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TRANSITION METAL CATALYSIS IN THE PHARMACEUTICAL INDUSTRY

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1.1 OVERVIEW OF CATALYSIS

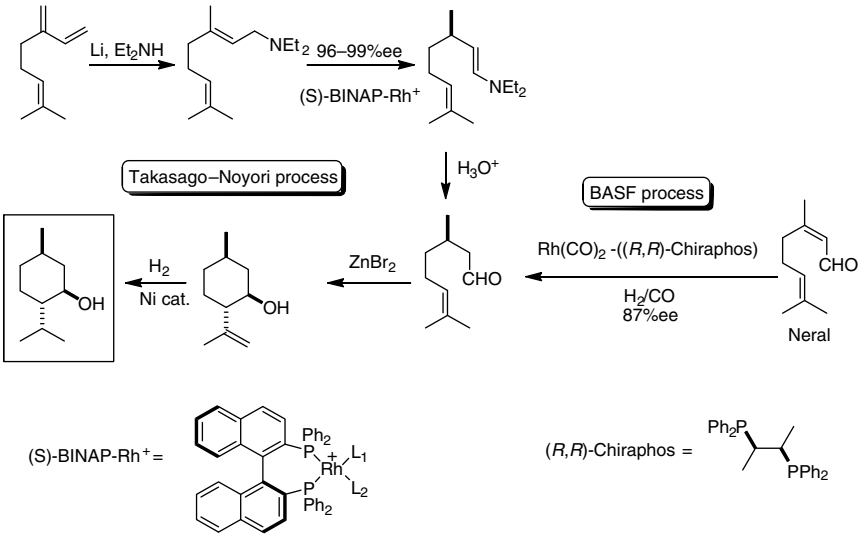
Catalysis typically provides the technology to enable the efficient and cost-effective synthesis of pharmaceutical products. By definition, catalysis increases the reaction rate by lowering the activation energy of the reaction, therefore allowing the chemical transformation to take place under much milder conditions over the uncatalyzed process. Furthermore, the catalyst typically imparts chemo-, regio-, or stereoselectivities over the course of the reaction to enable highly efficient syntheses of target molecules.

Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective, First Edition. Edited by Matthew L. Crawley and Barry M. Trost.

Catalysis is one of the principle drivers for the modern economy. Catalysis-based industries contribute more than 35% of the global GDP [1]. It has been estimated that about 90% of the chemicals are derived in some fashion from catalytic processes [2]. The annual worldwide demand for catalysts is approaching one million metric tons, and further growth in this sector was projected to continue [3]. Furthermore, catalysis is one of the 12 green chemistry principles [4]. The use of catalysis can significantly reduce waste streams, simplify synthetic processes, and reduce both cycle times and volume requirements, especially in chemical manufacturing. Catalysis often enables a business to enhance the value of the product while minimizing the overall carbon-footprint of their activities.

The significance of catalysis and its proven impact on the advancement of science was recognized by several Nobel Prizes in Chemistry. In 1909, Wilhelm Ostwald won the Nobel Prize for "his work on catalysis and for his investigation into the fundamental principles governing chemical equilibria and rates of reaction." During the first decade of this century, four transition-metal catalyzed reactions were honored with Nobel Prizes in Chemistry: asymmetric hydrogenation and oxidation (2001; Knowles, Noyori, and Sharpless), metathesis (2005, Chauvin, Grubbs, and Schrock), and cross-coupling reactions (2010; Heck, Negishi, and Suzuki). These reactions not only have academic significance but also proved to be critical for the production of industrially important products.

Noyori's BINAP-Rh-catalyzed asymmetric allylic amine isomerization reaction was used to develop an industrial process for menthol (Scheme 1.1) [5]. Menthol is one of the most widely utilized natural products. In 2007, the total world production of menthol was $>19{,}000$ tons, over a quarter of which was used for pharmaceutical purposes, while the remainder was used for consumer products such as toothpaste,



SCHEME 1.1 Industrial menthol processes.

cosmetics, confectionary, and tobacco products [6]. Natural menthol is supplied via isolation from mint cultivated primarily in Asian countries. However, the market demand greatly exceeded the natural supply. In addition, the reliability of natural supply is affected by weather and climate of the mint-growing region. A need existed for an efficient and economical method for synthetic menthol to close the supply gap and also to alleviate the volatility of price on the market.

The new Takasago–Noyori menthol process commenced with the conversion of myrcene to geranyldiethylamine by treatment with lithium and diethylamine. Then asymmetric isomerization of the allylic amine with a cationic BINAP-Rh catalyst afforded a chiral enamine, which was hydrolyzed to (*R*)-citronellal (96–99%ee). Elaboration of (*R*)-citronellal to (−)-menthol was accomplished in two additional straightforward steps. This new process allowed Takasago to produce 1000–3000 tons of synthetic menthol every year for the past 30 years.

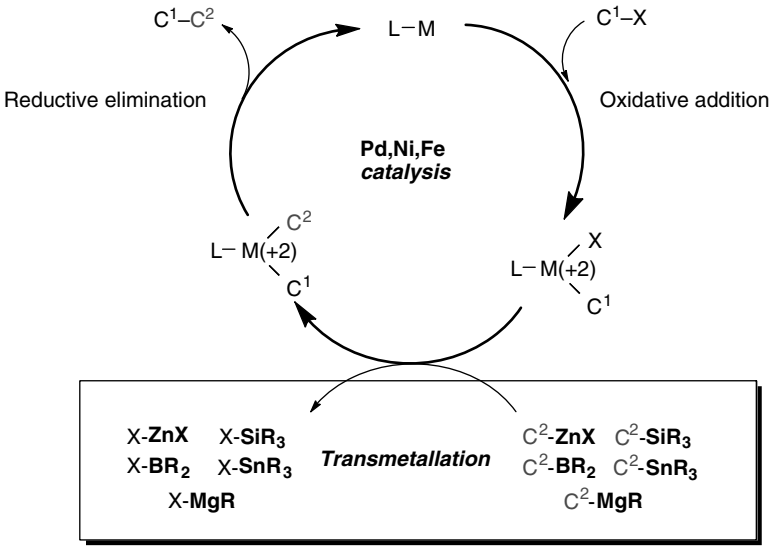
BASF recently disclosed a new menthol process using Chiraphos-Rh-catalyzed hydrogenation reaction as the key step [7]. They were able to achieve the direct asymmetric hydrogenation of neral to give (*R*)-citronellal with 87%ee. The projected production capacity of the BASF menthol process was 3000–5000 tons/year [8]. This menthol process described here clearly underscored the importance of catalysis to our everyday life.

1.2 TRANSITION METAL CATALYSIS IN THE PHARMACEUTICAL INDUSTRY

Transition metal catalyzed processes have been extensively utilized in the pharmaceutical industry for over the past 30 years. They have been employed for library preparations, discovery syntheses, and large-scale preparation of active pharmaceutical ingredients. This use relates to the efficiency to conduct a large number of chemical transformations with tolerance of numerous functional groups, and high enantio-, diastereo-, and chemoselectivities. The most commonly applied transition metal catalyzed applications relate to the transformations that result in a cross-coupling for the formation of carbon–carbon and carbon–heteroatom bonds, asymmetric hydrogenation, oxidation, asymmetric addition, and metathesis. The emergence of each technology, evolution into its current status, impact, and recent advances that are projected to provide additional value to the pharmaceutical industry deserve further discussion.

1.2.1 Cross-Couplings for the Formation of Carbon–Carbon Bonds

The importance of cross-couplings for the formation of carbon–carbon bonds to the chemical industry is best appreciated by awarding the 2010 Nobel Prize to Heck, Negishi, and Suzuki for "palladium-catalyzed cross-couplings in organic synthesis." The basis of cross-coupling is the reductive elimination of two organic components from a high valent late transition metal for the formation of a C–C bond (Scheme 1.2) [9]. The utility of this reaction was realized by the development of



SCHEME 1.2 General cross-coupling mechanism and extensions.

suitable components for the selective formation of the mixed bis-organometallic intermediate. In 1971, Kochi demonstrated that a Fe(III) complex can catalyze the coupling of organo-magnesium reagents with haloalkenes [10]. The following year in 1972, Kumada, Tamao, and Corriu independently reported the cross-coupling of organo-magnesium reagents with alkenyl or aryl halides catalyzed by a Ni(II) complex [11]. Since these seminal reports, palladium and nickel complexes have emerged as the mainstream catalysts employing organo-boronates, silicon, tin, magnesium, and zinc reagents as the nucleophilic components wherein the corresponding cross-couplings are referred to as Suzuki-Miyaura [12], Hiyama [13], Stille [14], Kumada [15], and Negishi [16] couplings. The transmetallation operation can also be replaced by a migratory insertion with an olefin or carbon monoxide to achieve a Heck coupling [17] or carbonylation [18]. Since the advent of these technologies and by proper choice of reaction components, catalyst, and conditions, most carbon–carbon single bonds can be constructed through this process.

