Catalytic asymmetric synthesis of all-carbon quaternary stereocenters

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Only a few catalytic asymmetric C–C bond-forming reactions have been shown to be useful for constructing all-carbon quaternary stereocenters. This Perspective examines the current state of such methods.

Carbon atoms bonded to four carbon substituents (all-carbon quaternary centers) pose a particular challenge for synthesis because creation of such centers is complicated by steric repulsion between the carbon substituents. When the four substituents differ, quaternary stereocenters become a singular challenge for achieving efficient asymmetric syntheses of chiral organic molecules (1–4). The invention of catalytic methods for asymmetric synthesis is one of the foremost recent achievements of chemistry (5), with the 2001 Nobel Prize in Chemistry recognizing William S. Knowles, Ryoji Noyori, and K. Barry Sharpless for their pioneering development of catalytic asymmetric hydrogenation and oxidation reactions. At present, many broadly useful methods for catalytic asymmetric oxidation and reduction exist; however, far fewer catalytic asymmetric methods for forming C–C bonds have been invented to date (5). As disclosures in this special feature will attest, this latter area of catalytic asymmetric synthesis is a current focus of intense investigation worldwide.

At present only a few catalytic asymmetric C–C bond-forming reactions have been shown to be useful for constructing quaternary carbons, undoubtedly reflecting the additional steric challenge involved in forming all-carbon quaternary centers. This Perspective will examine the current state of such methods. The focus will be on reactions for which some generality has been documented, and several examples exist of reactions that proceed with enantioselective meric selecivities of at least 9:1 [enantiomeric excesses (ees) >80%].

The asymmetric Diels–Alder reaction provides two approaches for forming quaternary stereocenters contained within the cyclohexene framework (Scheme 1). In reactions of type I, electron-rich dienes condense with electron-poor prochiral dienophiles containing a 1,1-disubstituted or trisubstituted double bond to generate a quaternary carbon. The diene is activated, and one prochiral face selected, by complexation of the electron-withdrawing group (EWG; EDG indicates electron-donating group) with a Lewis acid (L. A.) possessing chiral and nonracemic ligands.

Numerous chiral Lewis acids have been used to catalyze Diels–Alder reactions (6–9). Although many reactions of this type employ cyclopentadiene as the diene and 2-alkyl acrolein derivatives as the dienophile, several examples involve more intricate dienes or dienophiles. For example, a salen–Cr-catalyzed type I Diels–Alder reaction of siloxydiene carbamate 1 and 2-ethylpropenal (2) to form 3 was the key step in a recent total synthesis of (+)-aspidospermidine (Scheme 2; TBS, tert-butyldimethylsilyl) (10). Other examples of noteworthy enantio- and regioselectivity are found in oxazaborolidine-catalyzed cycloadditions of acyclic dienes with substituted quinones, such as the synthesis of dienedione 5 by using the Lewis acid catalyst 4 (ref. 11; Tf, trifluoromethanesulfonyl). Sm and Gd complexes of chiral pyridyl-bis(oxazoline) ligands have also been used with much success in asymmetric Diels–Alder reactions employing 2-acylquinones (12).

In a less developed strategy, the geminal substituents are incorporated in the diene rather than the dienophile (type II). To our knowledge, this strategy has been implemented only in inverse electron-demand Diels–Alder reactions. For example, high enantioselectivity has been reported for the cycloaddition of 3-carboxymethyl-2-pyrene with thiophene-2,5-diyl-3,4-dihydroxy-1,1′-binaphthyl (BINOL)–Yb complex (13). This catalytic approach to...
all-carbon quaternary stereocenters remains largely undeveloped.

Combination of Chiral Carbon Nucleophiles with Carbon Electrophiles

The C—C bond-forming step of three approaches for forming quaternary stereocenters by the union of catalytically generated chiral car- bon nucleophiles with carbon electrophiles are depicted in Scheme 3. In reactions of type I, a carbon with three disparate carbon sub- stituents is activated for bond formation by conversion to a carbanion or organo- metallic intermediate; diastereoselection in the catalytic asymmetric step arises when the counter ions, or ligands on the metal, are chiral and nonracemic. As summarized in Scheme 3, various metals and counter-ions have been used in these reactions.

