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Why Is Organo/Metal Combined Catalysis Necessary?

1.1 Introduction

Molecular chirality has played an important role in a broad scope of fields, including synthetic chemistry, drug discovery, biological system, and materials science and will continue to exert a great impact on physical science. Such unparalleled significance of chirality leads to increasing demand for efficient asymmetric protocols to build up chiral structures.

Chiral resolution is the oldest way to isolate optically pure chiral molecules from the racemic form. Chiral pool- and auxiliary-induced asymmetric synthesis has frequently been synthetic strategies of choice to create chiral elements in organic synthesis [1]. Although chiral auxiliary-induced asymmetric synthesis has been prevalently applied to the asymmetric synthesis of natural products and pharmaceutically significant substances, and thus held the historical impact on synthetic chemistry [2], the installation and removal of chiral auxiliary basically require additional reaction steps to thereby attenuate the synthetic efficiency.

Asymmetric catalysis has globally been accepted as the most efficient concept to stereoselectively build up molecular chirality. Since the advent of asymmetric cyclopropanation and hydrogenation catalyzed by chiral copper and rhodium complexes, respectively [3, 4], asymmetric metal catalysis has continuously been the central focus of asymmetric synthesis. The versatility and robustness of metals in the activation of a wide spectrum of chemical bonds, even those with high bond energy, have rendered many families of asymmetric transformations to be accessed by either Lewis acid or transition metal catalysis [5, 6].

The control of stereochemistry in asymmetric metal catalysis principally relies on the chiral ligand and to a large degree on the ligand acceleration [7]. The stereochemical control events involved in the transition metal catalysis might be one or some of the typical elementary reactions including chiral ligand coordination, oxidative addition, insertion, and reductive elimination. The oxidative addition occurs more easily with an electronically richer and low-valent metal to increase the oxidation state and coordination number of the metal center; therefore the ligand coordination facilitates this reaction. The global and long-standing interest in the design and development of chiral ligands has culminated in the explosive appearance of privileged ligands [8], which actually propel the proliferation of elegant and practical

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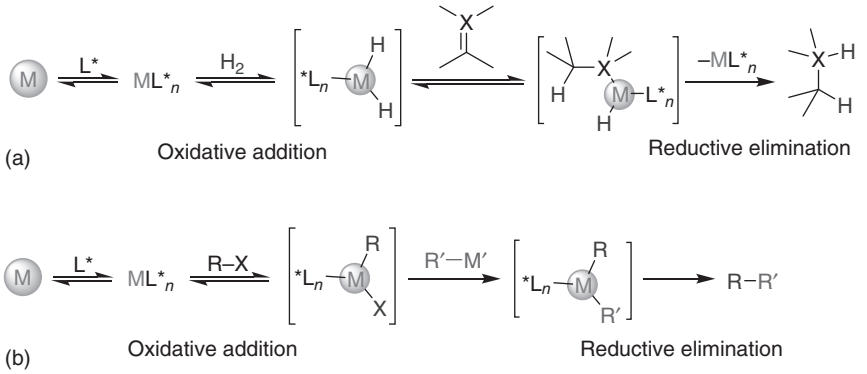


Figure 1.1 Transition metal-catalyzed reactions initiated with oxidative addition. (a) Hydrogenation. (b) Cross coupling.

asymmetric processes commencing with the oxidative addition, for example, asymmetric hydrogenation and cross-coupling reaction (Figure 1.1).

High-valent transition metals have also been found to enable a tremendous number of organic reactions. In contrast to abundantly available chiral ligands for asymmetric catalysis beginning with the oxidative addition, which undergoes with low oxidation state metals, rather fewer chiral ligands are compatible with high-valent metal catalysis and reactions undergoing under oxidation conditions to pose a great challenge to the control of stereoselectivity. For example, although the high-valent metal-catalyzed transformations commencing with nucleometallation (Eq. (1), Figure 1.2), aryl and allylic C–H activation (Eqs. (2) and (3)), have been well established, a very limited number of chiral ligands can enable highly enantioselective variants, in particular, those using molecular oxygen as the terminal oxidant [9]. So far, chiral Lewis acids are successful representatives among massive asymmetric high-valent metal catalysis [10]. As such, a new concept to break the conventional wisdom that relies on the chiral ligand to control the stereochemistry of transition metal catalysis is greatly desirable.

Asymmetric organocatalysis represents an important tool, independent, and conceptually distinct from metal catalysis, to build up molecular chirality [11, 12]. The typical principles in organocatalysis for the activation of chemical bonds cover a broad scope of concepts, including amine catalysis by enamine raising highest occupied molecular orbital (HOMO) and iminium lowering lowest unoccupied molecular orbital (LUMO), Brønsted acid catalysis by hydrogen-bonding interaction or protonation, NHC catalysis via umpolung of aldehyde, Lewis base catalysis by nucleophilic addition to either carboxylic acid derivatives or electron-deficient carbon–carbon double bonds to form reactive enolate or acylammonium species, and phase transfer catalysis by using ammonium and phosphonium to form ion pairs with anionic nucleophiles [13]. Such versatile principles in the activation of chemical bonds and structural diversity of organocatalysts have enabled the explosive appearance of fundamentally novel asymmetric reactions and processes featured by environmentally benign, atom, and step economies. Nevertheless, the

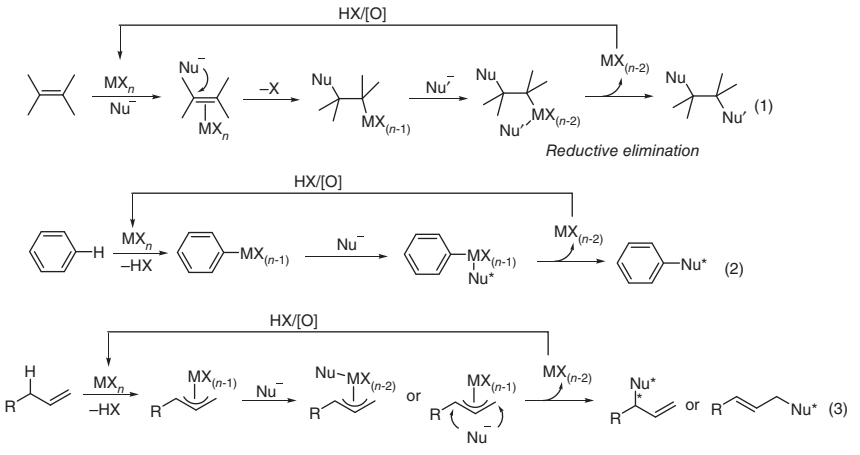


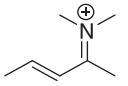
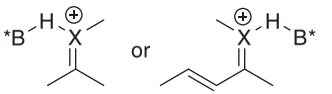
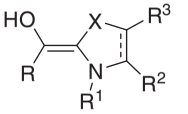
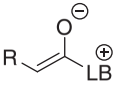
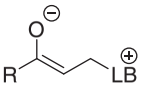
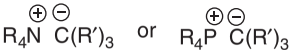
Figure 1.2 Representatives of high-valent metal catalysis.

complete dependence upon the interactions between a highly active functionality and the organocatalyst (Table 1.1) poses the organocatalysis essential constraints to activate relatively inactive chemical bonds and unfunctionalized substrates.

