Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters

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Abstract: Catalytic enantioselective construction of all-carbon quaternary stereocenters, i.e. carbon atoms bearing four different carbon substituents, poses a particular challenge in organic synthesis. This review gives a comprehensive account on the currently available methods of the above transformation that afford high enantioselectivities and synthetically useful yields.

1 Introduction

In biological systems, two enantiomers of a molecule usually exhibit different biological activities. In extreme cases, one enantiomer may be effective therapeutically while the other enantiomer is toxic. Therefore, the synthesis of chiral compounds in an enantioselective fashion is of great importance. Impressive progress has been made in asymmetric organic synthesis during the last two decades. Among the processes developed, catalytic enantioselective synthesis is the method of choice for several reasons: first, large quantities of chiral product can be generated with high enantioselectivity from a small amount of chiral catalyst; second, it allows simple and atom-economic processes without the need to install and remove the chiral auxiliary; third, compared to enzyme catalysis, it allows much broader substrate scope and provides access to both enantiomers of products by simply switching the chirality of the chiral catalyst.

All-carbon quaternary stereocenters, i.e. carbon atoms bearing four different carbon substituents, pose a particular challenge in organic synthesis. At present, few methods are reported for the catalytic enantioselective construction of all-carbon quaternary stereocenters.1 This review provides a survey of methods that give high enantioselectivities and synthetically useful yields. The approach by desymmetrization of two enantiotopic substituents on a prochiral quaternary center will also be discussed, but completeness is not claimed, since in theory every catalytic asymmetric reaction can be used in this approach. Chirality transfer, resolution and kinetic resolution, non-catalytic and biochemical methods will not be discussed here.

2 Cycloadditions

2.1 Diels–Alder Reactions

The asymmetric Diels–Alder reaction is one of the most powerful transformations to construct quaternary stereocenters enantioselectively. In theory the quaternary stereocenters can be derived from either 1,1-disubstituted dienophiles or 1,1-disubstituted dienes. However, the first approach has received most attention. The reaction between 2-methylacrolein and cyclopentadiene is the most commonly studied Diels–Alder reaction and many chiral Lewis acid catalysts were developed for this transformation (Figure 1). The best results with different kinds of Lewis acid catalysts are summarized in Table 1.2–13 Extremely high enantio- and diastereoselectivities can be achieved with many catalysts.

Asymmetric Diels–Alder reactions between various dienes and α,β-unsaturated aldehydes were also conducted with excellent results.14 Two examples are illustrated in Scheme 15 and Scheme 2,15 both of which generate only one diastereomer and enantiomer.
Biographical Sketches

Born in Philadelphia, Pennsylvania in 1941 where he began his university training at the University of Pennsylvania (BA, 1962), he obtained a Ph.D. degree in Chemistry just three years later at the Massachusetts Institute of Technology (1965). He directly moved to the University of Wisconsin where he was promoted to Professor of Chemistry in 1969 and subsequently became the Vilas Research Professor in 1982. He joined the faculty at Stanford as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition, he has been Visiting Professor of Chemistry in Germany (Universities of Marburg, Hamburg and Munich), Denmark (University of Copenhagen), France (Universities of Paris VI and Paris-Sud), Italy (University of Pisa) and Spain (University of Barcelona). In 1994 he was presented with a Docteur honoris causa of the Université Claude-Bernard (Lyon I), France, and in 1997 a Doctor Scientiarum Honoris Causa of the Technion, Haifa, Israel. Professor Trost’s work has been characterized by a very high order of imagination, innovation and scholarship. He has ranged over the entire field of organic synthesis, particularly emphasizing extraordinarily novel methodology. In recognition of his many contributions, Professor Trost has received a number of awards, including the ACS Award in Pure Chemistry (1977), the ACS Award for Creative Work in Synthetic Organic Chemistry (1981), the Baekeland Award (1981), Arthur C. Cope Scholar Award (1989), Guenther Award in the Chemistry of Essential Oils and Related Products (1990), the Dr. Paul Janssen Prize (1990), the ASSU Graduate Teaching Award (1991), Bing Teaching Award (1993), the ACS Roger Adams Award (1995), the Presidential Green Chemistry Challenge Award (1998), the Herbert C. Brown Award for Creative Research in Synthetic Methods (1999), the Belgian Organic Synthesis Symposium Elsevier Award (2000), the Nichols Medal (2000), the Yamada Prize (2001), the ACS Nobel Laureate Signature Award for Graduate Education in Chemistry (2002), the ACS Cope Award (2004) and The City of Philadelphia John Scott Award (2004). Professor Trost has been elected a fellow of the American Academy of Sciences (1992) and a member of the National Academy of Sciences (1990). He has published two books and over 750 scientific articles and served as Editor-in-Chief of the major compendium Comprehensive Organic Synthesis.

Chunhui Jiang received her B.Sc. in chemistry from Beijing University in 1997 and was then matriculated to State University of New York at Stony Brook. She did graduate research with Prof. Iwao Ojima and received her M.Sc. degree in 1999. She then obtained her Ph.D. in organic chemistry from Stanford University in 2004 under the supervision of Prof. Barry M. Trost. Her research includes the development of palladium-catalyzed regio- and enantio-selective ring-opening reactions of vinyl epoxide with carbon- and nitrogen-centered nucleophiles and their synthetic applications. Upon graduation, she took a process chemistry position at DuPont located in Newark, Delaware.
For the asymmetric Diels–Alder reactions between substituted 1-amino-1,3-butadienes and 2-methylacrolein, typical catalysts are Co-salen\(^{16}\) or Cr-salen\(^{17}\) complexes, as shown in Scheme 3.

The asymmetric Diels–Alder reactions between 2-alkylacrolein and acyclic dienes have been used in the total syntheses of many natural products, such as cassiol,\(^{18}\) tabersonine, aspidospermidine and quebrachamine,\(^{19}\) as illustrated in Scheme 4 and Scheme 5.

