New Strategies for the Development of an Asymmetric Version of the Baylis–Hillman Reaction**

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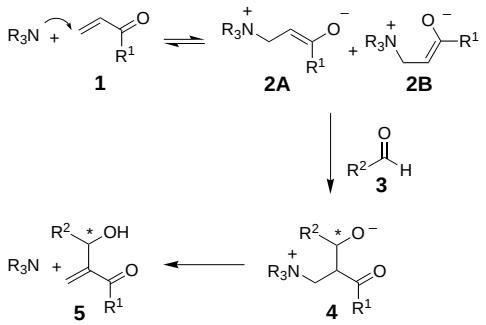
1. Variations, Preparative Scope and Mechanism of the Baylis–Hillman Reaction

The stereoselective formation of carbon–carbon bonds is an important challenge in organic chemistry. The Baylis–Hillman reaction allows the direct preparation of α-methylene-β-hydroxycarbonyl compounds by base-catalyzed reaction of α,β-unsaturated carbonyl compounds with aldehydes.[1–3] The first step of this reaction involves nucleophilic attack of the catalyst on the Michael acceptor **1** leading to the formation of the zwitterionic intermediate **2**. Subsequently, this intermediate reacts in the rate-determing step of the Baylis–Hillman reaction with the aldehyde **3** to give the alcoholate **4** (Scheme 1). The product **5** is finally formed by a



Scheme 1. The mechanism of the Baylis–Hillman reaction.

shift of a proton from the α-carbon to the oxygen atom of the alcoholate and extrusion of the catalyst.[4] The densely functionalized Baylis–Hillman products can be stereoselectively transformed, for example, into azirines,[5] epoxides,[6] triols[7] and *anti*-aldol products.[8] In addition, α-methylene-β-hydroxycarbonyl compounds are versatile starting materials for the synthesis of a variety of natural and nonnatural target molecules.[9, 10]

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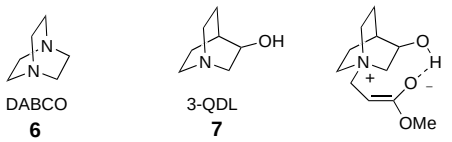
Unfortunately, the applicability of the Baylis–Hillman reaction is very often limited by low rates and conversions and low, highly substrate-dependent yields. It is particularly important for the development of an efficient asymmetric version of the Baylis–Hillman reaction that these problems are adequately addressed. The use of high pressure or of the microwave technique resulted in a significant increase in the rate of the reaction; however, only for a few substrates.[11] Increasing the reaction temperature above 20 °C resulted in polymerization of the sensitive acrylates. Recent work by Leahy and co-workers suggested that, counter-intentively, better yields and higher rates were observed at lower temperatures.[12] These results can be explained by the different rates of the formation of the diastereomeric base–acrylate adducts (**2A** and **2B**).

The rate and the conversion of the Baylis–Hillman reaction was significantly improved when nucleophilic non-hindered bases, such as diaza[2.2.2]bicyclooctane (DABCO, **6**), rather than simple tertiary amines were used. Further



improvements were observed when 3-quinuclidinole (3-QDL, **7**) was employed, due to stabilization of the zwitterionic intermediate **2** by formation of intramolecular hydrogen bonds.[13a–c] Similar effects were observed by the addition of methanol[13d] or acetic acid[13e] to the reaction mixture (formation of intermolecular hydrogen bonds) or by the presence of a hydroxy group in the acrylate.[13f] The rate of the reaction was decreased by the presence of bulky substituents in the α-position of tertiary amines. This was explained by the decrease in the rate of the addition of the catalyst to the acrylate.[14] Recent work by Aggarwal and co-workers has shown that very good rates and chemical yields could be obtained by using the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[15] However, the use of enolizable ketones led to formation of aldol products. The success of the use of DBU was explained by the assumption that the reaction of the zwitterionic intermediate with the acrylate rather than the attack of the catalyst on the acrylate