1.2 Early Stage of Organo/Metal Combined Catalysis and General Principles

The combination of asymmetric organocatalysis and metal catalysis integrates the catalytic activity of metals and organocatalysts, hence allows the simultaneous or sequential occurrence of multiply bond-breaking and forming events in stereochemical control to provide much more diverse ranges of concepts or principles capable of enabling unconventional enantioselective transformations that are toughly accessed by the individual catalyst [14]. Very early reports on the asymmetric organo/metal combined catalysis describe a Pd-catalyzed asymmetric allylic alkylation of an imino ester, in concert with chiral phase transfer catalysis [15]. Gong and coworkers found that the use of a cinchona alkaloid-derived ammonium bromide **4a** that Corey developed [16] as the chiral phase transfer catalyst, in combination with an achiral palladium complex of triphenylphosphine, is able to enable the reaction to deliver 59% ee [15]. Takemoto identified that the electron density of the trivalent phosphorus ligand exerts considerable impact on the reaction performance and the highest enantioselectivity of 94% ee was obtained with **4b** that Lygo introduced [17] in the presence of triphenyl phosphite ligand. In both the cases, the respective and synergistic action of the palladium complex and chiral PTC on the allylic ester **1** and nucleophile **2** renders the reaction to proceed more efficiently via a transition state **TS-1** and allows the stereochemical control to be accessed by chiral phase transfer catalyst, alone (Figure 1.3). This strategy indicates that the stereoselection of metal-catalyzed reactions can be controlled without chiral ligand, instead, by a co-organocatalyst, thus

Table 1.1 Typical activation modes in organocatalysis (OC).

Concepts of OC	Active intermediates	Applicable substrates	Reaction types
Enamine catalysis		Enolizable aldehydes and ketones	Aldol reaction Mannich reaction Michael addition
Iminium catalysis		Enal and enones	Michael addition Diels–Alder reaction Friedel–Crafts reaction
Brønsted acid catalysis		Aldehydes, ketones, and imines, enal, and enones	Reduction Friedel–Crafts reaction Michael addition
NHC catalysis		Aldehydes	Annulation Benzoin reaction Stetter reaction
Lewis base catalysis		Ketene, acylhalides, anhydride, and other analogues	[2+2] cyclization [4+2] cyclization Kinetic resolution
		Enals, enones, and α,β-unsaturated esters	[3+2] cycloaddition Baylis–Hillman reaction
Phase transfer catalysis		Acidic nucleophiles	Alkylation Aldol reaction Mannich reaction Michael addition

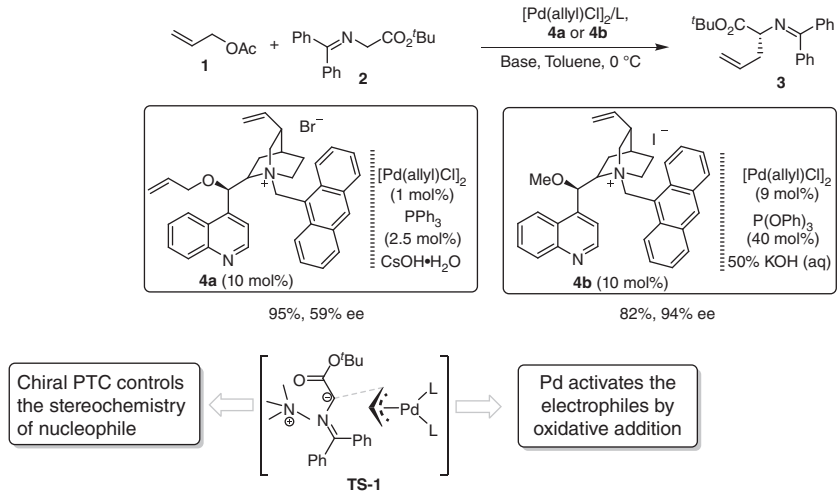


Figure 1.3 Pd and PTC cooperative catalysis.

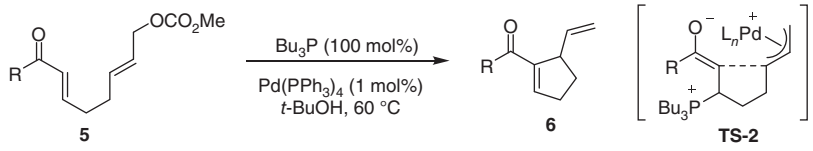


Figure 1.4 Pd and phosphine cooperative catalysis.

opens up a window to seek unconventional modes to address issues of the stereochemical control encountered in the asymmetric metal catalysis.

The cooperative catalysis of transition metal and Lewis base was first showcased by Krische and coworkers [18]. Tributylphosphine undergoes Rauhut–Currier type addition [19] with the enone moiety of **5** to generate a transient enolate and simultaneously, the palladium complex reacts with the allylic carbonate part to give a π-allylpalladium species. A subsequent intramolecular substitution occurs via a transition state **TS-2**, and followed by elimination of tributylphosphine, to yield the final product **6** (Figure 1.4). The perfect integration of the Lewis base and palladium catalysis offers a unique activation mode to make the reaction that is otherwise unable to proceed possible.

The cooperative catalysis of Lewis base and Lewis acid to drive an asymmetric [2+2] annulation of acetyl chloride **7** and imino esters **8** was reported by Lectka and coworkers [20]. The chelation of indium triflate to the imino ester **8** enhances the reactivity of the imine functionality. Thus, the nonmetal-coordinated zwitterionic enolate **Int-1** generated from the acetyl chloride **7** with BQ **10** and base **11** is able to undergo an enantioselective Mannich-type reaction with an In(III) cocatalyst-bound imino ester **Int-2** to form an intermediate **Int-3**. Finally, an intramolecular amide bond formation delivers β-lactams **9** and regenerates the catalyst (Figure 1.5).

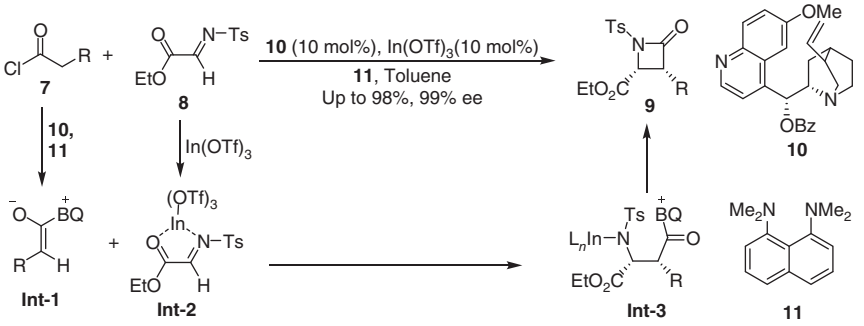


Figure 1.5 Lewis acid and Lewis base cooperative catalysis.