Dienophiles other than \(\alpha,\beta\)-unsaturated aldehydes can also be good partners for asymmetric Diels–Alder reactions. The cycloaddition of doubly activated \(\alpha\)-methylene \(\beta\)-ketoester and cyclopentadiene is successfully catalyzed by either bis(oxazoline)/\(\text{MgI}_2\)\(^{18}\) or the mono(oxazoline) complex \(^{19}\) (Scheme 6). Both catalysts provide comparable yield and enantioselectivity.\(^{20}\)

The asymmetric formation of azaspiro[5.6]dodec-9-ene systems is accomplished by the Diels–Alder reactions of \(\alpha\)-methylene caprolactam and dienes (Scheme 7).\(^{21}\) The resulting products are synthetic building blocks of a class of marine natural toxins.
The asymmetric Diels–Alder reactions of benzoquinone derivatives were recently developed. While simple 2,5-dimethyl-1,4-benzoquinone gives only poor regioselectivity when reacting with unsymmetrical dienes, an iodide substituent controls the regioselectivity excellently without affecting the high yield and enantioselectivity (Scheme 8). Evans developed a lanthanide(pybox) complex (22) to catalyze the Diels–Alder reactions of carbomethoxy-substituted quinones and naphthoquinones (Scheme 9). Both samarium and gadolinium complexes are effective catalysts to give excellent yields and selectivities. The reactions are highly regioselective when reacting with unsymmetrical dienes. For example, when $R_1 = \text{Et}$ and $R_2 = \text{H}$ in the diene partner, the small differentiation between methyl and ethyl substitutions on the diene results in a 5:1 regioselectivity; while changing $R_1$ to $n$-propyl increases the selectivity to 15:1.

**Scheme 4** Enantioselective total synthesis of (+)-cassiol

**Scheme 5** Enantioselective total synthesis of (+)-tabersonine, (+)-aspidospermidine and (–)-quebrachamine

The asymmetric Diels–Alder reactions of benzoquinone derivatives were recently developed. While simple 2,5-dimethyl-1,4-benzoquinone gives only poor regioselectivity when reacting with unsymmetrical dienes, an iodide substituent controls the regioselectivity excellently without affecting the high yield and enantioselectivity (Scheme 8). Evans developed a lanthanide(pybox) complex (22) to catalyze the Diels–Alder reactions of carbomethoxy-substituted quinones and naphthoquinones (Scheme 9). Both samarium and gadolinium complexes are effective catalysts to give excellent yields and selectivities. The reactions are highly regioselective when reacting with unsymmetrical dienes. For example, when $R_1 = \text{Et}$ and $R_2 = \text{H}$ in the diene partner, the small differentiation between methyl and ethyl substitutions on the diene results in a 5:1 regioselectivity; while changing $R_1$ to $n$-propyl increases the selectivity to 15:1.

**Scheme 6**

**Scheme 7**

**Scheme 8**

**Scheme 9**
The asymmetric Diels–Alder reactions with unsymmetrical 1,1-disubstituted dienes are only implemented in inverse-electron-demand reactions. As illustrated in Scheme 10, high enantioselectivity has been reported for the cycloaddition of 3-carbomethoxy-2-pyrone with a series of dienophiles catalyzed by (BINOL)–Yb(OTf)$_3$ or (BINOL)–TiCl$_2$(Oi-Pr)$_2$ complex.

### 2.2 [3+2] Cycloadditions

The enantioselective 1,3-dipolar [3+2] cycloadditions between an α,β-unsaturated aldehyde and a series of nitrones are implemented under the catalysis of the chiral Co(III) Lewis acid 24. The corresponding isoxazolidine products are obtained in high yields and enantioselectivities with almost exclusive endo selectivities (Scheme 11).

### 2.3 [2+2] Synthesis of β-Lactams

The enantioselective Staudinger reaction, an overall [2+2] cycloaddition of a ketene with an imine, provides an effective route to chiral β-lactams. When an unsymmetrical ketene is used, both enantio- and diastereoselectivities are well-controlled by the planar-chiral heterocycle catalyst 25, affording the β-lactam products with two adjacent stereogenic centers (Scheme 12). The reaction is proposed to proceed via the stepwise mechanism shown in Scheme 13.

Copper-catalyzed Kinugasa reactions between terminal alkynes and nitrones were also reported for the inter- or intramolecular asymmetric constructions of β-lactams. Fu discovered a method to trap the reaction intermediate with an electrophile, generating a quaternary stereocenter at the α-position (Scheme 14). Thus, two C–C bonds, a C–N bond, two new rings, a carbonyl group, and adjacent quaternary and tertiary stereocenters are generated in a single reaction, significantly increasing the complexity of the molecule. The reaction mechanism involves an initial [3+2] cycloaddition followed by rearrangement, as shown in Scheme 15.
2.4 Cyclopropanations

The enantioselective synthesis of chiral cyclopropanes from olefins can be achieved by two classes of methods: 1) the transition-metal (Rh, Cu, Co, etc.) catalyzed addition of diazocarbonyl compounds to olefins; and 2) addition of zinc-based carbenoid reagents derived from geminal dihaloalkanes. Both are used for asymmetric construction of cyclopropanes with quaternary stereo-centers. By far, the first method is studied more extensively and achieves higher selectivity. However, since the formation of diazo compounds requires the presence of an $\alpha$-carbonyl functionality, the products are restricted to carbonyl-substituted cyclopropanes. On the other hand, the second method provides access for the delivery of non-functionalized carbenes, such as a simple methylene group. However, this method usually requires the olefin to possess an allylic functional group, such as an allylic alcohol, to increase the enantioselectivity.

2.4.1 Intermolecular Cyclopropanation

2.4.1.1 Reactions with Diazocarbonyl Compounds

The rhodium-catalyzed intermolecular asymmetric cyclopropanation often affords good enantioselectivity but low diastereoselectivity. A noteworthy system was developed by Davies, utilizing methyl ($E$)-2-diazo-4-phenylbut-3-enooate as the carbenoid precursor and rhodium(II) $\text{N}^\text{SO}_2\text{Ar}$ as the catalyst, as shown in Scheme 16.31

The cyclopropanation of methyl phenyldiazoacetate was studied by both the Davies32 and Doyle33 groups, utilizing catalyst 27 as described above. With monosubstituted olefins, the reactions afford consistently good yields and diastereoselectivities, but the enantioselectivities are slightly inferior to the above-mentioned ($E$)-2-diazo-4-phenylbut-3-enooate system (Scheme 17). Doyle demonstrated that the cyclopropanes with two quaternary centers can also be constructed with very good yields. However, when unsymmetrical 1,1-disubstituted alkenes are used, only low $E/Z$ selectivities are observed (Scheme 18).

