Abstracts

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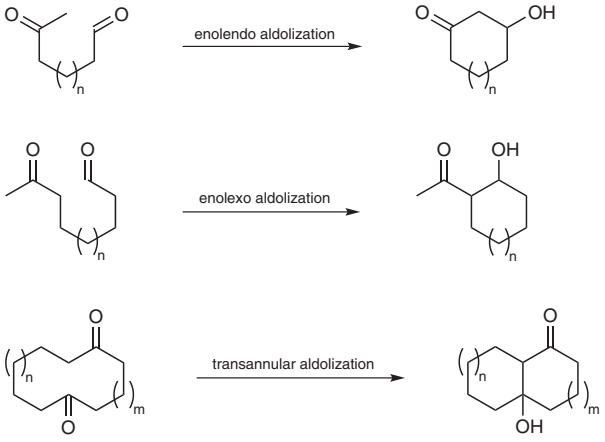
1.1.1 Enamine Catalysis of Intramolecular Aldol Reactions

X.-W. Wang, Y. Wang, and J. Jia

In this review, organocatalytic intramolecular aldol reactions are classified into three different types according to their enolization mode: enolendo aldolizations, enolexo aldolizations, and transannular aldolizations. The enantioselective enamine catalysis of these reactions using chiral, enantiomerically pure primary and secondary amines as catalysts is discussed. Following the logic of this volume, the chapter focuses on the more synthetically useful approaches.



Keywords: intramolecular · aldol · enamine · catalysis · enolendo · enolexo · transannular

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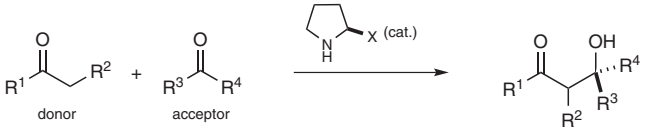
1.1.2 Enamine Catalysis of Intermolecular Aldol Reactions

S. M. Yliniemelä-Sipari, A. Piisola, and P. M. Pihko

This review discusses enamine catalysis of intermolecular aldol reactions. The organocatalytic approach to these carbon—carbon bond-forming reactions between enolizable carbonyl compounds and aldehydes or ketones is discussed from a practical standpoint, and is illustrated with examples from the literature. The scope and the current limitations of the protocols are presented. The origins of the limitations, based on chemoselectivity problems related to the activation of starting materials, are also described.



Keywords: intermolecular aldol reaction · asymmetric synthesis · enamine catalysis · organocatalysis

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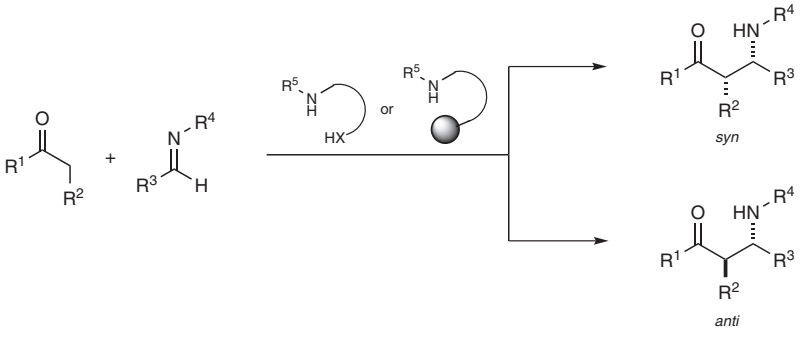
1.1.3 Enamine Catalysis of Mannich Reactions

M. Benohoud and Y. Hayashi

Chiral primary and secondary amines catalyze the Mannich reaction of imines and carbonyl compounds to diastereoselectively generate β-amino carbonyl compounds with excellent enantioselectivity. The design of amine catalysts and the judicious choice of the substituent on the nitrogen of the imine allows the selective formation of the *syn*- or *anti*-Mannich products. The imine component can be preformed or generated in situ from an amine and an aldehyde or by desulfonylation of α-amido sulfones. Imines can bear aromatic, carbamate, or sulfonate N-substituents. Since the initial development of amine-catalyzed Mannich reactions, the scope of carbonyl compounds has been extended from simple acetone to cyclic ketones, ketones substituted with heteroatoms, and aldehydes such as acetaldehyde, which is known to be difficult to handle because of its high reactivity. Mannich adducts formed in these asymmetric organocatalyzed processes are generally obtained with good yields and high diastereo- and enantioselectivities. There are several noteworthy features of this reaction: (1) the reactions are operationally simple; (2) water and air do not need to be strictly excluded; (3) amine catalysts are available, or can be prepared, in both enantiomeric forms; (4) in several procedures the catalyst loading can be reduced to <5 mol%; and (5) high enantioselectivities can be obtained. The asymmetric amine-catalyzed Mannich reaction is a practical and useful method for the synthesis of nitrogen-containing chiral molecules.