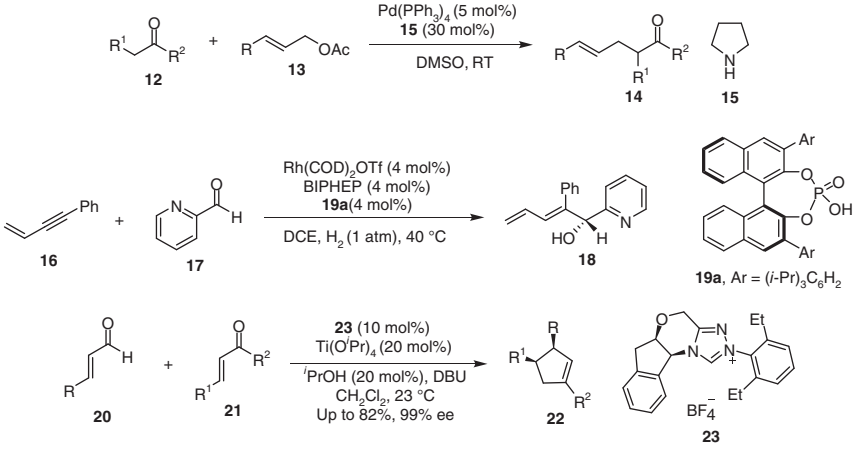


Figure 1.6 Typical organo/metal combined catalysis in the early stage. Source: Modified from Arndtsen and Gong [25].

In the same period, the enamine and palladium [21], Brønsted acids and transition metals [22, 23], NHC and metal complexes [24], and some other combined catalyst systems were successively reported, providing unusual fundamental bond activation modes that turn out to be versatile platforms to allow for the proliferation of unprecedented transformations (Figure 1.6) [25].

Most organocatalysts contain heteroatoms, which basically coordinate to metal catalysts to change the catalytic activity and to result in the "self-quenching" in some cases. As a consequence, the compatibility of metals and organocatalysts turns out to be the key to success in the organo/metal combined catalysis. On the other hand, the synergistic effect among the components of the combined systems is actually most desirable. Based on the activation modes and reaction pathway, the asymmetric organocatalysis combined with metal catalysis generally consists of cooperative catalysis, relay catalysis (also known as cascade, demino, and tandem catalysis), and sequential catalysis as well (Figure 1.7) [26].

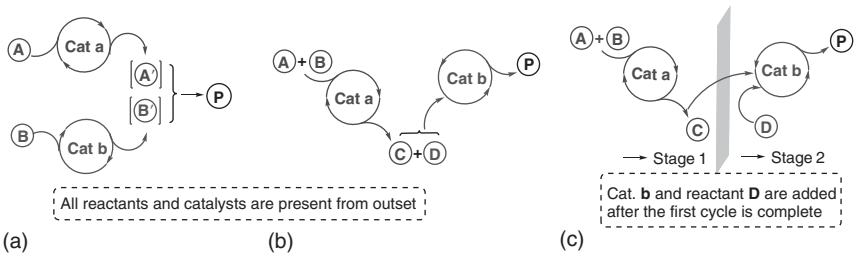


Figure 1.7 Categories of asymmetric organocatalysis combined with metal catalysis. (a) Cooperative catalysis. (b) Relay catalysis. (c) Sequential catalysis. Source: Chen et al. [26].

1.3 Organo/Metal Cooperative Catalysis

1.3.1 Control of Stereochemistry

Cooperative catalysis refers to a catalytic process, which is initiated via the simultaneous and respective activation of two or more substrates, functionalities, or chemical bonds enabled by two or more individual metal and organocatalysts (Figure 1.7a). The cooperative catalysis actually provides more possibilities to control the stereochemistry of an asymmetric transformation by tuning the chirality of each individual catalyst. For example, if the metal only works efficiently for breaking or assembling the chemical bonds, but is unable to control the stereochemistry by varying chiral ligands, the chiral organocatalysis concepts can be adapted to conquer the stereochemical control issue (Figure 1.8a). In case no appropriate organocatalysts are able to efficiently induce the stereoselectivity, chiral metal complexes would stand in for addressing the stereochemical issue while the organocatalyst solely acts to activate

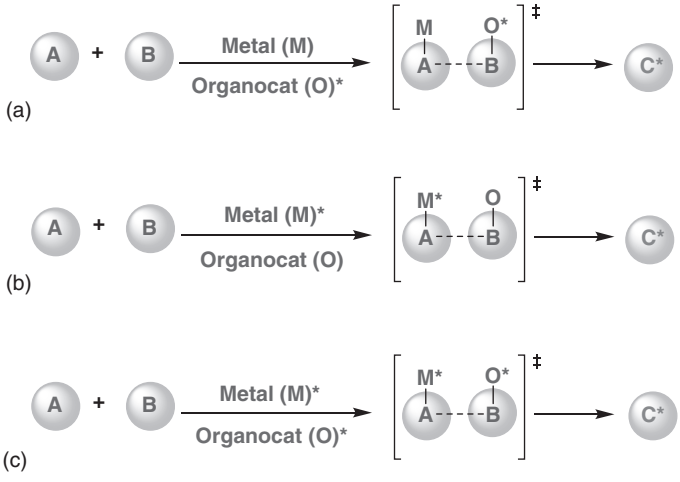


Figure 1.8 Strategies of stereochemical control in cooperative catalysis. (a) Combine achiral metal complex with chiral organocatalyst. (b) Combine chiral metal complex with achiral organocatalyst. (c) Combine chiral metal complex with chiral organocatalyst. Source: Han et al. [27].

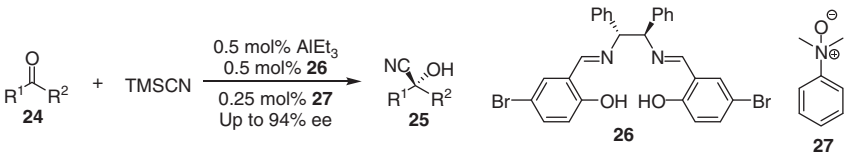


Figure 1.9 Chiral Lewis acid and achiral Lewis base cooperative catalysis. Source: Chen et al. [28].

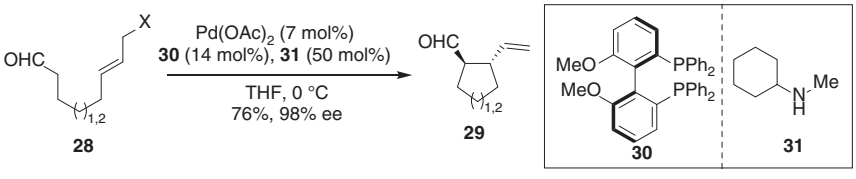


Figure 1.10 Asymmetric allylation enabled by chiral palladium complex and achiral amine. Source: Bihelovic et al. [29].

the substrates (Figure 1.8b). If neither of the concepts offers high stereoselectivity, both chiral metal complex and chiral organocatalyst can be applied to synergistically control the stereoselectivity (Figure 1.8c) [27].

The combination of achiral metal catalysts and chiral organocatalysts appeared at the beginning of this field [15]. In the same period, one of the earliest examples describing merging the chiral metal complex and achiral organocatalyst was introduced by Feng and coworkers who identified that the combination of an aluminum complex of chiral salen **26** and an *N*-oxide Lewis base **27** was able to afford a highly efficient and enantioselective cyanosilylation of ketones **24** (Figure 1.9) [28].

Saicic and coworkers described the combined use of a chiral palladium complex of (*R*)-Ph-MeOBiPHEP **30** and an achiral amine **31** to establish a highly enantioselective intramolecular α-allylation of aldehydes **28** (Figure 1.10) [29].

