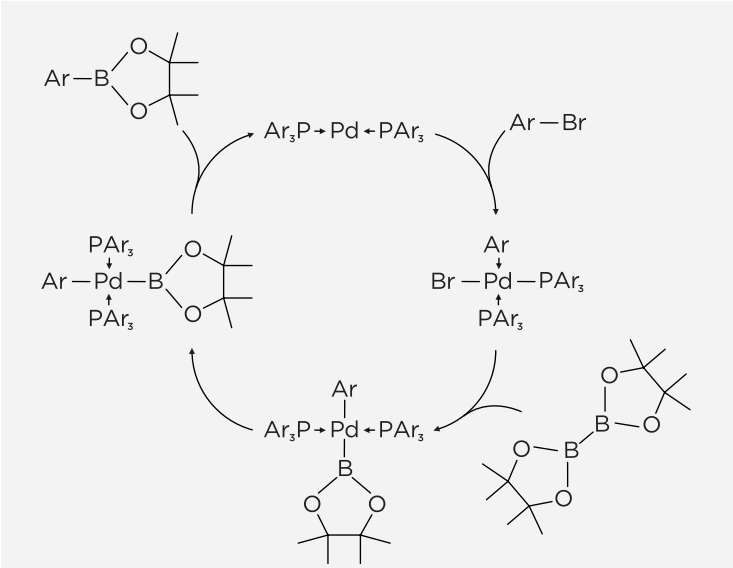
CATALYSIS CONSULTING

Case Study: Knowledge Based Problem Solving

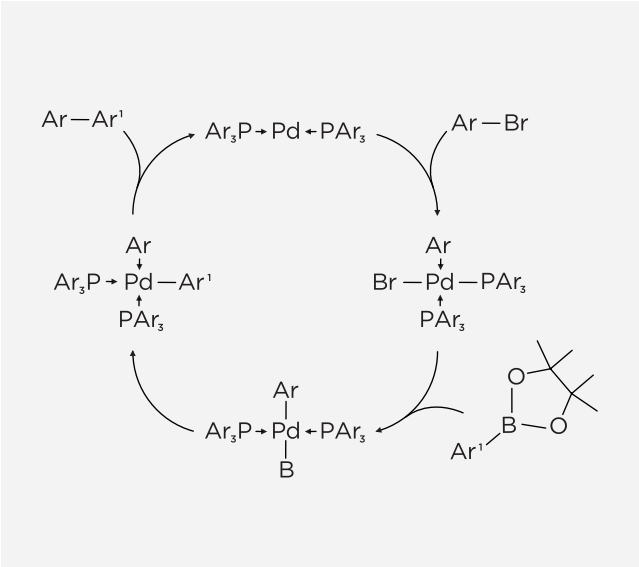
A Miyaura borylation which had previously operated successfully for a 50kg delivery suddenly developed a significant new impurity which was difficult to remove from the product. Problem analysis linked with a deep mechanistic understanding of catalytic chemistry highlighted the likely cause of the impurity. The 1 day it took to resolve the problem allowed the successful manufacture of 100kg of the required boronic ester with a clear understanding of how to eliminate the problem for all future production runs.



A Miyaura borylation reaction enables the synthesis of boronic esters by cross-coupling of bis(pinacolato) diboron (B2pin2) with aryl halides and vinyl halides. The pinacol boronic esters derived from B2pin2 are stable in air, slow to hydrolyse and serve as coupling partners in Suzuki Miyaura and similar reactions without prior hydrolysis. Both reactions require the use of a palladium catalyst and a base.



Miyaura Borylation



Suzuki Miyaura

The new impurity in the borylation reaction was identified as a symmetrical biphenyl. The biphenyl could be formed by one of the following mechanisms:

- Reduction of the Pd(II) catalyst:
  - If the impurity was formed at the beginning of the reaction then it could be due to the reduction of the Pd(II) precatalyst, or;
  - If it was generated throughout the reaction it could be an indication of oxygen ingress or some other mode of oxidation of the catalyst.
- A Suzuki Miyaura reaction.

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A Suzuki Miyaura reaction typically benefits from the presence of water. Water increases the rate of transmetallation of the boronate ester or acid onto the Pd (II) intermediate. The presence of water would facilitate the reaction of the formed pinicole boronic ester with unreacted starting material.

Problem analysis highlighted the most likely cause being the presence of water, even though it was not being deliberately added to the reaction. A review of the manufacturing protocol and the previous use of the equipment highlighted a methanol wash of the vessel prior to the problem batch. A lab reaction with 5-volume % methanol added to a typical reaction resulted in significant levels of biphenyl formation. In this reaction methanol mimics the effects of water. The use of a non-alcohol solvent for plant vessel cleaning prior to carrying out the next manufacture resulted in no biphenyl being formed.

In summary, an understanding of the mechanism of catalytic reactions and how impurities are formed enabled the rapid problem analysis resulting in the successful manufacture of very high quality pinacol boronic ester.

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