Nucleophilic Carbenes in Asymmetric Organocatalysis

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ABSTRACT

The coenzyme thiamine (vitamin B_1), a natural thiazolium salt, is involved in many enzymatic catalyses. Since it has been proposed that the catalytically active species of these reactions is a nucleophilic carbene, many chemists have tried to perform enzyme mimetic asymmetric carbene catalysis. After a long and difficult search, stable carbenes are finally isolated, characterized, and in the chemist's hands. The experiments of decades have finally resulted in successful enantioselective benzoin condensations and enantioselective intramolecular Stetter reactions as important examples of carbene catalyzed asymmetric nucleophilic acylation processes.

Enzymes Set the Standards

In its everlasting evolution processes, nature has brought forth countless mechanisms for complex biochemical reactions. Nucleophilic acylation reactions catalyzed by transketolase enzymes together with the coenzyme thiamine (**1**, vitamin B_1, a natural thiazolium salt shown in Figure 1) might serve as examples for highly selective chemical reactions that are accomplished in vivo.

In the 1990s, Schneider et al. revealed the structure of a transketolase enzyme that uses thiamine (contained in baker's yeast) as coenzyme to catalyze a number of important biochemical reactions.[1] As depicted in Figure 2, the thiamine molecule (shown as space-filling model) is embedded into a narrow channel in the very heart of the enzyme body. Regarding these elaborate chemical surroundings, it is easily understandable that chemical reactions taking place at the catalytically active center in the middle of the channel must inevitably be very selective. The biochemical processes of thiamine-dependent

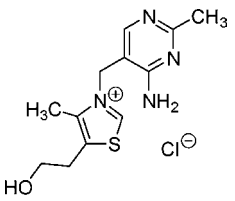

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FIGURE 1. Thiamine (vitamin B_1), a coenzyme.

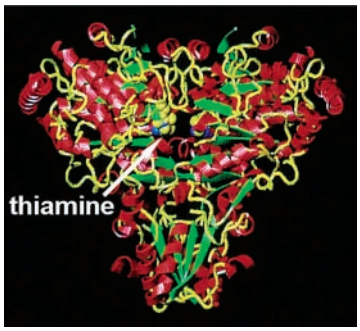

FIGURE 2. Structure of a transketolase enzyme determined by Schneider et al. Reproduced with kind permission of Prof. Schneider.

enzymes have been largely elucidated, and the enzymes have been used as synthetic tools.[2] Much research has been done to determine the actual catalytically active species of these reactions and to develop synthetic catalysts that mimic the enzymatic systems but do not need the bulky enzyme proteins around them to catalyze organic reactions selectively and efficiently.

Catalytic Nucleophilic Acylation Reactions

Reaction systems involving thiamine catalysts and catalytic nucleophilic acylation reactions in general have been thoroughly studied by numerous scientists. The first investigations date back as far as 1832 when F. Wöhler and J. Liebig discovered the so-called benzoin condensation catalyzed by cyanide anions.[3] In 1903, A. Lapworth proposed a mechanism for this remarkable reaction that would proceed via a carbanion generated from the benzaldehyde substrate in a hydrogen cyanide addition followed by deprotonation.[4] The intermediate carbanion species represents an active aldehyde with an inverted (i.e., nucleophilic) reactivity of the carbonyl carbon atom. This phenomenon was later on embedded into the comprehensive Umpolung concept developed by D. Seebach and co-workers.[5] Ukai et al. found in 1943 that, as well as cyanide ions, thiazolium salts can be used as catalysts for the benzoin condensation.[6] Some years later, Mizuhara et al. showed that the catalytic activity of the natural thiamine is based on its thiazolium unit as well.[7]

How are the identical effects of the cyanide catalyst and the thiazolium catalyst in the benzoin condensation reaction explained? Would there be a mechanism conceivable for thiazolium catalysis similar to the well-established Lapworth mechanism for cyanide catalysis?