A binary catalyst made up of a chiral phosphoric acid and an iridium complex **34** adorned with Noyori-diamine ligand allows a highly efficient asymmetric hydrogenation of acyclic imines **32** to give chiral amine **33** in almost perfect levels of enantioselectivity. In this case, the matched chirality between the chiral diamine ligand of the iridium complex **34** and the chiral phosphoric acid (*R*)-**19a** offers high stereoselectivity (Figure 1.11) [30].

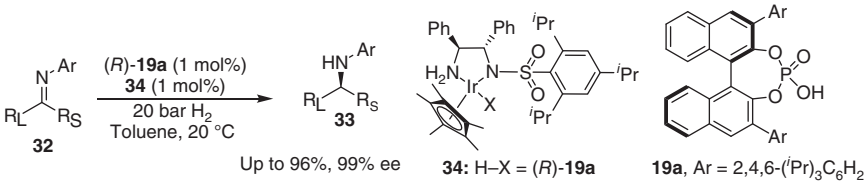


Figure 1.11 Asymmetric hydrogenation enabled by chiral iridium complex and phosphoric acid. Source: Modified from Li et al. [30].

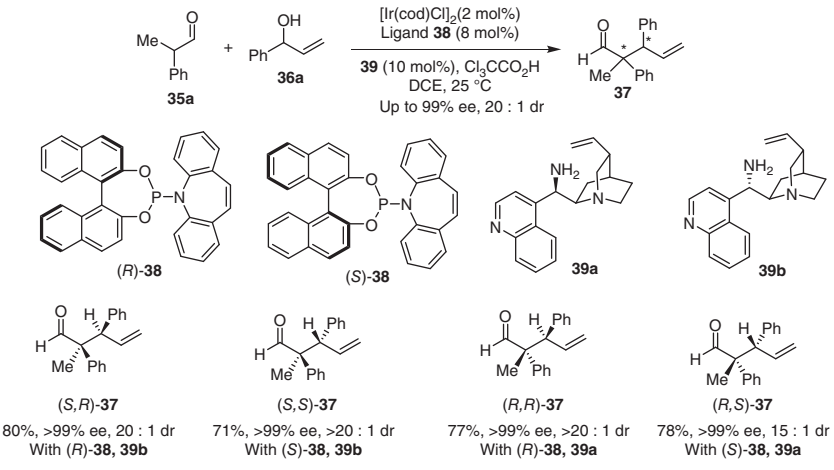


Figure 1.12 Stereodivergent cooperative catalysis. Source: Modified from Krautwald et al. [31].

In the cases of combining chiral metal and chiral organocatalysts, if both of them are robust enough to control the stereochemistry, the cooperative catalysis will be able to establish the stereodivergent construction of chiral structures by simply varying the stereochemistry of each individual chiral catalyst. The proof of concept in this field was demonstrated by Carriera who first reported a stereodivergent allylic alkylation between α-enolizable aldehyde **35a** and an allylic alcohol **36a** based on the asymmetric cooperative catalysis of iridium complex of chiral phosphoramidite **38** and chiral primary amine **39**, allowing access to four stereomers by altering the stereochemistry of the chiral ligand and chiral amine (Figure 1.12) [31]. Afterward, the cooperative catalysis of chiral rhodium complex and chiral amine, chiral iridium complex and chiral Lewis base, as well as the iridium complex and chiral NHC carbene was successively discovered by different research groups for the establishment of stereodivergent processes [32].

1.3.2 Cooperative Activation of Chemical Bonds

Simultaneous action of both the metal and organocatalyst on the same substrate actually provides a unique tool to activate a chemical bond and thereby makes the reaction that may not work upon, being promoted by either of individual catalysts probably occur. The feasibility and robustness of this strategy have been implicit in the activation of relatively inactive chemical bonds. For instance, both the allylic C—N bond of allyl amines **40** and C—O bond of allylic alcohols **41** can be activated by protonation as shown in **Int-4** and hydrogen-bonding interaction as shown in **Int-5** with the chiral phosphoric acid, respectively, to facilitate the oxidative addition of the palladium complex to give the π-allylpalladium phosphate complex intermediate, which smoothly undergoes the enantioselective substitution reaction with the enamine **Int-6** via a transition state **TS-4** to give α-allylic aldehydes **42** (Figure 1.13) [33]. It is worthy to mention that neither the allyl amine nor the allylic

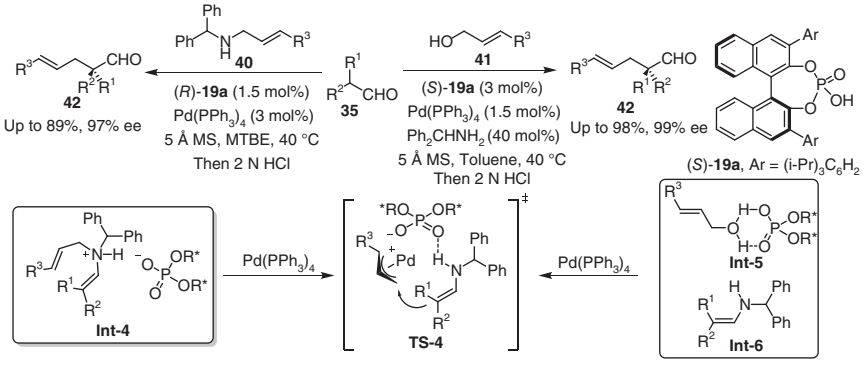


Figure 1.13 Allylation of aldehydes by cooperative catalysis of Pd, chiral Brønsted acid, and amine. Source: Mukherjee et al. [33].

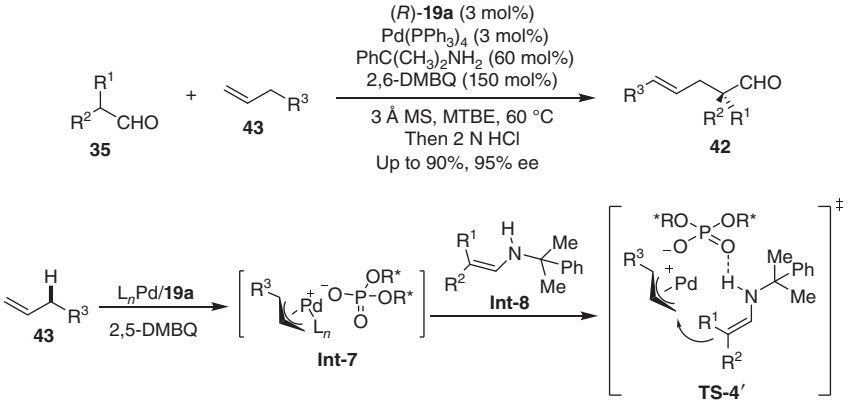


Figure 1.14 Asymmetric allylic C–H functionalization by cooperative catalysis.

alcohol can undergo the oxidative addition without the assistance of the Brønsted acid [34].

