Organocatalysis by N-Heterocyclic Carbenes

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Contents

1. Introduction

In the investigation of efficient chemical transformations, the carbon−carbon bond-forming reactions play an outstanding role. In this context, organocatalytic processes have achieved considerable attention.[1] Beside their facile reaction course, selectivity, and environmental friendliness, new synthetic strategies are made possible. Particularly, the inversion of the classical reactivity (Umpolung) opens up new synthetic pathways.[2] In nature, the coenzyme thiamine (vitamin B_1), a natural thiazolium salt, utilizes a catalytic variant of this concept in biochemical processes as nucleophilic acylations.[3] The catalytically active species is a nucleophilic carbene.[4]

Carbenes belong to the most investigated reactive species in the field of organic chemistry. As typical structural features, all carbenes are neutral and possess a bivalent carbon atom with an electron sextet. First evidence for the existence of carbenes is found in the pioneering work of Buchner and Curtius and Staudinger and Kupfer in the late 19th and early 20th century.[5] Because of their pronounced reactivity, carbenes could not be isolated until recently and were regarded as reactive intermediates.[6,7]

Since the first reports of stable nucleophilic carbenes by Bertrand and co-workers[8] and Arduengo et al.[9] in the late 1980s and early 1990s, the broad application of N-heterocyclic carbenes (NHCs) in organic synthesis has been impressively demonstrated. Beside their role as excellent ligands in metal-based catalytic reactions,[10] organocatalytic carbene catalysis has emerged as an exceptionally fruitful research area in synthetic organic chemistry.[11] This review highlights the extensive applications and reaction pathways of thiazol- (**A**), triazol- (**B**), imidazol- (**C**), and imidazolin-2-ylidenes (**D**) as versatile synthetic methods (Figure 1).

2. Enzymes as Archetypes

In nature, realms of complex biochemical reactions are catalyzed by enzymes, many of which lack metals in their active site. Among them, nucleophilic acylation reactions are catalyzed by transketolase enzymes[12] in the presence of coenzyme thiamine (**1**, vitamin B_1).[3] Inter alia, this coenzyme is present in baker's yeast and might serve as an example of highly selective chemical reactions that are accomplished in vivo. In 1954, Mizuhara et al. found that the catalytic active species of the coenzyme thiamine is a nucleophilic carbene (Figure 2).[4] The biochemistry of thiamine-dependent enzymes has been studied in detail, resulting in broad applications as synthetic tools.[13]

An X-ray structure of a thiamine-dependent transketolase enzyme was determined by Schneider et al. after isolation from *Saccharomyces cerevisiae* in the 1990s and is shown in Figure 3.[14] The thiamine cofactor is embedded in a narrow channel in the center of the enzyme. From the complex surrounding of the heart of this enzyme, it seems to be obvious that chemical reactions at the catalytically active site in this channel proceed inevitably with high selectivities.

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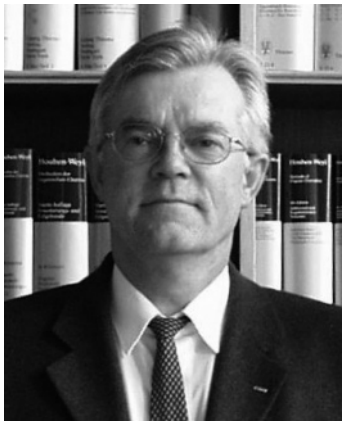

Dieter Enders was born in 1946 in Butzbach, Germany. He studied chemistry at the Justus Liebig University Giessen and received his Dr. rer. nat. under the supervision of Professor D. Seebach in 1974. After postdoctoral studies at Harvard University with Professor E. J. Corey, he returned to Giessen, obtaining his habilitation in 1979. In 1980 he moved to the University of Bonn as an associate professor, and in 1985 he moved to his present position as Professor of Organic Chemistry at the RWTH Aachen University. His current research interests are asymmetric synthesis, new synthetic methods using organometallics, the stereoselective synthesis of biologically active compounds, and organocatalysis. He has been the recipient of many prizes, among them the Leibniz Prize (Deutsche Forschungsgemeinschaft), the Yamada Prize (Japan), the Max Planck Research Award (Max Planck Gesellschaft and Alexander von Humboldt Foundation), and the Emil Fischer Medal (Gesellschaft Deutscher Chemiker).

Oliver Niemeier was born in 1976 in Leverkusen, Germany. He studied chemistry at the RWTH Aachen University, where he received his diploma degree in 2004. In 2006 he obtained his Ph.D. under the supervision of Professor D. Enders. His research was concerned with the development of novel chiral triazolium salts, their application in carbene-catalyzed intramolecular crossed benzoin cyclizations, and organocatalytic asymmetric intramolecular aldol reactions. From May on, he is carrying out postdoctoral research at Imperial College London with Professor A. G. M. Barrett.

The aim of many organic chemists is to develop synthetic catalysts that mimic this enzymatic system. Therefore, only the actually catalytically active site, without the necessity of the huge enzyme proteins around it, is the goal, as well as to use it efficiently and selectively in organic reactions.

3. Benzoin Condensation

3.1. Breslow Mechanism

The benzoin condensation catalyzed by N-heterocyclic carbenes has been intensively investigated. First investigations date back to 1832 when Wöhler and Liebig discovered the cyanide-catalyzed coupling of benzaldehyde to benzoin.[15]

Alexander Henseler was born in Bonn in 1979. He studied chemistry in Cologne and Sheffield and received his diploma from the Universität zu Köln in 2006. As a scholarship holder of the RWTH Aachen Graduiertenkolleg, he is now working on his Ph.D. in the research group of Professor D. Enders. His research studies focus on the development of new chiral N-heterocyclic carbene catalysts and their application in asymmetric synthesis.

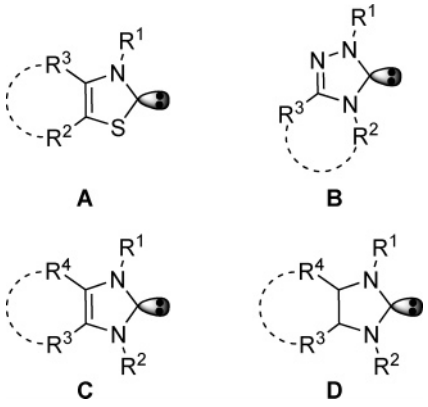

Figure 1. General types of N-heterocyclic carbenes.

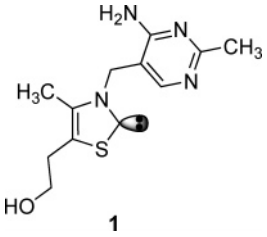

Figure 2. Coenzyme thiamine (vitamin B_1).

In 1903, Lapworth postulated a mechanism for this reaction in which an intermediate carbanion is formed by hydrogen cyanide addition to benzaldehyde followed by deprotonation.[16] Here, the former carbonyl carbon features an inverted, nucleophilic reactivity. This intermediate "active aldehyde" exemplifies the "Umpolung" concept of Seebach and coworkers.[2] In 1943, Ugai et al. recognized that thiazolium salts could also be used as catalysts in the benzoin condensation.[17] In 1958, on the basis of the work of Lapworth, Breslow proposed a mechanistic model for the thiazolium salt-catalyzed benzoin condensation.[18] In this mechanism, the catalytically active species is thiazolin-2-ylidene **3**, a carbene compound, which is formed in situ by deprotonation of the thiazolium salt **2**. The postulated catalytic cycle is shown in Scheme 1.

Breslow assumed that the thiazolium salt **2** is deprotonated at its most acidic position to form the thiazolin-2-ylidene **3**,

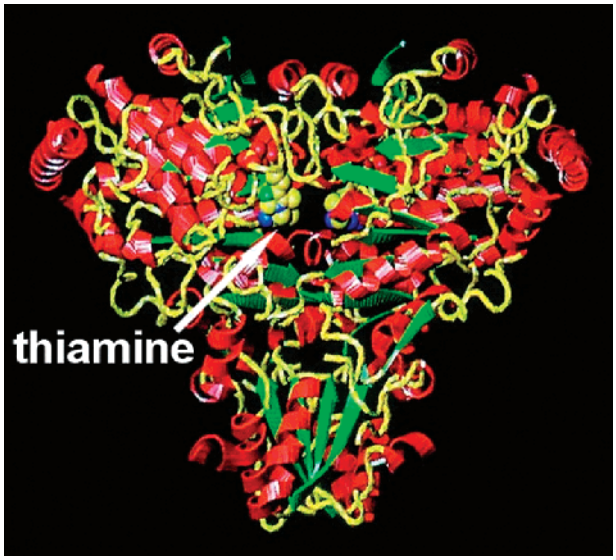

Figure 3. Structure of the transketolase enzyme isolated from *Saccharomyces cerevisiae*.

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

originally drawn as a mesomeric zwitterion. Nucleophilic attack of the carbonyl function of an aldehyde **4** then generates the thiazolium salt adduct **5**. Deprotonation/reprotonation leads to the active aldehyde in the form of the resonance-stabilized enaminol-type Breslow intermediate **6**. This nucleophilic acylation reagent **6** (equivalent to a d^1-synthon in the terminology of Seebach et al.) reacts again with an electrophilic substrate such as the carbonyl group of a second aldehyde molecule. The intermediate **7** eliminates benzoin (**8**), and the original carbene catalyst **3** is regenerated.

Lemal et al.[19] postulated an alternative mechanistic model based on the facile formation of carbene dimers **9**, and this was extended by López Calahorra and co-workers (Figure 4).[20] These two competing models have been intensely discussed. Finally, the carbene dimer mechanism could not stand up to the Breslow mechanism.[21]

Stetter et al. were the first to use thiazolium salts as catalysts for the preparation of acyloin and benzoin compounds on a preparative scale. They could utilize this

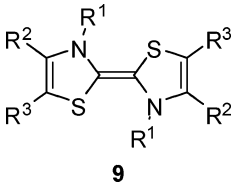

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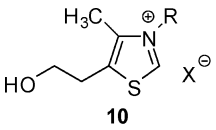
Figure 4. Thiazolin-2-ylidene dimer.

synthetic concept for the preparation of numerous α-hydroxyketones. Aliphatic aldehydes showed the best results with catalyst **10a**, whereas for aromatic substrates, the thiazolium salts **10b** or **10c** were better catalysts (Figure 5).[22,23]



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10a, R = Bn, X = Cl
10b, R = Me, X = I
10c, R = Et, X = Br

Figure 5. Thiazolium salts utilized by Stetter et al.

3.2. First Asymmetric Benzoin Condensations

As the product of the benzoin condensation is an α-hydroxyketone **8**, a new stereogenic center is formed. Consequently, many chemists have tried to develop heterazolium-catalyzed asymmetric benzoin condensations and, later, other nucleophilic acylation reactions (Scheme 2).