2.4.2 Intramolecular Cyclopropanation

Doyle and co-workers reported excellent enantiocontrol in intramolecular cyclopropanations of 3,3-disubstituted allylic diazoacetates by using Rh$_2$(5S-MEPY)$_4$ (29) as catalyst, as shown in Scheme 20.35

Poulter applied this method to the synthesis of presqualene diphosphate. The cyclopropanation key step occurs in high yield and enantioselectivity (Scheme 21).

The reactions of 2-substituted allylic diazoacetates were also studied (Scheme 22 and Table 2). Although the Rh$_2$(5$S$-MEPY)$_4$-catalyzed cyclization of the 2-methylallyl diazoacetate proceeds with only 7% ee, the modified chiral catalyst Rh$_2$(4$S$-MPPIM)$_4$ (30; Figure 2) can increase the level of enantiocontrol to 89%. Alternatively, chiral copper catalyst Cu(MeCN)$_4$PF$_6$/20 provides comparable enantioselectivity (87% ee) but lower yield. When the 2-substituent is changed to a butyl group, the copper system becomes inferior. The formation of a [4.1.0] bicyclic system by intramolecular cyclopropanation of 3-methyl-3-butenyl diazoacetate can be catalyzed by Rh$_2$(5$S$-MEPY)$_4$ (29) to afford an 83% ee (Scheme 23).

Corey also developed an asymmetric intramolecular cyclopropanation of substrate 32 catalyzed by chiral copper complex 34. This method provides a concise synthesis of the chemotactic factor sirenin (Scheme 25).

### Table 2: Comparative Study of Cu(I)- and Rh(II)-Catalyzed Cyclopropanations

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Rh$_2$(5$S$-MEPY)$_4$ (29)</th>
<th>Rh$_2$(4$S$-MPPIM)$_4$ (30)</th>
<th>Cu(MeCN)$_4$PF$_6$/20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yield (%)  ee (%)</td>
<td>Yield (%)  ee (%)</td>
<td>Yield (%)  ee (%)</td>
</tr>
<tr>
<td>Me</td>
<td>72  7a</td>
<td>75  89</td>
<td>58  87</td>
</tr>
<tr>
<td>Bu</td>
<td>72  35</td>
<td>82  93</td>
<td>73  82</td>
</tr>
</tbody>
</table>

*The opposite enantiomer.*
Cu(MeCN)₄(PF₆)/20 complex catalyzed macrocyclization of 35 affords the 10-membered macrocyclic compound 36 with high enantio- and diastereoselectivities (Scheme 26). In contrast to the intermolecular reactions of diazoesters, in which the E diastereomers are normally the predominant product, the macrocyclizations provide the Z isomers as the only products.

Interestingly, in a competitive cyclopropanation that would produce either macrocyclic product 38 or the five-membered-ring compound 39, the macrocycle formation is predominant with the copper catalyst, while allylic cyclopropanation is the sole result with the rhodium catalyst (Scheme 27).

When substrate 40 is set up to test the competition between the formation of 10- and 15-membered rings, a greater than 25:1 chemoselectivity is observed, favoring the formation of 15-membered product 41 with Cu(MeCN)₄(PF₆)/20 as catalyst (Scheme 28). Doyle explains this differentiation as being due to the different ability of the olefins to form stable intermediate π-complexes with the carbene center.

### 3 Combination of Carbon Nucleophiles and Carbon Electrophiles

#### 3.1 Michael Addition and Direct Alkylation

Conjugate additions of carbon nucleophiles to acceptor-activated carbon–carbon multiple bonds (Michael addition) or their Sₐₐ₂ substitution to haloalkanes are very useful and versatile reactions for the synthesis of quaternary carbon centers. However, very limited success has been achieved in the development of highly enantioselective catalytic versions until recently.

3.1.1 Transition-Metal-Catalyzed Michael Addition and Alkylation of Stabilized Carbon Nucleophiles

An important breakthrough in the studies of transition-metal-catalyzed Michael additions was the introduction of a chiral rhodium catalyst in 1992 by Ito and co-workers. The unique chiral ligand 42, with both planar and central chiral elements, forms a trans-chelating rhodium complex in situ under the reaction conditions. Under its catalysis, α-methyl-substituted cyanoacetates and cyanoacetic acid Weinreb amides can add to vinyl ketones or acrolein with excellent yields and enantioselectivities (Scheme 29).
Another chiral ligand (Figure 3) was also developed for the rhodium-catalyzed addition of 43a to acrolein. The resultant enantioselectivity is up to 86%.

Figure 3

In 1996, Shibasaki reported that the heterobimetallic catalyst La–Na–BINOL complex 44 effectively catalyzed the asymmetric Michael additions of a series of cyclic and acyclic \( \beta \)-ketoesters to methyl vinyl ketone. The ee values range from 74–93% with satisfactory yields, as shown in Scheme 30. When the Michael acceptor is changed to an acrylate, the reaction becomes significantly slower with deteriorated yield and ee. A slightly modified nucleophile 45 gives improved results (Scheme 31).

Scheme 30

Scheme 31

The Pd-BINAP and Pd-tol-BINAP aqua complexes developed by Sodeoka prove to be very effective and general catalysts for asymmetric Michael reactions of 1,3-diketones and \( \beta \)-ketoesters to vinyl ketone acceptors. Scheme 32 shows some representative results. When \((E)\)3-penten-2-one is employed as the Michael acceptor, 8:1 diastereoselectivity is obtained with an exceptional 99% ee for the major product.

In the methodologies discussed above, almost all reactions employ vinyl ketones as Michael acceptors. Recently, Jacobsen extended the scope of the asymmetric Michael reaction to \( \alpha,\beta \)-unsaturated imides, in the presence of [(salen)Al]_2O 47 as catalyst. The reactions proceed smoothly, providing excellent yields and enantio- and diastereoselectivities (Scheme 33).