Dieter Enders was born in 1946 in Butzbach, Germany. He studied chemistry at the Justus Liebig Universität Giessen and received his Dr. Rer. Nat. in 1974 under the supervision of Prof. Dieter Seebach. After postdoctoral studies at Harvard University with Prof. E. J. Corey, he went back to Giessen and obtained his habilitation in 1979. In 1980 he moved to the Universität Bonn as an associate professor before he changed again in 1985 to his present position as Professor of Organic Chemistry at the Rheinisch-Westfälische Technische Hochschule Aachen. He received many awards, among them the Prize of the Justus Liebig Universität Giessen (1978), the Leibniz Award (Deutsche Forschungsgemeinschaft, 1993), the Yamada Prize (Japan, 1995), the Max-Planck Research Award (Alexander von Humboldt- and Max-Planck-Gesellschaft, 2000), and the Emil Fischer Medal (Gesellschaft Deutscher Chemiker, 2002). His current research interests are asymmetric synthesis, especially the stereoselective synthesis of biologically active compounds, nucleophilic carbenes, and new synthetic methods using organometallics.

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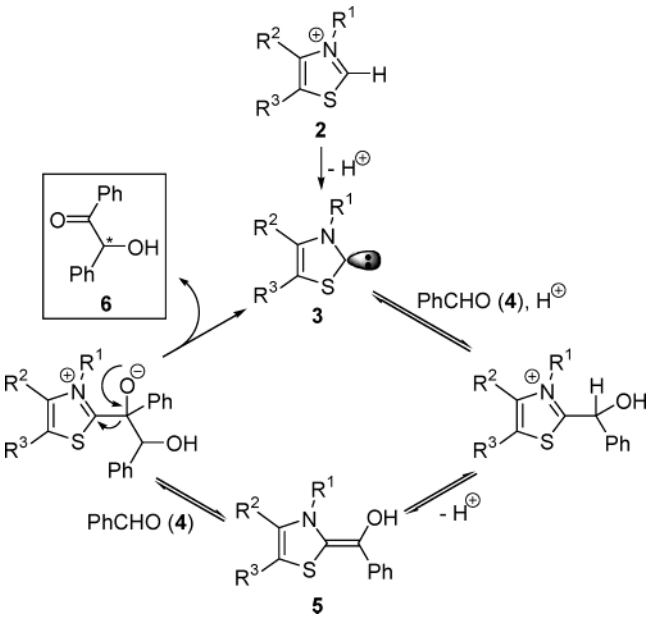
Scheme 1. Catalytic Cycle of the Benzoin Condensation as Proposed by R. Breslow



Indeed, R. Breslow based his mechanistic model for the thiazolium salt catalyzed benzoin condensation on the works of Lapworth. In 1958, he presented a mechanism that has a thiazol-2-ylidene, a carbene compound, as the catalytically active species.[8] His mechanistical model is displayed in Scheme 1.

The carbene compound would be formed in situ by deprotonation of the thiazolium salt **2** at its most acidic position. The resulting thiazol-2-ylidene, **3**, the actual catalyst, couples with an aldehyde molecule (**4**) to generate an active aldehyde, the hydroxy-enamine-type Breslow intermediate **5** that subsequently functions as the nucleophilic acylation reagent (d^1-synthon in the terminology of Seebach et al.). Reaction with an electrophilic substrate such as a second aldehyde molecule (**4**) yields the α-hydroxy ketone product **6** and the original carbene catalyst. An alternative mechanistic model of the thiazolium salt catalyzed benzoin condensation based on the formation of carbene dimers **7** (Figure 3) was presented by Lemal et al.[9] and extended by López Calahorra et al. in the 1980s.[10] Since then, the competing models have been widely discussed.[11]

Stable Carbenes

The catalytic cycle proposed by Breslow describes the intermediate formation of carbenes, a class of highly reactive molecules bearing a divalent carbon atom as the characteristic feature. More precisely, the thiazol-2-ylidene

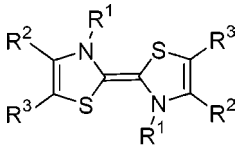


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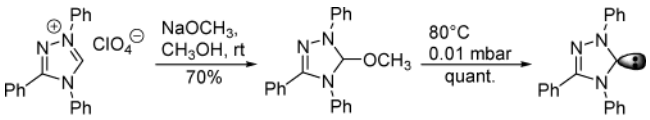
FIGURE 3. Thiazol-2-ylidene dimer.

8 **9**

FIGURE 4. Stable carbenes by Arduengo et al. (**8**) and Enders et al. (**9**).

Scheme 2. Synthesis of the Stable Carbene 9 Developed by Enders et al.