The utility of cross-couplings for the accessibility of bi-aryl, aryl-alkenyl, and aryl-alkynyl moieties has made these structures common synthetic intermediates for APIs and as pharmacophores rationally designed into numerous drugs and clinical candidates as exemplified by Losartan, Naratriptan, and Singulair (Fig. 1.1) [19]. A survey of reactions scaled in Pfizer's GMP facility at the Groton site showed a steady increase in the use of cross-couplings over the past two decades [20]. Of the 14% of reactions that generate a C–C bond, 4.3% were cross-couplings from 1985 to 1996, which increased to 14.5% for the period between 1997 and 2007. Further utility of cross-couplings will be due to advances in broadening the substrate scope for incorporation into a cross coupling. Extension to less reactive electrophiles such as aryl chlorides [21], phenolates [22], carbon-nitriles [23], and aryl ammonium

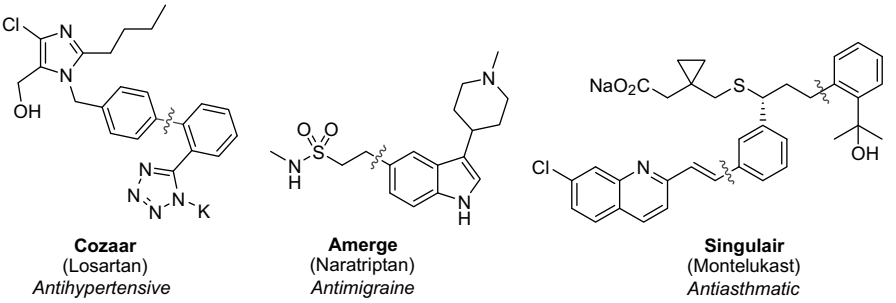
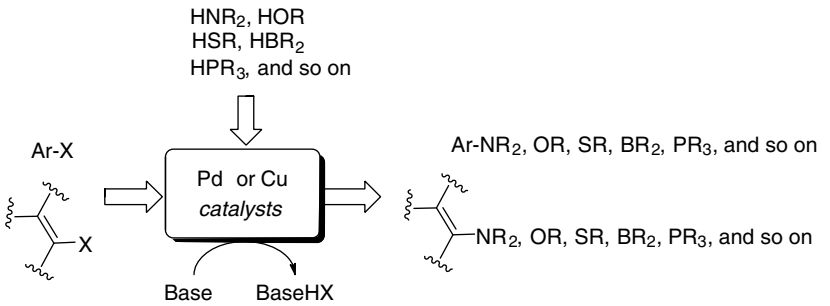


FIGURE 1.1 Selected examples for application of C–C cross-couplings.

salts [24] has greatly increased the flexibility for incorporating a larger pool of commercially available materials into a synthesis. Recently, some progress for the cross-coupling of aryl fluorides has been achieved [25]. Complementary to the advances with the electrophile, the nucleophile scope has also expanded to include aldol equivalents [26], carboxylic acids (decarboxylative couplings) [27], perfluorinated alkanes [28], and C–H insertions [29]. Progress has also been made for enantioselective cross-couplings [30] to provide access to atropisomers, which are emerging as pharmacophores [31]. More promising are the developments of enantioselective cross-couplings for the generation of classical carbon stereocenters, which provide general access to otherwise difficult structures [32]. These advances in cross-couplings are growing exponentially, a trend that will add additional value to the pharmaceutical industry.

1.2.2 Cross-Couplings for the Formation of Carbon–Heteroatom Bonds

The impact of cross-couplings for the formation of carbon–heteroatom bonds is more significant to the pharmaceutical industry than cross-couplings for the formation of C–C bonds. The process for heteroatom coupling is based on principles similar to those used for carbon–carbon bonds but varies with mechanism due to the influences of metal, ligand, and nucleophilic component (Scheme 1.3) [33]. Although the copper mediated C–N coupling has been known for over a century, that is, Ullmann [34] and



SCHEME 1.3 General scope of C–X bond formation through a cross-coupling.

Goldberg [35] reactions, the use of harsh conditions prevented general application to complex molecule synthesis. The discovery and development of ligand-mediated copper catalyzed couplings by Buchwald and coworkers [36] and Goodbrand et al. [37] allowed for much milder conditions and tolerance of numerous functional groups. These reactions have been extended to the coupling of nitrogen, phosphorous, oxygen, and sulfur providing general access to the respective carbon sp^2–X bond. Complementary to copper-catalyzed reactions, the palladium-catalyzed process has been known since the pioneering research of Migita and coworkers with amide-tin reagents [38]. The expansion in the palladium process originated from the independent developments of tin-free processes by Buchwald [39], Louie and Hartwig [40]. The palladium-catalyzed process was then extended to the formation of C–O, C–P, and C–B bonds. The recent application for the formation of a C–B bond by Ishiyama and coworkers [41] presented a valuable process for the preparation of organo-boronates for Suzuki couplings with significant functional group tolerance that simply cannot be achieved by traditional Grignard or organo-lithium-mediated approaches. The breadth of bond formations that are possible with cross-couplings for the formation of carbon–heteroatom bonds is nearly unmatched when compared to other methodologies.

The impact of cross-couplings for carbon–heteroatom bond formation for the pharmaceutical industry is considerable. These methodologies provide the robustness required for the formation of a large diversity of structures that are necessary for discovery and development (Fig. 1.2). Some notable examples are the multibillion dollar drugs Gleevec from Novartis [42], Abilify from Otsuka Pharmaceuticals [43], and Pfizer's Phase III candidate Torcetrapid [44]. The advances in broadening the electrophile scope for cross-couplings for carbon–carbon bonds are often extended to the formation of carbon–heteroatom bonds. The use of aryl chlorides [45] and aryl ethers [46] are routinely depicted in the recent literature. Other significant developments in cross-couplings are related to C–H activations and numerous reports are published on the efficient amination of C–H bonds [47]. One promising methodology reported by Hartwig is the C–H borolation promoted by an iridium catalyst, which provides interesting regioselectivities that are not achievable by existing methodologies [48]. These seminal advances will further increase the substrate scope and applicability for pharmaceutical synthesis.

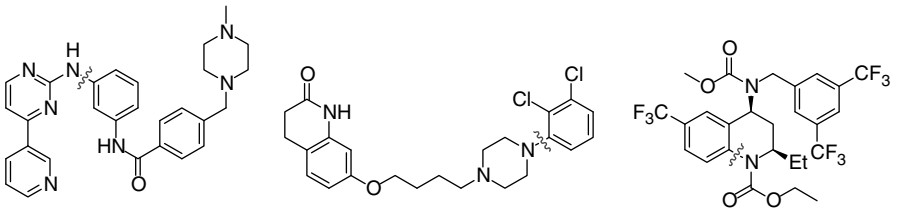
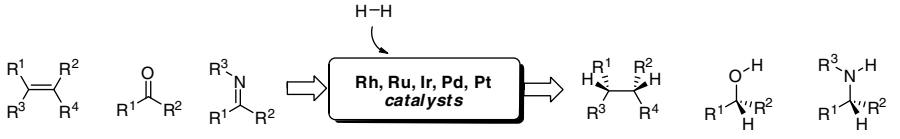


FIGURE 1.2 Selected examples for application of heteroatom cross-couplings.

