Heck and Cross-Coupling Reactions: Two Core Chemistries in Metal-Catalyzed Organic Syntheses

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The field of organic chemistry has undergone many dramatic developments during the past forty years. Among them, reactions emphasizing the use of transition metals in organic synthesis have contributed greatly to the simplification of methodology for selectively obtaining a target molecule in a short synthetic process. Indeed, innumerable organic syntheses that are not achievable by traditional methods have been realized by reactions catalyzed by transition metal complexes. Heck and cross-coupling reactions are two core chemistries that have provided a great impact on the development of the new area of "metal-catalyzed organic syntheses".

A very powerful and flexible catalytic cycle for carbon-carbon bond formation was discovered in 1971–1972 by the coupling reaction of Grignard reagents at the sp^2-carbon. In the past 30 years, the protocol has been substantially improved and expanded to analogous coupling reactions of other organometallic and metalloid compounds, which include Li, B, Al, Si, Cu, Mn, Zn, In, Sn, and Hg. Coupling reactions of C–H, O–H, N–H, S–H and P–H bonds in the presence of a base as well as a palladium catalyst are other useful variants closely related to the original cross-coupling chemistry. These reactions provide an indispensable and simple methodology for preparative organic chemists in academic and industrial laboratories. Due to the simplicity and reliability in the carbon-carbon, carbon-heteroatom (O, N, S, P) and carbon-metalloid (B, Si, Sn) bond formation, as well as the high efficiency of the catalytic process, the reactions have been widely accepted by organic chemists in various fields. Application of the protocols range from various syntheses of complex natural products and biologically relevant molecules including drugs, to the preparation of supramolecules and of functional materials. Reactions on polymer surfaces have allowed robot synthesis and combinatorial synthesis. Palladium-phosphine complexes are the most common catalysts which achieve a high activity and the efficiency often exceeds 1,000,000 turnover number of the catalyst (TON). Significant tolerance of palladium catalysts to most functional groups is also advantageous for the syntheses of complex molecules having multiple functional groups. A recent topic in this field is the oxidative addition of chloroarenes to palladium(0) complexes, which has been studied extensively from the viewpoints of cost and availability, especially in the industrial process of Heck and cross-coupling reactions. Palladium catalysts based on bulky, electron-donating alkylphosphines and N-heterocyclic carbenes have been newly developed as ligands for carrying out these reactions of chloroarenes. Another recent topic that expanded the limitation of substrates is the oxidative addition of haloalkanes possessing β-hydrogen atoms. C–C bond formation between two sp^3 carbons is a protocol that has been long-awaited by synthetic organic chemists, but the reaction has been much less successful among the possible combinations of different types of nucleophiles and electrophiles. Coordinatively unsaturated palladium complexes possessing electron-donating phosphines have been found to catalyze cross-coupling reactions between alkylboranes with primary and even secondary alkyl halides with no significant β-hydride elimination. Thus, representative combinations of metals and halides of alkyl, allyl, 1-alkenyl, 1-alkynyl, and aryl derivatives are now available for such C–C bond-forming reactions.

Several monographs on the cross-coupling reactions and other metal-catalyzed C–C bond-forming reactions have appeared.[1–4] This fascinating field is still growing

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and continues to provide essential tools for precise synthesis of organic compounds of practical significance. The hope of the editors is that this thematic issue on Heck and cross-coupling reactions will help both expert and novice practitioners to use metal-catalyzed reactions for organic syntheses.

References

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