10 **11** **9**

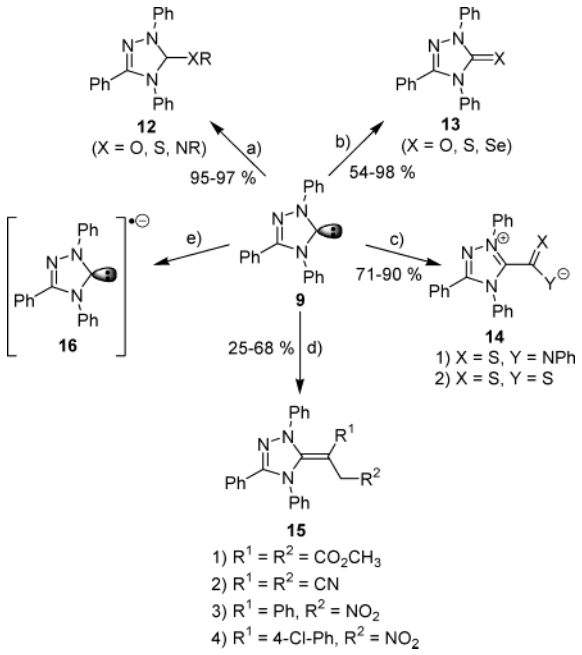
3 belongs to the family of heterocyclic nucleophilic carbenes that have been intensely studied as reaction intermediates by Wanzlick et al. in the 1960s.[12] Yet, it seemed to be impossible at that time to isolate the actual carbenes due to their pronounced reactivity (e.g., their easy dimerization).

Twenty years later, however, decisive progress in carbene chemistry was achieved by Bertrand et al.[13] and Arduengo et al.[14], who presented compounds that are stable at room temperature and that can be regarded as carbene structures. In many respects, Bertrand's phosphinocarbene rather reacts like a phosphaacetylene. It was suspected not to possess a predominant carbene character,[15] although recent studies seem to support again the assumption of a carbene structure.[16] However, the imidazol-2-ylidene **8** synthesized by Arduengo et al. in 1991 and depicted in Figure 4 became reputed to be the first stable carbene that has been isolated and characterized. In the meantime, a number of stable *N*-heterocyclic carbenes has been isolated and characterized by different groups.[17]

Inspired by this success, our research group cooperated with Teles et al. to investigate the chemistry of carbene structures derived from the triazol heterocycle. We synthesized the triazol-5-ylidene **9** (see Figure 4) that proved to be stable at temperatures up to 150 °C in absence of air and moisture.[18] Of stable carbenes, bottled and in a multigram scale—this has finally come true: compound **9** was the first carbene to be commercially available. As shown in Scheme 2, the crystalline carbene has been obtained from the corresponding triazolium salt precursor **10** by the addition of methanolate and subsequent thermal decomposition of the adduct **11** in vacuo via α-elimination of methanol.[19]

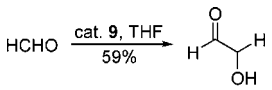
As depicted in Scheme 3, **9** shows the characteristic behavior of a nucleophilic Wanzlick-type carbene.[20] Alkoxy-, alkylthio-, or alkylaminotriazoles **12** are obtained via the insertion of the carbene **9** into the OH, SH, or NH bonds of alcohols, thiols, or amines. Compound **9** reacts with oxygen, sulfur, and selenium to form the triazolinone, -thione, and -selenone **13**, respectively. Reactions with heterocumulenes such as phenylisothiocyanates and car-

Scheme 3. Typical Reactions of the Stable Carbene 9[a]



[a] Reaction conditions: (a) RXH, rt; (b) O_2 or S_8 or Se, toluene, reflux; (c) PhNCS, THF or CS_2, toluene, rt; (d) $R_1CH{=}CHR_2$, THF, rt; (e) e^-, cyclic voltammetry in DMF.

Scheme 4. Formoin Condensation Reported by Teles et al.



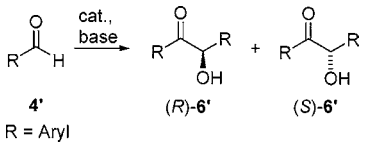
bon disulfide lead to the corresponding betaines **14**, reactions with doubly activated double bonds such as fumaric and maleic esters, nitriles, maleic imides, and nitro olefins afford the open-chain allylic systems **15**.