Even more remarkably, the Brønsted acid can facilitate the palladium-mediated allylic C–H cleavage. Thus, the combination of the palladium complex, chiral Brønsted acid, and primary amine allows an enantioselective oxidative α-allylation of aldehydes **35** with α-olefins **43** [35]. The Pd-mediated allylic C–H oxidation generates the π-allylpalladium phosphate complex **Int-7** that undergoes asymmetric allylation with enamine **Int-8** via the transition state **TS-4′** similar to List's model **TS-4** to smoothly give the chiral aldehydes **42** in excellent enantioselectivity (Figure 1.14).

Adoption of visible light photocatalysis to combine with chiral organocatalysis leads to another versatile concept for the development of asymmetric transformations that are unable to work based on traditional bond-activation and assembly strategies [36]. MacMillan and coworker first described the integration of a photocatalyst **48** and a chiral amine catalyst **47a** to establish an efficient α-alkylation of aldehydes **44** with α-bromocarbonyls **45** (Figure 1.15) [37]. Subsequently, merging the

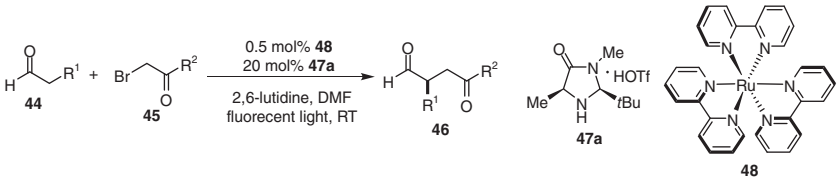


Figure 1.15 Asymmetric organocatalysis combined with photocatalysis. Source: Modified from Nicewicz and MacMillan [37].

ruthenium(II) or iridium(III) visible photocatalysts and chiral Brønsted acids [38], NHC carbene [39], or other organocatalysts [40] were disclosed to promote asymmetric transformations that proceed via transient radical intermediates in excellent stereochemical control.

The organo/metal combined catalysts aforementioned are typical representatives in the field of hybrid cooperative catalysis. Each of them consists of a large family of chiral catalyst systems that provide plentiful synergistic activation of chemical bonds and many possibilities to induce the stereoselectivity, allowing for the creation of new asymmetric transformations. A detailed description of this field will be presented in Chapters 2–9.

1.4 Organo/Metal Relay and Sequential Catalysis

Relay catalysis is defined as a cascade process in which two or more sequential bond-forming events are independently promoted by two or more catalysts in a cascade manner. Based on the substrates, either the linear ligation (Figure 1.16a) or annulation (Figure 1.16b) can be accessed by this catalytic strategy.

The sequential catalysis generally describes a one-pot reaction promoted by different catalysts, which are chemically incompatible, and therefore parts of the catalysts or, in some cases, reagents must be added after the previous catalytic reaction is complete (Figure 1.7c) [26]. Both relay and sequential catalysis can provide general platforms to design new protocols for the enantioselective construction of molecular complexity from readily available starting materials, featured by avoiding the additional workup of either isolable or transient intermediates to thereby reduce labor, save time, and minimize waste. This book will be focusing on discussion of cooperative and relay catalysis, both of which are chemically compatible. Thus, sequential catalytic processes that proceed based on artificial operation, will be excluded from this book except the very original ones that have inspired the following developments.

Rovis coined the name of relay catalysis defining a cascade reaction constituted of elementary steps promoted by the individual catalyst, respectively, and reported a nucleophilic carbene and HOAt (**53**) relay catalysis for an amidation of α-reducible aldehydes **49** and amines **50** to produce α-reduced amides **51** [41]. The aldehyde **49** undergoes a redox reaction with carbene to yield an acyl azolium **Int-8**, which then condenses with **53** to give an even more reactive intermediate **Int-9** capable of participating in the subsequent amidation reaction (Figure 1.17).

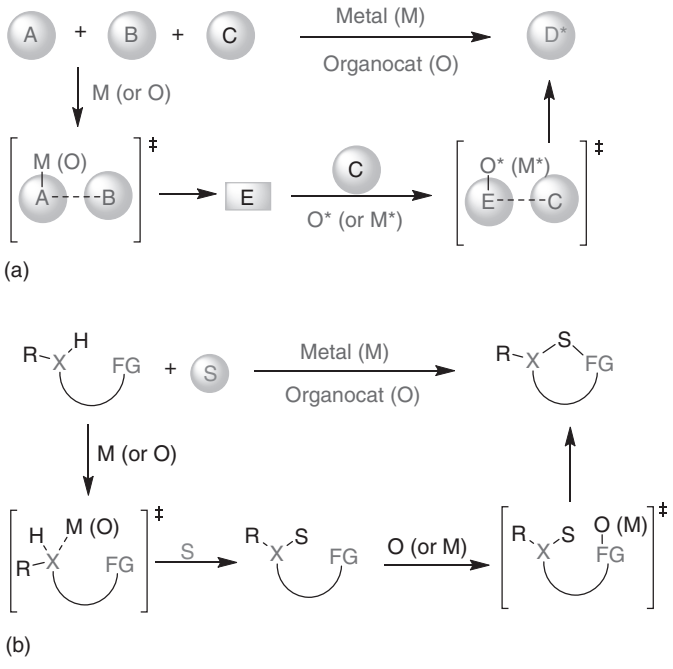


Figure 1.16 General principal of organo/metal relay catalysis. (a) Intermolecular relay catalysis. (b) Relay catalysis for annulation. Source: Han et al. [27].

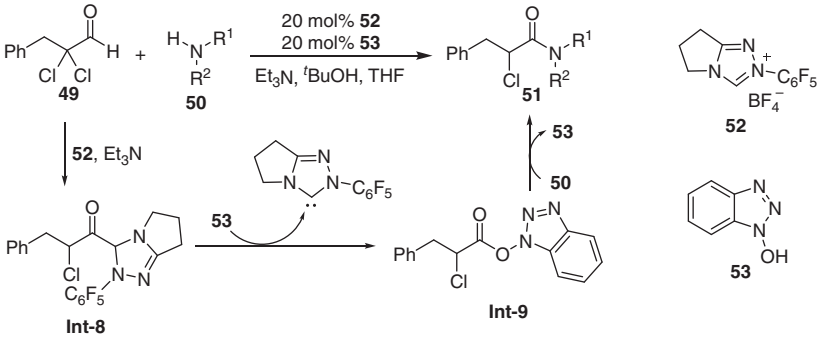


Figure 1.17 Proof of concept of relay catalysis.

One of the earliest organo/metal relay catalysis describes cascade hydroformylation and asymmetric aldol reaction (Figure 1.18). The styrene derivatives **54** prefer to undergo branch-selective hydroformylation catalyzed by rhodium complex of **57** to generate α-branched aldehydes, which then undergo a proline-catalyzed asymmetric direct aldol reaction to give β-hydroxyketones **56**. In contrast, α-alkenes **58** favorably undergo the linear-selective hydroformylation to give enolizable aldehydes, which then participate in the subsequent proline-catalyzed cross-aldol reaction with another aldehyde **59** [42].