Scheme 2. Asymmetric Benzoin Condensation

In 1966, Sheehan and Hunneman presented the first results of an asymmetric benzoin condensation utilizing the chiral thiazolium salt **11** as precatalyst.[24] However, the enantiomeric excess of the synthesized benzoin was only 22%. Some years later, they were able to obtain enantiomeric excesses of up to 51% with modified thiazolium salts such as **12**. Unfortunately, the products were formed in low yields (6%).[25] Many years later, Dvorak and Rawal improved the protocol of Sheehan and co-workers, obtaining 48% enantiomeric excess (ee) with better yields.[26] Menthyl-substituted thiazolium salts such as **13** were developed by Takagi et al. and catalyzed the formation of benzoin in a micellar two-phase reaction system with an enantiomeric excess of 35% and an improved yield of 20%.[27] Zhao et al. combined the Sheehan catalysts with the Takagi reaction conditions and obtained moderate enantiomeric excesses of 47−57% and yields of 20−30%.[28] On the basis of their mechanistic model, in 1993 López Calahorra and co-workers synthesized bisthiazolium salt catalysts such as compound **14**, affording benzoin with 27% ee and a yield of 21% (Figure 6).[29]

3.3. Stable Carbenes

Side by side with the research on carbene-catalyzed benzoin condensations, much effort has been devoted toward the isolation of stable carbenes. The chemistry of nucleophilc carbenes was intensively studied by Wanzlick et al. in the 1960s.[30] Until then, the divalent carbenes were considered as highly reactive intermediates. In retrospective, Wanzlick et al. had N-heterocyclic carbenes in their hands, but they did not believe that they would be able to actually isolate

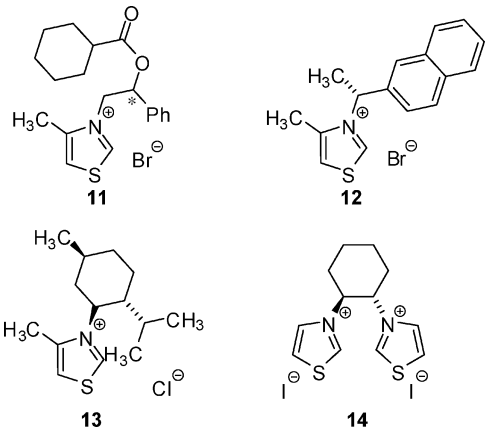


Figure 6. Chiral thiazolium salts for the asymmetric benzoin condensation.

them. Only the dimeric forms, the electron-rich olefins, were reported. It was more than 28 years later that Bertrand and co-workers[8] and Arduengo et al.[9,31] presented carbene compounds that were stable at room temperature. The best known representatives, the imidazolin-2-ylidenes, e.g., **15**, and derivatives, e.g., **16**, are today often called Wanzlick carbenes (Figure 7).

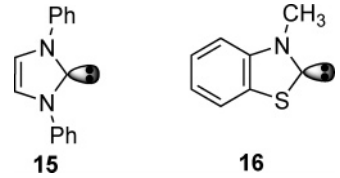
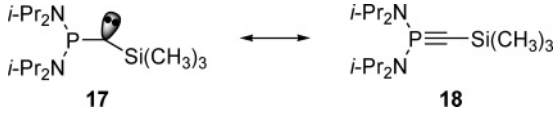


Figure 7. Typical Wanzlick carbenes.

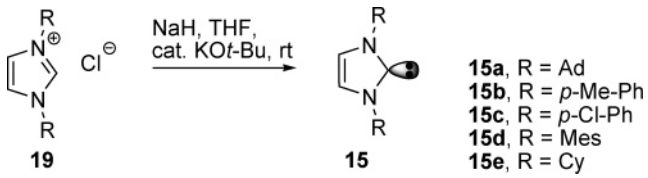
However, the carbene character of Bertrand's phosphinocarbene **17** was initially doubted, as its chemical reactivity appeared to resemble more a phosphaacetylene **18**.[32] Recent studies seem to support its carbene character again (Scheme 3).[33]

Scheme 3. Phosphinocarbene Reported by Bertrand and Co-workers

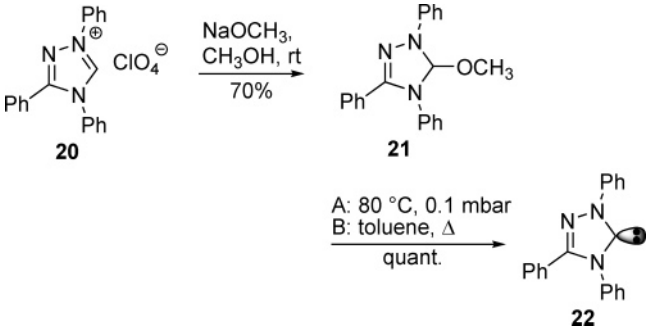


Thus, the imidazolin-2-ylidene **15a** synthesized by Arduengo et al. in 1991 is now referred to as the first N-heterocyclic carbene to be isolated and characterized. Its preparation was achieved by deprotonation of the corresponding imidazolium salt **19**. Later on, Arduengo et al. could also synthesize stable carbenes with less bulky substituents. It should be noted that the structure of these carbenes is identical with that of the Wanzlick carbenes. Progress in laboratory methods was finally decisive for the successful isolation of these carbenes (Scheme 4).

Scheme 4. Preparation of Stable Imidazolin-2-ylidenes by Arduengo and Co-workers



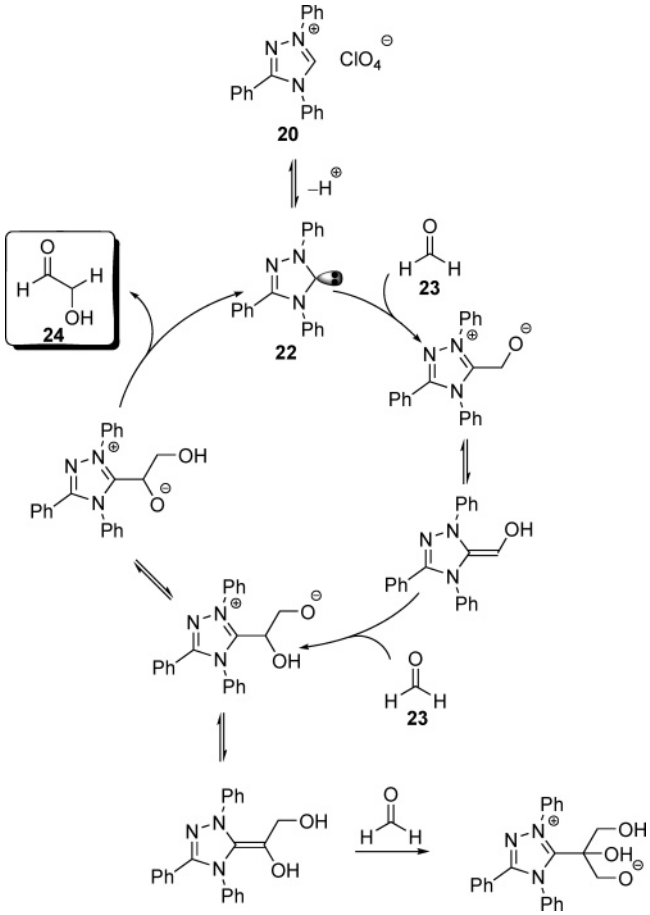
Scheme 5. Synthesis of the Stable Carbene 22 Developed by Enders and Teles and Co-workers



Since Arduengo et al.'s initial reports, numerous stable N-hereocyclic carbenes of various types have been synthesized.[6,10,34,35] Applications in organocatalysis and metal-based catalysis have developed rapidly.

Inspired by this success and based on our work on the asymmetric Stetter reaction in the late 1980s, our research group together with Teles and co-workers studied the triazole heterocycle as an alternative carbene structure. In 1995, we reported the synthesis of the triazolin-5-ylidene **22** starting from the triazole precursor **20**.[36] The crystalline carbene **22** was obtained from **20** by addition of sodium methanolate to give the stable adduct **21** followed by α-elimination of methanol, either at 80 °C under vacuum or in refluxing toluene. Compound **22** proved to be stable at temperatures up to 150 °C in the absence of air and moisture.[37] Compound **22** was the first carbene to be commercially available (Scheme 5).

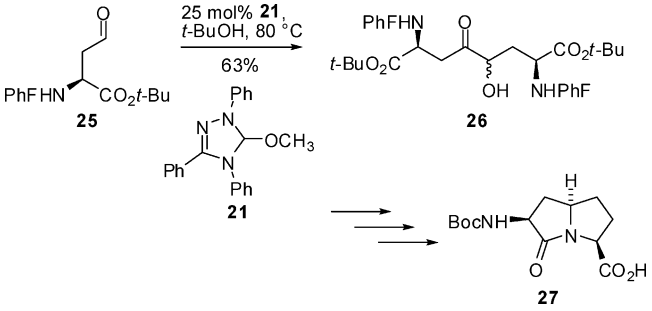
Scheme 6. Postulated Mechanism of the Formoin Condensation Reported by Teles and Co-workers



The triazolin-5-ylidene **22** turned out to be a powerful catalyst for the conversion of formaldehyde (**23**) to glycolaldehyde (**24**) in the "formoin reaction".[38] This reactivity is a useful complement to the catalytic properties of thiazolium salts, which mainly afford 1,3-dihydroxyacetone as product (Scheme 6).[39] As triazolium ylides are more stable than thiazolium ylides, the elimination of glycolaldehyde occurs faster than the addition of the third formaldehyde molecule.

An interesting application of the benzoin condensation utilizing precatalyst **21** was published by Dietrich and Lubell in their synthesis of the enantiopure pyrrolizidinone amino acid **27**.[40] Acyloin condensation of aspartate β-aldehyde **25** in *tert*-butyl alcohol at 80 °C yielded the corresponding α-hydroxyketone **26** in good yield with no need of a base to activate the catalyst (Scheme 7). The pyrrolizidone dipeptide structure **27** can be used to study conformation−activity relationships of biologically active peptides.

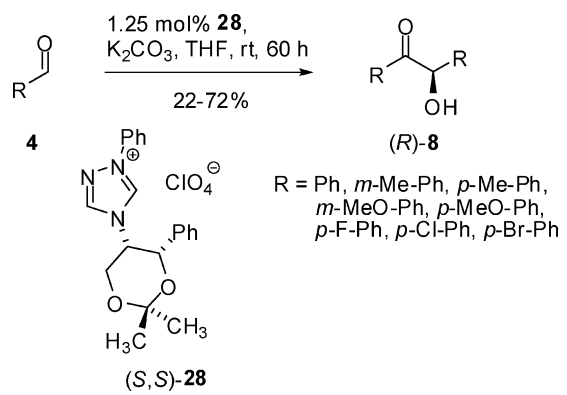
Scheme 7. Synthesis of the Enantiopure Pyrrolizidinone Amino Acid 27 by Dietrich and Lubell



3.4. Asymmetric Benzoin Condensations

The promising results of triazolium salt catalysis inspired our research group to synthesize a variety of chiral triazolium salts for the asymmetric benzoin condensation.[41] Extensive investigations have shown that the enantiomeric excesses and catalytic activities are highly dependent on the substitution pattern of the triazolium system. The most active catalyst (*S*,*S*)-**28** provided benzoin (**8**) in its (*R*)-configuration with 75% ee and a good yield of 66%. Remarkably, only low catalyst loadings were necessary (1.25 mol %), which indicated that the activity increased by almost 2 orders of magnitude compared to that of the chiral thiazolium salts used before. The application of the catalyst system to other electron-rich aromatic aldehydes **4** gave the corresponding α-hydroxyketones **8** with enantiomeric excesses up to 86%.

Scheme 8. Asymmetric Benzoin Condensation by Enders et al.