Electrochemical reduction of the stable carbene **9** in the cyclic voltammetry affords the corresponding radical anion **16** bearing a radical center and a carbenic center in the same molecule.[21] Wanzlick-type carbenes such as **9** can also be used as promising substitutes for phosphane ligands in organometallic chemistry since the resulting complexes proved to be considerably more stable than their phosphane analogues.[22]

In addition to the carbene chemistry described previously, triazol-5-ylidene **9** turned out to be a powerful catalyst for the formoin condensation converting formaldehyde **17** to glycolaldehyde **18** as illustrated in Scheme 4.[23] This reactivity complements the catalytic properties of thiazolium salts, which have been known for a long time to catalyze the formoin reaction affording 1,3-dihydroxyacetone as product.[24] In comparison with thiazolium salts, carbene **9** is much more stable when exposed to traces of water and oxygen at elevated temperatures, allowing high turnover numbers in organocatalysis.

Triazolium salts seemed to be promising catalyst precursors for benzoin-type condensation reactions. These results encouraged us to do more research on heterocyclic structures derived from triazol, especially on chiral triazolium salts regarding their possible use in asymmetric catalysis.

Scheme 5. Base Induced Catalytic Asymmetric Benzoin Condensation



Asymmetric Catalysis with Carbenes

It has always been the ambition of research chemists to imitate nature in its magnificent methods for generating complex chemical structures. A crucial aspect of these natural processes is the prevalent chirality of their products. Therefore, syntheses strategies that attempt to mimic naturally occurring enzyme-catalyzed reactions are always jugded regarding their stereoselectivity.

Benzoin Condensation. Since the product of the benzoin condensation discovered by Wöhler and Liebig, benzoin **6**, bears a new stereogenic center, this reaction caught the attention of many chemists who tried to develop heterazolium-catalyzed asymmetric nucleophilic acylation reactions with the base induced benzoin condensation of Scheme 5 being a test reaction.

The first research on the asymmetric benzoin condensation was presented by Sheehan et al. in 1966 employing the chiral thiazolium salt **19** shown in Figure 5 as the catalyst precursor.[25]

Yet, the observed enantiomeric excess of the synthesized benzoin was as low as 2%. Using modified thiazolium salts such as **20**, Sheehan et al. could obtain enantiomeric excesses up to 52% with the yield unfortunately being reduced to 6%.[26] Many years later, though, Rawal et al. showed that the yield of the reaction reported by Sheehan et al. could be improved to 48%.[27] Takagi et al. reported chiral menthyl-substituted thiazolium salts such as compound **21** shown in Figure 5, the best of which catalyzed the formation of benzoin with an enantiomeric excess of 35% and an improved yield of 20% by carrying out the reaction in a micellar two-phase system.[28] The superior Sheehan catalysts were combined with the Takagi reaction conditions by Zhao et al. who obtained moderate enantiomeric excesses of 47−57% and yields of 20−30%.[29] In 1993, López Calahorra et al. presented bisthiazolium

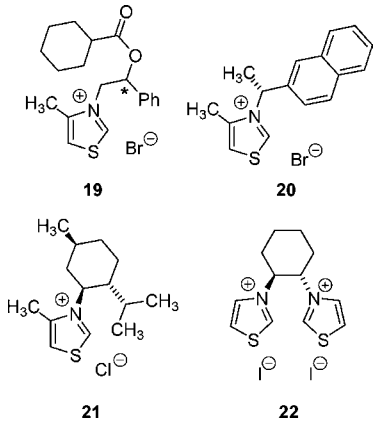
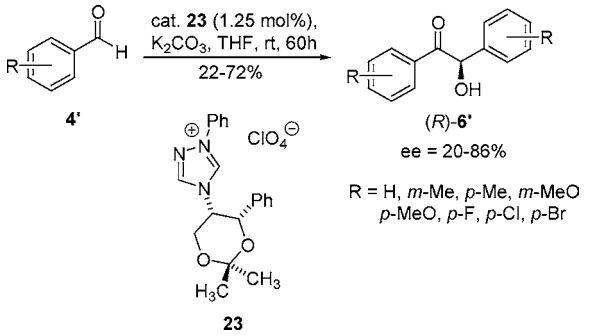


FIGURE 5. Chiral thiazolium salts for the enantioselective benzoin condensation.