Keywords: asymmetric Mannich reaction · chiral amines · enamines · imines · β-amino carbonyls

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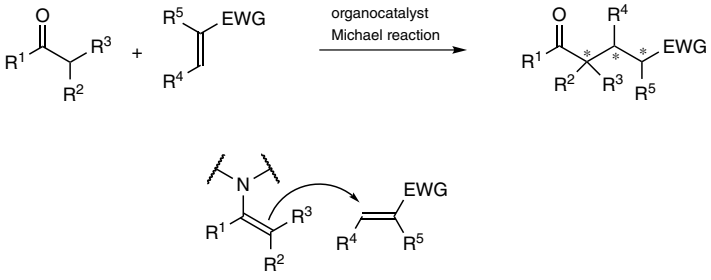
1.1.4 Enamine Catalysis of Michael Reactions

N. Mase

This chapter addresses significant achievements in asymmetric synthesis focusing on enamine-based organocatalytic direct Michael reactions. The description of methods for Michael reactions is subdivided on the basis of various classes of intramolecular, intermolecular, and domino reactions. In addition, these are further subdivided on the basis of donors (nucleophiles) and acceptors (electrophiles): ketones and aldehydes as the donors and α,β-unsaturated carbonyl compounds, nitroalkenes, vinyl sulfones, and vinylphosphonates as the acceptors.



Keywords: conjugate addition reactions · domino reactions · enamine catalysis · enamines · iminium catalysis · intermolecular reactions · intramolecular reactions · Michael acceptors · Michael addition · Michael donors · one-pot process · organocatalysis · reductive Michael reactions

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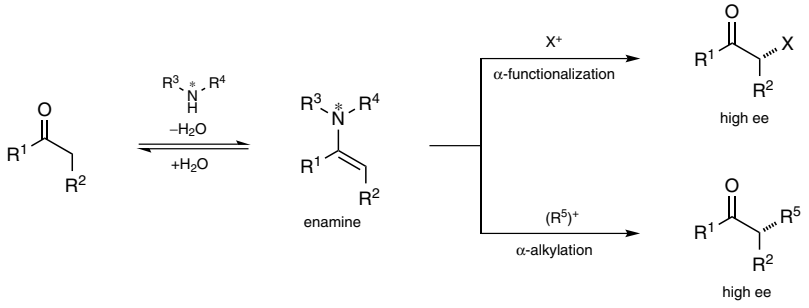
1.1.5 Enamine Catalysis of α-Functionalizations and Alkylations

S. Mukherjee

Since the turn of this century, asymmetric enamine catalysis has given rise to a plethora of synthetically useful transformations. This section describes some of the most efficient and practical methods for enamine catalyzed asymmetric α-functionalizations and alkylations. The first part of this review deals with the introduction of different heteroatom functionalities (e.g., nitrogen, oxygen, halogens, sulfur, or selenium) at the α-position of aldehydes and ketones, whereas methods for the formation of C—C bonds (e.g., alkylation, allylation, or arylation) are described in the latter part.



Keywords: alkylation · allylation · arylation · asymmetric catalysis · enamine · α-functionalization · organocatalysis