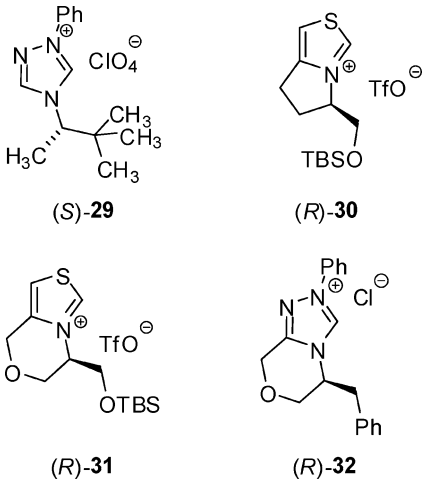


Figure 8. Chiral heterazolium salts of Enders [(*S*)-**29**] and Knight and Leeper [(*R*)-**30**−(*R*)-**32**].

Electron-deficient aldehydes showed significantly lower inductions (Scheme 8).

Attempts to apply catalyst (*S*,*S*)-**28** to aliphatic aldehydes resulted in very low enantiomeric excesses and yields. Utilizing triazolium salt (*S*)-**29** yielded only low enantiomeric excesses of up to 26% and only moderate yields (Figure 8).[42]

In 1997, Leeper and co-workers introduced novel bicyclic thiazolium salts for the asymmetric benzoin condensation. Utilizing catalyst (*R*)-**30**, an enantiomeric excess of 21% accompanied by a yield of 50% was obtained. With an optimized catalyst structure (*R*)-**31** aliphatic butyroin could be obtained with an enantiomeric excess of 33% (75% yield).[43] Another thiazolium salt containing a norbornane backbone gave benzoin in quantitative yields but only 26% ee.[44] By developing chiral, bicyclic triazolium salts, such as compound (*R*)-**32**, they could significantly improve their results. Various aromatic acyloins were produced with modest-to-good enantioselectivities (20−83% ee) (Figure 8).[45]

Scheme 9. Asymmetric Benzoin Condensation of Aromatic Aldehydes by Enders et al.

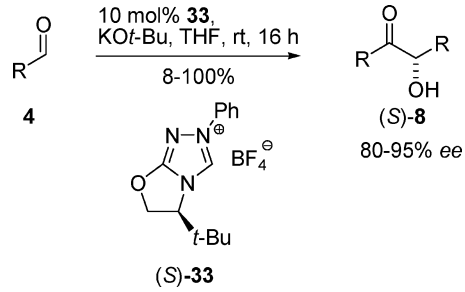


Table 1. Scope of the Asymmetric Benzoin Condensation by Enders et al.

R	*T* (°C)	yield (%)	ee (%)	R	*T* (°C)	yield (%)	ee (%)
Ph	18	83	90	*m*-Cl-Ph	18	92	62
Ph[a]	18	46	93	*m*-Cl-Ph	0	85	86
Ph[b]	18	33	99	*p*-Me-Ph	18	16	93
p-F-Ph	18	81	83	*m*-Me-Ph	18	70	86
p-F-Ph	0	61	91	*m*-Me-Ph	0	36	91
p-Cl-Ph	18	80	64	*p*-MeO-Ph	18	8	95
p-Cl-Ph	0	44	89	*o*-furyl	0	100	64
p-Br-Ph	18	82	53	*o*-furyl	−78	41	88
p-Br-Ph	0	59	91	*o*-naphthyl	18	69	80

[a] 5 mol % **33**. [b] 2.5 mol % **33**.

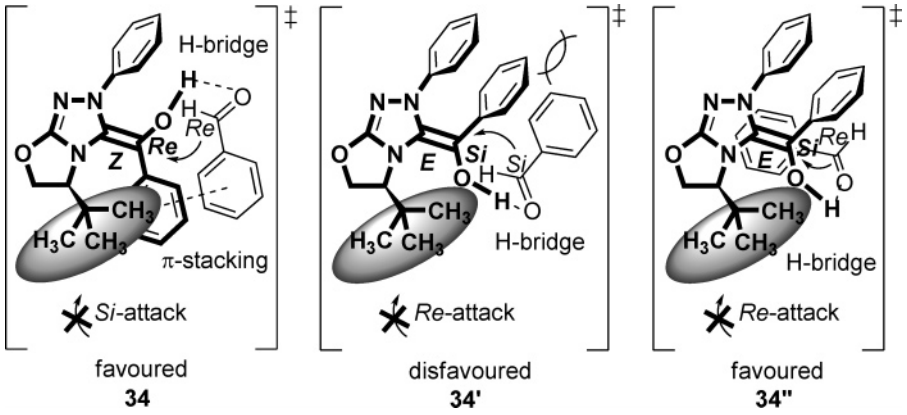


Figure 9. Transition states for the asymmetric benzoin condensation proposed by Enders et al. and Dudding and Houk.

Inspired by these results, another chiral bicyclic triazolium salt was developed in our research group in 2002. Triazolium salt (*S*)-**33**, derived from (*S*)-*tert*-leucine, was applied in the asymmetric benzoin condensation.[46] (*S*)-Benzoin (**8**) was produced in a very good enantioselectivity (90% ee, 83% yield). The condensation of numerous other aromatic aldehydes **4** yielded the corresponding α-hydroxyketones **8** with exellent enantiomeric excesses up to 99%. As previously observed, electron-rich aldehydes gave higher asymmetric inductions than the electron-deficient ones. Lower reaction temperatures (0 °C instead of room temperature) or lower amounts of catalyst caused decreasing yields but slightly enhanced enantiomeric excesses (Scheme 9, Table 1).

The transition state **34**, shown in Figure 9, has been proposed to explain the observed absolute configuration. The *Si*-face of the assumed Breslow-type intermediate would be steric shielded by the *tert*-butyl group of the bicyclic catalyst. The second aldehyde molecule would then attack the hydroxyenamine from its *Re*-face, leading to an (*S*)-configured product, which is actually observed in the experiments. In addition, interactions of the phenyl substituent of the enol moiety (via π-stacking) as well as intermolecular H-bridge activation of the aldehyde function with the hydroxyl group of the Breslow intermediate may lead to a preorganized transition state.

However, the (*E*/*Z*)-geometry of the Breslow intermediate has not yet been determined but is relevant for the preorientation of the second aldehyde molecule. As shown in transition state **34′**, the corresponding (*E*)-isomer would probably favor a *Si*−*Si*-attack and, therefore, a (*R*)-configuration in the product. An unfavorable steric interaction between the phenyl substituent of the enol moiety and the phenyl substituent of the attacking aldehyde in **34′** probably disfavors this transition state. The most favorable transition state has been determined to be **34″** through computational calculation by Dudding and Houk.[47] In this transition state, no π-stacking occurs, but the substituent of the approaching aldehyde resides in an open pocket of the catalyst with minimum steric repulsion. Thus, the formation of (*S*)-benzoin would again be favored.

Besides the catalysis of the benzoin condensation with a variety of central chiral N-heterocyclic carbenes, Bach and co-workers recently utilized axially chiral *N*-arylthiazolium salts such as **35** as precatalysts.[48] The best results obtained with this catalyst were 85% yield and up to 40% ee of the benzoin product (*R*)-**8**. The rather low inductions were explained by the not-sufficiently-restricted rotation around the stereogenic axis of the corresponding active carbene intermediate (Figure 10).

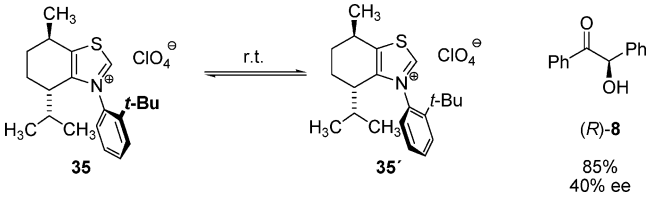


Figure 10. Axially chiral thiazolium salt used by Bach and co-workers.

Further catalyst concepts range from C_1- and C_2-symmetric *N*-alkylbenzimidazolium and thiazolium salts, e.g., **36**,[49] to chiral rotaxanes tethering a thiazolium salt moiety as **37**. However, the enantioselectivity obtained with the conceptually new C_2-symmetric enantiomerically pure bisthiazolium salt **36** remained with 15% ee in a low range. Takaka and co-workers have recently applied rotaxanes such as **37** in the asymmetric benzoin condensation; however, the enantiomeric excesses with up to 32% remained rather low (Figure 11).[50]

Davis and Forrester[51] and, later, Xu et al.[52] showed that thiazolium- and imidazolium-ion based ionic liquids also promote the benzoin condensation effectively. The room-

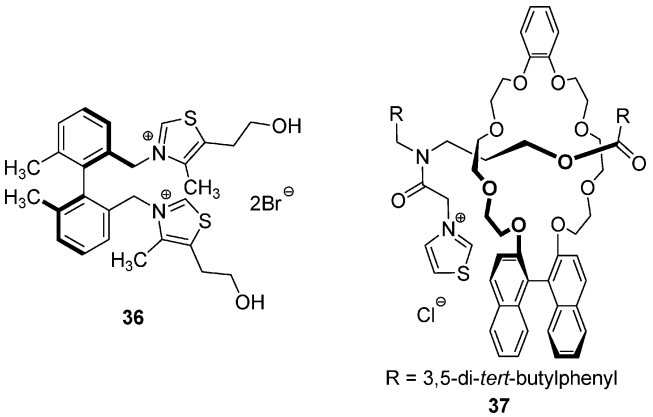


Figure 11. Conceptually new chiral thiazolium salts **33** and **34**.

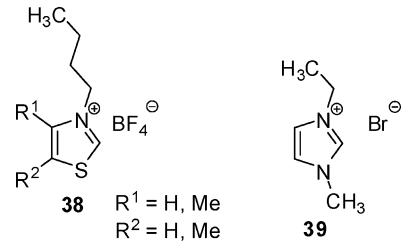


Figure 12. Ionic liquids as catalysts for the benzoin condensation.

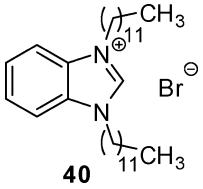


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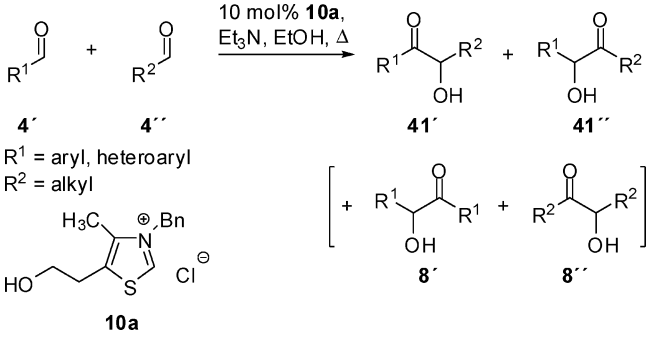
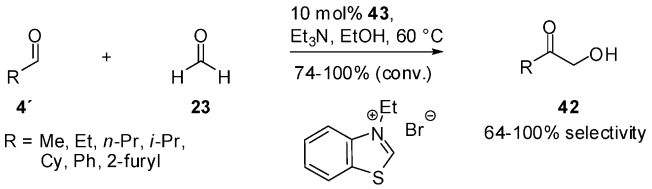
Figure 13. Benzimidazolium salt used for the benzoin reaction in water.