Scheme 32

Scheme 33

Jacobsen also used a similar catalyst, (salen)CrCl, to catalyze the enantioselective alkylation of \( \alpha \)-substituted five- to seven-membered cyclic ketones in excellent ee (Scheme 34).
### 3.1.2 Phase-Transfer Catalytic Alkylation and Michael Addition

Chiral crown ether complexes have been used as phase-transfer catalysts for asymmetric Michael reactions. An early example used 4 mol% KO(t-Bu)-chiral crown ether complex (49) as a catalyst to afford the Michael adduct with up to 99% ee (Scheme 35).\(^\text{50}\)

![Scheme 35](image)

In 1984, Merck scientists reported the first catalytic enantioselective alkylation mediated by a phase-transfer catalyst. N-[p-(Trifluoromethyl)benzyl]cinchonium bromide 50 was used as the phase-transfer reagent to catalyze the alkylation of substituted indanones 51. High yields and enantioselectivities were reported on different substrates (Scheme 36).\(^\text{51}\) However, the enantiomer of cinchonine is not available from a natural source so it is not trivial to synthesize the enantiomers of 52 and 53. Using a diastereomeric compound 54 (30 mol%), ent-53 can be synthesized in 78% ee and 99% yield.

The Michael addition of 51 catalyzed by the same phase transfer reagent 50 was reported to give good ee’s (up to 80%) with excellent yield (Scheme 37).\(^\text{52}\) In most asymmetric Michael reactions, two activating groups are attached to the acidic carbon. However, this example shows that a single carbonyl group can suffice.

![Scheme 37](image)

The binaphthyl-based chiral ammonium salt 55 is also used as a phase-transfer catalyst for the alkylation and Michael addition of β-ketoesters.\(^\text{53}\) Excellent ee’s are obtained for the alkylation of both cyclic and acyclic tert-butyl β-ketoesters (Scheme 38). Michael additions of tert-butyl β-ketoesters result in lower ee’s than the alkylation reactions, while use of the corresponding fluorenyl ester as substrate dramatically improves the enantioselectivity (Scheme 39).

![Scheme 38](image)

![Scheme 39](image)
3.1.3 Organocatalytic Michael Addition

The first catalytic enantioselective conjugate addition to alkynes was reported by Jörgensen in 2004, utilizing [DHQ]2PHAL as organocatalyst (Scheme 40).54 The reactions proceed in close to quantitative yields and good to high enantioselectivities, giving a mixture of E and Z enones in a 1:1 ratio. The product mixture can be transformed completely to the more stable E isomer in the same pot by addition of a catalytic amount of Bu3P or I2.

Scheme 40

Recently Takemoto reported a bifunctional thiourea catalyzed enantio- and diastereoselective Michael addition to nitroolefins.55 While the enantioselectivity was excellent in most cases, the diastereoselectivity ranged from poor to excellent. Scheme 41 shows an example with excellent enantio- and diastereoselectivities.

Scheme 41

3.1.4 Michael Addition with Hard Nucleophiles

The copper-catalyzed conjugate addition with alkylzinc or alkylaluminum reagents to α,β-unsaturated ketones is a well-known method for enantioselective alkylation. However, since the sterically hindered trisubstituted enones are not good partners for asymmetric conjugate additions, this approach has only very limited success in constructing quaternary stereocenters. The first successful example was reported by Hoveyda in 2002 as a tandem Michael addition–alkylation, as shown in Scheme 42.56 Impressively, 92% ee and greater than 20:1 diastereoselectivity was achieved using benzyl bromide as the trapping reagent.

Scheme 42

Recently, Hoveyda developed a copper-catalyzed conjugate addition to 2,2-disubstituted nitroolefines with a peptide-based ligand (Scheme 43),57 while Alexakis reported a similar conjugate addition to 3-substituted cyclohexenones in the presence of phosphoramidite ligands (Scheme 44).58

Scheme 43

Scheme 44

The desymmetrization of enone-diones via Rh-BINAP-catalyzed tandem conjugate-addition–aldol cyclization is a newly developed method to generate quaternary stereocenters. As shown in Scheme 45, two C–C bonds, one new ring and four adjacent stereogenic centers are formed with exclusive diastereoselectivity and high yield and enantioselectivity in a single transformation. Both cyclic and acyclic substrates are well-tolerated in the reaction.59
3.2 Allylation via Palladium $\pi$-Allyl Intermediate

Palladium-catalyzed asymmetric allylic alkylation reactions have emerged as one of the most powerful tools for the controlled introduction of various chemical bonds with high chemo-, regio- and stereoselectivities. The reaction involves a common palladium $\pi$-allyl intermediate as electrophile with a variety of nucleophiles. With suitable carbon nucleophiles and $\pi$-allyl precursors, the quaternary carbon stereocenters can be generated in both the nucleophile and the electrophile sides.

3.2.1 Quaternary Stereocenter on the Nucleophile Side

Chiral ferrocenylphosphine ligands $^{58a}$ and $^{58b}$ were developed in 1988 and 1992 and promoted good enantioselectivities in the palladium-catalyzed allylation of 1,3-diketones (Scheme 46). It is noteworthy that the products produced by the two catalytic systems have opposite absolute configurations, indicating that the interaction of the two ligands with the nucleophile may be fundamentally different.

The first asymmetric allylation of $\beta$-ketoesters with high ee was reported by Trost in 1997, using the chiral ligand $^{59}$. Impressively, 86–95% ee was reported for the allylation reaction of 2-carboalkoxy cyclohexanones and tetralone derivatives with simple or 2-substituted allyl acetates (Scheme 47). A concise synthesis of (–)-nitramine was realized from the allylation product (Scheme 48).

When reacting with 1,3-disubstituted allylation reagents, both enantio- and diastereoselectivities are controlled by the chiral ligand. Using a tetralone derivative as the nucleophile, excellent (88–98%) diastereoselectivity was achieved, with the enantioselectivity further improved to 96–99% (Scheme 49).