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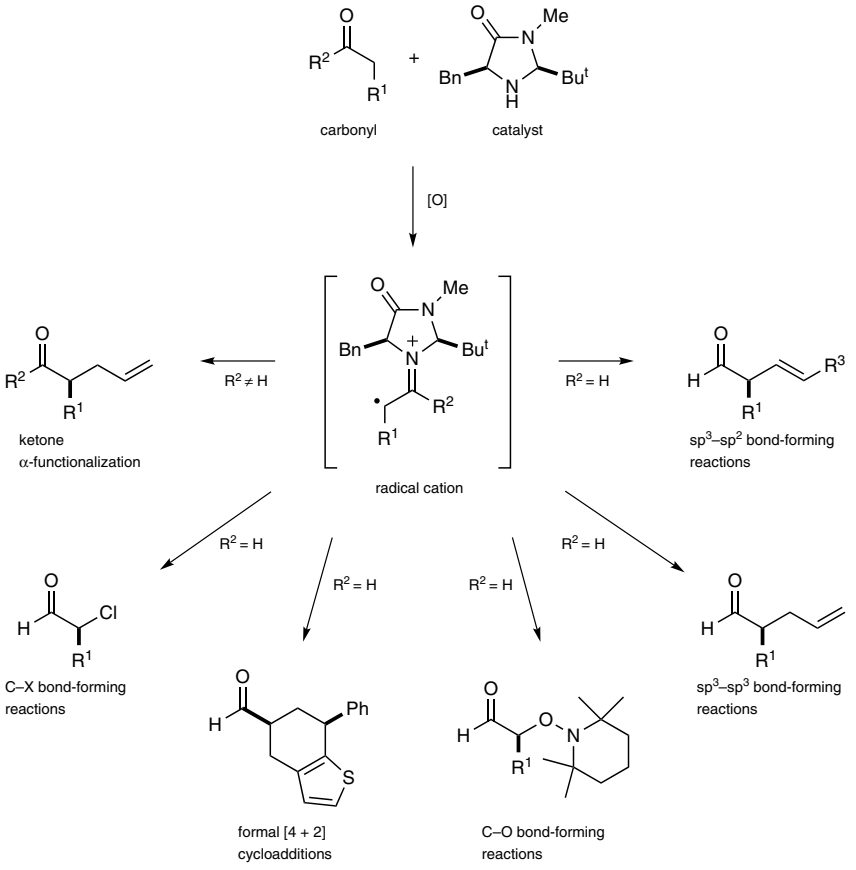
1.1.6 SOMO and Radical Chemistry in Organocatalysis

D. W. C. MacMillan and T. D. Beeson

This chapter describes the design and development of singly occupied molecular orbital (SOMO) catalysis. This new mode of organocatalytic activation is founded upon the mechanistic hypothesis that the one-electron oxidation of a transient enamine intermediate, derived from a carbonyl compound and a chiral amine catalyst, will render a 3π-electron SOMO radical cation that is subject to enantiofacial discrimination. This chiral SOMO-activated species can readily combine with SOMO nucleophiles in unique asymmetric bond constructions to enable previously unknown transformations. Many SOMO nucleophiles have been shown to participate with radical cations and, correspondingly, a diverse range

of chemistry, such as carbon—carbon and carbon—heteroatom bond formations, formal [4+2] cycloadditions, and polyene cyclizations, has been implemented.



Keywords: SOMO · nucleophile · radical cation · iminium · enamine · aldehydes · ketones · carbon—carbon bond formation · carbon—heteroatom bond formation · cycloaddition · cyclization

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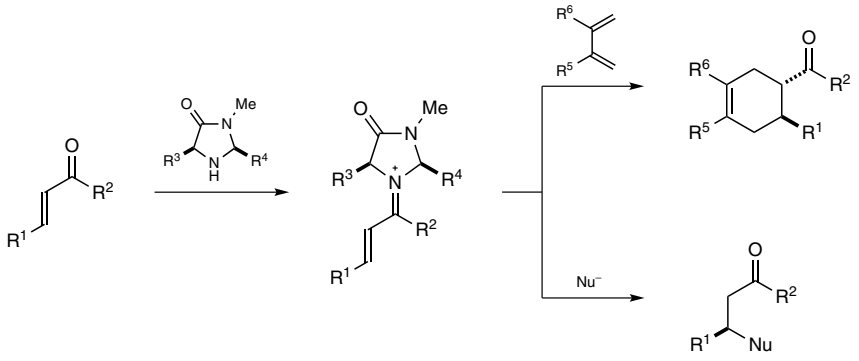
1.1.7 Iminium Catalysis

D. W. C. MacMillan and A. J. B. Watson

Chiral amine catalysts condense with α,β-unsaturated carbonyl compounds to generate transient chiral iminium ions. These activated intermediates are then able to participate in enantioselective carbon—carbon and carbon—heteroatom bond formation with a broad range of nucleophilic partners.



Keywords: aldehydes · amines · asymmetric catalysis · asymmetric synthesis · chiral compounds · chirality · conjugate addition · diastereoselectivity · enals · enamines · enones · iminium salts · Michael addition · nucleophilic addition

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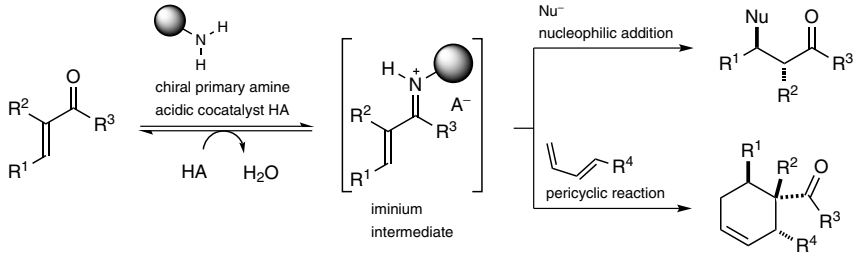
1.1.8 Iminium Catalysis with Primary Amines