Many useful catalytic asymmetric phase-transfer alkylation reactions have been developed where the chiral counter-cation \((Y^+)^+\) is a quaternary ammonium salt \((14, 15)\). The synthesis of 6 is exemplary (Scheme 4) \((16)\). In most transformations of this type disclosed to date, two activating groups flank the acidic carbon; however, this example shows that a single carbonyl group can suffice. The chiral counter- cation also can be a complex containing an electropositive metal, although useful enantioselection in forming quaternary stereocenters has been achieved only rarely \((17)\). High enantioselectivity was reported recently for the reaction of cyanooacetates with \(\alpha,\beta\)-unsaturated imi- des catalyzed by salen—Al complex 7, as illustrated in the synthesis of indole derivative 8 \((18)\). Palladium- and nickel- catalyzed arylation/vinylation reactions of carbonyl compounds and related species have been shown to have fairly broad scope \((19, 20)\). These processes have now been documented for anions generated from several carbon acids: lactones \[e.g., synthetic of 9; dba, diben- zylideneacetone; BINA P, 2,2’-bis(diphe- nylphosphino)-1,1’-binaphthyl; HMDS, hexamethyldisilazane], ketones, and ox- indoles \((19)\).

Much less developed is the related strategy in which the electrophile is prochiral (Scheme 3, type II). For example, notably absent are useful proce- dures involving conjugate addition to \(\alpha,\beta\)-unsaturated carbonyl compounds (or related electrophiles) in which the \(\beta\) carbon is disubstituted \((21)\). Copper- catalyzed \(S_{\text{N}}^2\) displacement of pro- chiral allylic phosphates with achiral or- ganozinc nucleophiles is one example of a useful type II process \((22)\). The sto-ichiometric reaction of enamines derived from chiral amines with carbon electrophiles has notable utility for preparing all-carbon quaternary centers \((\text{cf. ref. 23})\). Nonetheless, few catalytic reactions of type III have been reported \((24)\) and none of the related reaction in which \(R^1\) and \(R^2\) are hydrogen and the carbon electrophile is prochiral.

Reactions of Chiral Allymetal Electrophiles with Carbon Nucleophiles

Two approaches for generating all-car- bon quaternary stereocenters by reaction of catalytically generated allylmetal complexes with carbon nucleophiles are shown in Scheme 5 \((25-27)\). In reactions of type I, a carbon nucleophile containing three diversified carbon substituents is alkylated by an allymetal intermediate in which the ancillary ligands \((L)\) on the metal \((M)\) are chiral and nonrace- mic. Many type I reactions have been developed wherein the ligands are chiral bidentate phosphines; an example is syn- thesis of tetralin 10 catalyzed by the Pd complex of diphosphine 11 (Scheme 6; LDA, lithium diisopropylamide; rt, room temperature) \((28)\). Although most exam- ples of reactions of this type employ nu- cleophiles having two electron-withdraw- ing groups attached to the acidic carbon, the synthesis of 10 demonstrates that one carbonyl group can be suffi- cient. This example also illustrates a cur- rent limitation in alkylations of this type: the carbon nucleophile must pos- sess only a single acidic \(\alpha\)-hydrogen to prevent reaction at other acidic sites.

In reactions of type II, diastereomeric chiral and nonracemic allymetal inter- mediates containing two different sub- stituents at one allyl terminus are gener- ated from either an achiral or a racemic chiral allylic precursor. Although two diastereomeric allymetal intermediates can be formed, enantioselection is achieved by preferential reaction of one of these intermediates at its dissubstituted terminus. In an example of dy- namic kinetic resolution of a racemic precursor, high enantioselection is ob- tained in joining isoprene oxide \((12)\) with nitromethane to form nitroalkene 13 by using diphosphine 14 (Scheme 6) \((29)\). Other nucleophiles \((Nu)\) such as carbonyl compounds containing two ac- tivating groups have been used in similar reactions; however, little is known regarding the types of allylic leaving groups \((LG)\) that can be used. Type II reactions of allyl metal intermediates...
have received less attention than type I reactions for the synthesis of all-carbon quaternary stereocenters.

Intramolecular Heck Reactions

Intramolecular Pd(0)-catalyzed coupling of an aryl or vinyl halide [or triflate (Tf)] with a tethered alkene containing an additional substituent on the proximal alkene terminus is a broadly applicable method for simultaneously forming rings and all-carbon quaternary stereocenters (Scheme 7). Since the first reports of the catalytic asymmetric variant of this chemistry in 1989 (30, 31), this method has been used widely for the asymmetric construction of quaternary stereocenters. Numerous examples of fashioning five- and six-membered rings in this way have been documented (32–34). No other method for catalytic asymmetric synthesis of all-carbon quaternary stereocenters has been verified with as broad a range of substrates.