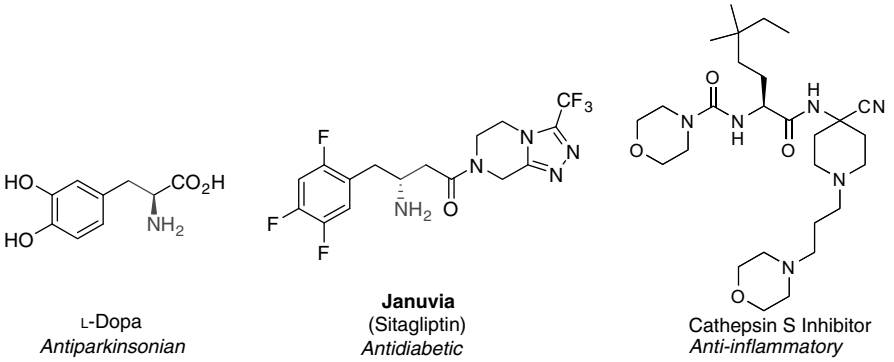
1.2.3 Asymmetric Hydrogenation

Asymmetric hydrogenation is the most significant asymmetric technology utilized to establish chirality in pharmaceutical products. Half of the 2001 Nobel Prize was awarded to William Knowles and Ryoji Noyori "for their work on chirally catalyzed hydrogenation reactions." A hydrogenation is the transfer of a molecule of hydrogen to a pi-bond resulting in a formal reduction, typically catalyzed by a transition metal (Scheme 1.4) [49]. The utility of the process is the ability to control reduction of one enantiotopic face of the pi-bond by a chiral ligand resulting in asymmetric induction. Since the advent of transition metal catalyzed asymmetric hydrogenations by Knowles and Noyori, an exceedingly large pool of chiral ligands have been invented typically based on the class of biaryl diphosphines, monophosphines, phospholanes, ferrocenyl-based diphosphines, and miscellaneous phosphines, which have comparable performance [50]. As coined by Jacobsen, the selected few that are routinely applied to large-scale production of commercially relevant molecules are referred to as "privileged ligands [51]." Intellectual protection for the initial structures has expired, and the industry has free access to utilize the technology. Some structures are still protected by patents. However, since the variation based on the ligand structure can be considerable while retaining similar performance to known systems, modification of the initial ligand design to circumvent IP protection is often achievable [52]. Asymmetric hydrogenation has been applied to the saturation of C=C, C=O, and C=N bonds most typically with Rh, Ru, and Ir-based catalysts. Due to the high levels of discrimination exhibited for these processes, multiple stereocenters can often be established in a single transformation through a hydrogenation that proceeds through a dynamic kinetic asymmetric transformation.

Asymmetric hydrogenation can be considered as the powerhouse for installation of chirality into a drug substance [53]. Numerous examples attest to this importance (Fig. 1.3). The classical example of multiton applications are the synthesis of L-Dopa by Monsanto as well as the menthol processes described earlier in this chapter [54]. Sitagliptin from Merck [44b] and a Cathepsin *S* inhibitor from Boehringer Ingelheim [55] highlight the usefulness of this technology for the synthesis of human pharmaceuticals. The value of asymmetric hydrogenation for the establishment of chirality is due to the low cost for hydrogen, high levels of asymmetric induction, and most importantly the typical high turnover allowing for exceedingly low catalyst loadings. Achievement of 10,000–1,000,000 turnovers is common and expected for production processes. Due to the large pool of available ligands, pharmaceutical companies and specialized CROs built catalysis or automation groups that can conduct high throughput optimization to establish the optimal ligand and conditions for a particular transformation.



SCHEME 1.4 General hydrogenation scope.



L-Dopa
Antiparkinsonian

Januvia
(Sitagliptin)
Antidiabetic

Cathepsin S Inhibitor
Anti-inflammatory

FIGURE 1.3 Selected examples for application of asymmetric hydrogenation.

Clearly asymmetric hydrogenation is one of the most mature of all asymmetric catalytic technologies employed by the pharmaceutical and agrochemical industries. There are several reasons why this methodology has been so fully embraced. From an operations perspective, asymmetric hydrogenation requires no significant changes to equipment that has been used for many years for standard hydrogenations at scale. Thus, minimal capital investments and limited operator retraining are needed to use the technology. The steady march of chiral ligand development in the past 35 years has led to reasonably good scope with respect to the substrate classes which can be successfully reduced. In parallel, there have been dramatic improvements in the efficiency of these chiral catalysts, leading to ever higher TON's (turnover numbers) and TOF's (turnover frequencies) and lower catalyst loadings. Hydrogen, particularly on a mole basis, is also by far the cheapest reducing agent available. When these advantages are coupled with a transformation that is inherently "atom economical," which also provides value-added (chiral) products the broad acceptance of asymmetric hydrogenation can be understood.

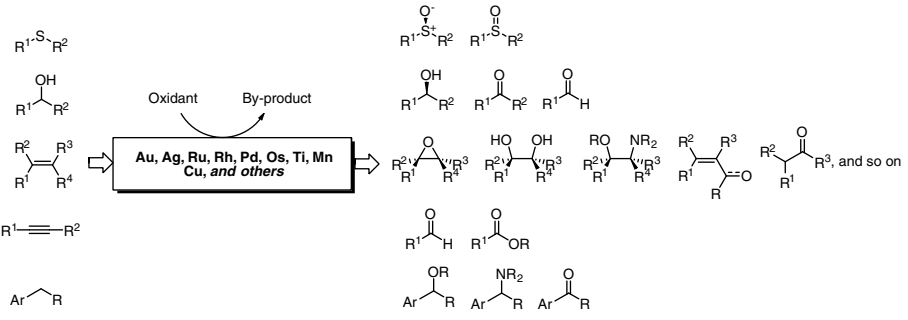
However, asymmetric hydrogenation of certain substrates is still challenging. For example, only recently has a general process for the asymmetric hydrogenation of some tetra-substituted and unfunctionalized olefins been reported by Pfaltz and coworkers [56]. These catalysts normally require the relatively expensive BAr^F counterion, which also has a high molecular weight. There is also nearly exclusive use of iridium for these hydrogenations, rather than cheaper precious metals such as ruthenium. Achieving very low catalyst loadings thus becomes a critical part of the cost analysis in these processes as well. These outstanding issues of expanding the substrate scope and improving the economics of asymmetric hydrogenation will likely form the basis of future academic and industrial research in this critical area.

1.2.4 Oxidative Catalysis

Oxidative catalysis, the complementary process to hydrogenation, has also impacted pharmaceutical research and development albeit to a lesser degree than for academic total synthesis. Oxidations catalyzed by transition metals involve a broad class of

transformations to generate pro-chiral, racemic, and chiral products. The significance of asymmetric oxidations was recognized by awarding half of the 2001 Nobel Prize to Sharpless "for his work on chirally catalyzed oxidation reactions." The general utility for transition metals to catalyze an oxidation is through a metal-mediated oxidation wherein the oxidized metal is regenerated by a stoichiometric oxidant (Scheme 1.5). Use of the transition metal allows for use of less reactive and desirable oxidants as well as providing the chemo- and stereoselectivity necessary for an efficient process. The classical example for this mechanism was developed by Ley for the oxidation of alcohols and aldehydes with a ruthenium oxide catalyst [57]. Some extensions have been applied to allylic C–H oxidations [58], but the vast utility of transition metal oxidations was realized by pi-bond oxidations. The Wacker process enables access to aldehydes and ketones by the oxidation of olefins; however, utilization of the methodology on highly functionalized compounds is restricted due to limited chemoselectivity [59]. Alternatively, stereoselective olefin oxidation can efficiently provide chiral epoxides, through a Sharpless [60] or Jacobsen–Katsuki [61] asymmetric epoxidation, as well as chiral diols or amino-alcohols through a Sharpless dihydroxylation [62] or amino-hydroxylation [63], respectively. Application of a slight modification of the Sharpless asymmetric epoxidation conditions to the oxidation of sulfides has provided a general access to the chiral sulfoxide pharmacophore [64].

Transition metal catalyzed oxidation has had limited applications in the pharmaceutical industry to date. The decreased use of oxidations in API syntheses in relation to academic total syntheses [9] is due to the inefficiency of introducing elements in an oxidation state that requires adjustment, associated waste, and safety concerns. The typical use of nongreen solvents, such as chlorinated hydrocarbons, further limits the utility for oxidations to the pharmaceutical industry. This issue is reflected by one goal of the American Chemical Society Green Initiative for oxidations without a chlorinated solvent [65]. The notable application to the synthesis of esomepraxol [66], rosavastatin [67], and indinavir [68] underscores the value of transition metal catalyzed oxidations (Fig. 1.4). The utility of asymmetric oxidations for the formation of C–O bonds has also been extended to the synthesis of other more complicated stereocenters. The use of a Sharpless asymmetric epoxidation by Eisai provided the stereochemistry to construct a quaternary carbon stereocenter through a



SCHEME 1.5 Transition metal catalyzed oxidation and extensions.

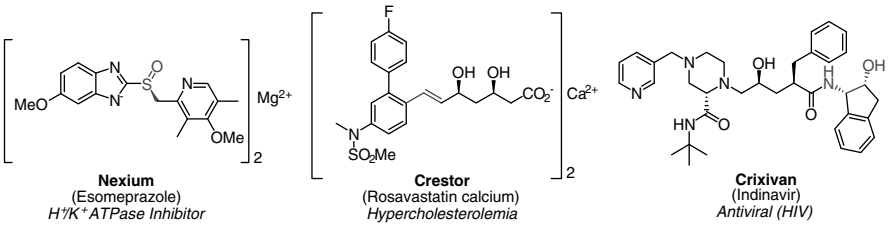
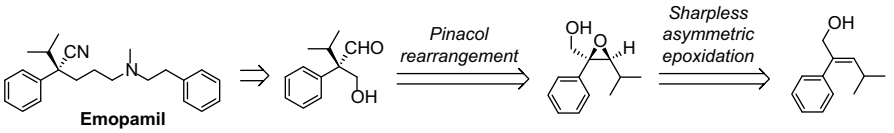


FIGURE 1.4 Selected examples for application of oxidations.