Y. Liu and P. Melchiorre

Advances in catalytic, enantioselective additions of a variety of nucleophiles to enals and enones under the iminium activation of chiral primary amines are described. Primary amine catalysis offers the unique possibility of chemical reactions between sterically demanding partners, thus overcoming the inherent difficulties of chiral secondary amines in generating congested covalent intermediates. This has allowed for the expansion of iminium catalysis to include difficult carbonyl substrates such as α,β-unsaturated ketones and α-branched α,β-unsaturated aldehydes. The selected methods represent the state of the art in the rapidly evolving area of iminium catalysis with primary amines, which provides a suitable synthetic tool to enantioselectively functionalize hindered unsaturated carbonyl compounds at their α- and β-positions.



R^2 = alkyl, R^3 = H; α-branched aldehydes
R^2 = H, R^3 = alkyl; α,β-unsaturated ketones

Keywords: aldehydes · amines · asymmetric catalysis · asymmetric synthesis · conjugate addition · cycloaddition · ketones · iminium catalysis · organocatalysis

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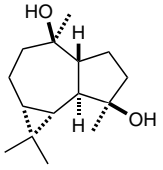
1.1.9 Applications of Aminocatalysis in Target-Oriented Synthesis

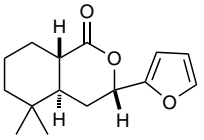
M. Christmann

This chapter covers applications of aminocatalysis to the synthesis of natural products and active pharmaceutical ingredients. The activation modes discussed include enamine activation, iminium activation, and dienamine activation. Following the organocatalytic

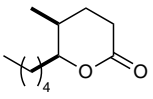
key step, a detailed description of the completion of the individual syntheses is provided. Finally, an outlook on future prospects concludes this section.



aromadendranediol



ricciocarpin A



cis-aerangis lactone

Keywords: natural products · total synthesis · Mannich reaction · Aldol reaction · Michael reaction · prolines · enamines · Diels–Alder reaction · iminium salts · carbonyl compounds · catalysts · drugs

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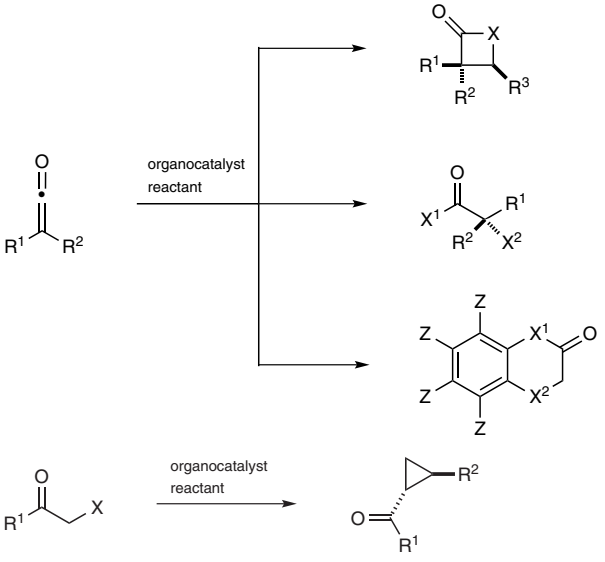
1.1.10 Tertiary Amine and Phosphine-Catalyzed Reactions of Ketenes and α-Halo Ketones

S. Chen, E. C. Salo, and N. J. Kerrigan

Although the chemistry of ketenes has been well explored over the last 100 years, it has only been since the late 1990s that a number of catalytic asymmetric methodologies for accessing important privileged structural motifs have been discovered. For many years cinchona alkaloid systems have been the most widely used for the development of reactions involving ketenes, but more recently ferrocenylamine, N-heterocyclic carbene, and phosphine systems have been introduced, and these have provided many new opportunities for the development of reactions. The above-mentioned catalysts promote enantioselective reactions that provide access to such valued molecules as four-membered rings (β-lactones, β-lactams, as well as oxa- and aza-β-lactams), six-membered rings (δ-lactones and thiazinones), bicyclic ring systems (bicyclic β-lactones, *o*-quinone adducts, benzoxazinones, and quinoxalinones), α-halogenated products, and α-chiral esters and amides. Cinchona alkaloid systems have also seen use as catalysts for the reactions of α-halo ketones (cyclopropanation).