Scheme 10. Crossed Benzoin Condensation by Stetter and Dämbkes



4′ 4′′ 41′ 41′′ 8′ 8′′ 10a

Scheme 11. Selective Cross-Acyloin Condensation by Inoue and Co-workers



4′ 23 42 43

temperature organic ionic liquids **38** promoted the benzoin condensation of benzaldehyde, when treated with small quantities of triethylamine, with 80% conversion after 1 week. Recently, the first example of simple 1-*N*-alkyl-3-methylimidazolium salts, e.g., **39** (EMIMBr), as precatalysts in the benzoin condensation has been demonstrated. Several aliphatic and aromatic aldehydes could be utilized to yield the corresponding α-hydroxyketones (Figure 12).

A short time ago, the first benzoin reaction in water catalyzed by benzimidazolium salts was presented.[53] A long hydrophobic N-alkyl chain as in **40** was proven to give the best yields, since it was considered to play an important role in the micelle formation. Because the obtained α-hydroxyketones can simply be filtered without need for further purification, this protocol seems to be quite interesting from the viewpoint of green chemistry (Figure 13).

Almost simultaneously, the research group of Degani developed a very fast microwave-assisted benzoin condensation in aqueous reaction media.[54] The utilized vitamin B_1 catalyst gave good yields of the benzoin products, and the reaction could be run to completion within 20 s.

3.5. Crossed Benzoin Condensations

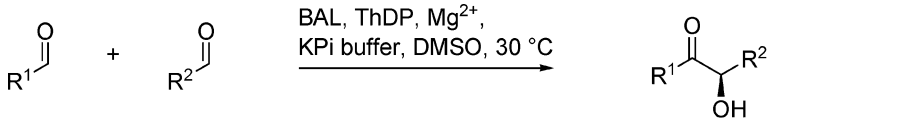
An obvious extension of the benzoin reaction is the cross-coupling of different aldehydes or of aldehydes and ketones. In crossed acyloin condensations, usually a mixture of all possible symmetric and asymmetric acyloins **8′**−**8′′** and **41′**−**41′′** is obtained. Stetter and Dämbkes could show that, in some special cases, an excess of aliphatic aldehyde (R^2 = *i*-Bu) in combination with an aromatic or heteroaromatic aldehyde (R^1 = *o*-Cl-Ph, thiophenyl) (3:1) could yield selectively one of the two asymmetric acyloins **41′** (Scheme 10).[55] This chemoselective outcome can be explained by the reaction of the more stable Breslow intermediate, derived from the aromatic aldehyde, with the more reactive aliphatic aldehyde. A crossed acyloin condensation of aliphatic aldehydes could also be achieved with this method but can be explained by statistical arguments.[56] Because the yields are based on the minor aldehyde, which must mainly give the crossed acyloin for statistical reasons, no direct crossed condensation is obtained.

A selective cross-acyloin condensation of formaldehyde (**23**) and another aldehyde **4′** to yield exclusively 1-hydroxy-2-ones **42** was reported by Inoue and co-workers.[57] Among different screened catalysts, 3-ethylbenzothiazolium bromide **43** in combination with an alcohol as solvent showed the best results with respect to reactivity and selectivity (Scheme 11). In the proposed catalytic cycle, the carbene catalyst initially selectively attacks the aldehyde because of the stabilizing effects of the R-groups in the Breslow intermediate **6** (Scheme 1). The following selective attack to formaldehyde was explained by the higher electrophilic character in comparison with the other aldehyde.

Müller and co-workers could obtain enantiopure α-hydroxyketones, benzoins, and acyloins using the thiamine-dependent enzymes benzaldehyde lyase (BAL)[58] or benzoylformate decarboxylase (BFD).[59] Mostly aromatic aldehydes were linked to acetaldehyde chemo- and stereoselectively. In 2002, the first asymmetric crossed benzoin condensation was reported by the same group.[60] Mixed benzoins **41′** were obtained with high selectivities and enantiomeric excesses utilizing thiamine diphosphate (ThDP)-dependent enzymes by taking advantage of the aldehyde donor−acceptor behavior (Scheme 12).

The crossed benzoin condensation is not limited to aldehyde−aldehyde coupling; the reaction between aldehydes and aldimines is also possible. Murry et al. developed a thiazolium-catalyzed (**10a**) addition of aldehydes **4** to *N*-acylimines, which is analogous to an azabenzoin condensa-

Scheme 12. Enzymatic Asymmetric Cross-Benzoin Condensation

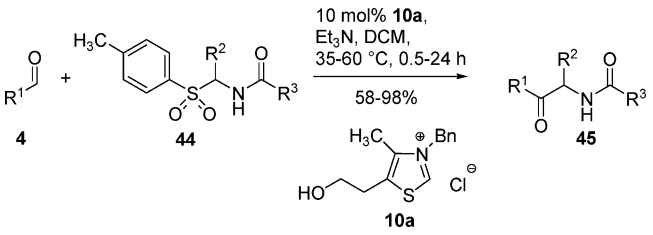


4′ 4′′ conversion, selectivity, *ee* up to > 99%

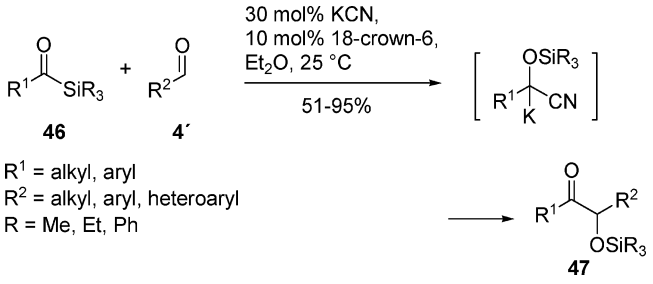
(*S*)-**41′**

R^1 = Ph, 3-CN-Ph, 4-Br-Ph, 4-CF_3-Ph, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl,
R^2 = 2-Cl-Ph, 2,6-difluorophenyl, 2,3,5-trifluorophenyl, 2,3,4,5,6-pentafluorophenyl

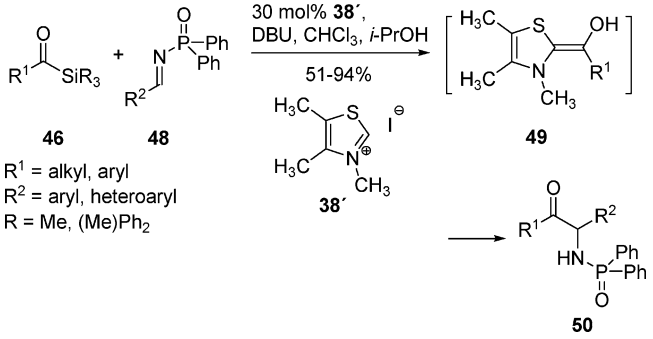
Scheme 13. Azabenzoin Reaction by Murry et al.



Scheme 14. Cyanide Catalyzed Crossed Silyl Benzoin Condensation by Johnson and Co-workers



Scheme 15. Synthesis of α-Aminoketones by Mattson and Scheidt



tion.[61] Arylsulfonylamides **44** served as precursors for the *N*-acylimines and were generated by elimination. The proposed mechanism is analogous to that for the benzoin reaction with in situ generation of the Breslow intermediate and attack on the *N*-acylimine acceptor. Different biochemically relevant α-amidoketones **45** could be synthesized with this strategy (Scheme 13, Table 2). Electron-deficient aldehydes performed much better in this reaction than electron-rich ones. Aliphatic aldehydes (entry 15) as well as α,*β*-unsaturated aldehydes (entry 17) were shown to be suitable.

Table 2. Scope of the α-Amidoketones 45 Synthesized by Murry et al.

entry	R^1	R^2	R^3	time	yield (%)
1	4-pyridinyl	Ph	H	30 min	86
2	4-pyridinyl	Ph	Me	30 min	93
3	4-pyridinyl	Ph	Cy	30 min	98
4	4-pyridinyl	Ph	Ph	30 min	88
5	4-pyridinyl	Ph	*p*-F-Ph	30 min	90
6	4-pyridinyl	Ph	*p*-MeO-Ph	30 min	97
7	4-pyridinyl	Ph	OBn	15 min	96
8	4-pyridinyl	Ph	O*t*-Bu	15 min	85
9	Ph	Ph	O*t*-Bu	24 h	75
10	*m*-Br−Ph	Ph	O*t*-Bu	8 h	86
11	*p*-MeO-Ph	Ph	O*t*-Bu	48 h	68
12	*p*-CN-Ph	Ph	O*t*-Bu	15 min	80
13	2-furyl	Ph	O*t*-Bu	24 h	73
14	3-pyridinyl	Ph	O*t*-Bu	24 h	93
15	Me	Ph	O*t*-Bu	24 h	62
16	$BnOCH_2$	Ph	O*t*-Bu	24 h	75
17	PhCH=CH	Ph	Cy	24 h	80
18	4-pyridinyl	*p*-F-Ph	Cy	30 min	76
19	4-pyridinyl	*p*-MeO-Ph	Cy	30 min	84
20	4-pyridinyl	H	Ph	24 h	58

A nonenzyme-catalyzed crossed benzoin condensation should be mentioned, although so far not catalyzed by N-heterocyclic carbenes. Johnson and co-workers have recently reported crossed silyl benzoin condensations catalyzed by cyanide. The acylsilanes **46** serve as superior acylanion precursors, which avoid the usual problem of self-condensation.[62] α-Siloxyketones **47** could be synthesized via a Brook rearrangement with complete regiocontrol with the catalyst system KCN/**18**-crown-**6** (Scheme 14). By applying $La(CN)_3$ as a catalyst, alkyl- and α,*β*-unsaturated substrates could also be used.[63] An enantioselective version was also developed by the same group using chiral metallophosphites as Umpolung catalysts.[64]

Mattson and Scheidt were able to use a similar strategy with the catalytic addition of acylsilanes **46** to imines **48** in a synthesis of α-aminoketones **50**.[65] By employing a readily available thiazolium salt **38′** as carbene precursor, the direct formation of *N*-phosphinylated aminoketones was made possible (Scheme 15). The formation of benzoin was completely avoided. In the proposed catalytic cycle, after Brook rearrangement,[66] an enolsilane is formed and undergoes conversion to the Breslow intermediate **49** in the presence of an alcohol (*i*-PrOH).