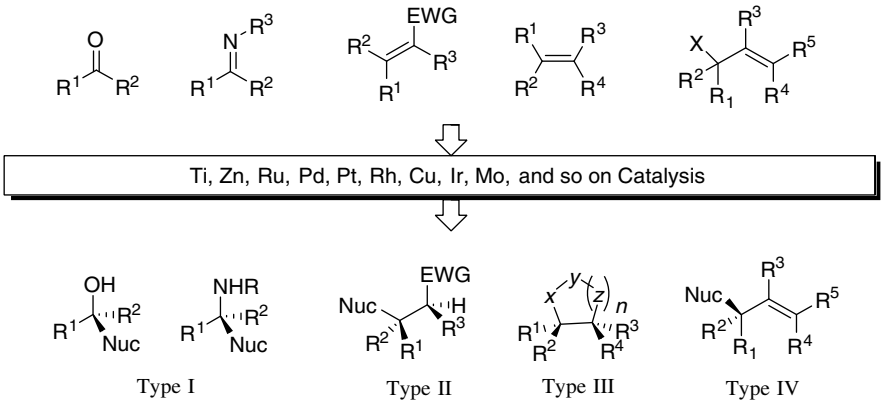
subsequent Pinacol rearrangement (Scheme 1.6) [69]. This type of stereocenter cannot be readily accessed by other more traditional asymmetric transformations thereby demonstrating the significant utility of asymmetric oxidations toward API synthesis. Recent advances in transition metal catalyzed oxidations toward asymmetric allylic oxidation [70], oxidative coupling [71], and C–H oxidations [72] have provided increased utility for complex molecule synthesis. Adaptation of these new methodologies by medicinal chemists for the design and discovery of new APIs and the utilization of these new methods by process chemists will increase the use of these valuable transition metal catalyzed oxidations.

1.2.5 Asymmetric Addition Reactions

Asymmetric addition reactions comprise a wide variety of transformations, which due to their versatility provide access to chiral structures that are not otherwise efficiently accessible by other technologies. The utility of transition metals for these additions stems from the ability to use a substoichiometric amount of a chiral ligand that provides a more efficient asymmetric transformation relative to more traditional chiral auxiliary–based technologies. Although some reports on enantioselective additions to aldehydes date back to the 1940s [73], the first reproducible reaction was the addition of Grignard reagents to carbonyl species with a chiral ethereal solvent reported by Cohen and Wright in 1953 [74]. Oguni et al. in 1984 reported the (*S*)-leucinol catalyzed addition of diethylzinc to benzaldehyde with 49%ee [75]. This seminal achievement sparked the dramatic developments in transition metal catalyzed asymmetric additions with hundreds of methodological developments and thousands of applications. These types of transition metal–based addition reactions can be crudely divided into four types of transformations (Scheme 1.7). The first involves addition to C=O and C=N bonds. These additions provide chiral alcohol or amine products by the addition of a carbon-based nucleophile such as through an asymmetric organo-zinc-mediated, aldol, and cyanide addition reactions. The second



SCHEME 1.6 Eisai SAE and application to a quaternary carbon stereocenter.



SCHEME 1.7 General types of asymmetric addition reactions.

reaction type is the asymmetric addition to C=C bonds through a conjugate (1,4) addition. The third class of additions is cycloadditions achieved by cyclopropanations, dipolar [3 + 2] cycloadditions, and more traditional Diels–Alder [4 + 2] reactions. The final addition type involves asymmetric allylic alkylations that provide chiral allylic stereocenters.

The utility of asymmetric addition reactions for pharmaceutical companies comes from the ability to access stereocenters that are not amenable to efficient construction through asymmetric hydrogenation. This general trend is due to the higher catalyst loadings and costs typically associated with implementing an asymmetric addition. The suggestion of Pfizer's Hawkins that the chances of using an asymmetric transformation on commercial scale is greater if the process was implemented early in development and applied to a late synthetic step [76] is more relevant for asymmetric addition reactions than for hydrogenations. The costs associated with resolution of an early intermediate can be lower than implementing the asymmetric addition reaction. Several applications of asymmetric additions have been reported by pharmaceutical companies (Fig. 1.5). The applications to GSK 3082 [77], oseltamivir [78], and tipranavir [79] highlight the utility of the technology. Significant advances in asymmetric additions have recently emerged that can change these perceptions. C–H activation for the stereoselective insertion of a heteroatom provides

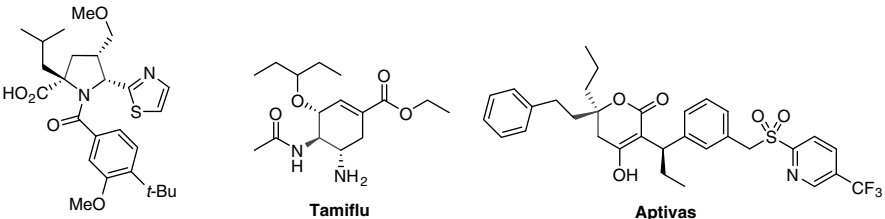


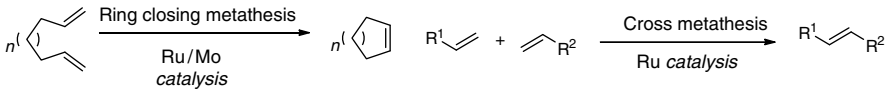
FIGURE 1.5 Selected examples of the application of asymmetric additions.

the opportunity to establish stereocenters from readily available materials [80]. The asymmetric addition to ketones has efficiently afforded chiral tertiary alcohols [81]. Recent advances in asymmetric allylations [82] and propargylations [83] provide access to chiral homoallylic and propargylic alcohols that are not readily accessed by hydrogenation of the corresponding 2,3-unsaturated ketones, due to their propensity to isomerize the pi-bond into conjugation. The ability to access a large number of chiral moieties and scaffolds through these advances will increase the value of asymmetric addition reactions in pharmaceutical production.

1.2.6 Metathesis

Metathesis has also impacted academic research more significantly than for the pharmaceutical industry. However, the scientific impact of metathesis technology cannot be overstated, as exemplified by the awarding of the 2005 Nobel Prize to Chauvin, Grubbs, and Schrock "for the development of the metathesis method in organic synthesis." Industrial application of the metathesis reaction dates back to the 1950s as exemplified by the Shell Higher Olefin Process (SHOP) [84]. Over the past several decades, the emergence of highly active and well-defined molybdenum and ruthenium metathesis catalysts allowed the chemoselectivity required for fine chemical and complex organic molecule synthesis. The notable catalysts are those developed by Grubbs and coworkers [85], Hoveyda and coworkers [86], Nolan and coworkers [87], Grela and coworkers [88], Schrock et al. [89], and Zhan [90]. Applications to the pharmaceutical industry are generally limited to the ring closing metathesis (RCM) for the construction of medium to large rings and cross metathesis (Scheme 1.8). The well-known tolerance of numerous functional groups to the metathesis conditions and the ability to utilize unactivated olefins presents significant utility for the incorporation into complex molecule synthesis.

The use of metathesis is more significant in early discovery with limited examples in development. Some notable examples are depicted in Figure 1.6, which include BILN 2061 [91], telcagepant [92], and SB-462795 [93]. The drawback to the incorporation of metathesis into a multikilogram batch is often the limited catalyst turnover and typical high dilution necessary to prevent dimerization. When conditions and the substrate are thoroughly optimized, <1 mol% catalysts loadings with reasonable concentrations can often be achieved. The importance for substrate optimization is exemplified by the process reported by Boehringer Ingelheim for the synthesis of the macrocycle BILN 2061. By derivatizing an amide nitrogen, the molecule was shown to adopt a more favorable conformation for cyclization, which enabled the reaction to be conducted at 20 times the initial reaction concentration. Achieving a concentration of 0.2 M for the RCM equates to a 20-fold improvement



SCHEME 1.8 General types of metathesis utilized in the pharmaceutical industry.

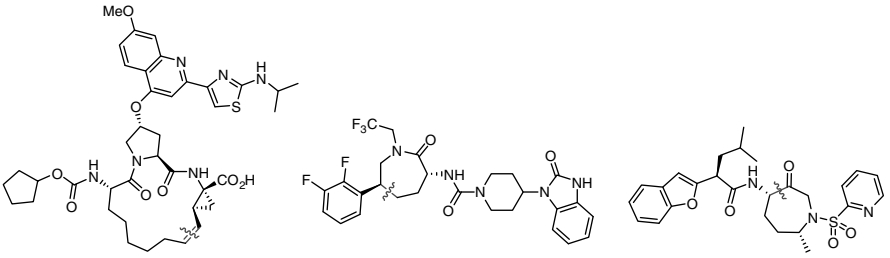


FIGURE 1.6 Selected examples for application of metathesis.

in the volume–time factor for production (*vida infra*). Similar to other transition metal catalysts processes, recent advances in metathesis chemistry have enabled formation of tetra-substituted olefins [94], asymmetric metatheses [95], and the metatheses of alkynes [96]. This research has directly increased the ability to construct the increasingly complex biologically active molecules that are being discovered and developed as the next generation of medicines.