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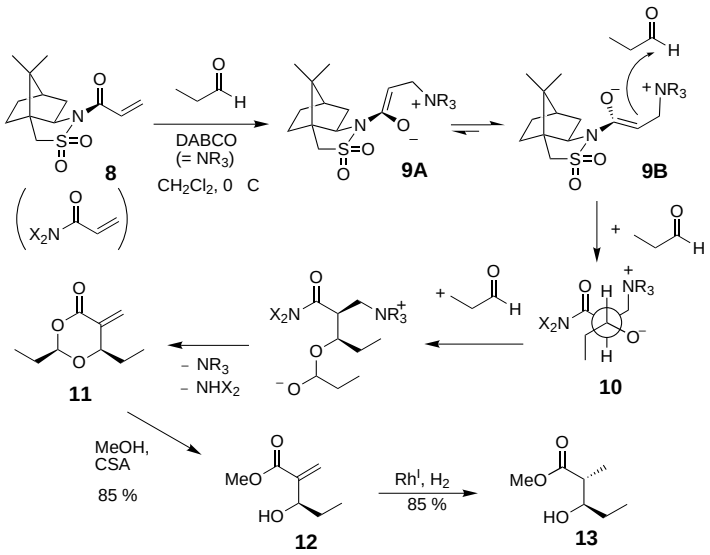
represents the rate-determing step of the reaction: although DBU represents a sterically hindered base, the zwitterionic intermediate is stabilized by delocalization of the positive charge. The concentration of the intermediate in the equilibrium is increased and, hence, the overall rate of the reaction is enhanced. However, this explanation is contradictory to the Curtin–Hammett principle. A stabilization of the zwitterionic intermediate and a significant enhancement of the rate of the reaction was also induced by the use of metal salts, such as $La(OTf)_3$ and $LiClO_4$ (OTf = triflate = trifluoromethanesulfonate).[16]

2. Asymmetric Baylis–Hillman Reactions of Chiral Michael Acceptors

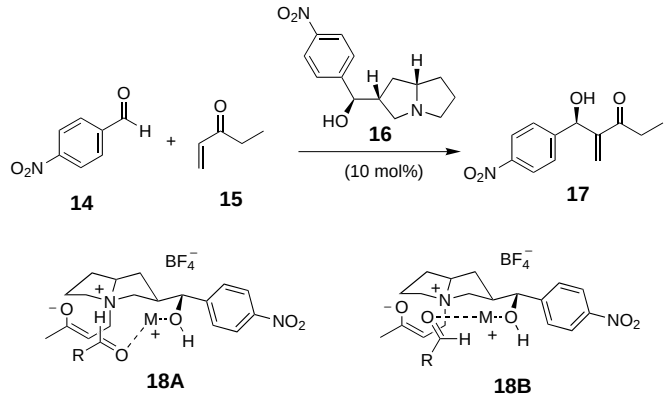
During the course of the Baylis–Hillman reaction two stereocenters are formed, one of which remains in the Baylis–Hillman product. An obvious concept for the development of an asymmetric version of the reaction lies in the use of an enantiomerically pure acrylic acid derivative. The use of enantiomerically pure menthyl acrylates resulted, however only in certain cases, in respectable diastereomeric excesses.[17] A significant improvement was reported in 1997 by Leahy and co-workers who used the Oppolzer sultame as a chiral auxiliary in DABCO-catalyzed Baylis–Hillman reactions (Scheme 2).[18] In this reaction, the 1,3-dioxan-4-one **11** was obtained, which was transformed by methanolysis into the α-methylene-β-hydroxyester **12** which was subsequently diastereoselectively hydrogenated to give the *anti*-aldol product **13**. The esters **12** were isolated in good yields. However, 15 equivalents of the aldehyde were required. The stereoselectivity can be explained by the following: Michael addition of the catalyst to the acrylate **8** results in formation of a *Z*-enolate which mainly resides in the *anti*-conformation **9B**, since in this case the dipole-repulsion between the sulfonyl and the carbonyl group is minimized. Owing to the steric interaction with the axial oxygen atom of the sulfonyl group, the attack of the aldehyde proceeds diastereoselectively from the *re* side of the acrylate to give the adduct **10**, which subsequently reacts with a second aldehyde molecule to give a hemiacetal. Extrusion of the catalyst and cyclization with extrusion of the chiral auxiliary finally afforded the 1,3-dioxan-4-one **11**.



Scheme 2. DABCO-catalyzed Baylis–Hillman reaction according to Leahy et al. CSA = camphorsulfonic acid.