A successful asymmetric variant of the azabenzoin reaction has recently been presented by Miller and co-workers, who

Scheme 16. Enantioselective Intermolecular Aldehyde−Imine Cross-coupling by Miller and Co-workers

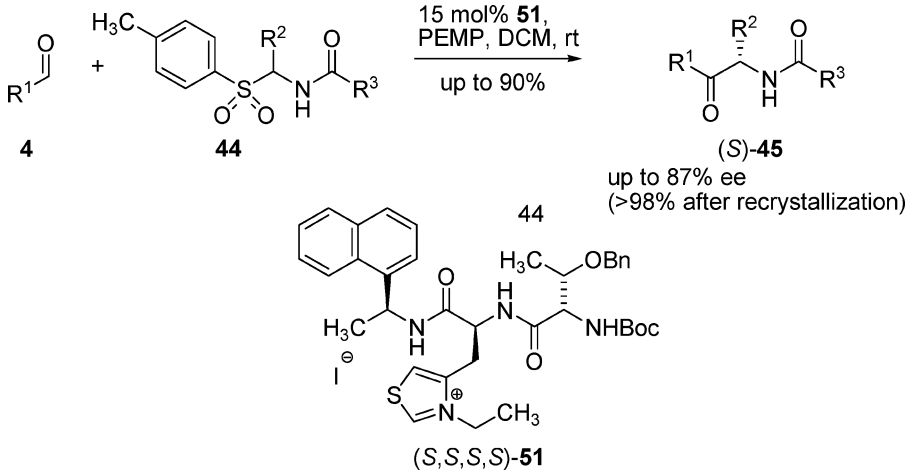


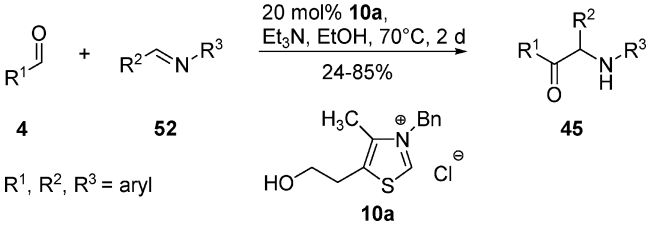
Table 3. Enantioselective Synthesis of α-Amidoketones by Miller and Co-workers

R^1	R^2	R^3	time	yield (%)	ee (%)
p-Cl-Ph	Ph	Ph	2 h	100	78
p-Cl-Ph	*p*-MeO-Ph	Ph	2 h	90	87
o-NO_2-Ph	*p*-MeO-Ph	Ph	15 min	77	82
o-NO_2-Ph	*p*-MeO-Ph	*i*-Pr	15 min	63	79
p-Cl-Ph	Ph	*i*-Pr	2 h	97	75
p-Cl-Ph	2,4-dimethoxyphenyl	Ph	1 h	80	81
Ph	Ph	Ph	2 h	15	83

employed chiral peptidic thiazolium salts such as the compound (*S*,*S*,*S*,*S*)-**51** (see Scheme 16).[67] They observed that the structure and stoichiometry of the base significantly influenced the activity of the catalyst. The hindered base pentamethyl piperidine (PEMP) gave the highest ee values (Scheme 16, Table 3).

You and co-workers have recently shown that aromatic aldehydes **4** can also be coupled to unactivated imines **52** (R^2, R^3 = aryl) to form α-aminoketones **45** under thermodynamic control.[68] In contrast, in the investigations of Murry et al. and Miller and co-workers, the product was formed under kinetic control, as the imine must react faster with the Breslow intermediate than with another aldehyde molecule. By utilizing the thiazolium chloride **10a**, a wide range of substrates was successfully used in this reaction with varying yields (Scheme 17). Studies to understand the reaction mechanism revealed at least a partial thermodynamic control, as the desired product was also formed with benzoin as substrate.

Scheme 17. Intermolecular Aldehyde−Imine Cross-coupling by You and Co-workers

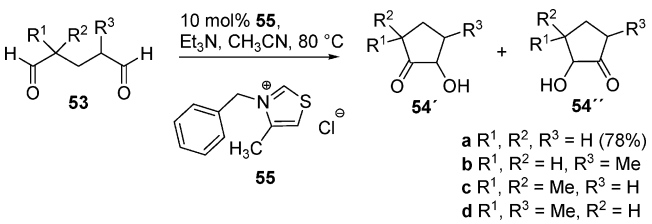


3.6. Intramolecular Crossed Benzoin Condensations

In contrast to the previously described intermolecular condensation reaction, intramolecular crossed benzoin reactions have been developed for a much shorter time. In 1976, Cookson and Lane reported a cyclization of glutaric aldehydes **53** with thiazolium salts as precatalysts (**55**) to the corresponding hydroxylcyclopentanones **54′** and **54″**.[69] Unfortunately, asymmetric dialdehydes (**53b−c**) only yielded the isomeric α-ketoles **54′b−c** and **54″b−c** (Scheme 18).

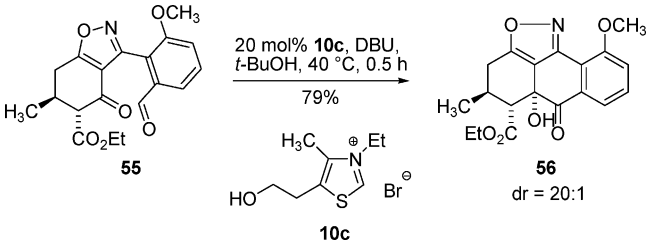
Synthetic thiazolium salts (**10c**), developed by Stetter and his co-workers, similar to thiamine itself,[70] have been

Scheme 18. Intramolecular Acyloin Condensation by Cookson and Lane



successfully used by Suzuki et al. for a diastereoselective intramolecular crossed aldehyde−ketone benzoin reaction in the course of an elegant synthesis of preanthraquinones.[72] By employing the highly functionalized isoxazole **55** as substrate, the tetracyclic α-hydroxyketone **56** was obtained by base-promoted cyclocondensation in good yield. The high diastereoselectivity was induced by the pre-existing stereocenters in the substrates (Scheme 19).

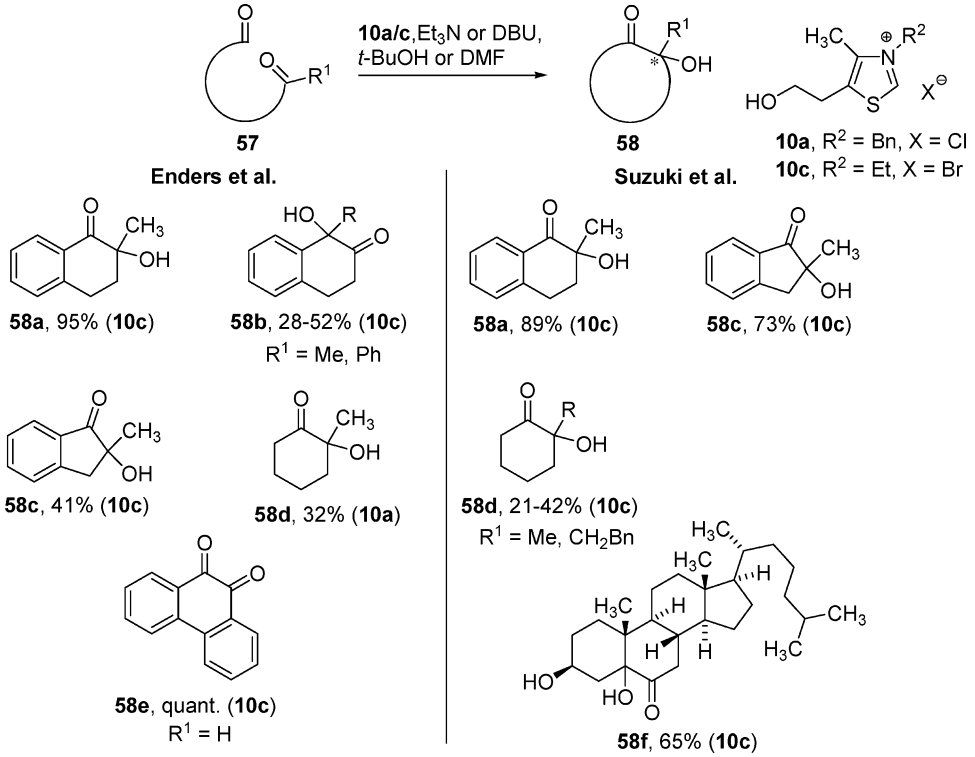
Scheme 19. Intramolecular Crossed Benzoin Reaction by Suzuki and Co-workers



In order to develop a general method, our group started investigations on simple aldehyde ketones **57** as substrates for the carbene-catalyzed crossed intramolecular benzoin condensation. Independently, both our group and Suzuki and co-workers reported that various five- and six-membered cyclic acyloins **58** can indeed be obtained as their racemic mixtures by employing commercially available thiazolium salts as precatalysts (Scheme 20).[74] The tetralone **58a** was obtained in a significantly higher yield than tetralone **58b** with interchanged functionalities. This may be due to the activating effect of the aromatic aldehyde in the precursor of **58a**. Substrates lacking the obviously favorable benzannulation in the resulting acyloin (**58d**) showed only moderate yields because the competing intermolecular reaction was also observed. The quinone **58e** was isolated starting from the corresponding dialdehyde. The α-hydroxyketone is only formed as an intermediate and undergoes air oxidation to the quinone **58e** during workup.

The next goal, of course, has been to develop an enantioselective variant. Unfortunately, the chiral bicyclic triazolium salt (*S*)-**33**, that had been found to be an excellent catalyst for the enantioselective intermolecular benzoin condensation, proved to be ineffective in the intramolecular reaction. Searching for alternative catalysts, our group synthesized the novel triazolium salts **59** and **60** starting from easily accessible enantiopure polycyclic γ-lactams. The precatalyst **59** led to excellent results in the intramolecular crossed benzoin condensation of aldehyde ketones **57**, as shown in Scheme 21. The acyloins **58** bearing a quaternary stereocenter were synthesized with very good yields and excellent enantiomeric excess (93−98% ee).[75] The precatalyst **60**, easy available from the very cheap chirality source L-pyroglutamic acid, proved to be even more active and the yields were consistently excellent, albeit accompanied by lower enantiomeric excesses (63−84% ee). The substrates of the enantioselective intramolecular crossed benzoin condensation were varied to widen the scope of the reaction. Promising results were achieved with substrates where the aldehyde and the ketone function are interchanged and with substrates where a five-membered ring is formed. The stereochemical outcome was explained by the transition state shown in Scheme 21. The *Si*-face of the Breslow intermediate, which is formed as its (*E*)-isomer, is sterically shielded by the tetrahydronaphthalene residue of the tetracyclic

Scheme 20. Thiazolin-2-ylidene Catalyzed Intramolecular Crossed Benzoin Reactions



catalyst. The *Re*-face of the intermediate would attack the ketone function at its *Re*-face (R ≠ Bn). Furthermore, a favorable prearrangement might be caused by the activation of the ketone function by an intramolecular H-bridge. Thus, the (*S*)-configuration of the new stereocenter would be preferred, which is the case. Encouraged by our report, Suzuki and co-workers[76] published their results utilizing Rovis' aminoindanol-derived chiral triazolium salt **61**[77] as catalyst for the asymmetric intramolecular crossed bezoin condensation. They could widen the scope to aliphatic (**58d**) and biaryl aldehyde−ketones (**58g**). The observed facial selectivity with **58g** was opposed to that of all other substrates. The authors assumed that this unexpected reversal was caused by changes in the enol geometry of the Breslow intermediate.

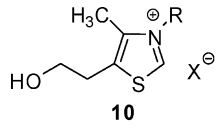
Suzuki and co-workers could also apply this approach to the asymmetric synthesis of 4-chromanones, which are characteristic features in natural products, such as (*S*)-eucomol (Scheme 22).[78]

Starting from the corresponding aldehyde−ketones **65**, our group could develop a general N-heterocyclic carbene-catalyzed protocol for the asymmetric synthesis of various 3-hydroxy-4-chromanones **63′** (Scheme 23, Table 4).[79] The application of three different triazolium salts as precatalysts, previously developed in our research group, enabled the adaptation to the steric and electronic demands of the catalyst system. Again, the tetracyclic catalyst (*R,S*)-**59** was shown to be suitable for a broad range of substrates. Activated substrates only required short reaction times and could be converted with the help of the bulkier catalyst (*S*)-**33**, resulting, in most cases, in better inductions.