Keywords: α-halo ketones · ketenes · cinchona alkaloids · ferrocenylamine · N-heterocyclic carbenes · Binaphane · Josiphos · azaferrocene · alcoholysis · Naminolysis · aldol–lactonization · [2+2] cycloaddition · catalytic asymmetric halogenation · α-halogenation ·

[4+2] cycloaddition · *o*-quinones · *N*-(thioacyl)imines · β-lactams · lactones · ketene dienolates · asymmetric cyclopropanation

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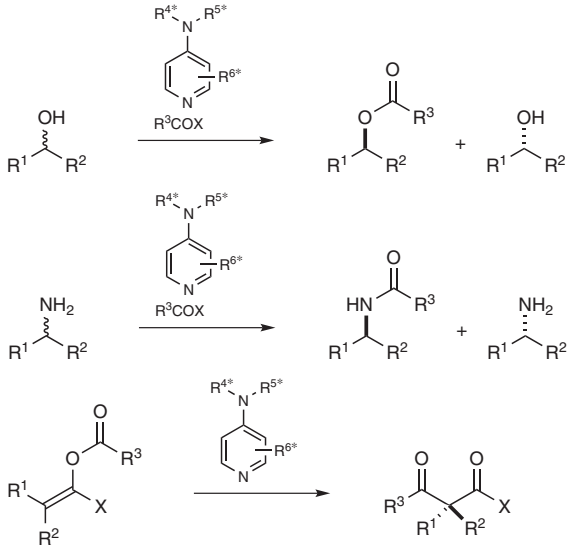
1.1.11 Chiral DMAP-Type Catalysts for Acyl-Transfer Reactions

T. Furuta and T. Kawabata

4-(Dimethylamino)pyridine (DMAP) and 4-(pyrrolidin-1-yl)pyridine (PPY) are powerful catalysts for acylation and many other reactions. Chiral DMAP-type and PPY-type catalysts promote O-acylation, N-acylation, and C-acylation in an enantioselective manner. As examples, catalytic enantioselective O-acylation, kinetic resolution of racemic alcohols, dynamic kinetic resolution of hemiaminals and azlactones, and desymmetrization of *meso*-diols are described. Addition of phenols, enols, and pyrroles to ketenes is also catalyzed by a chiral PPY-type catalyst in a highly enantioselective manner. Regioselective O-acylation of monosaccharides, disaccharides, a natural glycoside, and tetrasubstituted alkene diols is also effectively promoted by chiral PPY-type catalysts. Kinetic resolution of racemic amines by catalytic acylation with PPY-type catalysts is also described. An anion-binding approach by dual catalysis with chiral thioureas and 4-(dimethylamino)pyridine has recently been developed for acylative kinetic resolution of racemic amines. Asymmetric C-acylation via O-to-C acyl rearrangement of O-acylated azlactones and benzo[*b*]furans is effectively catalyzed by chiral PPY- and DMAP-type catalysts. Intermolecular C-acylation of ketene silyl acetals and imines is also described.



Keywords: nucleophilic catalyst · acylation · acyl transfer · (dimethylamino)pyridine · pyrrolidin-1-ylpyridine · kinetic resolution · parallel kinetic resolution · desymmetrization · dynamic kinetic resolution · regioselective acylation · hydrogen bond · *meso*-diols · acylpyridinium ion · planar chirality · axial chirality · C_2-symmetry · thiourea · ferrocene · rearrangement

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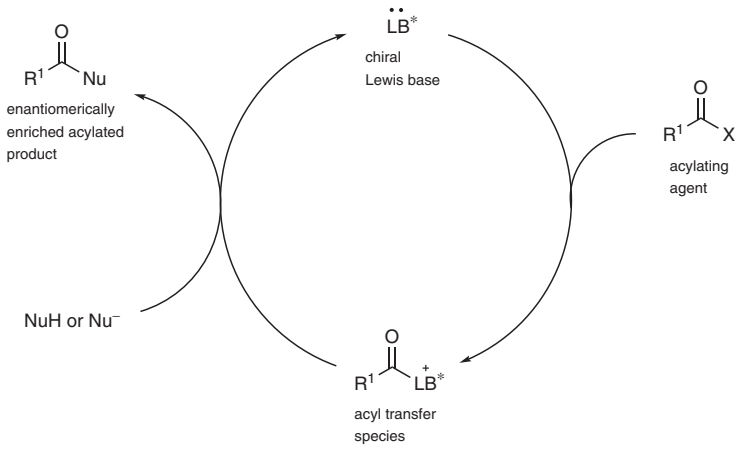
1.1.12 Non-DMAP-Type Catalysts for Acyl-Transfer Reactions

A. D. Smith and P. A. Woods

The ability of organic Lewis bases other than 4-(dimethylamino)pyridine-based catalysts to promote a range of asymmetric O-, N-, and C-acyl-transfer processes has evolved rapidly

and is a highly active field of research. This section summarizes the developments in catalyst architectures and approaches to these processes that have been uncovered to date in this thriving area of organocatalysis.