The same ligand system can also be used in the intramolecular allylation. As illustrated in Scheme 50, the bicyclo[2.2.2] system is formed with 4.6:1 dr and >99% ee of the major diastereomer. Addition of 10 mol% Eu(fod)$_3$ as an additive inverts the diastereoselectivity to 1:8, but the enantioselectivity of the major isomer decreases to 68%.
In addition to doubly activated nucleophiles, a series of simple ketones also proved suitable for the asymmetric allylation. Figure 4 lists some representative ketones along with the yields and enantioselectivities of their reactions with allyl acetate or allyl carbonate in the presence of the palladium catalysts and chiral ligands of Figure 5. Treatment of the enol allyl carbonates with chiral catalysts induces loss of carbon dioxide and C-allylation with high ee, both with the S,S-anthracenyl Trost ligand and the S-(t-Bu)-PHOX ligand (Scheme 51).68

This methodology has been used in the total syntheses of benzomorphans (Scheme 52), and hamigeran B (Scheme 53), and allocyathin B.71

BINAP (46a) is also employed as a chiral ligand for the palladium catalyzed allylation of various 1,3-diketones with cinnamyl acetate.72 The palladium catalyst of 46a facilitates the allylation of five-to-eight-membered cyclic
diketones as well as some acyclic diketones in good ee (77–89%) (Scheme 54).

While most chiral ligands used in the palladium-catalyzed allylation reactions are bidentate chelating ligands, a novel monodentate ligand, 64, was recently developed for this transformation. The active catalytic species is proposed to be complex 65. It successfully catalyzes the allylation of five-to-eight-membered cyclic β-ketoesters with a series of allyl acetates with good to high enantioselectivities, as shown in Scheme 55.

Scheme 54

An enantioselective allylation catalyzed by a Pd–Rh two-component catalyst system provides another solution to stereochemical control. While palladium activates the electrophile by forming the palladium β-allyl species, the rhodium species can coordinate to the cyano group of the cyanoester substrate to control the enantioselectivity, as in the asymmetric Michael additions. As shown in Scheme 56, while the standard TRAP ligand 42 gives 93% ee, its modified form 66 improves the enantioselectivity further to 99%. The primary source of chirality is proved to be the rhodium catalyst, because the same reaction in the absence of rhodium catalyst generates a racemic product in 91% yield. Interestingly, using only half an equivalent of chiral ligand 42 along with half an equivalent achiral ligand dppb is sufficient to provide the same 93% ee. A similar reaction can also be carried out with the corresponding α-cyano Weinreb amide with 87% ee.

3.2.2 Quaternary Stereocenter on the Electrophile Side

Enantioselective nucleophilic addition on the geminal disubstituted terminal of a palladium π-allyl species is much less developed because of the significant steric hindrance. The only example was reported by Trost, utilizing racemic isoprene monoxide as a substrate via a dynamic kinetic asymmetric transformation (DYKAT) process. Catalyzed by a Pd(0) catalyst and chiral ligand 59 or 67, a series of β-ketoesters can be selectively added to the sterically more hindered 2-position of isoprene monoxide to afford the chiral 1,2-adducts as major products in good yields and excellent enantioselectivities (Scheme 57). In addition to β-ketoesters, nitromethane can also serve as the pronucleophile to afford the 1,2-adduct in 51% yield and 97% ee.

Scheme 55  BSA = N,O-bis(trimethylsilyl)acetamide

Scheme 56  Pd–Rh catalyzed allylation reaction

Scheme 57

The above-described method serves as the key step in a concise asymmetric synthesis of the cyclopentyl core of viridenomycin, as shown in Scheme 58.
In addition, the Trost group reported a Pd(0)-catalyzed enantioselective Wagner–Meerwein ring-expansion reaction of 1-vinyl-1-propanols or 1-vinyl-1-butanol (Scheme 59). The palladium π-allyl intermediate promoted the hydroxyl-assisted ring expansion to produce the cyclobutanone or cyclopentanone products with quaternary centers.

3.3 Copper-Catalyzed S₈₂’ Allylation

Hoveyda reported a copper-catalyzed regio- and enantioselective allylic S₈₂’ substitution reaction to construct quaternary stereocenters. Two different peptide ligands, as well as a heterocyclic carbene ligand, could be used to afford high enantioselectivities, as shown in Scheme 61.79

3.4 Reactions with Carbonyl and Imine Electrophiles

3.4.1 Carbon-Acylation Reactions

In 2003, Fu reported the first catalytic enantioselective carbon-acylation reaction.80 A modified planar chiral derivative of DMAP, compound 69, proved to be the most effective catalyst. The cyclic silyl ketene acetal is acylated by carboxylic anhydride with high yields and enantioselectivities (up to 99%) (Scheme 62). In addition, an acyclic silyl ketene acetal, in a 2:1 mixture of olefin isomers, is also acylated with excellent enantiomeric excess (Scheme 63), indicating that both olefin geometric isomers are being converted efficiently into the same product enantiomer.

The intramolecular acylations of oxindoles and benzo furanones are also catalyzed with efficient stereocontrol (Scheme 64). The proposed mechanism is illustrated in Scheme 65.
3.4.2 Mannich Reactions

Recently Jörgensen and co-workers developed the first catalytic asymmetric direct Mannich reaction of β-ketoesters, catalyzed by Cu(OTf)₂/20 (Scheme 67). Two adjacent quaternary and tertiary centers are generated with very good enantio- and diastereoselectivities.83

Scheme 66

3.4.3 Addition of Allylmetal Reagents to Aldehydes

Although the enantioselective addition of allylmetal reagents to aldehydes is a well-developed general method for stereoselective C–C bond formation, its application to the construction of quaternary stereocenters is a recent achievement. Rationally designed 2,2¢-bispyrrolidine-based bisphosphoramidate 71 catalyzes the addition of unsymmetrical γ-disubstituted allylic trichlorosilanes to aromatic aldehydes. Excellent diastereo- and enantioselectivities are achieved with good yields (Scheme 68).84 This process is also used in the synthesis of serotonin antagonist LY426965 (Scheme 69).85 However, this allylation method has yet to achieve satisfactory results with aliphatic aldehydes.