Scheme 6. Asymmetric Benzoin Reactions by Enders et al.



salt catalysts (e.g., compound **22** in Figure 5) for the asymmetric benzoin condensation leading to optical inductions up to 27% ee and yields up to 21%.[30]

Pursuing the idea of triazolium salt catalysis, our research group synthesized a variety of chiral triazolium salts and examined their ability to catalyze the benzoin reaction.[31] However, the enantiomeric excesses and catalytic activities proved to vary strongly with slight structural changes in the substitution pattern of the triazolium system. The most active catalyst **23** provided benzoin **6** in its (*R*)-configuration with 75% ee and a satisfactory yield of 66% using a significantly reduced catalyst amount of 1.25 mol % (Scheme 6). This represented an increase of activity of almost 2 orders of magnitude as compared with the results obtained with chiral thiazolium salts before.

The applicability of this new catalyst type was subsequently extended to other aromatic aldehydes **4′** to give the respective aromatic α-hydroxy ketones **6′** listed in Scheme 6. Electron-rich aldehydes generally furnished the respective benzoins in moderate to good enantiomeric excesses up to 86%, whereas the asymmetric inductions achieved with electron-deficient aldehydes were significantly lower. Apparently, deactivation of the aldehyde function led to lower catalytic activities but higher enantioselectivities. Accordingly, the highest enantioselectivity of 86% (and the lowest yield) was obtained with *p*-methoxybenzaldehyde, in which the carbonyl function is considerably deactivated due to the +M effect of the methoxy group. The reaction had to be carried out in the absence of oxygen and water; otherwise, the intermediate nucleophilic carbene was oxidized to the triazolinone or suffered hydrolysis with subsequent aminal-type ring opening.

Attempts to apply catalyst **23** to the synthesis of aliphatic acyloins gave very low yields and low enantioselectivities. Adaptation of the catalyst structure resulted in triazolium salt **24**, depicted in Figure 6, as the best catalyst for the condensation of aliphatic aldehydes. However, only low enantiomeric excesses up to 26% and moderate yields that varied widely were obtained.[31a]

Further contributions to the research on asymmetric benzoin condensation were made by Leeper et al. using novel thiazolium salts. In 1997, they reported chiral, bicyclic thiazolium salt catalysts that led to enantiomeric excesses up to 21% and yields up to 50% when used for the asymmetric benzoin condensation and enantiomeric

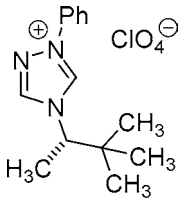
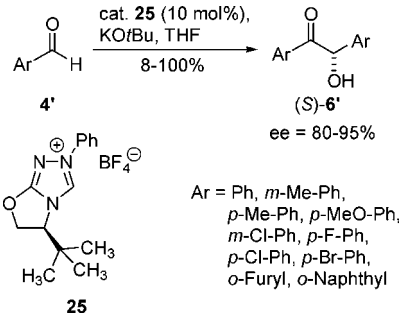


FIGURE 6. Chiral triazolium salt synthesized by Enders et al. as catalyst for the condensation of aliphatic aldehydes.

Scheme 7. Highly Enantioselective Triazolium Salt Catalyzed Condensation of Aromatic Aldehydes Reported by Enders et al.



excesses up to 33% (yields up to 75%) when used for the synthesis of aliphatic butyroin.[32] Another thiazolium catalyst containing a norbornane backbone gave benzoin in quantitative yield with an enantiomeric excess of 26%.[33] In 1998, Leeper et al. reported novel chiral, bicyclic triazolium salts that produced aromatic acyloins with varying enantioselectivities (20−83% ee).[34]

On the basis of their protocol, another chiral, bicyclic triazolium salt was developed in our research group. In 2002, we published our results regarding asymmetric benzoin condensations (shown in Scheme 7) using the novel triazolium salt **25** as a catalyst precursor.[35]

Benzoin **6** was obtained in very good yield and with the best enantioselectivity reported so far (yield 83%; 90% ee). The condensation of numerous other aromatic aldehydes **4′** provided the corresponding α-hydroxy ketones **6′** in varying yields with excellent enantiomeric excesses up to 95%. As previously observed, electron-rich aromatic aldehydes gave significantly better asymmetric inductions than electron-deficient (i.e., activated aromatic aldehydes). Lower reaction temperatures (0 °C instead of room temperature) led to higher enantioselectivities coupled with lower yields. The use of a reduced amount of catalyst (5 or even 2.5 mol % instead of the standard 10 mol %) led to a dramatic degradation of the chemical yields together with only slightly enhanced enantiomeric excesses.