4. Stetter Reaction

4.1. Intermolecular Stetter Reactions

In the early 1970s, Stetter and co-workers succeeded in transferring the concept of the thiazolium-catalyzed nucleophilc acylation to the substrate class of Michael acceptors.[70] Since then, the catalytic 1,4-addition of aldehydes **4** to an acceptor bearing an activated double bond **66** carries his name. The Stetter reaction enables a new catalytic pathway for the synthesis of 1,4-bifunctional molecules **67**, such as 1,4-diketones, 4-ketoesters, and 4-ketonitriles.[23,71] The reaction can be catalyzed by a broad range of thiazolium salts. Stetter and co-workers found that the benzyl-substituted thiazolium salt **10a** gave the best results for the addition of aliphatic aldehydes, whereas **10b** and **10c** were chosen for the addition of aromatic aldehydes. Any one of these three was found to be suitable for additions with heterocyclic aldehydes. Salt **10d** was utilized with α,β-unsaturated esters (Figure 14).



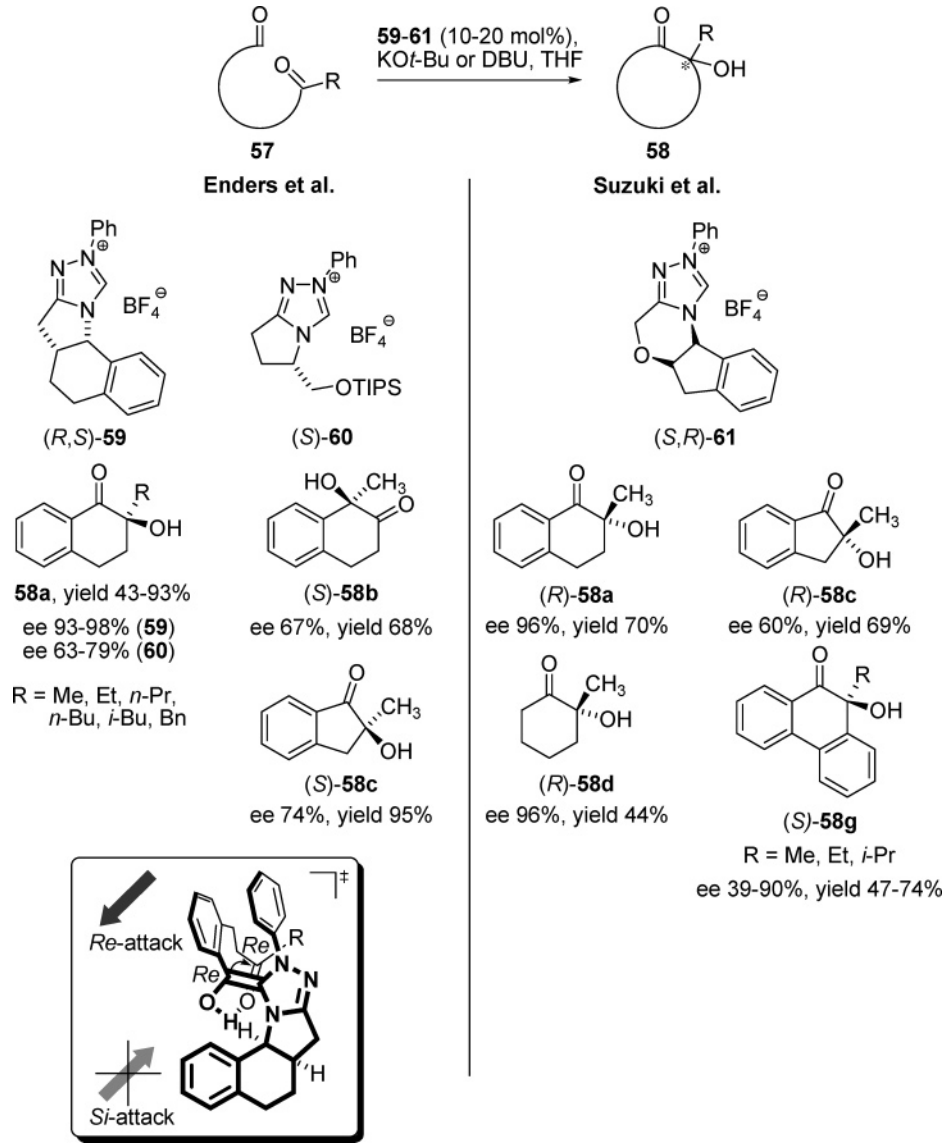
10

10a, R = Bn, X = Cl
10b, R = Me, X = I
10c, R = Et, X = Br
10d, R = $(CH_2)_2OEt$, X = Br

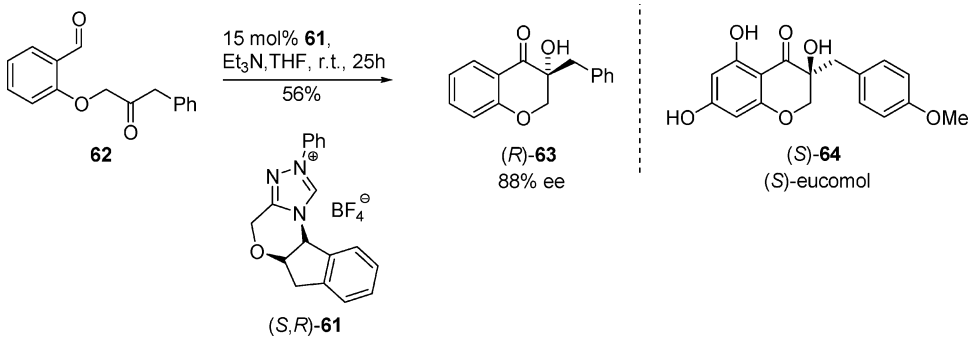
Figure 14. Thiazolium salts **10** for the intermolecular Stetter reaction.

With linear-chain aldehydes, yields in the range of 60−80% are usually obtained. α-Branched aliphatic aldehydes cause lower yields. Unsaturated aldehydes with conjugated or isolated double bonds can be employed as well as aldehydes with isolated triple bonds. For the synthesis of 1,4-diketones, most α,β-unsaturated ketones can serve as acceptors. Aromatic and heterocyclic α,β-unsaturated ketones are particularly well-suited.[80] This versatile method has found broad application in the synthesis of organic key intermediates and diverse natural products. In the catalytic cycle, the aldehyde **4** is activated by the carbene under generation of the Breslow intermediate **6** and subsequent nucleophilic attack of the acyl anion equivalent to the Michael acceptor **66** (Scheme 24).

Scheme 21. Asymmetric Intramolecular Crossed Benzoin Condensation by Enders et al. and Suzuki and co-workers



Scheme 22. Enantioselective Synthesis of the Eucomol Core by Suzuki and Co-workers

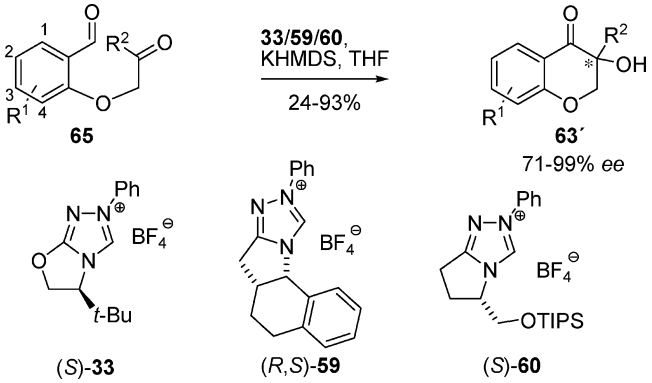


First attempts of an asymmetric Stetter reation were done in our research group in 1989 with the investigation of chiral thiazolium salts such as **71** as precatalysts. The reaction of *n*-butanal (**68**) with chalcone (**69**) in a two-phase system gave the 1,4-diketone **70** with an enantiomeric excess of 39% but a low yield of only 4% (Scheme 25).[81] The catalytic activity of thiazolium as well as triazolium salts in the Stetter reaction persisted in being rather low. Triazolium salts have been shown to possess a catalytic activity in the nonenantioselective Stetter reaction,[23] but in some cases, stable adducts with Michael acceptors have been observed,[37a] which might be a possible reason for their failure in catalysis.

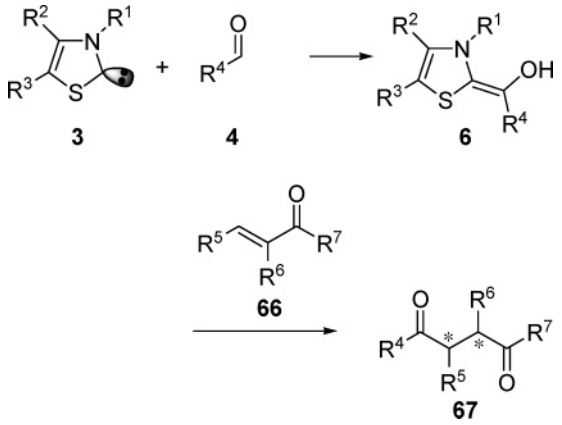
4.2. Intramolecular Stetter Reactions

In 1995, Ciganek reported an intramolecular version of the Stetter reaction.[82] 2-Formylphenoxycrotonates and formylphenoxyacrylates **72** have been shown to be highly active substrates for the Stetter reaction. The reactivity of the substrates was considerably enhanced, which may be due to entropic factors (Scheme 26). The reaction also proceeds

Scheme 23. Asymmetric Synthesis of 4-Chromanones 63′ by Enders et al.



Scheme 24. Stetter Reaction



in the absence of triethylamine as base. The catalyst is presumably activated by DMF taking the place of the amine.

In 1996, our research group observed an activity of triazolium salts, e.g., (*S*,*S*)-**28**, as precatalysts in this intramolecular Stetter reaction. The enantioselective synthesis of various 4-chromanones (*R*)-**73** was performed with enantiomeric excesses of 41−74% and yields of 22−73% (Scheme 27).[83]

In order to compare the NHC catalyst efficiency, the cyclization of the salicylaldehyde derived substrate **72** (R^1 = H) to the corresponding chromanone **73** has, meanwhile, become a benchmark reaction. After these first results, not much attention was paid to this important reaction. However, during the last few years, Rovis and co-workers have achieved significant progress.[84] Using 20 mol % of the aminoindanol-derived triazolium salt **74** or the phenylalanine-based salt **75**, a broad range of different chromanones as well as their aza-, thia-, and carbacyclic analogues **73′** could be obtained with enantiomeric excesses of 82−97% and yields of 63−95% (Scheme 28, Table 5).