Keywords: acyl transfer · carboxyl transfer · kinetic resolution · dynamic kinetic resolution · parallel kinetic resolution · desymmetrization

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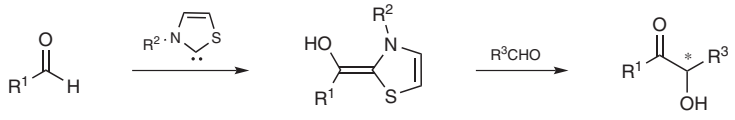
1.1.13 Carbene-Catalyzed Benzoin Reactions

K. Suzuki and H. Takikawa

Benzoin condensation catalyzed by N-heterocyclic carbenes (NHCs) has been widely studied. The catalytic, synthetic, mechanistic, and stereochemical aspects of this reaction have been thoroughly examined. The combination of N-heterocyclic carbenes and aldehydes allows for the formation of a nucleophilic enamine intermediate, which reacts with various electrophilic substrates such as carbonyl groups. This section focuses on the asymmetric benzoin reaction catalyzed by chiral N-heterocyclic carbenes, including not only the homocoupling of aldehydes, but also the crossed reaction with other acceptors.



Keywords: asymmetric benzoin condensation · carbon—carbon bonds · aldehydes · N-heterocyclic carbenes · triazolium salts · thiazolium salts · enzyme catalysis · α-hydroxy ketones · α-amino ketones · carbocyclic compounds

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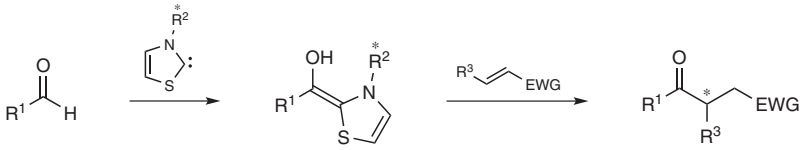
1.1.14 Carbene-Catalyzed Stetter Reactions

D. A. DiRocco and T. Rovis

N-Heterocyclic carbenes have proven efficient and selective catalysts for asymmetric Stetter and benzoin reactions. These catalysts allow the stereoselective synthesis of a variety of 1,4- and 1,2-functionalized compounds in a mild and unconventional manner. Utilizing "umpolung" reactivity, aldehydes can be transformed efficiently to the corresponding ketone products without the use of traditionally harsh and forcing conditions. The Stetter reaction allows an entry into the stereoselective synthesis of 1,4-functionalized com-

pounds by coupling aldehydes with a variety of Michael-acceptors. Intra- and intermolecular Stetter reactions can be catalyzed highly efficiently and stereoselectively by N-heterocyclic carbenes. The scalability of this reaction has also been demonstrated many times, often with dramatically reduced catalyst loadings.



Keywords: benzoin · Stetter · triazolium · thiazolium · aryl · aliphatic · aldehyde · ketone · cyclization · intramolecular · quaternary · desymmetrization · cyclohexadienone · intermolecular · glyoxamide · alkylidenemalonate · hetaryl · nitroalkene

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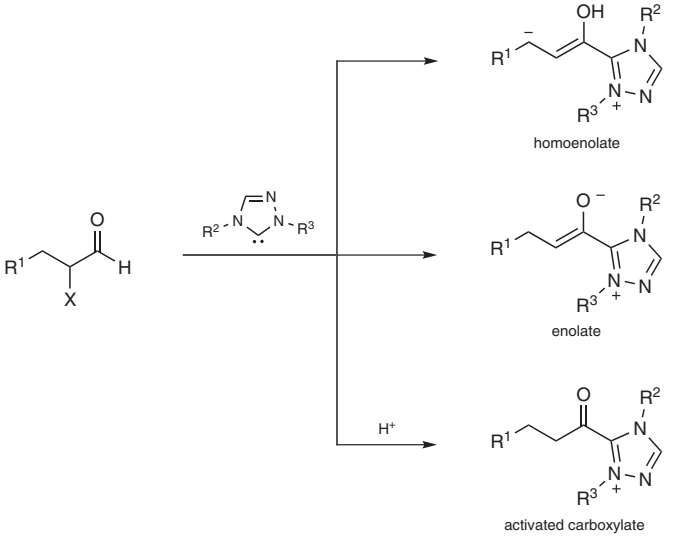
1.1.15 N-Heterocyclic Carbene Catalyzed Reactions of α-Functionalized Aldehydes