3. Asymmetric Baylis–Hillman Reactions of Achiral Michael Acceptors

Much work related to the development of a catalytic, enantioselective version of the Baylis–Hillman reaction by the use *chiral bases* has been reported. Only low enantiomeric excesses were obtained when brucin, *N*-methylprolinol, *N*-methylephedrine, and nicotine were employed. The use of cinchona alkaloids and of enantiopure 3-QDL **7** resulted in a significant increase of the rate of the reaction, but only in low enantiomeric excesses which decreased when the reactions were carried out under pressure.[1b,17,19a] Enantiomeric excesses of 9–44% *ee* were obtained in the reaction of pyrimidine-5-carbaldehydes with acrylates using (*S*)-BINAP as the catalyst.[19b] Enantioselectivities of 21–70% *ee* were observed in the reaction of ethyl- and methylvinyl ketone with aromatic aldehydes **14** using the chiral hydroxypyrrolizidine catalyst **16**, which was prepared in four steps starting from BOC-L-prolinol (Scheme 3).[20] The enantioselectivity was explained by the predominant formation of intermediate **18A**, which is less sterically hindered than the isomeric intermediate **18B**. The employment of a reaction temperature of $-40\,^{\circ}C$, the use of $NaBF_4$ as a cocatalyst, and the presence of a hydroxy group in the base (which allows the formation of intramolecular hydrogen bonds) resulted in good conversions and rates.



Scheme 3. Asymmetric Baylis–Hillman reaction using a chiral hydroxypyrrolizidine catalyst.

Very good enantioselectivities were recently reported by Hatakeyama and co-workers.[21] The reaction of a variety of aldehydes **20** with the highly reactive 1,1,1,3,3,3-hexafluoroisopropylacrylate **19** using modified cinchona alkaloids as the catalyst resulted, at a temperature of $-55\,^{\circ}C$, in the formation of the Baylis–Hillman products **22** in 31–58% yields with 91–99% *ee* (Scheme 4). The use of the tricyclic derivative **21**, which was prepared from quinidine in one step,[22] proved crucial for obtaining high enantioselectivities. The success of catalyst **21** can be explained by the (compared with quinidine)

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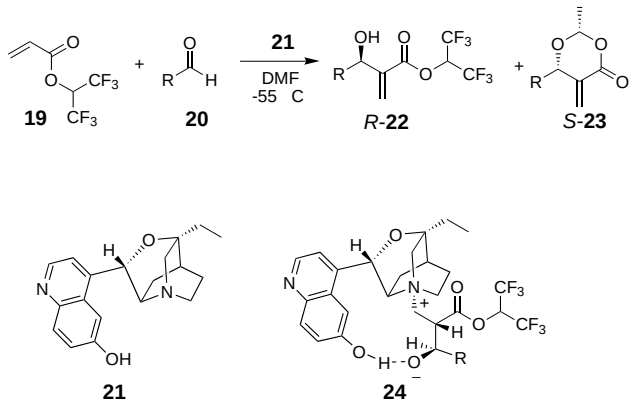
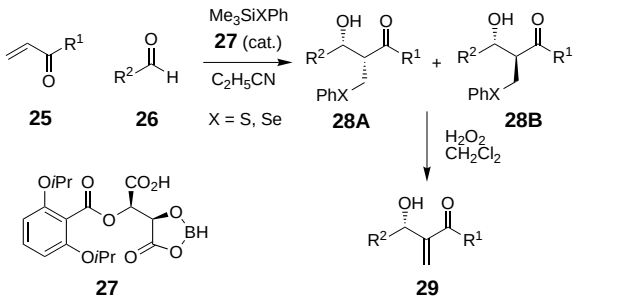


Scheme 4. Asymmetric Baylis–Hillman reaction using a chiral cinchona alkaloid catalyst.

increased nucleophilicity, by the presence of a free hydroxy group at the quinoline moiety, and by the *anti-open* conformation[23] of the alkaloid which allow an optimal stabilization of the zwitterionic intermediate **24** by formation of intramolecular hydrogen bonds. Using the Oppolzer auxiliary (see above) only low enantioselectivities could be obtained for aldehydes branched at the α-position. In contrast, the Baylis–Hillman products derived from isobutyric aldehyde and cyclohexane carbaldehyde could be prepared in 31 and 36% yields with 99% *ee* when the catalyst **21** was used. A disadvantage of the method of Hatakeyama et al. results from the decrease of the yields due to formation of the dioxanones **23**, which were generated with opposite absolute configurations and with lower enantioselectivities compared with the products **22**. However, the formation of these undesired side products was helpful for the elucidation of the mechanism of the reaction.