Scheme 67

Scheme 68

Vedejs reported a different chiral DMAP derivative 70 to catalyze acyl transfer reactions similar to those shown in Scheme 64. Up to 92% ee is obtained with excellent yields. In addition, the rearrangement of furan enol carbonate is also achieved (Scheme 66). A 12:1 mixture of α- and γ-carboxylated isomers is isolated in good yield and enantioselectivity.82
3.4.4 Aldol Reactions

The scandium-catalyzed aldol reaction of cyclic silicon enolates to formaldehyde is also used to construct quaternary stereocenters asymmetrically (Scheme 70).86

Asymmetric Robinson annulation is one of the earliest-described methods to generate quaternary stereocenters enantioselectively. In 1974, Hajos and Parrish reported an extremely efficient aldol cyclization of a triketone substrate (Scheme 71).87 A quantitative yield and 93% ee are obtained for the alcoholic product, which can be further dehydrated to provide the Robinson annulation product with high yield. It is noteworthy that only 3 mol% of (S)-proline is used in this reaction as catalyst, in contrary to many other cases which employ stoichiometric or sub-stoichiometric amounts of chirality-inducing reagents.

4 Arylation and Vinylation Reactions

4.1 Intramolecular Heck Reactions

Palladium-catalyzed asymmetric Heck reactions, first developed in 1989,88 have become a powerful tool to construct quaternary stereocenters, and have been applied in the total syntheses of many natural products.89 Two general approaches are used in this area: 1) direct construction of the quaternary stereocenter by differentiating between enantiotopic faces of an olefin; and 2) differentiating two enantiotopic olefins in a molecule containing a prochiral quaternary center.

4.1.1 Direct Construction of Quaternary Stereocenters

The two major contributors in this area are Overman and Shibasaki. While Overman’s main focus is on the construction of heterocyclic systems, especially oxindoles, Shibasaki conducts research to generate carbocyclic compounds.

4.1.1.1 Construction of Oxindole and Other Heterocyclic Systems

Overman’s early research was conducted on the intramolecular Heck reactions of cyclic olefins, as shown in Scheme 72. Modest enantioselectivities (55–75%) are observed in most cases. Interestingly, the opposite enantiomers of the chiral products are obtained using the same enantiomer of BINAP ligand, but by adding different additives (Ag3PO4 or 1,2,2,6,6-pentamethylpiperidine). In some cases excellent enantioselectivities can be observed (Scheme 73), but are likely caused by an in situ kinetic resolution in the double-bond migration step.90,91

Additive: Ag3PO4: 74%, 79–81% ee (S)            8%  
PMP:      45%, 89–95% ee (R)          44%

Scheme 72

Additive: Ag3PO4: 74%, 79–81% ee (S)            8%  
PMP:      45%, 89–95% ee (R)          44%

Scheme 73
In the studies of asymmetric Heck cyclization of acyclic olefins, it was found that the Z geometry of the olefin is required to obtain high enantioselectivity. For example, in Scheme 74, excellent ee (95%) is obtained from the reaction of \((Z)\)-butenanilide, which can be further enriched to >99% by an efficient recrystallization of the aldehyde product.\(^{92}\) This method was used in the asymmetric synthesis of physostigmine and physovenine.\(^{92,93}\)

**Scheme 74** Heck cyclization of \((Z)\)-2-butenanilide and the asymmetric synthesis of physostigmine and physovenine. PMP = 1,2,2,6,6-pentamethylpiperidine; DMAC = \(N, N\)-dimethylacetamide.

Although BINAP is the most effective chiral ligand in many asymmetric Heck reactions, a modification is necessary in some cases to obtain improved results. For example, in the total synthesis of quadrigemine C and psycholeine (Scheme 75), a novel double Heck cyclization is achieved on the complicated polycyclic meso-substrate in the presence of tol-BINAP (46b) ligand. A reasonable 62% yield of the desired diastereomer is obtained with excellent 90% ee, along with 21% of meso-isomers.\(^{94}\)

The construction of quaternary stereocenters bearing two aryl substituents by Heck cyclization was further studied in order to investigate the ligand choice and determine reaction scope (Scheme 76).\(^{95}\) It was found that BINAP and Tol-BINAP give comparable results in most cases in terms of both yield and enantioselectivity. Good to excellent stereocontrol is achieved for a series of aromatic- and heteroaromatic-substituted substrates.

**4.1.1.2 Construction of Carbocyclic Systems**

In a similar way, Shibasaki uses all-carbon instead of heteroatom linkers to construct carbocyclic compounds with quaternary stereocenters. Again, the olefin geometry is important for the stereocontrol. While the \(Z\) olefin affords excellent enantioselectivity, the \(E\) olefin gives only modest ee with the opposite enantiomer enriched (Scheme 77). The total syntheses of \((-\)-eptazocine,\(^{96}\) halenaquinone and halenaquinol\(^{97}\) are realized with this methodology as the key steps, as shown in Scheme 78 and Scheme 79.

The regioselectivity in the asymmetric Heck cyclization was also studied. When both 5-exo and 6-exo cyclization pathways are possible, as in the substrate 73 in Scheme 80, only the 6-exo cyclization product 74 and its double-bond isomerization product 75 are formed. The reaction yield can be optimized to 62–71% with 95% ee.
The source of the regioselectivity is discussed in the paper. The resulting products can be used in the synthesis of various diterpenes.

A new chiral ligand BINAPAs (76) was synthesized and tested in an asymmetric Heck cyclization reaction, as shown in Scheme 81. It affords enantioselectivity comparable to that of BINAP, but superior reaction yield.

Chiral oxazoline ligand 77 also provides favorable results in the Heck cyclization of substituted N-formyltetrahydropyridine 78. While using BINAP as a chiral ligand results in low yield and enantioselectivity with serious double-bond scrambling, 77 successfully controls the double-bond migration and affords good enantioselectivity as well as yield (Scheme 82).

4.1.1.3 Other Transformations of the Carbopalladation Intermediate

With suitable substrates, the carbopalladation intermediate in Heck cyclizations can proceed through reaction pathways other than the normal β-hydride elimination. For example, when there is no β-hydride available, the intermediate can be trapped intramolecularly by another...
olefin to form a polyene cyclization product,\textsuperscript{101} or can react with an intermolecular hydride source to form the reduced product,\textsuperscript{102} as shown in Scheme 83 and Scheme 84.

