14 Asymmetric palladium-catalysed coupling reactions
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14.1 Introduction

Organometallic chemistry offers special effects in bond-forming reactions. Of all the new metal-mediated processes to be applied in synthesis, it is palladium-catalysed coupling reactions that have found the most immediate and enthusiastic reception in industrial laboratories. The key to the attraction of this type of chemistry is that two components that would normally be combined can be linked in a single step, often in a highly selective and efficient way. What is more, in many cases and in contrast to the use of organocuprate, lithium and magnesium methodologies, protection of hydroxylic functionality in the substrates is often unnecessary with palladium-catalysed coupling. There are two main classes of coupling reaction: the Heck coupling reaction and cross-coupling reactions of the types pioneered by Stille (organotin precursors) and Suzuki (organoboron precursors). In 1989, the first examples of enantioselective Heck coupling were described independently by the groups of Shibasaki and Overman. Since then, there has been a rapid development of the asymmetric modification of all classes of palladium-catalysed coupling reaction, providing a synthetically direct and versatile new approach to the enantioselective preparation of intermediates for use in organic synthesis. It is these developments that are the subject of this chapter.

Heck coupling combines substituted vinyl or aryl derivatives (typically bromides, iodides or triflates) with an alkene (typically an α,β-unsaturated carbonyl compound or styrene derivative, though many other types of alkene can also be employed). The two reactants are coupled to form (1) without consuming the unsaturation in the alkene portion (Scheme 14.1). Cross-coupling reactions also combine unsaturated reactants in a way that retains the unsaturation in the product. For example, the vinyl arene target molecule (2) can be prepared by a cross coupling between an aryl bromide (ArX) and a vinlytin reagent (Scheme 14.2). In terms of disconnections retrosynthesis design, consideration of the preparation of both (1) (ɛ = CO₂Me) and (2), for example, indicates that in both cases an aryl bromide and a substituted alkene would be appropriate starting materials.

Schemes 14.1 and 14.2 show the similarity between the disconnections afforded by the two bond-forming processes. Although giving rise to products that are similar in structural type, these two coupling procedures follow different mechanisms. These are illustrated in Schemes 14.3 and 14.4. In both
Heck and cross-coupling reactions, vinyl coreactants \( \text{CH}_2=\text{CHX} \) can be used to good effect in place of the aryl-X derivative.

**14.1.1 Mechanism of Heck coupling**

Heck coupling with aryl halides begins with an oxidative addition into the Ar–X bond. In this way, the aryl group becomes attached to the transition metal catalyst. The alkene approaches initially as a side-on \( \eta^2 \) ligand. Carbon–carbon bond formation is achieved by \( \sigma \)-bond migration, displacing the palladium to the far end of the alkene. The metal is lost by \( \beta \)-elimination, so reforming the alkene in the organic product, which is liberated in this step. Heck coupling is typically performed in the presence of the base, so that loss of HX (which is picked up by the base to form, for example, \( \text{Et}_3\text{NH}^+\text{X}^- \)) completes the catalytic cycle.