Table 4. Scope of the N-Heterocyclic Carbene-Catalyzed Synthesis of 4-Chromanones 63′

R^1	R^2	precat.	T	time (h)	yield (%)	ee (%) (config.)
H	Et	(*R*,*S*)-**59**	5 °C	48	88[a]	94 (*S*)
H	Me	(*R*,*S*)-**59**	rt	18	70[b]	90 (*S*)
H	Me	(*R*,*S*)-**59**	5 °C	48	62[a]	93 (*S*)
H	*i*-Bu	(*R*,*S*)-**59**	rt	40	78[c]	92 (*S*)
H	*i*-Bu	(*R*,*S*)-**59**	5 °C	24	46[a]	95 (*S*)
H	Cy	(*R*,*S*)-**59**	rt	72	53[a]	94 (*S*)
2,4-dibromo	Et	(*R*,*S*)-**59**	0 °C	18	92[a]	76 (*S*)
2,4-dibromo	Et	(*S*)-**33**	rt	18	87[a]	86 (*R*)
2,4-dibromo	*i*-Bu	(*R*,*S*)-**59**	0 °C	24	93[a]	92 (*S*)
2,4-dibromo	*i*-Bu	(*S*)-**33**	5 °C	24	84[a]	81 (*R*)
2-nitro	*i*-Bu	(*R*,*S*)-**59**	5 °C	19	54[b]	89 (*S*)
2-nitro	*i*-Bu	(*S*)-**33**	5 °C	65	51[b]	99 (*R*)
2,4-di-*tert*-butyl	Me	(*R*,*S*)-**59**	rt	65	30[a]	82 (*S*)
2,4-di-*tert*-butyl	Me	(*R*,*S*)-**59**	45 °C	24	50[a]	78 (*S*)
2,3-methylendioxo	*n*-Pr	(*R*,*S*)-**59**	rt	72	24[b]	91 (*S*)
2,3-methylendioxo	*n*-Pr	(*R*,*S*)-**59**	45 °C	72	43[a]	88 (*S*)
2,3-methylendioxo	*n*-Pr	(*S*)-**60**	rt	48	61[a]	71 (*S*)

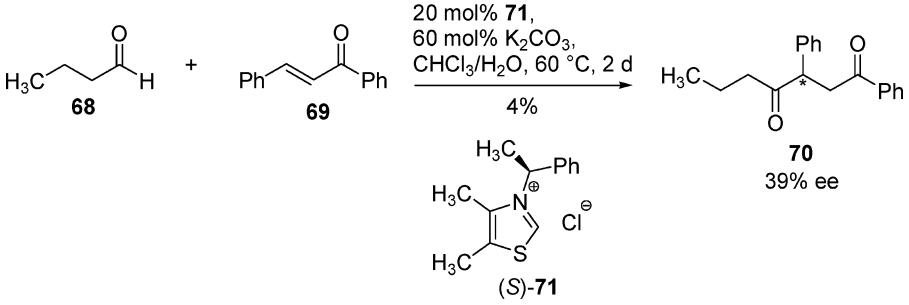
[a] Reaction with 20 mol % precat. and 19 mol % KHMDS. [b] Reaction with 10 mol % precat. and 9 mol % KHMDS. [c] Reaction with 12 mol % precat. and 9 mol % KHMDS.

However, the reaction is limited to (*E*)-alkenes as Michael acceptors, because only this configuration is active enough.[85] Aliphatic substrates lacking a heteroatom in the γ-position of the acceptor were also utilized as substrates in this reaction with catalyst (*R*)-**75**. As a result of the greater conformational freedom, an increase of the electrophilic character of the Michael acceptor was necessary to enable the formation of the corresponding cycloalkanones. An activation with one ester substituent for a five-membered ring (**76**) and two ester substituents for a six-membered ring (**77**) was found to be adequate. Enantioselectivities up to 95% and chemical yields up to 97% could be obtained (Figure 15).

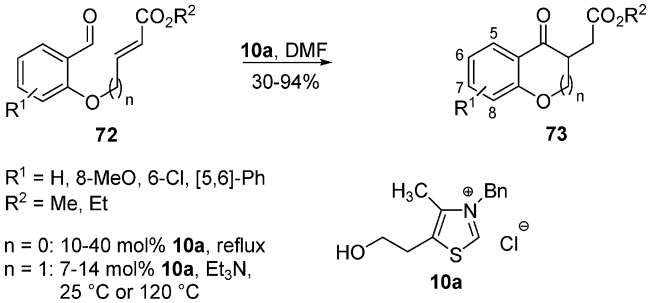
Rovis and co-workers[86] and, later, Hamada and co-workers[87] also accepted the challenge of generating quaternary stereocenters. The substitution pattern of the phenyl ring of the catalyst was found to be a decisive factor. In this case, the *N*-pentafluorophenyl-substituted catalyst (*R*,*S*)-**80** proved to be the most effective for the conversion of the β,β-disubstituted substrates **78** to the corresponding cyclized products **79** with up to 99% enantiomeric excess (Scheme 29, Table 6). A variety of heteroatoms such as oxygen and sulfur tethering the aldehyde and Michael acceptor was suitable. (*E*)-Isomers provided uniformly higher yields and enantioselectivities than the corresponding (*Z*)-configured substrates. The generation of analogue six-membered rings proved to be a challenging target. Only strongly activated substrates as a ketone Michael acceptor provided the desired product in moderate yield, albeit with 99% ee.

The method could be extended to substrates with aliphatic backbones. As with the aromatic substrates, (*E*)-alkenes **81**

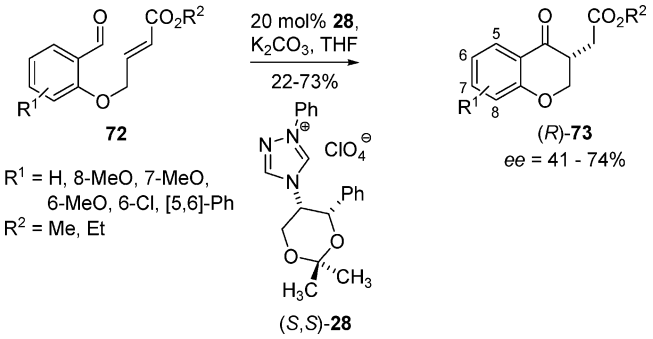
Scheme 25. First Attempts of an Asymmetric Stetter Reaction by Enders et al.



Scheme 26. Intramolecular Stetter Reaction by Ciganek



Scheme 27. First Asymmetric Intramolecular Stetter Reaction by Enders et al.



Scheme 28. Asymmetric Intramolecular Stetter Reaction by Rovis and Co-workers

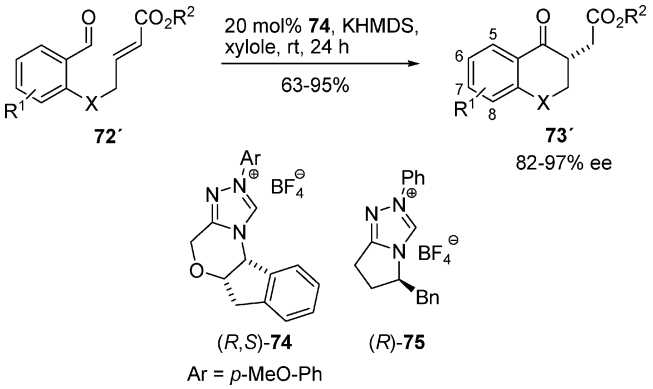
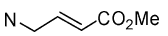


Table 5. Scope of the Asymmetric Intramolecular Stetter Reaction by Rovis and Co-workers

R^1	R^2	X	precat.	yield (%)	ee (%)
H	Et	O	(*R*,*S*)-**74**	94	94
6-Me	Et	O	(*R*,*S*)-**74**	80[a]	97
8-Me	Et	O	(*R*,*S*)-**74**	90	84
8-MeO	Et	O	(*R*,*S*)-**74**	95[a]	87
H	Me	S	(*R*,*S*)-**74**	63	96
H	Me	NMe	(*R*,*S*)-**74**	64	82
H	Me		(*R*,*S*)-**74**	72	84
H	Et	CH_2	(*R*,*S*)-**74**	35	94
H	Et	CH_2	(*R*)-**75**	90	92

[a] Reaction with 10 mol % cat. and 10 mol % KHMDS.

gave better results. The corresponding thioethers proved to be not suitable as substrates. In contrast, by tethering with an electron-withdrawing sulfone instead of sulfide, the product **82** could be obtained in 98% yield and 80% ee. Nitrogen-containing substrates were also included in the scope of substrates, although with a slight decrease of the yield (Scheme 30, Table 7).

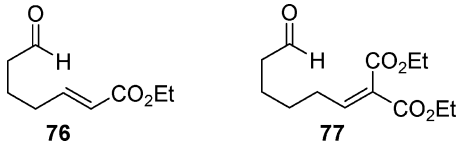


Figure 15. Aliphatic substrates in the intramolecular Stetter reaction by Rovis and co-workers.

Scheme 29. Generation of Quaternary Stereocenters by Rovis and Co-workers

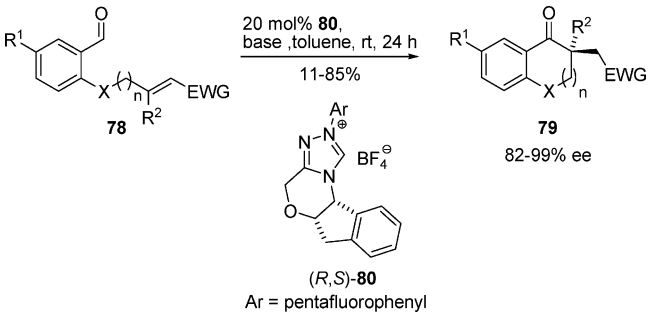
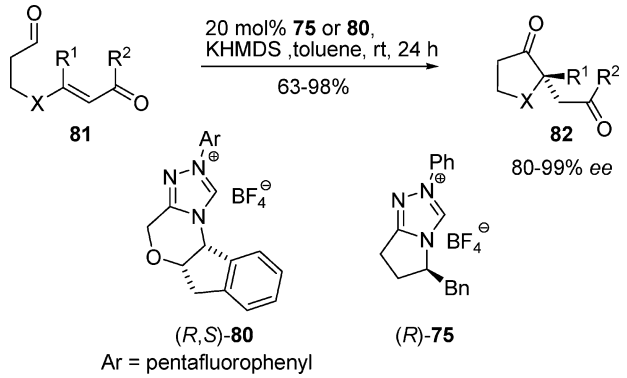


Table 6. Scope of Subtrates and Effect of Substrate Geometry ($n = 0$)

R^1	R^2	X	EWG	base	yield (%)	ee (%)
H	Et	O	CO_2Me	Et_3N	96	97
Br	Et	O	CO_2Me	Et_3N	92	89
H	Et	S	CO_2Me	KO*t*-Bu	90	97
H	Et	S	CO_2Me	KO*t*-Bu	89	86[a]
H	*n*-Pr	S	CO_2Me	KO*t*-Bu	83	98
H	*n*-Pr	S	CO_2Me	KO*t*-Bu	85	89[a]
H	CH_2CH_2Ph	S	CO_2Me	KO*t*-Bu	91	99
H	CH_2CH_2Ph	S	CO_2Me	KO*t*-Bu	92	84[a]
H	Ph	S	CO_2Me	KO*t*-Bu	15	82
H	CO_2Me	S	CO_2Me	KO*t*-Bu	85	90[a]
H	Me	CH_2	CO_2Et	Et_3N	95	99
H	Ph	O	COMe	Et_3N	55[b]	99

[a] Utilizing of the (*Z*)-isomer. [b] $n = 1$, 10 equiv of Et_3N.