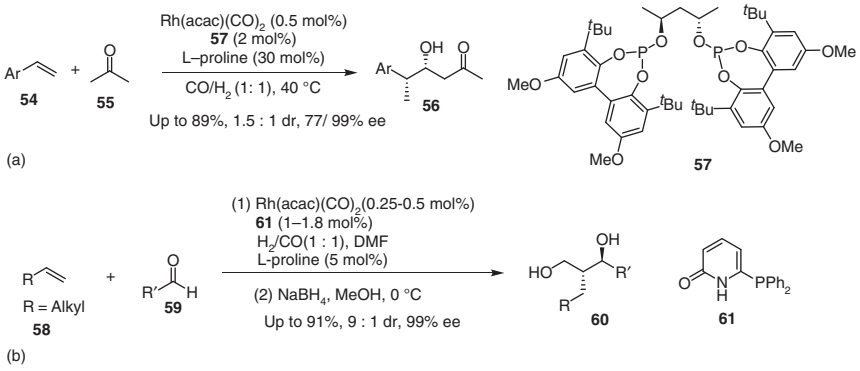


Figure 1.18 Relay catalytic cascade hydroformylation and aldol reaction. (a) Eilbracht's work. (b) Breit's work.

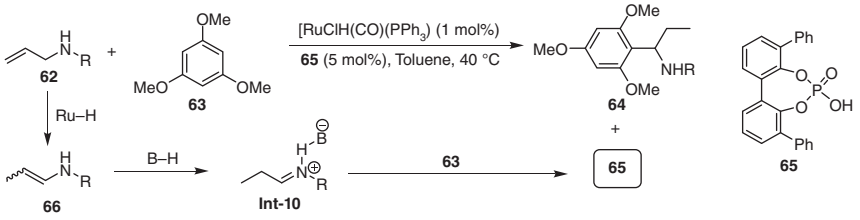


Figure 1.19 Ru/Brønsted relay catalysis. Source: Modified from Sorimachi and Terada [43].

Terada and coworker established a one-pot tandem isomerization/carbon–carbon bond-forming sequence of allylamines **62** and **63** enabled by the relay catalysis of a ruthenium complex and Brønsted acid **65**. The readily available allylamines **62** initially undergoes a double-bond migration catalyzed by ruthenium complex to give an enamine **66**, which then participates in a Brønsted acid-catalyzed addition reaction with 1,3,5-trimethoxybenzene (**63**) via the intermediate **Int-10** to yield **64** and regenerate phosphoric acid **65** (Figure 1.19) [43].

Soon after these events, hydroamination of alkynes and asymmetric transfer hydrogenation cascade processes, enabling the direct transformation of a linear functionality, the carbon–carbon triple bond, to a stereogenic center, were established by relay catalysis of gold complex and chiral phosphoric acid [44]. Gong and coworkers elaborated a gold complex/chiral phosphoric acid relay catalytic transformation to directly convert the propargylic anilines **67** to a number of chiral tetrahydroquinolines **69** in excellent yields and with high levels of enantioselectivity (Figure 1.20a) [44]. Coincidently, Liu and Che also found a cascade intermolecular hydroamination and transfer hydrogenation reaction of alkynes **71** and anilines **72** rendered by gold and chiral phosphoric acid relay catalysis to furnish chiral secondary amine products **73** in excellent yields and enantioselectivities (Figure 1.20b) [44].

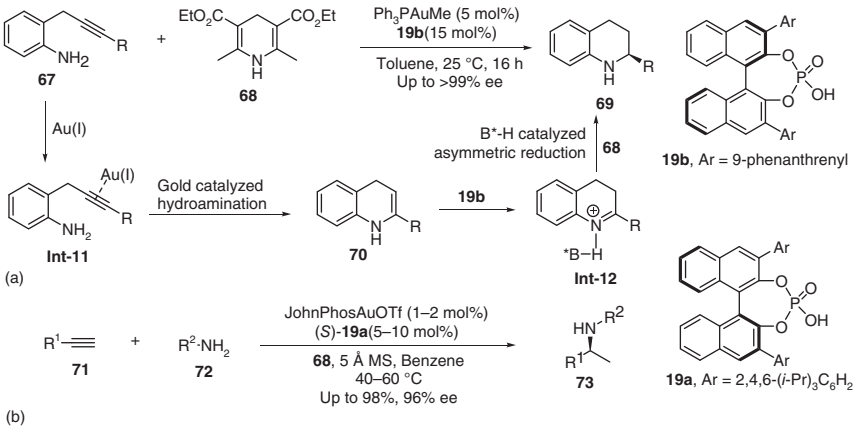


Figure 1.20 Gold/chiral Brønsted acid relay catalysis. Source: Modified from Liu and Che [40].

Dixon combined a gold(I)-catalyzed intramolecular hydroalkoxylation of 3-butylnoic acids **74** to generate furan-2(3*H*)-one intermediates **77**, a chiral phosphoric acid-mediated condensation with tryptamine **75** to form *N*-acyliminium phosphate **Int-13**, and *N*-acyliminium cyclization, to accomplish a one-pot process enabling the direct transformation of the 3-butylnoic acids **74** and the tryptamine **75** into chiral *N*-heterocyclic compounds **76** in great yields and stereoselectivities (Figure 1.21) [45].

In the same year, You and coworkers reported a relay catalytic cascade cross-metathesis and asymmetric Friedel–Crafts alkylation between indole derivatives **78** and unsaturated carbonyls **79** [46]. The presence of the Grubbs catalyst is sufficient to drive cascade reaction but in the racemic version [47]. The addition of the chiral phosphoric acid **19a** as co-catalyst allows the Friedel–Crafts alkylation to proceed much faster and thus offers high stereoselectivity (Figure 1.22).

The earliest combination of iminium activation mode and transition metal for sequential catalysis was described by MacMillan et al. The Grubbs II catalyst **81b**,

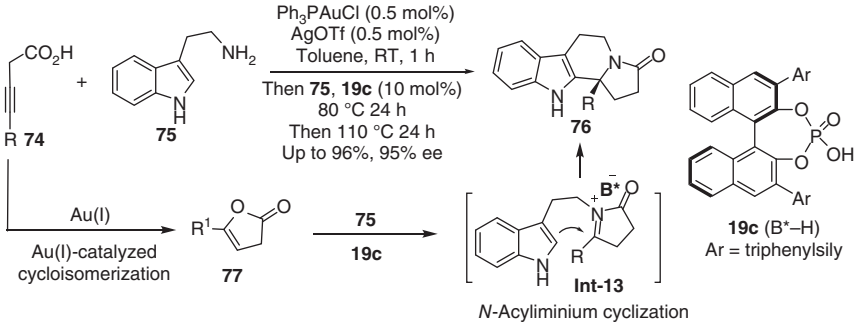


Figure 1.21 Gold/chiral Brønsted acid sequential catalysis. Source: Modified from Yang et al. [45].

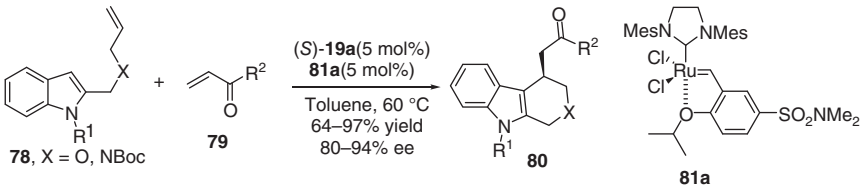


Figure 1.22 Relay catalytic cascade metathesis and Friedel–Crafts reaction.