1.3 CHALLENGES IN TAKING CATALYSIS TO INDUSTRIAL SCALES

In recent years, transition-metal catalysis has become a truly indispensible technology for industrial scale production of APIs. This is due to several inter-related factors (a) the constantly increasing regulatory requirements, for example, the strong regulatory pressure to develop a single-enantiomer of a drug as well as more stringent environmental protection legislations; (b) the pressure to reduce cost and time to market (a single day delay to the market will result in $>\$1$ million loss for a \$400 million annual revenue drug); and (c) the discovery of more efficient catalytic reactions from both academia and industry. The interplay of all these elements has resulted in the uptake of many of these catalytic methods for industrial scale API production. Successful examples of catalytic reactions on commercial scales are now routinely reported in the literature, yet there still exists a time delay between the initial (usually academic) reports on new catalysis and their implementation in industry.

The development and implementation of a catalytic reaction for industrial scale production is not trivial and many considerations have to be taken into account. The major factors that might hamper the technology transfer from lab-scale to large-scale production involve (a) the limited availability of the catalysts; (b) high cost of catalysts; (c) nonscalable operations (such as column chromatography, high dilution, extreme temperatures/pressures, unsafe reagents, etc.); and (d) the intellectual property (IP) issues (Fig. 1.7). Thus, a significant amount of process research and evaluation is almost always required to translate the chemistry demonstrated in initial reports into a "process-friendly" state.

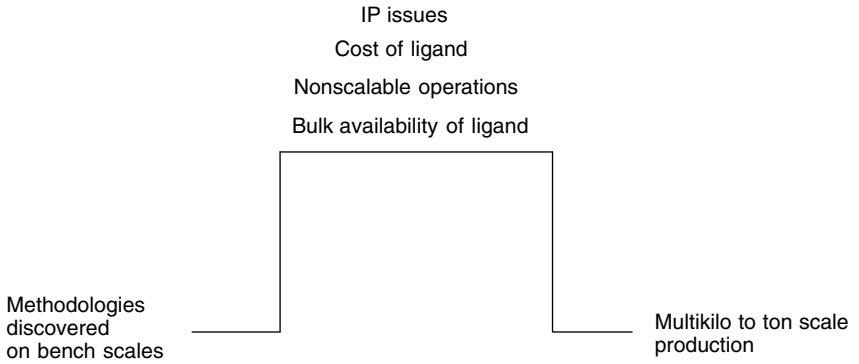


FIGURE 1.7 Taking Benchtop reactions to large scales.

Perhaps most importantly though, it is generally in industry where the new catalysis is truly "stressed" with complex substrates containing multiple potentially interfering functional groups. At this time one often finds that the chemo-, stereo-, or regioselectivity of a catalyst is not as good as the performance shown for a limited number of substrates lacking true steric and electronic breadth. When catalysis performs poorly at this early stage, the reasons for this are rarely apparent. The substrate, the product, or the catalyst itself might be responsible, and significant effort is often required to elucidate these effects. This is likely the critical juncture where the speed with which new methodologies are embraced by industry is decided. When time and resource investments are not made for new chemistries that are capable of being truly transformative to API synthesis, their acceptance and use will be clearly delayed and an early opportunity missed.

To overcome these hurdles, it therefore takes the efforts and collaboration from both industry and academia. From the industry perspective, more efforts should be directed at enhancing collaboration with academia on catalysis research and proactively increasing investment in strategic technologies. The companies should encourage forward thinking and a long-term vision. They should ideally provide incentives and rewards for industrial scientists to take smart risks to innovate and explore new chemistry.

Along this line, several major pharmaceutical companies have already invested heavily in setting up new technological platforms such as high throughput catalysis screening. Boehringer Ingelheim, Merck, and Pfizer all have their own in-house catalysis groups dedicated to catalyst development and these organizations have proven to be very successful [97].

Academic researchers by contrast should become more aware of and appreciate the constraints of industry. The research programs should be designed in such a way that barriers for technology transfer of the newly developed chemistry into the industrial setting are minimized. Environmental friendly solvents and reagents should be included in the routine optimization for new methodologies. Another encouraging trend is that more research groups partner with chemical suppliers to make their new catalysts commercially available for initial testing. Simple steps like

these can greatly facilitate the uptake of new catalytic methods for pharmaceutical applications.

To better understand the complexity of technology transfer to large-scale production and how the factors described above play out in the pharmaceutical industry, it is instructive to further consider Boehringer Ingelheim's BILN 2061 process. BILN 2061 (Ciluprevir, Fig. 1.8) was discovered by Boehringer Ingelheim (BI) as an HCV NS3 protease inhibitor [98] and entered the development phase in the late 2000 as the first small molecule therapy for hepatitis C infection. The most unique structural feature of the molecule was the 15-membered macrocycle ring containing a *cis*-double bond. The macrocyclization was achieved via a ruthenium-catalyzed RCM reaction. Back in 2000, RCM was largely an academic exercise [99] and there were no industrial applications of this reaction to large-scale API synthesis. In order to support clinical studies and the projected market supplies, BI required the development of a manufacturing process suitable for multiton production. A strategic decision was, therefore, made to invest in the development of the metathesis reaction for production scales [100].

At the outset of the project, Grubbs' first generation catalyst (**1**) [101] was used to cyclize the tripeptide diene **2** (Scheme 1.9). When the acyclic precursor was treated with >5 mol% catalyst in refluxing dichloromethane for 24 h, the desired macrocycle **3** was formed along with up to 50% of the *epi*-RCM product (epi-**3**). The extent of epimerization varied from batch to batch and was scale-dependent. In addition to the stereochemical concerns, other critical scale up issues for this key RCM reaction were identified, which included: (1) the high dilution (0.01 M) required to minimize the unproductive intermolecular metathesis side reactions, (2) high catalyst loadings, (3) a projected multimillion-dollar capital investment due to the high solvent volume, (4) the uncertain supply of the catalyst due to cost and availability concerns, and (5) a complicated IP situation. All of these issues need to be resolved before the RCM reaction could be reliably scaled up to support the clinical development of BILN 2061.

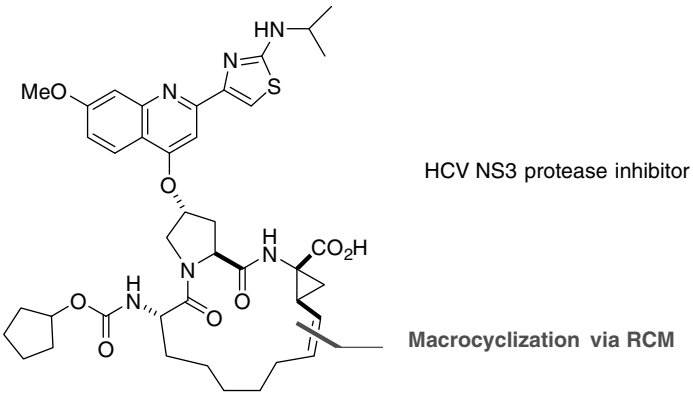
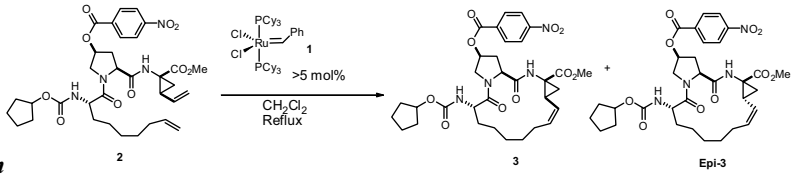


FIGURE 1.8 BILN 2061.



SCHEME 1.9 Initial results for RCM reaction.