When the Heck reaction of substrate 81 was studied, the unusual β-methoxide elimination product 83 was observed as the major product with excellent ee. Its occurrence is rationalized by the intermediacy of palladacycle 84, which preferentially undergoes β-methoxide elimination (Scheme 85). When the β-methoxide is not available, the corresponding palladacycle intermediate can be isolated as a stable compound.

4.1.2 Generation of Quaternary Stereocenters by Desymmetrization

Desymmetrization of a prochiral molecule containing quaternary centers by the asymmetric Heck reaction is another general method to construct quaternary stereocenters asymmetrically. A variety of decalin derivatives can be synthesized efficiently by this method (Scheme 86). Some results are summarized in Table 3.\textsuperscript{103–106}

<table>
<thead>
<tr>
<th>X</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>Ligand</th>
<th>Other conditions</th>
<th>Yield</th>
<th>ee</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CH\textsubscript{2}OTBS H</td>
<td>BINAP</td>
<td>PdCl\textsubscript{2}, Ag\textsubscript{2}PO\textsubscript{4}, CaCO\textsubscript{3}, NMP, 60 °C</td>
<td>67%</td>
<td>80%</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>CH\textsubscript{2}OTBS H</td>
<td>BINAS (85)</td>
<td>Pd\textsubscript{2}(dba)\textsubscript{3}, Ag\textsubscript{2}PO\textsubscript{4}, CaCO\textsubscript{3}, NMP, 60 °C</td>
<td>90%</td>
<td>82%</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>CH\textsubscript{2}OTBS CH\textsubscript{2}OAc</td>
<td>BINAP</td>
<td>PdCl\textsubscript{2}, Ag\textsubscript{2}PO\textsubscript{4}, CaCO\textsubscript{3}, NMP, 60 °C</td>
<td>67%</td>
<td>87%</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>OTf</td>
<td>CH\textsubscript{2}OPv H</td>
<td>BINAP</td>
<td>Pd(OAc)\textsubscript{2}, K\textsubscript{2}CO\textsubscript{3}, pinacol, DCE, 60 °C</td>
<td>78%</td>
<td>95%</td>
<td>106</td>
<td></td>
</tr>
</tbody>
</table>

Hydrindane derivatives can also be synthesized by a similar method from a slightly revised substrate, as shown in Scheme 89. Up to 86% ee is obtained.\textsuperscript{109} This reaction has been employed to synthesize a key intermediate of (−)-oppositol and (−)-prepinnaterpene.\textsuperscript{110}
The asymmetric Heck cyclization of substituted cyclopentadienes followed by anion capture further demonstrates the versatility of asymmetric Heck reactions. As illustrated in Scheme 90, the carbopalladation intermediate further tautomerizes to a palladium π-allyl species, which is regioselectively captured by various nucleophiles to form a product with three adjacent stereogenic centers, one of which is quaternary. It sets up the framework for the synthesis of (−)-capnellene.

4.2 α-Arylation and Vinaylation Reactions of Ketones and Lactones

The first catalytic asymmetric α-arylation of ketones to produce all-carbon quaternary stereocenters was reported by Buchwald in 1998. Pd-BINAP efficiently catalyzes the arylation of 2-methyl-α-tetralone in up to 88% ee. α'-Blocked α-alkyl-substituted cyclopentanones are even superior substrates, giving the arylation products in good yields and high enantioselectivities, in the presence of either BINAP or modified ligand 86, which provides a more reactive catalyst system (Scheme 91). The vinlylation on similar substrates is also successfully developed, in the presence of chiral ligand 87 (Scheme 92).
Recently, Jörgensen reported an α-arylation of α-ethoxy-carbonyl-substituted cyclic ketones and lactams via an S_NAr mechanism. The best result is illustrated in Scheme 94.

**4.3 Desymmetrizing Suzuki Couplings**

An enantioselective Suzuki coupling to generate quaternary stereocenters was recently reported by Willis et al. One of the two enantiotopic triflate groups in a geminal-substituted cyclopentadiene was selectively inserted by the chiral palladium catalyst and coupled with aryl borate to afford the chiral product with a quaternary stereocenter (Scheme 95). Up to 86% ee was obtained with modest but still synthetically useful yields.

**5 Metal-Catalyzed Diene and Enyne Cyclizations**

**5.1 Diene Cyclizations**

The zirconium-catalyzed asymmetric diene cyclization was investigated with the zirconium complex 89 as a catalyst in the presence of stoichiometric Grignard reagent. Excellent enantioselectivities are achieved in many cases, but the reaction yields and diastereoselectivities are often modest or poor. Depending on the substrate structure and reaction conditions, different products can be obtained, as illustrated in Scheme 96.
5.2 Enyne Cyclizations

Pd(II)-catalyzed enyne cyclizations are reported to produce the chiral five-membered ring products with extremely high yields and enantioselectivities in the presence of BINAP and modified BINAP ligands shown in Figure 6. The results for a representative 1,6-enyne substrate are summarized in Table 4. The cyclizations of substrates with nitrogen in the tether are also developed successfully. Two examples are given in Scheme 98 and Scheme 99, the former also illustrating the cyclization of a 1,7-enyne.

**Table 4** Pd(II)-Catalyzed Asymmetric Carbocyclization of a 1,6-Enyne Substrate

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Pd source (5%)</th>
<th>Other conditions</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47b</td>
<td>Pd(OOCF3)2</td>
<td>C6D6, 100 °C</td>
<td>&gt;99</td>
<td>94</td>
</tr>
<tr>
<td>90</td>
<td>Pd(OOCF3)2</td>
<td>C6D6, 100 °C</td>
<td>&gt;99</td>
<td>95</td>
</tr>
<tr>
<td>92</td>
<td>Pd(OOCF3)2</td>
<td>C6D6, 100 °C</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>91</td>
<td>[MeCN]Pd(BF4)2</td>
<td>DMSO, 80 °C</td>
<td>&gt;99</td>
<td>94</td>
</tr>
<tr>
<td>93</td>
<td>[MeCN]Pd(BF4)2</td>
<td>DMSO, 80 °C</td>
<td>&gt;99</td>
<td>96</td>
</tr>
</tbody>
</table>

**Scheme 98**

**Scheme 99**

6 Intramolecular Hydroacylations

6.1 Intramolecular Stetter Reactions

Very recently, Rovis and Kerr extended the scope of asymmetric Stetter reactions to the construction of quaternary stereocenters. Chiral carbene precursors 95 and 96 are employed as pre-catalyst to afford excellent enantioselectivities and good to excellent yields. Both α,β-unsaturated ketones and esters can serve as the intramolecular acceptors, as shown in Scheme 100 and Scheme 101.

