

PREFACE TO VOLUME 83

The two chapters in Volume 83 describe reactions that represent two major (and growing) franchises in the *Organic Reactions* series, namely, transition metal catalyzed cross-coupling reactions and multicomponent reactions. These two processes not only have a rich history in synthetic organic chemistry, but also represent some of the most commonly employed transformations in the modern practice of molecule construction.

The first chapter authored by Eiichi Nakamura, Takuji Hatakeyama, Shingo Ito, Kentaro Ishizuka, Laurean Ilies, and Masaharu Nakamura describes one of the most exiting advances in the field of transition metal catalyzed cross-coupling reactions: the use of iron catalysts. Despite the fact that iron catalysis was documented very early in the evolution of cross-coupling reactions, the advent of palladium catalysts has dominated the development of these 2010 Nobel Prize winning reactions. However, concerns about cost and toxicity of palladium have stimulated a renaissance in the use of iron catalysts, given its earth abundance, low cost, and low toxicity. More importantly, many of the applications of iron catalysis show complementary behavior in scope and rate compared to palladium-catalyzed reactions. For example, chlorides, phosphates, and sulfides perform well as electrophiles in a variety of structural settings. In addition, organometallic reagents based on magnesium, zinc, copper, manganese, and boron are competent nucleophiles in this coupling process. These reactions are all the more intriguing given the mechanistic complexity of first-row elements which are prone to one-electron processes and possess much weaker bonds to carbon. Fortunately, the mechanistic ambiguity of these reactions has not hampered their development and applications in total synthesis endeavors are already on record. Eiichi Nakamura is a leader in this field and has provided the reader with clear guidelines about the choice of iron catalyst, electrophile, and nucleophile to achieve many different pairwise combinations of organic moieties. As this is Prof. Nakamura's second *Organic Reactions* chapter, we are highly indebted to him for his outstanding support of the series. Together with the well-known Stille coupling of organotin compounds (Volume 50, by Vittorio Farina, Venkat Krishnamurthy, and William J. Scott) and the Hiyama-Denmark coupling of organosilicon compounds (Volume 75, by Timothy W.-t. Chang, Russell C. Smith, Aaron D. Bailey, Christopher S. Regens, Nathan S. Werner, and Scott E. Denmark), this chapter completes a powerful trinity of the most modern methods for formation of carbon-carbon single bonds.

The second chapter authored by Stephen G. Pyne and Minyan Tang describes the latest in a long line of multicomponent reactions published in this series: the boronic acid Mannich reaction, sometimes called the Petasis reaction. Although the Mannich reaction chapter is seriously out of date (Volume 1!, by F. F. Blicke), more modern variants such as the Biginelli Reaction (Volume 63, by C. Oliver Kappe and Alexander Stadler), the Passerini reaction (Volume 65, by Luca Banfi

and Renata Riva) and the Strecker reaction (Volume 70, by Masakatsu Shibasaki, Motomu Kanai, and Tsuyoshi Mita) illustrate the growing importance of creating molecules from multiple reaction partners in a single transformation. Many metrics of synthetic efficiency have been introduced (atoms, electrons, steps, etc.) but it is undeniable that the more connections to diverse molecular subunits that can be created per manipulation is a significant component of efficiency. Interestingly, all of the above-mentioned name reactions have a common feature in the formation of an azomethine unit from a carbonyl compound and a nitrogen-containing compound, which then undergoes addition by various nucleophiles that define the different variants. As the title implies, in this variant the nucleophile is a boronic acid (or the recently introduced trifluoroborate) attached to an aryl, heteroaryl, alkenyl, or allyl unit. The reactions are operationally rather simple and the conditions are decidedly mild; no strong acids or bases are required. The products, invariably chiral amines, are extremely important compounds estimated to comprise 45% of all drug substances. Accordingly, methods for the stereocontrolled construction of these amines using the boronic acid Mannich reaction have been developed including diastereoselective, auxiliary-controlled, and catalytic enantioselective variants. The significant synthetic potential of the products and the high levels of stereocontrol available for their construction assure that the transformations described in this chapter will find widespread use in academic and industrial laboratories alike.

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