4. Alternative Syntheses of Nonracemic Baylis–Hillman Products

An alternative approach for the synthesis of nonracemic Baylis–Hillman products was reported by Barrett and coworkers. In a two-step synthesis, which was preparatively equivalent to an asymmetric Baylis–Hillman reaction, α-methylene-β-hydroxyketones **29** were prepared with 34–94% *ee* (Scheme 5).[24] The overall yields of the sequence ranged between 18 (X = S, R^1 = Me, R^2 = Et) and 52% (X = Se, R^1 = Me, R^2 = Me). In the first step, the enantioselective condensation of the α,β-unsaturated ketone **25** with the aldehyde **26** and trimethylsilylphenyl sulfide or selenide



Scheme 5. Baylis–Hillman analogous reaction according to Barrett et al.

afforded the diastereomeric β-hydroxyketones **28A** and **28B** with 63–97% *ee*. This reaction was catalyzed by the chiral acyloxyborane **27**. The Baylis–Hillman products **29** were subsequently prepared by oxidative elimination using *m*-chloroperoxybenzoic acid or H_2O_2. The enantioselectivities of this step were in the range of 50 to 96% *ee*.

Outlook

Many groups have contributed to the development of an efficient and enantioselective Baylis–Hillman reaction. All this work leads the way to the development of a useful and broadly applicable methodology in the future. In this context, the design of new catalysts based on the modification of cinchona alkaloids could play an important role. Besides the optimization of the enantioselectivities, the increase of the chemical yields, the conversions, and the reaction rates continue to represent important issues, particularly for "difficult" substrates.

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Nanoporous Structures by Design

Michael J. Zaworotko*

Whereas the development of reliable methods for crystal-structure prediction remains an elusive scientific challenge,[1] its relevance to aspects of pharmaceutical and materials science has fueled rapid development of the concept of crystal engineering.[2] Is crystal engineering synonymous with crystal-structure prediction? The simplest answer is, not yet. However, crystal engineering has emerged as a paradigm for the design and synthesis of new solid phases because its fundamental precept is that most crystal structures can be regarded as self-assembled entities,[3] that is, they are "supermolecules par excellence".[4] In other words, crystal engineering can be regarded as being synonymous with supramolecular synthesis.

Crystal engineering has thus far focused upon chemical entities that are predisposed to form predictable, self-assembled networks that is, molecules or ions that are exofunctional and capable of forming 1D, 2D, or 3D networks. Crystal structure prediction is therefore simplified to an issue more related to the design of networks. That such a strategy can be successful is perhaps best exemplified by the recent observation of several new classes of open framework solids that exhibit the property of microporosity.

Zeolites represent the prototypal microporous solids, have channels and cavities of 4 – 10 Å,[5] and have found widespread application in catalysis and separations.[6] The first generation of synthetic "zeolite analogues" that were generated by crystal-engineering strategies consisted of rigid 3D networks based upon organic or metal – organic moieties. However, these zeolite analogues typically suffered from the phenomenon of interpenetration[7] or from the irreversible collapse of the structure upon the removal of the guest molecules. Subsequent studies revealed a second generation of frameworks that are more closely analogous to zeolites in that they are robust enough to survive the complete loss of the guest molecules and that they reversibly adsorb small volatile molecules. Interestingly, such structures can be purely organic and sustained by hydrogen bonds[8] or they can be based upon coordination-polymer frameworks.[9] However, these compounds do not compare to the inorganic (zeolite) structures in terms of either their surface area or their thermal stability.

Very recently, a third generation of synthetic frameworks that exhibit hitherto unseen levels of porosity, so called nanoporosity, and stability has been discovered. These structures are exemplified by the octahedral polymer $[Zn_4O(bdc)_3]$ (bdc = benzene-1,4-dicarboxylate).[10] $[Zn_4O(bdc)_3]$ is a relatively simple and inexpensive material to prepare, is remarkably stable to loss or exchange of guests, and remains crystalline at temperatures above 300 °C. The feature that makes $[Zn_4O(bdc)_3]$ special is that it exhibits a relative degree of porosity hitherto unprecedented in crystalline solids. Recently Kitagawa and co-workers reported the structure and porous nature of $[Cu(4,4'\text{-bipy})_2](SiF_6)$ (**1**)[11] (bipy = bipyridine). Complex **1** is the latest addition to this new family of nanoporous materials and is important because of its implications for future design principles and because of its properties.

Design Principles

It would be natural to assume that 3D architectures present a higher level of complexity than 1D and 2D architectures. In many ways 3D architectures represent the ultimate challenge to crystal engineers since success leads directly to the control and prediction of crystal structures. It is therefore somewhat ironic that two of the simplest examples of predictable networks are exemplified by 3D networks, that is, those generated by the assembly of tetrahedral or octahedral nodes. Tetrahedral nodes are predisposed to generate diamondoid architectures, whereas octahedral nodes are expected to afford octahedral networks.

Diamondoid architectures using a tetrahedral metal as the node and cyanide ligands (CN^-) as the spacer represent

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