The absolute configuration of the produced benzoin was determined to be (*S*) by comparison to the measured optical rotation value with the corresponding literature data.[36] This stereochemical outcome might be explained by transition state **26** shown in Figure 7. The *si*-face of the intermediate formed in the hypothetical catalytic cycle would be sterically shielded by the *tert*-butyl group of the bicyclic catalyst. Accordingly, the second aldehyde molecule would attack the Breslow intermediate at its *re*-face.

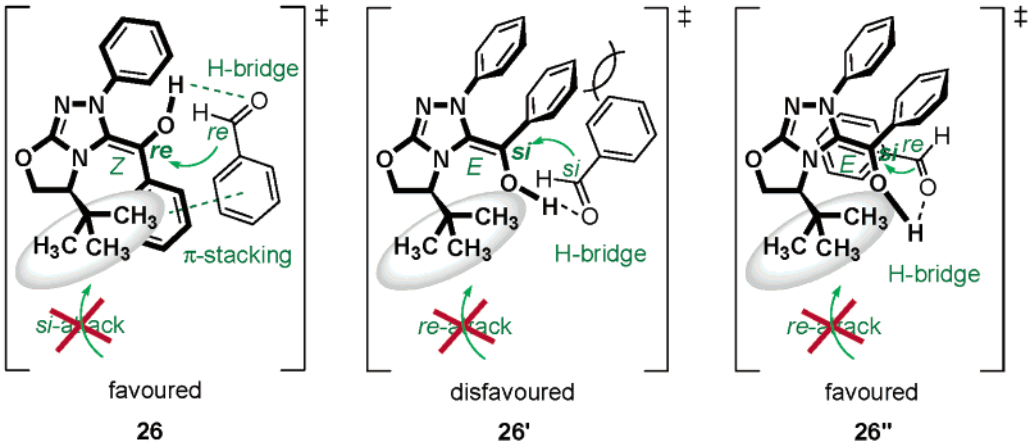


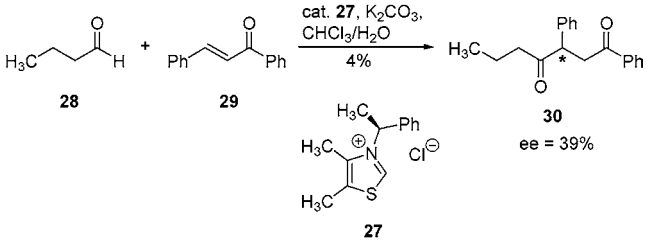
FIGURE 7. Possible transition states for the asymmetric benzoin condensation proposed by Enders et al. and Houk et al.

Furthermore, the phenyl substituent of the enol moiety might cause a preorientation of the approaching second aldehyde (via π-stacking and H-bridge activation of the aldehyde carbonyl group) that leads to a favorable arrangement for the formation of the new C−C bond. Thus, the *re*-face of the approaching aldehyde molecule would be preferred which in consequence leads to the (*S*) configuration of the new stereocenter in the benzoin product.

However, caution is advisable for such interpretations since the *E*/*Z* geometry of the Breslow intermediate has not been determined yet. The olefin geometry does not directly affect the stereoselectivity of the reaction because no stereocenter is formed there; the carbonyl group of the first aldehyde that is transformed into the enol moiety of the Breslow intermediate is regenerated in the product molecule. Nevertheless, the *E*/*Z* geometry of the enol intermediate is crucial for the preorientation of the second aldehyde molecule: the *E* isomer would, if one assumes the same H-bridge interactions, probably favor an *si*−*si*-attack as shown in transition state **26′**, leading to (*R*)-benzoin. This stereochemical outcome is not observed; this might be explained by an unfavorable sterical interaction in transition state **26′** between the twisted phenyl substituent of the enamine moiety and the phenyl substituent of the attacking aldehyde. Referring to computational calculations, Houk et al. recently proposed that **26″** should be the most stable transition state.[37] In this intermediate, π-stacking does not occur, but the substituent of the approaching aldehyde resides in an open pocket above the catalyst where steric repulsion is at a minimum. In summary, the proposed transition states seem to correlate well with the observed stereochemistry of the benzoin products.