**Scheme 100**

**Scheme 101**

6.2 Rhodium-Catalyzed Desymmetrization

Although the rhodium-catalyzed asymmetric intramolecular hydroacylation of olefins has been actively studied during the last two decades, using this method to introduce quaternary stereocenters is only accomplished by desymmetrization of prochiral 1,4-dienes. The cyclization is catalyzed by cationic Rh(BINAP)ClO4 species to afford the 3,3,4-trisubstituted cyclopentanones in high trans selectivity and excellent enantioselectivity, as shown in Scheme 102. Spiro[4.4]nonane systems are also syn-

thesized by two sequential intramolecular hydroacylations in the same manner.\textsuperscript{126}

7 Allylations Mediated by Tertiary Radicals or Cations

The first radical-mediated enantioselective formation of quaternary stereocenters was reported in 1997.\textsuperscript{127} The radical intermediates were generated from substituted racemic α-iodolactones in the presence of the chiral Lewis acid complex \textit{Me}_3\textit{Al}/\textit{97} and trapped by allylstannane reagent (Scheme 103). Addition of diethyl ether as an additive significantly increased the enantioselectivity. The amount of chiral Lewis acid can be decreased from a stoichiometric amount to 0.2 equivalent without significantly decreasing the yield and enantioselectivity.

A novel enantioselective atom-transfer radical cyclization was achieved in the presence of a sub-stoichiometric amount of Mg–bisoxazoline 20 complex (Scheme 105). An excellent 92\% ee is obtained but the catalyst turnover number is only 2.\textsuperscript{129}

8 Rhodium-Catalyzed C–H Insertions

In 1995, Doyle reported an enantioselective synthesis of β-lactams via intramolecular C–H insertion. When using diazoacetamide of \textit{cis}-2,6-dimethylpiperidine as substrate, the catalyst \textit{Rh}_2(4\textit{S}-\textit{MEOX})_4 (31) affords the desired β-lactam in 86\% ee and 69\% yield (Scheme 106).\textsuperscript{130}

Hashimoto investigated the enantiotopic selective aromatic C–H insertion using several chiral dirhodium(II) tetraakis(carboxylate) catalysts. As shown in Scheme 107 and Table 5, while 99 affords good results for only one substrate,\textsuperscript{131} the modified complex 100 is a much more general catalyst.\textsuperscript{132} Complex 100 also catalyzed a double insertion on benzylic hydrogens to form a spirocyclic product in 80\% ee (Scheme 108).\textsuperscript{133}

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>64</td>
<td>77</td>
</tr>
<tr>
<td>Et</td>
<td>86</td>
<td>95</td>
</tr>
<tr>
<td>\textit{n}-Pr</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>allyl</td>
<td>41</td>
<td>55</td>
</tr>
</tbody>
</table>

Table 5 Enantiotopic Selective Aromatic C–H Insertion (Scheme 107) Catalyzed by Different Chiral Rh(II) Complexes
Recently, the construction of a quaternary stereocenter by the reaction between a vinyldiazoacetate and cycloalkenes was described by Davies and Jin. As shown in Scheme 109, product \(101\), bearing a quaternary stereocenter, was prepared in synthetically useful yield with excellent enantio- and diastereoselectivities. Considering the reaction mechanism, although a tandem allylic C–H activation (to form \(102\)) followed by a Cope rearrangement from \(102\) to \(101\) is an obvious interpretation, there is no clear thermodynamic driving force for this conversion. In fact, compound \(101\) is quantitatively transformed to \(102\) at 110 °C with complete chirality transfer. Therefore, the reaction mechanism still needs more investigation.

### 9 Other Desymmetrization Methods

Several other desymmetrization methods for the enantioselective construction of all-carbon quaternary stereocenters are briefly discussed here. Completeness is not claimed since, in principle, any catalytic asymmetric reaction could be used in this approach.

The enantioselective iodocyclization products of 4-alkenylmalonate derivatives cyclize in situ with one of the two ester groups to form the bicyclic products with excellent enantioselectivities (Scheme 110). The titanium catalyst \(103\) is usually used. Impressively, when enantiotopic dienes are present in the molecules, both enantiofacial and enantiotopic selectivities are achieved, adding one more stereogenic center into the product molecules. The new chiral center can be located at any one of the three possible positions, depending on the substrate substitution patterns (Scheme 111).

---

**Scheme 107**

**Scheme 108**

**Scheme 109**

**Scheme 110**

**Scheme 111**

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Enantioselective opening of meso-epoxides is one of the most widely studied desymmetrization reactions. When the substrate is properly designed, an intramolecular opening of a prochiral epoxide can introduce a quaternary stereocenter enantioselectively, as shown in Scheme 112.136

**Scheme 112**

A palladium-catalyzed enantioselective C–C bond cleavage of a 1,3,3-trisubstituted cyclobutanol affords the ring-opened product in high yield and ee, as shown in Scheme 113. However, other substrates with different substituents give significantly lower enantioselectivities.137

**Scheme 113**

10 Summary and Outlook

The catalytic enantioselective construction of all-carbon quaternary stereocenters has received more attention over the last two decades and several powerful methods have been developed. However, despite the recent advances in this field, many problems remain unsolved, such as high catalyst loading, limited reaction scope, and inaccessibility to many compounds with certain substitution patterns. For example, the asymmetric Diels–Alder reaction with 1,1-disubstituted dienes and Michael additions to β-disubstituted enones are still intimidating challenges to synthetic chemists. This is a field full of challenges and opportunities for further discoveries.

References