P.-C. Chiang and J. W. Bode

The combination of an N-heterocyclic carbene catalyst and an α-functionalized aldehyde can lead to the generation of five discrete reactive intermediates: (i) acyl anion equivalents, (ii) homoenolate equivalents, (iii) ester enolate equivalents, (iv) saturated acyl azoliums (activated carboxylates), and (v) α,β-unsaturated acyl azoliums. In each case, chiral catalysts have been identified that allow for highly enantio- and diastereoselective reactions. Furthermore, complex annulation cascades that utilize multiple intermediates in a single catalytic process allow for the formation of carbocyclic and heterocyclic compounds bearing multiple functional groups and with exquisite control of absolute configuration. All of these intermediates can be generated from α-functionalized aldehydes, but can also be accessed from a number of surrogates, including α-hydroxyenones and ketenes. This chapter summarizes the development of new chemistry arising from each of these catalytically generated species and the state of the art in catalytic enantioselective variants using chiral N-heterocyclic carbenes.



Keywords: N-heterocyclic carbene · acyl anions · homoenolates · ester enolates · acyl azolium · activated carboxylates · enantioselective · diastereoselective · γ-lactone · γ-lactam · Diels–Alder · cyclopentene · redox neutral reactions · triazolium salts

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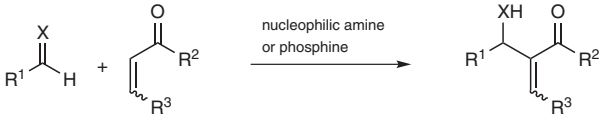
1.1.16 (Aza)-Morita–Baylis–Hillman Reactions

S. Hatakeyama

This manuscript describes enantioselective C—C bond-forming reactions between carbon electrophiles, such as aldehydes and imines, and activated alkenes, such as acyclic and cyclic α,β-unsaturated carbonyl compounds, using chiral nucleophilic amine or phosphine catalysts, or using achiral nucleophilic catalysts together with chiral Brønsted acid activators.



X = O, NR^3

Keywords: asymmetric Morita–Baylis–Hillman reaction · asymmetric aza-Morita–Baylis–Hillman reaction · carbon—carbon bond formation · chiral amine catalyst · chiral phosphine catalyst · chiral Brønsted acid activator

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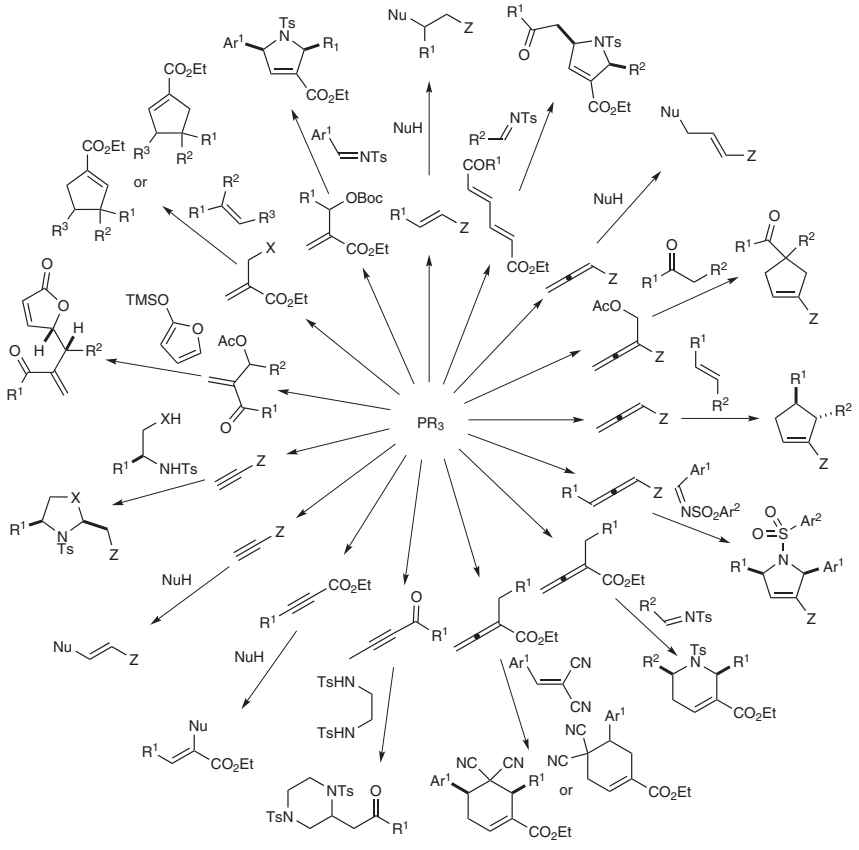
1.1.17 Phosphine Catalysis