In order to better understand the RCM reaction, additional catalysts were screened (Fig. 1.9). With the second generation, NHC-containing catalysts from Grubbs and coworkers [102], Hoveyda and coworkers [103], and Grela and coworkers [104] (**4**, **5**, and **6**), very little isomerization occurred in the RCM reaction. However, these more reactive catalysts led to the formation of 8–10 mol% of the cyclic dimer, which not only resulted in lower yields but also complicated product purification. In contrast, the first generation Hoveyda catalyst **7** [105] that has somewhat attenuated activity, gave a much cleaner reaction with almost no dimer formation and no epimerization. With 3–5 mol% catalyst at 0.01 M diene concentration, 90–95% yields of compound **3** were obtained after 24 h in refluxing dichloromethane. More than 100 kg API was manufactured by using these conditions. Several critical scale up concerns still remained. The most serious issue was the high dilution required to effect an efficient macrocyclization. When the initial diene concentration was increased from 0.01 to 0.1 M, the yield of **3** dropped from $>90\%$ to 40%. This challenge is certainly not unique to the Boehringer's substrate. In fact, most of the RCM-based macrocyclizations required a substrate concentration ranging between 0.2 and 8.5 mM, and a catalyst loading at 2–10 mol% [106].

From a business perspective to secure the projected market supplies, the large reaction volume requirement of the RCM would necessitate a multimillion dollar capital investment to build a new production facility at Boehringer's manufacturing site. Although the RCM reaction itself is intrinsically green by virtue of being a catalytic process with excellent atom economy [107], the need for high dilution resulted in an E-factor [108] of 370 kg/kg for this step alone. This means that to

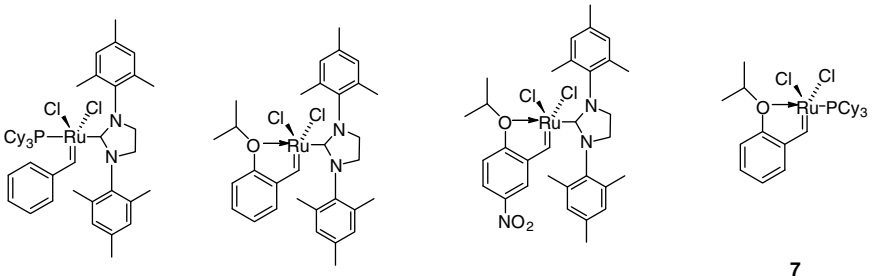


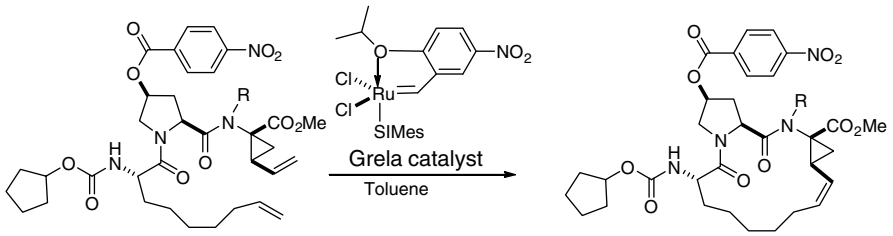
FIGURE 1.9 RCM catalysts.

cyclize 1 kg diene, ~370 kg of chemical waste would be generated. An average synthetic step should have an E-factor in the range of 5–30 kg/kg. In addition, it was highly desirable to replace dichloromethane with a greener solvent.

During the early work on the RCM reaction, a small but detectable effect on the RCM rate by varying the substituent on the remote C-4 position was noticed. Based on this observation, it was hypothesized that by changing the substituents on the acyclic precursor backbone, it might be possible to coil the molecule into a conformation that is more favorable for intramolecular cyclization. Indeed, it was found that the protecting group on the C-4 amide nitrogen has a profound influence on the conformation of the acyclic precursor and consequently the concentration requirement for the intramolecular macrocyclization.

A series of diene precursors with different substituents on the C-4 amide nitrogen were synthesized. Using Grela's catalyst, when R = H (**2**), an 82% yield of **3** was obtained at 0.01 M concentration (Scheme 1.10). The reaction was not only faster with Boc as a protecting group on the nitrogen as in compound **8** but also cleaner even at 0.2 M with lower catalyst loading (93% yield of **9**). Presumably, the introduction of the Boc group on the C-4 amide nitrogen relieved the ring strain of the acyclic precursor, thereby facilitating the desired intramolecular metathesis pathway. Detailed mechanistic studies using NMR techniques also showed that by changing from the unprotected substrate **2** to the Boc-protected diene **8**, the initiation site of metathesis shifted from the vinylcyclopropane to the nonenoic acid moiety (Scheme 1.11). It was hypothesized that initiation at the vinylcyclopropane leads to a slower reaction due to stabilization of the Ru carbene by chelation, whereas initiation at the nonenoic acid site accelerates the ring-closing step.

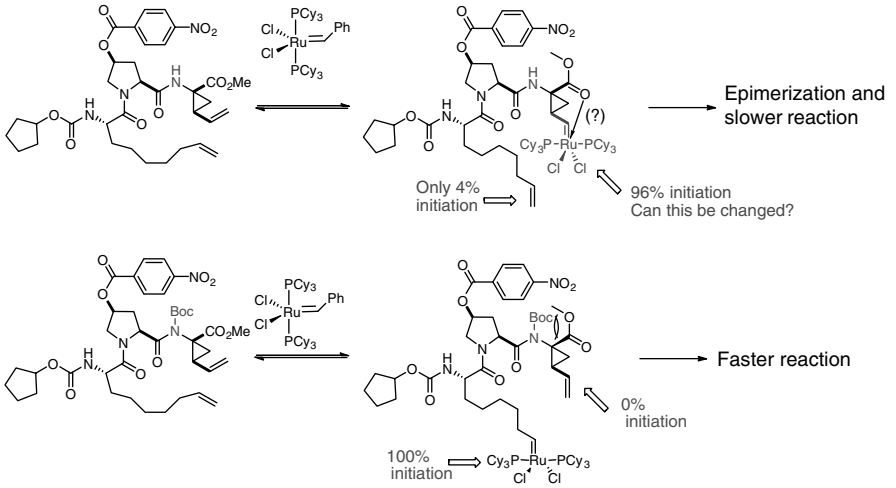
With this breakthrough discovery, the RCM reaction could be accomplished at more than 20-fold higher substrate concentration with the use of 0.05 mol% catalyst, to give 93% yield of the RCM product within a short reaction time. To prepare 1 kg of macrocycle intermediate **3**, only 0.5 g catalyst and 7.5 L of solvent were needed. As a result, the E-factor of this step was reduced from 370 to 52 kg/kg. The new RCM process thus improved the greenness of the reaction by about one order of magnitude. In addition, the reaction solvent was changed from dichloromethane to toluene without negatively impacting the performance of the RCM. More importantly, the



2: R = H
8: R = Boc

3: R = H: 82% at 0.01 M
R = H: 40% at 0.1 M
9: R = Boc: 93% at 0.2 M

SCHEME 1.10 RCM reaction with modified substrates.



SCHEME 1.11 Initiation of RCM reaction with modified substrates.

new RCM process could be readily accommodated in the existing standard multipurpose reactors in chemical production, and the need for a multimillion dollar capital investment was averted.

Securing the IP rights for various RCM catalysts was required to use this metathesis chemistry to supply the market with the HCV protease inhibitor. This "freedom-to-operate" is necessary to ensure the reliability of the drug supply once the compound is marketed. Any disruption of this supply could potentially affect patient safety, and was therefore unacceptable. The IP issue was taken very seriously and was handled with care throughout process development. In parallel to the scientific program, BI engaged in extensive contract negotiations with several technology owners and eventually was able to reach an agreement of collaboration with Professor Grela.

Through innovative chemical research and development, a breakthrough was achieved for the RCM reaction for BILN 2061 production. The new macrocyclization process runs at improved concentrations with a low catalyst loading (ca. 0.05%) to give the RCM product in $>90\%$ yield. Overall, these improvements significantly reduced the API cost. This achievement was highlighted in professor Grubbs' Nobel Prize Speech [109] as well as in Chemical & Engineering News [110]. The success story of BILN 2061 showed that in order to develop a commercially viable catalytic process, a multitude of inter-related factors need to be considered including reaction optimization, green chemistry, IP, the manufacturing facility, catalyst cost, and raw material sourcing. These challenges can only be met through the collaborative work of a multidisciplinary team.

1.4 SUMMARY AND FUTURE OUTLOOK

The rapid growth of transition-metal catalysis has enabled the pharmaceutical industry to accelerate both drug discovery and drug development. Future catalysis

research will undoubtedly bring more exciting chemistry and allow novel transformations to take place with ultra low catalyst loadings and good functional group compatibility. Collaboration of synthetic organic, physical organic, as well as organometallic, analytical and computational chemists provides the foundation to elucidate mechanistic pathways, rationalize catalyst behavior, invent new methodologies, and optimize and implement processes into chemical production. The ultimate goal of this effort is to develop catalysts that impart the selectivities, reactivity, and atom economy needed for cost-effective approaches to a variety of critical chemical transformations. Finally, a close collaboration between academia and industry is vitally important for the expedient implementation of catalysis on scale. It is our hope that this book will not only serve as an overview of the fast-growing field of transition-metal catalysis but also provide impetus and inspirations for the future discovery of more efficient and practical catalysts to help us tackle the economical and ecological challenges in the twenty-first century.

