

DUAL ROLE OF PALLADIUM CATALYST IN ALKYNYLATION OF ARYL HALIDES

Abstract

This thesis is aimed to introduce novel insights, systems and methods in Sonogashira alkylation of (hetero)aryl bromides and chlorides at room temperature in the absence of copper co-catalyst.

By simultaneous introduction of two different palladium pre-catalysts, one tuned to promote oxidative addition of (hetero)aryl bromides, and the other tuned to activate terminal acetylenes, novel catalytic system was developed based on effective Pd–Pd transmetallation. Herein described Pd–Pd system was used in the synthesis of alkyl, aryl and heteroaryl substituted alkynes at room temperature without any copper additives. Two key intermediates, oxidative addition adduct and palladium acetylide, were prepared independently, and used in the transmetallation reaction to produce desired cross-coupled products. Pd–Pd tandem was also used in the preparation of synthetic intermediate of active pharmaceutical ingredient (API), and in a multi-gram scale synthesis with as low as 0.125 mol % of total palladium loading.

In addition, two other catalytic systems for alkylation of (hetero)aryl halides at room temperature have been developed. The system $(\text{PhCN})_2\text{PdCl}_2/\text{JohnPhos}$ was able to cross-couple activated and deactivated (hetero)aryl bromides with only stoichiometric amounts of aryl and alkyl acetylenes at room temperature. Furthermore, it was also used on a multi-gram scale synthesis where only 0.0125 mol % of palladium was needed to achieve the desired results. The system $\text{PdCl}_2/\text{XPhos}$ enabled couplings of less reactive aryl chlorides and alkynes into desired alkylation products and represents the first catalytic system capable of alkylation of aryl chlorides with no copper additives at room temperature or at 60 °C.

Keywords: Palladium, Cross-coupling, Sonogashira, Transmetallation, Mechanism