Recently, Suzuki et al. reported an intramolecular crossed benzoin condensation starting from a bifunctional aldehyde−ketone that yielded polycyclic α-hydroxy ketones.[38] Chiral catalysts have not been used so far, but their nonchiral commercial thiazolium salts have been shown to catalyze some stereoselective variants of the reaction: a stereocenter introduced earlier into the substrate molecule induced diastereoselectivities in the benzoin reaction. In addition to these approaches, enzyme-based systems as well have brought forth promising results in thiazolium-catalyzed benzoin cross-coupling reactions.[39]

Scheme 8. First Attempts in the Asymmetric Stetter Reaction by Enders et al.



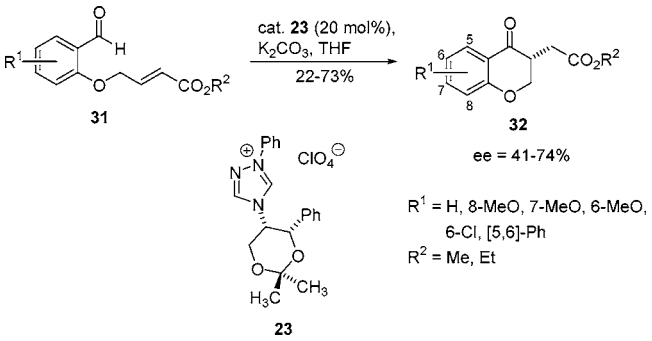
Stetter Reaction. In the 1970s, Stetter et al. succeeded in transferring the concept of thiazolium catalyzed nucleophilic acylation of aldehydes to the substrate class of Michael acceptors. The Stetter reaction, the addition of an activated aldehyde to an acceptor bearing an activated double bond, created a new catalytic pathway for the synthesis of 1,4-bifunctional molecules.[40]

Consequently, in our research group, new chiral thiazolium salts (e.g., catalyst **27**) were applied in the first investigations on the asymmetric Stetter reaction. The results are shown in Scheme 8. The reaction of butanal **28** with chalcone **29** in a two-phase system gave the 1,4-diketone **30** with a chemical yield of only 4%, but an encouraging enantiomeric excess of 39%.[41]

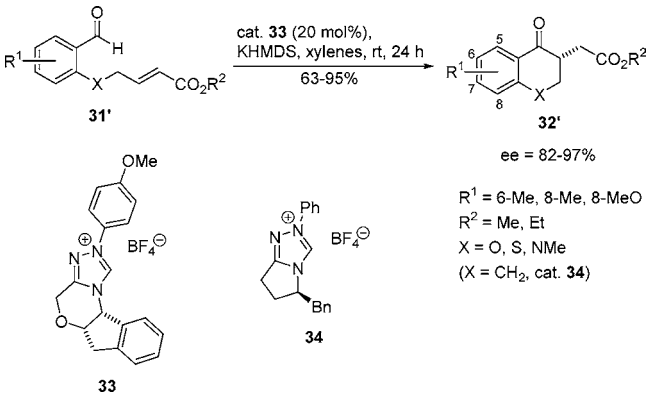
Unfortunately, the catalytic activity of thiazolium as well as triazolium salts in the Stetter reaction remained generally low. Although the activity of triazolium salts in the nonenantioselective Stetter reaction had been previously reported,[40a] some triazol-5-ylidenes have been shown to give stable adducts with several Michael acceptors—a possible reason for their failure in catalysis.[20b]

We envisaged an intramolecular variant where the reactivity of the substrate should be considerably enhanced due to entropic factors.[42] The stereoselective synthesis of various 4-chromanones via an intramolecular Stetter reaction, as can be seen in Scheme 9, was performed with yields in the range of 22−73% and enantiomeric excesses of 41−74%.[31c,43]

Scheme 9. First Asymmetric Intramolecular Stetter Reactions by Enders et al.



Scheme 10. Asymmetric Intramolecular Stetter Reaction of Aromatic Substrates Developed by Rovis et al.

