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Novel, highly chemo-selective metal catalyzed reactions for the preparation of key intermediates in organic synthesis/medicinal chemistry

Howard Alper

University of Ottawa, Canada

Transition metal catalyzed reactions are extensively used for organic synthesis, including in the preparation of key intermediates for drug synthesis. Of particular note are carbonylation reactions catalyzed by transition metal complexes. Why? Carbon monoxide is a rather inexpensive and easily available source of C1. While carbon monoxide is toxic and has to be handled under safe conditions, adhering to best practices enables one to work, with confidence, using this gas. Our laboratory has been utilizing this compound for 48 years without incident, by more than one hundred graduate students and postdoctoral fellows. Esters and amides are valuable in medicinal chemistry as pharmaceutical agents and/or as intermediates for the synthesis of pharmacologically active compounds. Conventional routes to esters and amides can produce substantial amounts of waste products, increasing the cost for manufacturing products of value in medicinal chemistry. In contrast, the atom-efficient palladium catalyzed carbonylation of aromatic halides has proven to be a remarkably chemo-selective route to amides and esters. Bifunctional and polyfunctional organic compounds containing both amino and hydroxyl functionalities occur in a number of drug intermediates. This presentation will demonstrate the unique chemo-selectivity for the preparation of amides and esters as dominant reaction products, depending on the nature of the added phosphine ligand and the base used for the reaction of aminophenols with haloarenes. The reaction of several amino alcohols with haloarenes was also observed. The scope and versatility of these reactions were investigated by treating aminophenols with styrenes. One can achieve by judicious choice of phosphine ligand, exceptionally high regioselectivity in these reactions, especially for the isolation of amides in high isolated yields. When the strategy is applied to the aminocarbonylation of aminophenols with easily accessible alkynes, then unsaturated amides are formed in high yields and with the excellent region- and chemo-selectivities. An example is the synthesis of avenanthramide A, which has anti-inflammatory properties. Additional chemical reactions to be discussed in this presentation include the synthesis of allyloxyphenols, the preparation of indolizines by oxidative alkoxycarbonylation of propargylic pyridines, as well as a novel route to N-fused heterocycles.

halper@uottawa.ca