Y. C. Fan and O. Kwon

The conjugate addition of tertiary phosphines to the activated carbon—carbon multiple bonds of alkenes, allenes, alkynes, and allylic carbonates generates β-phosphonium enolates, β-phosphonium dienolates, β-phosphonium enoate zwitterions, and vinylphosphonium ylides. These intermediates react with nucleophiles, electrophiles, and combinations of both in various modes to produce carbo- and heterocycles that are useful synthetic intermediates. This review provides a history and a summary of such nucleophilic phosphine catalyzed reactions, including asymmetric variations using chiral phosphines. It does not cover acyl transfer or Morita–Baylis–Hillman reactions.



Keywords: phosphine · alkenes · allenes · alkynes · Morita–Baylis–Hillman adduct · conjugate addition · phosphonium enolate · phosphonium ylide · zwitterion · umpolung addition · annulation · enantioselective

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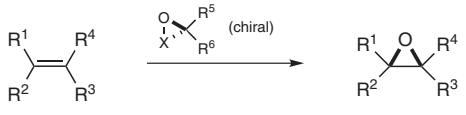
1.2.1 Asymmetric Ketone and Iminium Salt Catalyzed Epoxidations

O. A. Wong, T. A. Ramirez, and Y. Shi

Epoxides are extremely valuable as products or intermediates in organic synthesis. This chapter focuses on recent developments in the epoxidation of alkenes using chiral ketone and iminium salt catalysts and also highlights synthetic applications of chiral ketone catalyzed epoxidation.

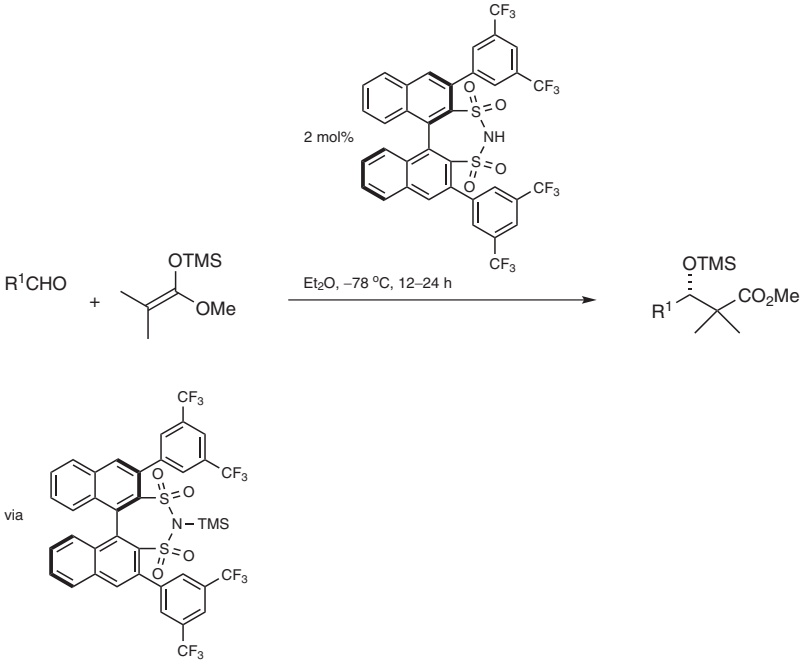


Keywords: epoxidation · epoxy compounds · dioxiranes · nonmetal catalysis · metal-free catalysis · organic catalysis · organocatalysis · enantioenriched epoxides · chiral ketones · oxidation · cascade cyclization · iminium salts · oxaziridines · oxaziridinium salts · alkenes · stereoselective

1.2.2 Lewis Acid Organocatalysts Other than Ketone and Iminium Salt Catalysts

P. García-García

This manuscript deals with the applications of Lewis acid organocatalysts in asymmetric catalysis. Chiral silanes, chiral compounds containing carbenium or phosphonium cations, as well as chiral ionic liquids promote fundamental reactions such as Diels–Alder cycloadditions, aldol reactions, and nucleophilic additions.



Keywords: Lewis acid organocatalysts · chiral silanes · chiral phosphonium salts · chiral trityl-based catalysts · chiral ionic liquids · asymmetric allylation · asymmetric aldol reaction · asymmetric nucleophilic addition