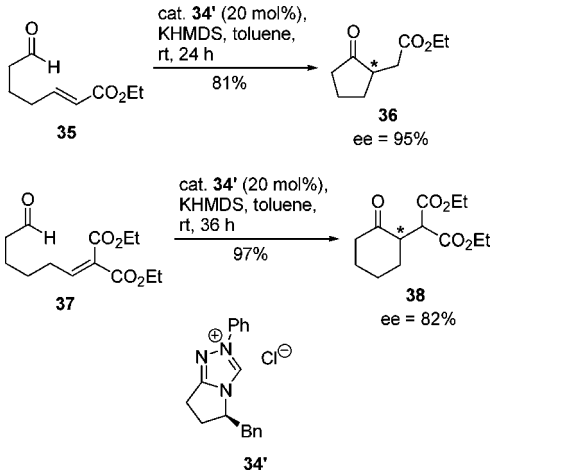


Recently, Rovis et al. achieved an improvement of the asymmetric intramolecular Stetter reaction using triazolium salts similar to those synthesized earlier by Leeper et al.[44] Employing catalysts of the types **33** and **34**, as depicted in Scheme 10, they obtained good enantioselectivities of 82−97% (chemical yields 63−95%) in the synthesis of numerous chromanones and aza-, thia-, and carbacyclic analogues **32′**. Thus, the scope of the reaction has been much expanded; however, it remains considerably restricted since only *E*-alkenes that are sufficiently activated for electrophilic attack can be used as Michael acceptors.[45]

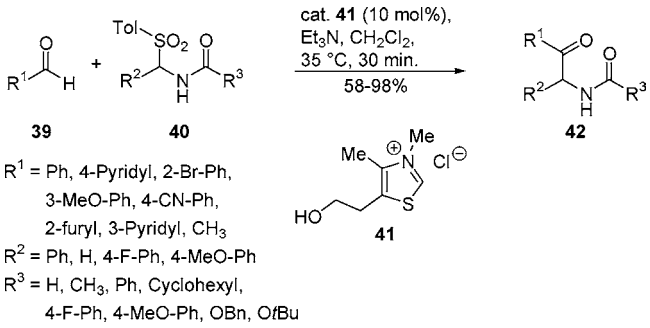
Rovis et al. also examined aliphatic substrates such as **35** and **37** that led to cyclopentanone **36** and cyclohexanone **38**, respectively, with good yields and good enantioselectivities in the asymmetric intramolecular Stetter reactions shown in Scheme 11. The olefin of substrate **37** is doubly activated by two ester substituents.[45] This reactivity enhancement of the Michael acceptor proved to be necessary because the greater conformational freedom of the aliphatic linker in compound **37** critically diminished the reactivity of the aliphatic substrate compared to the aromatic substrate **31′**.

Reider et al. reported the synthesis of α-amido ketones **42** in a cross-coupling reaction of aldehydes **39** and acylimines, catalyzed by the thiazolium salt **41**.[46] This aza-Stetter type system is shown in Scheme 12; the acylimine, formed in situ from an arylsulfonamide **40**, functions as the Michael acceptor. Although not enantioselective, this

Scheme 11. Asymmetric Intramolecular Stetter Reaction of Aliphatic Substrates Developed by Rovis et al.



Scheme 12. Stetter Reaction with Acylimine Acceptors Reported by Reider et al.



remarkable reaction demonstrates the versatility of the Stetter protocol.

Conclusion

It is still difficult to fulfill the standards set by nature in its enzymatic reactions, but the research done by many chemists in the field of carbene catalysis has already resulted in some impressive examples of efficiency and stereoselectivity. The achievement of the asymmetric benzoin condensation of aromatic aldehydes and of the intramolecular asymmetric Stetter reaction mark important steps on the way and might become powerful tools in the chemist's hands. The mechanisms of these reactions have been elucidated, and researchers have finally succeeded in isolating nucleophilic carbenes. Yet, the successful reactions reported so far are selective but restricted in scope and conditions, and more reactions are queued up: the condensation of aliphatic aldehydes has not yet found its optimum catalyst, the asymmetric intermolecular Stetter reaction is waiting for a breakthrough, and only a few crossed acyloin condensations have been reported. Recent reports on transesterification reactions[47] and ring-opening polymerizations[48] altogether catalyzed by *N*-heterocyclic carbenes provide only first examples for a further extension of the scope of organocatalytic systems involving nucleophilic carbenes. Much more work has to be done to really knock on nature's door.

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