Several illustrative applications of the use of catalytic asymmetric intramolecular Heck reactions in the synthesis of complex polycyclic molecules containing all-carbon quaternary stereocenters are shown in Scheme 8; PMP, 1,2,2,6,6-pentamethylpiperidine; Bn, benzyl. The preparation of hydrophenanthrene illustrates an asymmetric 6-exo Heck cyclization (35). The use of sequenced 6-exo and 6-endo Heck cyclizations is exemplified in the formation of oxapentacyclic ketone from tricyclic triflate (36). In this example, catalyst control in the initial 6-exo cyclization delivers in moderate enantiopurity. Two additional steps convert to the anthraquinone antibiotic xestoquinone (36). The first total synthesis of the dodecacyclic polyindoline alkaloid quadrigemine C (21) was realized in two additional steps from Heck product 20 (37). The use of catalytic asymmetric Heck cyclizations to desymmetrize a structurally elaborate meso intermediate is illustrated by double Heck cyclization of octacyclic difluoride 19 to provide the C1-symmetric bisoxindole 20 in 62% yield and 90% ee (37). This transformation highlights the structural complexity that can be tolerated, as cyclization substrate possesses both secondary and tertiary amine functionalities as well as a labile σ-bond linking its contiguous benzylic quaternary centers. However, the presence of the amines is likely responsible for the need for high catalyst loadings to achieve useful cyclization rates. The first combination of Chiral Carbon Electrophiles with Carbon Nucleophiles

Asymmetric nucleophilic catalysts can be used to generate chiral electrophiles. The union of these with prochiral carbon nucleophiles represents a promising catalytic approach to the synthesis of all-carbon quaternary stereocenters (Scheme 9). In reactions of this type, a chiral electrophile is generated and then alkylated in a C–C bond-forming event with a nucleophile containing three disparate carbon substituents to form quaternary carbon stereocenters as exemplified in 24.

Although many different types of catalytically generated chiral electrophiles are possible, acyl electrophiles have received the most attention to date (X = O, Scheme 9). Several catalytic acyl-transfer reactions have been developed wherein the chiral nucleophilic catalyst is a nonracemic amine nucleophile (38, 39). For example, oxindole 27 was formed in high enantiopurity from 2-acyloxindole precursor 25 by using planar chiral 4-aminopyridine catalyst 26 by using planar chiral 4-aminopyridine catalyst 26 (40). The related reaction of silylketene acetal 28 with acetic anhydride, catalyzed by 26, is reported to give β-ketoester 29 in good yield and enantiopurity (41). The use of chiral phosphines as nucleophilic catalysts in similar reactions to generate all-carbon quaternary stereocenters has been less successful to date (42, 43).

Cyclopropanations

Cyclopropanation of alkenes offers two distinct approaches for the synthesis of all-carbon quaternary stereocenters (Scheme 10) (44). In one approach...
of cyclopropyl carbinol from diiodomethane (45). The synthesis of allylic substituents and carbenoids derived with alkenes containing Lewis basic al- in type I processes has been achieved using successfully. High enantioselectivity sessing chiral nonracemic ligands coordi- metal carbenoid (Cu, Rh, or Co) pos- processes is achieved by employing a prochiral alkene (type II). Diastereo- different carbon substituents to any addition of a carbenoid containing two all-carbon stereocenters can arise from ent geminal substituents. Alternatively, prochiral alkene containing two differ- type II processes, diazo compounds are observed in intra- enantioselectivity and diastereoselectivity of these types, an alkene that is either 1,1-disubstituted or trisubstituted under- of these methods, Diels–Alder reactions, coupling reactions of allylmetal intermediates, and intramo- leukene Heck reactions, the demonstrated scope is quite limited. For example, practical catalytic asymmetric Diels–Alder reactions of α,β-unsaturated ketones, esters, or nitriles have yet to be developed. Similarly, of the three de- scribed methods for forming all-carbon quaternary stereocenters from catalytically generated chiral nucleophiles, only the type 1 process (Scheme 3) has been developed extensively. Likewise, cata- lytic asymmetric formation of quaternary stereocenters by using allylmetal electrophiles is currently documented only for η3-allylpalladium species. Even for catalytic asymmetric Heck reactions, which have shown the broadest scope to date, structural features required to achieve high ee are poorly understood.

There are bountiful opportunities for further discoveries. Large gaps in the known methods, some of which are noted in this brief survey, remain to be filled. In addition, many catalytic asymmetric C–C bond-forming reactions have yet to be used to forge quaternary
carbons. For example, practical examples of forming quaternary carbons by catalytic asymmetric hydrocarbonylation, hydrocyanation, or hydrovinylition of carbon-carbon double bonds have yet to be described. Likewise, Heck and other carbometallation reactions have not yet been engineered to form all-carbon quaternary stereocenters in bimolecular reactions. Moreover, as only a few metals other than palladium have been used in catalytic asymmetric reactions to form all-carbon stereocenters, the reactivity of many additional metals remains to be exploited. Also certain to play a role in future developments in this area are organocatalytic reactions in which catalytically generated chiral nracemic iminium ion and enamine intermediates are used to construct stereogenic quaternary carbons (38, 64).