REFERENCES

[1] North American Catalysis, Society. Available at http://www.nacatsoc.org/what.asp

[2] Recognizing the Best in Innovation: Breakthrough Catalyst. *R&D Magazine*, September 2005, p. 20.

[3] *World Catalyst Market*, June, 2008.

[4] Anastas, P. T.; Warner, J. C., Eds., *Green Chemistry Theory and Practice*; Oxford University Press: Oxford, 1998.

[5] Noyori, R. *Adv. Syn. Cat.* **2003**, *345*, 15.

[6] Clark, G. S. *Perfumer Flavorist* **2007**, *32*(12), 38.

[7] Jäkel, C.; Paciello, R. U.S. Patent 7534921 (05/19/2009).

[8] McCoy, M. *Chem. Eng. News* **2010**, *88*(35), 15.

[9] For a general review, see: Slagt, V. F.; Vries, A. H. M.; Vries, J. G.; Kellogg, R. M. *Org. Process Res. Dev.* **2010**, *14*, 30–47.

[10] Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487.

[11] (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374; (b) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc. Chem. Commun.* **1972**, 144.

[12] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[13] (a) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486; (b) Denmark, S. E. *J. Org. Chem.* **2009**, *74*, 2915.

[14] (a) Stille, J. *Angew. Chem. Int. Ed.* **1986**, *25*, 508; (b) Farina, V.; Krishnamurthy, D.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

[15] Tamao, K. In *Comprehensive Organic Synthesis*; Trost, B., Ed., Pergamon: Oxford, 1991; Vol. 3, p. 435.

[16] (a) Negishi, E.; King, A.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821; (b) Knochel, P.; Singer, R. *Chem. Rev.* **1993**, *93*, 2117.

[17] Heck, R. F. *Org. React.* **1982**, *27*, 345.

[18] Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163.

[19] (a) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149; (b) Blatcher, P.; Carter, M. W.; Butina, D.; Owen, M. R. U.S. Patent 4997841 (1991); (c) Labelle, M.; Belley, M.; Gareau, Y.; Gauthier, J. Y.; Guay, D.; Gordon, R.; Grossman, S. G.; Jones, T. R.; Leblanc, Y.; McAuliffe, M.; MaFarlane, C. S.; Masson, P.; Metters, K. M.; Quimet, N.; Patrick, D. H.; Piechuta, H.; Rochette, C.; Sawyer, N.; Xiang, Y. B.; Pickett, C. B.; Ford-Hutchinson, A. W.; Zamboni, R. J.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 283.

[20] Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Process Res. Dev.* **2005**, *9*, 253.

[21] For a selected example, see: Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

[22] Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4566.

[23] (a) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594; (b) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874; (c) Najera, C.; Sansano, J. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2452.

[24] Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Lee, H.; Yee, N. K.; Senenayake, C. H. *Org. Lett.* **2010**, *12*, 4388.

[25] (a) Littke, A. F. *Modern Arylation Methods*; Wiley-VCH: Weinheim, 2009; pp. 25–67; (b) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 5922; (c) Ohashi, M.; Kambara, T.; Hatanaka, T.; Saijo, H.; Doi, R.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 3256.

[26] (a) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176; (b) Kundig, E. P.; Seidel, T. M.; Jia, Y.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 8484; (c) Garcia-Fortanet, J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 8108.

[27] (a) Gooben, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 7103; (b) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248; (c) Gooben, L. J.; Rodriguez, N.; Lange, P. P.; Linder, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 1111.

[28] (a) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011**, *76*, 1174; (b) Zhang, C.-P.; Wang, Z.-L.; Chen, Q.-Y.; Zhang, C.-T.; Gu, Y.-C.; Xiao, J.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 1896.

[29] (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; (b) Peng, H. M.; Dai, L.-X.; You, S. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 5826; (c) Rousseaux, S.; Gorelsky, S. L.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692.

[30] (a) Bermejo, A.; Ros, A.; Fernandez, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 15798; (b) Shen X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 11278.

[31] LaPlante, S. R.; Edwards, P. J.; Fader, L. D.; Jakalian, A.; Hucke, O. *Chem. Med. Chem.* **2011**, *6*, 505.

[32] (a) For a selected review, see: Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 8347; (b) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908–11909; (c) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264.

[33] (a) For a comprehensive review, see: Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2004**, 2337.

[34] Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382.

[35] Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.

[36] Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett*. **1999**, *40*, 2657.

[37] Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670.

[38] Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

[39] Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348.

[40] Louie, J.; Hartwig, J. F. *Tetrahedron Lett*. **1995**, *36*, 3609.

[41] (a) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am.Chem. Soc.* **1993**, *115*, 11018; (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.

[42] Loiseleur, O.; Kaufmann, D.; Abel, S.; Buerger, H. M.; Meisenbach, M.; Schmitz, B.; Sedelmeier, G.W.O. Patent 03/066613 (2003).

[43] Morita, S.; Kitano, K.; Matsubara, J.; Ohtani, T.; Kawano, Y.; Otsubo, K.; Uchida, M. *Tetrahedron* **1998**, *54*, 4811.

[44] Damon, D. B.; Dugger, R. W.; Hubbs, S. E.; Scott, J. M.; Scott, R. *W. Org. Process Res. Dev.* **2006**, *10*, 472.

[45] (a) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109; (b) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049.

[46] Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.

[47] Sun, K.; Li, Y.; Xiong, T.; Zhange, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694.

[48] (a) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534; (b) Boebel, T. A.; Hartwig, J. F. *Organometallics* **2008**, *27*, 6013; (c) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058.

[49] (a) W. Tang, X. Zhang. *Chem. Rev.* **2003**, *103*, 3029; (b) Schenkel, L. B.; Ellman, J. A. *J. Org. Chem.* **2004**, *69*, 1800; (c) Barbaro, P.; Bianchini, C.; Giambastiani, G.; Parisel, S. L. *Coord. Chem. Rev.* **2004**. *248*, 2131; (d) Blaser, H.-U.; Studer, M. *Acc. Chem. Res.* **2007**, *40*, 1348.

[50] Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Cat.* **2003**, *343*, 103.

[51] Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

[52] Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.*, **2006**, *106*, 2734.

[53] (a) Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385; (b) Schultz, C. S.; Krska, S. W. *Acc. Chem. Res.* **2007**, *40*, 1320.

[54] (a) Knowles, W. S.In *Large Scale Asymmetric Catalysis*, Blaser, H.U.; Schmidt, E., Eds., Wiley-VCH: Weinheim, 2003; p. 23; (b) Selke, R. In *Large Scale Asymmetric Catalysis*, Blaser, H. U.; Schmidt, E., Eds., Wiley-VCH: Weinheim, **2003**; p. 39.

[55] Lorenz, J. C.; Busacca, C. A.; Feng, X. W.; Grinberg, N.; Haddad, N.; Johnson, J.; Kapadia, S.; Lee, H.; Saha, A.; Sarvestani, M.; Spinelli, E. M.; Varsolona, R.; Wei, X., Zeng, X.; Senanayake, C. H. *J. Org. Chem.* **2010**, *75*, 1155.

[56] Bell, S.; Wustenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, *311*, 642.

[57] Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

[58] For selected recent examples, see: (a) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547; (b) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 730; (c) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.*

2010, *12*, 824; (d) Pilarski, L. T.; Janson, P. G.; Szabo, K. J. *J. Org. Chem.* **2011**, *76*, 1503.

[59] (a) Tsuji, J. *Synthesis* **1984**, 369; (b) Feringa, B. L. Wacker oxidation. In *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, 1998; Vol. 2, p. 307.

[60] (a) Pfenninger, A. *Synthesis* **1986**, 89; (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

[61] Jacobsen, E. N. Asymmetric catalytic epoxidation of unfunctionalized olefins. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., Wiley-VCH: New York, 1993.

[62] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

[63] (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 451. (b) Reiser, O. *Angew. Chem. Int. Ed.* **1996**, *35*, 1308.

[64] (a) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135; (b) Donnoli, M. I.; Superchi, S.; Rosini, C. *J. Org. Chem.* **1998**, *63*, 9392.

[65] Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

[66] Wang, F.; Montemayor, L. K.; Che, D.; Horne, S. E. U.S. Patent 2007-797921 20070509 (2010).

[67] Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. *Bio Med. Chem. Lett.* **1997**, *5*, 437.

[68] Senanayake, C. H.; Smith, G. B.; Ryan, K. M.; Fredenburgh, L. E.; Liu, J. *Tetrahedron* **1996**, *37*, 3271.