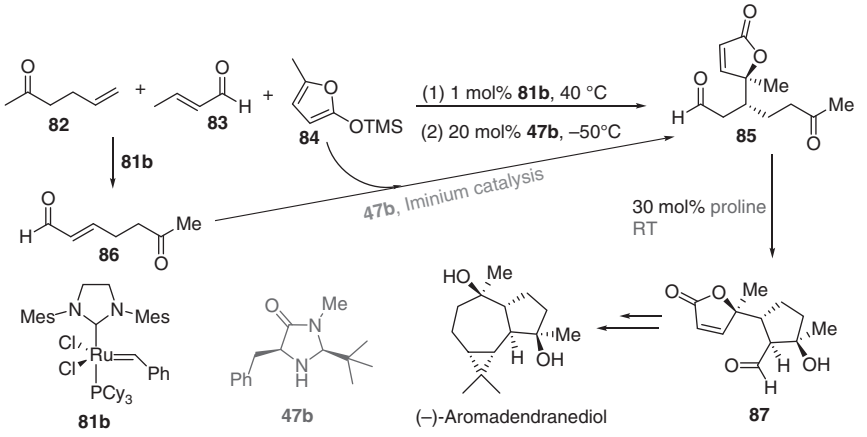


Figure 1.23 Sequential metathesis/Michael addition/aldol reaction. Source: Modified from Simmons et al. [48].

5-hexene-2-one **82**, and crotonaldehyde **83** are combined at 40 °C to undergo the metathesis to give a keto-enol **86**. The subsequent asymmetric Michael addition of trimethylsilyloxyfuran **84**–**86** catalyzed by imidazolidinone **47b** proceeds at −50 °C to generate **85**. Finally, the intramolecular aldol reaction of **85** catalyzed by L-proline allows the production of **87** in overall 64% yield and with 5/1 dr and 95% ee. This sequential one-pot process enabled by the triple catalysis provides the key intermediate **87** to access natural product (−)-aromadendranediol (Figure 1.23) [48].

As aforementioned and also implied in the working models of organocatalysis (Table 1.1), it is basically hard for organocatalysis to activate relatively inert chemical bonds. For example, hydrogen is highly inert for pure organocatalysts and unable to participate in the organocatalytic process. However, the adoption of transition metal catalysis in the relay catalytic process can allow asymmetric hydrogenation to occur by using the chiral organocatalyst to control the stereochemistry. Zhou and coworkers combined chiral ruthenium complex and chiral Brønsted acid to establish highly enantioselective hydrogenation of quinoxalines [49]. The Ru(II)-catalyzed hydrogenation of quinoxaline **88** initially proceeds to generate dihydroquinoxaline **90**, which undergoes either a Ru(II)-catalyzed non-enantioselective hydrogenation or a chiral phosphoric acid (*S*)-**19a**-catalyzed asymmetric disproportionation to give **89** (Figure 1.24). Since the chiral phosphoric acid-catalyzed self-transfer hydrogenation

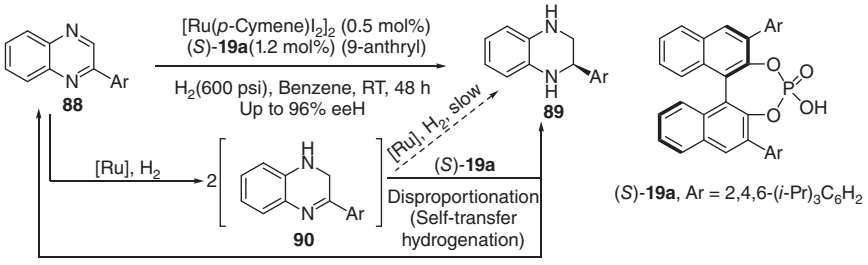


Figure 1.24 Relay catalytic hydrogenation.

is much faster than the Ru-catalyzed process, high levels of enantioselectivity are achieved for the entire relay catalytic hydrogenation reaction.

The relay catalytic systems listed before are typical representatives and actually provide the general reaction modes that are amenable to design new cascade processes. Since these events, hybrid multi-catalyst relay catalysis has gradually been blooming. Increasing attention has been paid to this field, leading to a large number of nonclassical asymmetric cascade transformations that will be highlighted and discussed in detail in the next chapters, in particular in Chapters 3, 4, and 6.

1.5 Conclusion

Since the advent of asymmetric metal catalysis, the incorporation of chiral ligands to the central metal has dominantly been the reliable strategy to address the stereoselective issue encountered in catalytic asymmetric reactions. The organo/metal combined catalysis changes and even actually refutes such conventional wisdom. The preponderance of activation modes and stereochemical options allocates unparalleled capacity to the organo/metal cooperative catalysis for the creation of asymmetric reactions. The sequential occurrence of multiply bond-breaking and forming events in stereoselective manner featured in relay catalysis propels the emergence of nonclassical cascade reactions. The last decades have indeed witnessed exciting progress in asymmetric organocatalysis combined with metal catalysis. It is not to overstate that the organo/metal combined catalysis is gradually altering the status quo of asymmetric catalysis, to some degree, and will continue to exert an essential impact on asymmetric catalysis.

References

1 (a) Ager, D. (ed.) (2005). *Handbook of Chiral Chemicals*, 2e. Boca Raton, FL: CRC Press, Taylor & Francis. (b) Christmann, M. and Bräse, S. (eds.) (2007). *Asymmetric Synthesis – The Essentials*. Weinheim: Wiley-VCH.

2 (a) Hanessian, S. (1983). *Total Synthesis of Natural Products: The Chiron Approach*. Oxford: Pergamon Press. (b) Roos, G. (ed.) (2014). *Key Chiral Auxiliary Applications*, 2e. Academic Press.

3 (a) Nozaki, H., Moriuti, S., Takaya, H. et al. (1966). *Tetrahedron Lett.* 7: 5239–5244. (b) Nozaki, H., Takaya, H., Moriuti, S. et al. (1968). *Tetrahedron* 24: 3655–3669.

4 (a) Knowles, W.S. and Sabacky, M.J. (1968). *J. Chem. Soc., Chem. Commun.*: 1445–1446. (b) Horner, L., Siegel, H., and Büthe, H. (1968). *Angew. Chem. Int. Ed.* 7: 942–942.

5 (a) Noyori, R. (1994). *Asymmetric Catalysis in the Organic Synthesis*. New York: Wiley. (b) Blaser, H.U. and Schmidt, E. (2004). *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*. Weinheim: Wiley-VCH.

6 Jacobson, E.N., Pfaltz, A., and Yamamoto, H. (eds.) (1999). *Comprehensive Asymmetric Catalysis*. Heidelberg: Springer-Verlag.

7 (a) Sharpless, K.B. (1988). *J. Am. Chem. Soc.* 110: 1968–1970. (b) Sharpless, K.B. (1995). *Angew. Chem. Int. Ed. Engl.* 34: 1059–1070.

8 Zhou, Q.L. (ed.) (2011). *Privileged Ligands and Catalysts*. Weinheim: Wiley-VCH.

9 (a) McDonald, R.I., Liu, G.S., and Stahl, S.S. (2011). *Chem. Rev.* 111: 2981. (b) Newton, C.G., Wang, S.G., Oliveira, C.C. et al. (2017). *Chem. Rev.* 117: 8908. (c) Saint-Denis, T.G., Zhu, R.Y., Chen, G. et al. (2018). *Science* 359: 759. (d) Wang, P.S. and Gong, L.Z. (2020). *Acc. Chem. Res.* 53: 2841–2854.