[69] Kimura, T.; Yamamoto, N.; Suzuki, Y.; Kawano, K.; Norimine, Y.; Ito, K.; Nagato, S.; Iimura, Y.; Yonaga, M. *J. Org. Chem.* **2002**, *67*, 6228.

[70] Covell, D. C.; White, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 6448.

[71] Xie, J.; Huang, Z.-Z. *Angew. Chem. Int. Ed.* **2010**, *49*, 10181.

[72] (a) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654; (b) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566.

[73] (a) Betti, M.; Lucchi, E. *Boll. Sci. Fac. Chim. Ind. Bologna* **1940**, 2–5; *Chem. Abstr.* **1940**, *34*, 2354; (b) Tarbell, D. S.; Paulson, M. C. *J. Am. Chem. Soc.* **1942**, *64*, 2842.

[74] Cohen, H. L.; Wright, G. F. *J. Org. Chem.* **1953**, *18*, 432.

[75] (a) Oguni, N.; Omi, T.; Yamomoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841; (b) Oguni, N.; Omi, T. *Tetrahedron Lett*. **1984**, *25*, 2823.

[76] Hawkins, J. M.; Watson, T. J. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 3224.

[77] Agbodjan, A. A.; Cooley, B. E.; Copley, R. C. B.; Corfield, J. A.; Flanagan, R. C.; Glover, B. N.; Guidetti, R.; Haigh, D.; Howes, P. D.; Jackson, M. M.; Matsuoka, R. T.; Medhurst, K. J.; Millar, A.; Sharp, M. J.; Slater, M. J.; Toczko, J. F.; Xie, S. *J. Org. Chem.* **2008**, *73*, 3094.

[78] Trost, B. M.; Zhang, T. *Eur. J. Org. Chem.* **2011**, *17*, 3630.

[79] Trost, B. M.; Andersen, N. G. *J. Am. Chem. Soc.* **2002**, *124*, 14320.

[80] (a) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594; (b) Lee, E. C.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 12066.

[81] Hatano, M.; Ishihara, K.; *Synthesis* **2008**, 1647.

[82] (a) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910; (b) Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638.

[83] Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K.; Senenayake, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 7600.

[84] Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerisation*; Academic Press: San Diego, 1997.

[85] Scholl, M.; Ding, S.; Lee, S. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

[86] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

[87] Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

[88] Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318.

[89] Schrock, R. R., Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

[90] Zhan, Z.-Y. U.S. Patent 0043180 (2007).

[91] (a) Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303; (b) Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2009**, *13*, 250.

[92] Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, C. M.; Graham, S., Vacca, J. P.; Williams, T. M. *Org. Lett.* **2008**, *10*, 3235.

[93] Marquis, R. W.; Ru, Y.; LoCastro, S. M.; Zeng, J.; Yamashita, D. S.; Oh, H.-J.; Erhard, K. F.; Davis, L. D.; Tomaszek, T. A.; Tew, D.; Salyers, K.; Proksch, J.; Ward, K.; Smith, B.; Levy, M.; Cummings, M. D.; Haltiwanger, R. C.; Trescher, G.; Wang, B.; Hemling, M. E.; Quinn, C. J.; Cheng, H.-Y.; Lin, F.; Smith, W. W.; Janson, C. A.; Zhao, B.; McQueney, M. S.; D'Alessio, K.; Lee, C.-P.; Marzulli, A.; Dodds, R. A.; Blake, S.; Hwang, S.-M.; James, I. E.; Gress, C. J.; Bradley, B. R.; Lark, M. W.; Gowen, M.; Veber, D. F. *J. Med. Chem.* **2001**, *44*, 1380.

[94] (a) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**. *9*, 1589; (b) Vorfalt, T.; Leuthausser, S.; Plenio, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 5191.

[95] Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943.

[96] Heppekausen, J.; Stade, R.; Goddard, R.; Furstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11045.

[97] (a) Tang, W.; Capacci, A. G.; Wei, X.; Li, W.; White, A.; Patel, N. D.; Savoie, J.; Gao, J. J.; Rodriguez, S.; Qu, B.; Haddad, N.; Lu, B. Z.; Krishnamurthy, D.; Yee, N. K.; Senanayake, C. H. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 5879; (b) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 7600; (c) Tang, W.; Capacci, A. G.; White, A.; Ma, S.; Rodriguez, S.; Qu, B.; Savoie, J.; Patel, N. D.; Wei, X.; Haddad, N.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 1104; (d) Lorenz, J. C.; Busacca, C. A.; Feng, X.; Grinberg, N.; Haddad, N.; Johnson, J.; Kapadia, S.; Lee, H.; Saha, A.; Sarvestani, M.; Spinelli, E. M.; Varsolona, R.; Wei, X.; Zeng, X.; Senanayake, C. H. *J. Org. Chem.* **2010**, *75*, 1155; (e) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Lee, H.; Li, Z.; Liang, M.; Reeves, D.; Saha, A.; Varsolona, R.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 341.

[98] (a) Lamarre, D.; Anderson, P. C.; Bailey, M.; Beaulieu, P.; Bolger, G.; Bonneau, P.; Boes, M.; Cameron, D. R.; Cartier, M.; Cordingley, M. G.; Faucher, A.-M.; Goudreau, N.; Kawai, S. H.; Kukolj, G.; Lagacé L.; LaPlante, S. R.; Narjes, H.; Poupart, M.-A.; Rancourt, J.; Sentjens, R. E.; St. George, R.; Simoneau, B.; Steinmann, G.; Thibeault, D.; Tsantrizos, Y. S.; Weldon, S. M.; Yong, C.-L.; Llinás-Brunet, M. *Nature* **2003**, *426*, 186; (b) Llinás-Brunet, M.; Bailey, M. D.; Bolger, G.; Brochu, C.; Faucher, A.-M.; Ferland, J. M.; Garneau, M.; Ghiro, E.; Gorys, V.; Grand-Maître, C.; Halmos, T.; Lapeyre-Paquette, N.; Liard, F.; Poirier, M.; Rhéaume, M.; Tsantrizos, Y. S.; Lamarre, D. *J. Med. Chem.* **2004**, *47*, 1605; (c) Tsantrizos, Y.; Bolger, G.; Bonneau, P.; Cameron, D. R.; Goudreau, N.; Kukolj, G.; LaPlante, S. R.; Llinás-Brunet, M.; Nar, H.; Lamarre, D. *Angew. Chem. Int. Ed.* **2003**, *42*, 1356; (d) Goudreau, N.; Cameron, D. R.; Bonneau, P.; Gorys, V.; Plouffe, C.; Poirier, M.; Lamarre, D.; Llinás-Brunet, M. *J. Med. Chem.* **2004**, *47*, 123; (e) Rancourt, J.; Cameron, D. R.; Gorys, V.; Lamarre, D.; Poirier, M.; Thibeault, D.; Llinás-Brunet, M. *J. Med. Chem.* **2004**, *47*, 2511.

[99] (a) Grubbs, R. H., Ed. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003; (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.

[100] (a) Medicinal Chemistry Synthesis: Faucher, A.-M.; Bailey, M. D.; Beaulieu, P. L.; Brochu, C.; Duceppe, J.-S.; Ferland, J.-M.; Ghiro, E.; Gorys, V.; Halmos, T.; Kawai, S. H.; Poirier, M.; Simoneau, B.; Tsantrizos, Y. S.; Llinás-Brunet, M. *Org. Lett.* **2004**, *4*, 2901; (b) First Large-Scale Synthesis: Yee, N. K.; Farina, V.; Houpis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.-J.; Wei, X.; Simpson, R. D.; Feng, X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, L.; Xu, J.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson, M.; Donsbach, K.; Nicola, T.; Brenner, M.; Winter, E.; Kreye, P.; Samstag, W. *J. Org. Chem.* **2006**, *71*, 7133; (c) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Proc. Res. Dev.* **2005**, *9*, 513; (d) Highly Practical Large-Scale Synthesis: Shu, C. et al. *Org. Lett.* **2008**, *10*, 1303; (e) Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanyake, C. H. *Org. Proc. Res. Dev.* **2009**, *13*, 250.

[101] Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

[102] Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

[103] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

[104] Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318.

[105] Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr., Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

[106] Gradillas, A.; Perez-Castells, J. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 6086.

[107] Anastas, P. T.; Warner, J. C., Eds., *Green Chemistry Theory and Practice*; Oxford University Press: Oxford, 1998.

[108] E-Factor Definition: (a) Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273; (b) Sheldon, R. A. *Chem. Ind.* **1992**, 903.

[109] Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 3760.

[110] (a) "Sustainable Syntheses," Thayer, A. M. in *Chemical & Engineering News* June 8, 2009; (b) "Drug Production: Boehringer-Ingelheim blazes trail in Scaling Up Metathesis Reaction" Thayer, A. M. in *Chemical & Engineering News* Feb. 12, 2007.