10 (a)Yamamoto, H. (ed.) (2000). *Lewis Acids in Organic Synthesis*. Weinheim: Wiley-VCH. (b) Mlynarski, J. (ed.) (2017). *Chiral Lewis Acids in Organic Synthesis*. Weinheim: Wiley-VCH.

11 MacMillan, D.W.C. (2008). *Nature* 455: 304.

12 List, B. and Yang, J.W. (2006). *Science* 313: 1584.

13 (a) Berkessel, A. and Gröger, H. (2005). *Asymmetric Oranocatalysis – From Biomimetic Concepts to Application in Asymmetric Synthesis*. Weinheim: Wiley-VCH. (b) Dalko, P.I. (2007). *Enantioselective Organocatalysis: Reactions and Experimental Procedures*. Weinheim: Wiley-VCH.

14 (a) Shao, Z.H. and Zhang, H.B. (2009). *Chem. Soc. Rev.* 38: 2745. (b) Du, Z.T. and Shao, Z.H. (2013). *Chem. Soc. Rev.* 42: 1337. (c) Allen, A.E. and MacMillan, D.W.C. (2012). *Chem. Sci.* 3: 633.

15 (a) Chen, G.S., Deng, Y.J., Gong, L.Z. et al. (2001). *Tetrahedron-Asymmetry* 12: 1567–1571. (b) Nakoji, M., Kanayama, T., Okino, T. et al. (2001). *Org. Lett.* 3: 3329–3331.

16 Corey, E.J., Xu, F., and Noe, M.C. (1997). *J. Am. Chem. Soc.* 119: 12414–12415.

17 Lygo, B. and Wainwright, P.G. (1997). *Tetrahedron Lett.* 38: 8595–8598.

18 Jellerichs, B.G., Kong, J.R., and Krische, M.J. (2003). *J. Am. Chem. Soc.* 125: 7758–7759.

19 Rauhut, M.M. and Currier, H. (1963). Repreparation of dialkyl 2-methylense galutarates (American Cyanamid Co.). US Patent 3,074,999; Chem. Abstr. 58, 11224a.

20 France, S., Wack, H., Hafez, A.M. et al. (2002). *Org. Lett.* 4: 1603–1605.

21 Ibrahem, I. and Córdova, A. (2006). *Angew. Chem. Int. Ed.* 45: 1952–1956.

22 Komanduri, V. and Krische, M.J. (2006). *J. Am. Chem. Soc.* 128: 16448–16449.

23 Mukherjee, S. and List, B. (2007). *J. Am. Chem. Soc.* 129: 11336–11337.

24 Cardinal-David, B., Raup, D.E.A., and Scheidt, K.A. (2010). *J. Am. Chem. Soc.* 132: 5345–5347.

25 Arndtsen, B.A. and Gong, L.Z. (eds.) (2020). *Topics in Current Chemistry Collections: Asymmetric Organocatalysis Combined with Metal Catalysis*. Springer.

26 Chen, D.F., Han, Z.Y., Zhou, X.L. et al. (2014). *Acc. Chem. Res.* 47: 2365.

27 Han, Z.Y., Wang, C., and Gong, L.Z. (eds.) (2012). *Science of Synthesis: Asymmetric Organocatalysis*, (ed. K. Maruoka), vol. 2, 697. Stuttgart: Georg Thieme Verlag.

28 (a) Chen, F., Feng, X., Qin, B. et al. (2003). *Org. Lett.* 5: 949–952. (b) Chen, F.X., Zhou, H., Liu, X. et al. (2004). *Chem. Eur. J.* 10: 4790–4797.

29 (a) Bihelovic, F., Matovic, R., Vulovic, B. et al. (2007). *Org. Lett.* 9: 5063–5066. (b) Vulovic, B., Bihelovic, F., Matovic, R. et al. (2009). *Tetrahedron* 65: 10485–10494.

30 Li, C., Wang, C., Villa-Marcos, B. et al. (2008). *J. Am. Chem. Soc.* 130: 14450–14451.

31 Krautwald, S., Sarlah, D., Schafroth, M.A. et al. (2013). *Science* 340: 1065–1068.

32 (a) Cruz, F.A. and Dong, V.M. (2017). *J. Am. Chem. Soc.* 139: 1029–1032. (b) Jiang, X., Beiger, J.J., and Hartwig, J.F. (2017). *J. Am. Chem. Soc.* 139: 87–90. (c) Singha, S., Serrano, E., Mondal, S. et al. (2020). *Nat. Catal.* 3: 48–54.

33 (a) Mukherjee, S. and List, B. (2007). *J. Am. Chem. Soc.* 129: 11336–11337. (b) Jiang, G. and List, B. (2011). *Angew. Chem. Int. Ed.* 50: 9471–9474.

34 Murahashi, S., Makabe, Y., and Kunita, K. (1988). *J. Org. Chem.* 53: 4489–4495.

35 Wang, P.S., Lin, H.C., Zhai, Y.J. et al. (2014). *Angew. Chem. Int. Ed.* 53: 12218–12221.

36 Prier, C.K., Rankic, D.A., and MacMillan, D.W. (2013). *Chem. Rev.* 113: 5322–5363.

37 Nicewicz, D.A. and MacMillan, D.W. (2008). *Science* 322: 77–80.

38 Rono, L.J., Yayla, H.G., Wang, D.Y. et al. (2013). *J. Am. Chem. Soc.* 135: 17735–17738.

39 DiRocco, D.A. and Rovis, T. (2012). *J. Am. Chem. Soc.* 134: 8094.

40 Liu, Y.-Y., Liu, J., Lu, L.-Q. et al. (2019). *Top. Curr. Chem.* 377: 37.

41 Vora, H.U. and Rovis, T. (2007). *J. Am. Chem. Soc.* 129: 13796.

42 (a) Abillard, O. and Breit, O. (2007). *Adv. Synth. Catal.* 349: 1891. (b) Chercheja, S. and Eilbracht, P. (2007). *Adv. Synth. Catal.* 349: 1897.

43 Sorimachi, K. and Terada, M. (2008). *J. Am. Chem. Soc.* 130: 14452.

44 (a) Han, Z.Y., Xiao, H., Chen, X.H. et al. (2009). *J. Am. Chem. Soc.* 131: 9182–9183. (b) Liu, X.Y. and Che, C.M. (2009). *Org. Lett.* 11: 4204–4207.

45 Yang, T., Campbell, L., and Dixon, D.J. (2007). *J. Am. Chem. Soc.* 129: 12070–12071.

46 Cai, Q., Zhao, Z.A., and You, S.L. (2009). *Angew. Chem. Int. Ed.* 48: 7428–7431.

47 Chen, J.R., Li, C.F., An, X.L. et al. (2008). *Angew. Chem. Int. Ed.* 47: 2489–2492.

48 Simmons, B., Walji, A.M., and MacMillan, D.W.C. (2009). *Angew. Chem. Int. Ed.* 48: 4349–4353.

49 Chen, Q.A., Wang, D.S., Zhou, Y.G. et al. (2011). *J. Am. Chem. Soc.* 133: 6126–6129.