Scheme 30. Asymmetric Intramolecular Stetter Reaction with Aliphatic Substrates

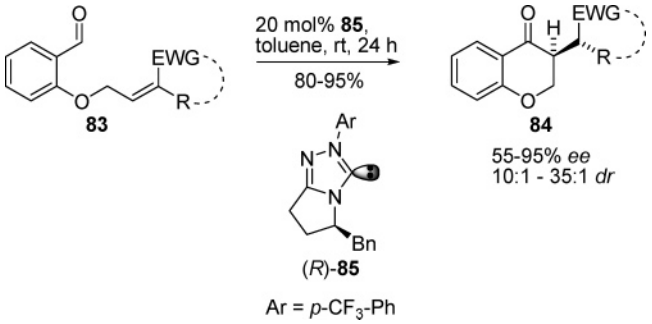


Recently, the same group was able to extend the scope of the intramolecular Stetter reaction for an enantio- and diastereoselective variant utilizing α,β-disubstituted acceptors **83**.[88] The key challenge was to secure a diastereoselective proton transfer onto the hypothetic enolate intermediate. It was shown that hexamethyldisiloxane (HMDS; formed from the base KHMDS) deteriorates the diastereoselectivity. This problem was overcome by using the free carbene catalyst (*R*)-**85**, i.e., HMDS was removed in high vacuum prior to the reaction (Scheme 31). The free carbene (*R*)-**85** afforded the chromanones **84** with enantiomeric excesses of up to 95% and diastereomeric ratios of up to 35:1 (Table 8).

Table 7. Substrate Scope for the Synthesis of 82 by Rovis and Co-workers

X	R^1	R^2	precat.	yield (%)	ee (%)
CH_2	Me	Ph	(*R*,*S*)-**80**	85	96
SO_2	*n*-Pr	OMe	(*R*)-**75**	98	80
NAc	Me	Me	(*R*,*S*)-**80**	65	95
CH_2	Me	4-pyridinyl	(*R*,*S*)-**80**	85	96
CH_2	Me	*p*-NO_2-Ph	(*R*,*S*)-**80**	90	84
CH_2	Me	Me	(*R*,*S*)-**80**	81	95
CH_2	Me	$(CH_2)_2$Ph	(*R*,*S*)-**80**	63	99
CH_2	*n*-Bu	Ph	(*R*,*S*)-**80**	71	98

Scheme 31. Enantio- and Diastereoselective Intramolecular Stetter Reaction by Rovis and Co-workers



Aliphatic aldehydes were also shown to be viable substrates with >80% yield and good enantio- and diastereoselectivities.

The syn selective formation of the new stereocenters was assumed to arise from a diastereoselective proton transfer of two possible enolate rotamers **86** or **87**. The hypothetical intramolecular proton transfer was supported by the fact that double-bond isomers afford the complementary diastereoselectivity (Scheme 32).

In related investigations, the Rovis group examined the effect of pre-existing stereocenters in the intramolecular asymmetric Stetter reaction with the catalyst (*R*,*S*)-**61** (Scheme 33).[89] The racemic substrates *rac*-**89**, containing one stereogenic center, were utilized in a parallel kinetic resolution for the synthesis of 2,3- and 2,4-disubstituted

Table 8. Scope of α,β-Disubstituted Acceptors in the Intramolecular Stetter Reaction

EWG	R	yield (%)	ee (%)	dr (%)
CO_2Me	Me	94	95	30:1
CO_2Et	Et	95	92	35:1
CO_2Et	*n*-Bu	53	94	12:1
CO_2Et	Bn	80	84	20:1
CO_2Me	allyl	95	83	13:1
		95	94	10:1
		80	95	18:1
COMe	Me	85	55	10:1

Table 9. Effect of the Pre-existing Stereocenters in 89

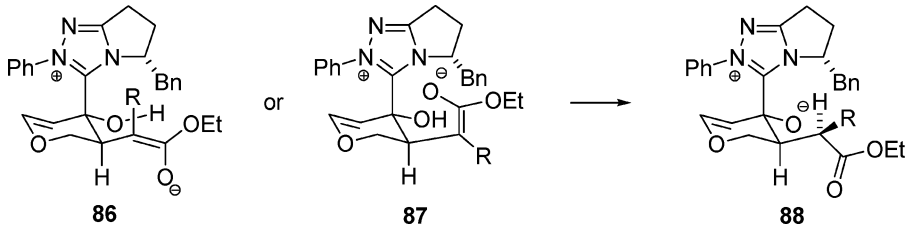
R^1	R^2	yield (%)	trans/cis	ee trans (%)	ee cis (%)
4-Me	Et	97	50:50	98	94
4-Ph	Et	96	50:50	98	96
3-Me	Et	90	50:50	90	95
3-*i*-Pr	Et	95	53:47	84	96
5-Bn	Me	95	15:85	<5	<5
Cy	Me	74[a]	3.5:96.5	20	6

[a] Conversion.

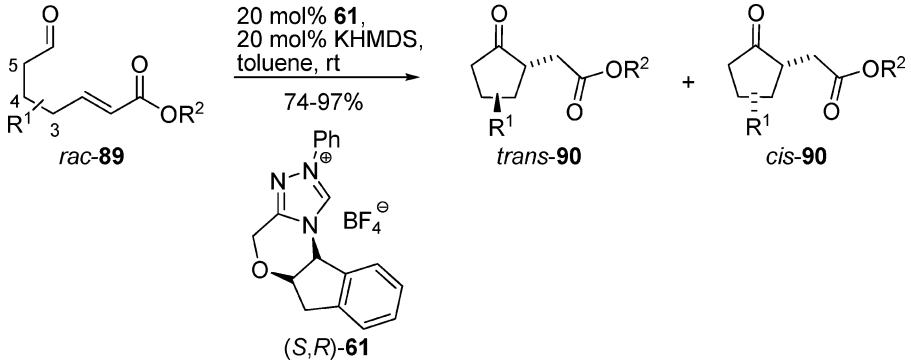
cyclopentanones **90**. The inseparable *cis*- and *trans*-diastereomers were obtained in an equimolar mixture, albeit with high ee's (84−98%). The corresponding 2,5-disubstituted cyclopentanones were generated with preference of the cis diastereomer with low ee, indicating the reaction was substrate controlled (Table 9).

Liu and Rovis could also utilize the concept of desymmetrization for the enantio- and diastereoselective synthesis of hydrobenzofuranones **92** in an intramolecular Stetter reaction (Scheme 34).[90] Cyclohexadienones **91** were utilized as substrates, providing **92** with three contiguous stereocenters. Moreover, the very short reaction time demonstrates the potential of this reaction.

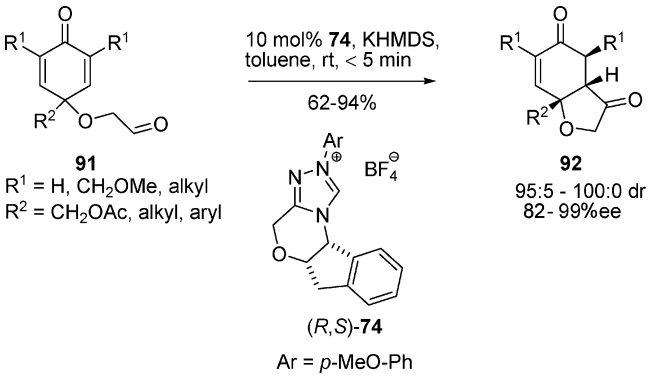
Scheme 32. Proposed Transition States for the Diastereo- and Enantioselective Stetter Reaction



Scheme 33. Pre-existing Stereocenters in the Intramolecular Stetter Reaction



Scheme 34. Asymmetric Synthesis of Hydrobenzofuranones



The concept of axial chirality was utilized by Bach and co-workers with the menthol-derived triazolium salt **35** (Figure 10) in the asymmetric intramolecular Stetter reaction and intermolecular benzoin condensation.[48] Using 20 mol % of this catalyst, they were able to isolate the Stetter product **73** (R^1 = H, R^2 = Me) with 50% ee in 75% yield. Presumably, an atropisomerization during the reaction diminishes the stereoselectivity.

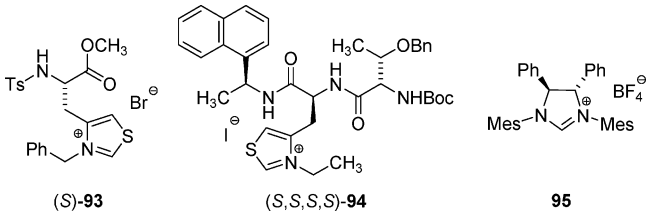


Figure 16. Chiral heterazolium salts for the Stetter reaction by Miller and co-workers[91] and Matsumoto and Tomoika.[92]

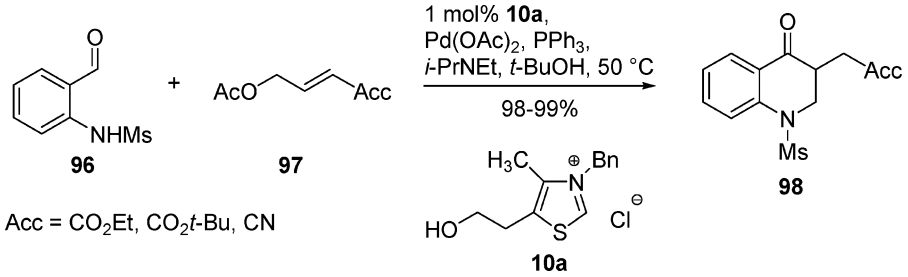
Applying the concept of small peptide catalysts to the intramolecular asymmetric Stetter reaction, the Miller group[91] replaced a histidine residue of amino acid derivatives with thiazolylalanine (Taz) derivatives. An initial screening with **72** (R^1 = H, R^2 = *t*-Bu) as the substrate and 20 mol % of the catalyst (*S*)-**93** afforded the corresponding chromanone **73** with up to 80% ee and 40% yield. In oder to improve the yield and selectivity of the reaction, Taz was embedded in an appropriate scaffold. The incorporation of Taz into peptide sequences yielded catalyst (*S*,*S*,*S*,*S*)-**94**, which led to the product **73** in a promising yield of 67% and 73% ee. Matsumoto and Tomoika recently showed that chiral C_2-symmetric dihydroimidazolium salts, such as **96**, are also efficient precatalysts in the asymmetric intramolecular Stetter reaction with aliphatic substrates, such as **76** (the corresponding methyl ester was used).[92] Using substoichiometric amounts of base, a racemization could be suppressed and the cyclohexanone derivative could be obtained with 76% ee and 74% yield (Figure 16).

Table 10. Substrate Scope for the Sila-Stetter Reaction by Scheidt and Co-workers

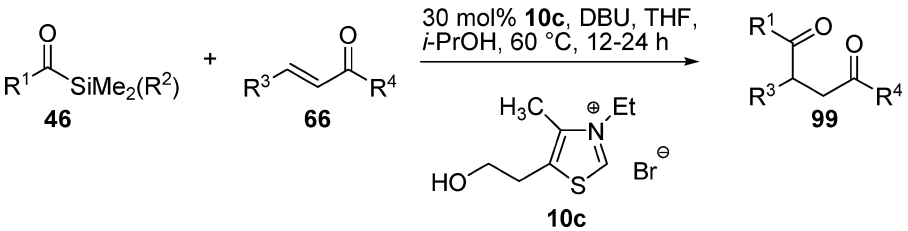
entry	R^1	R^2	R^3	R^4	yield (%)
1	Ph	Me	Ph	Ph	77
2	Ph	Me	Ph	*p*-Cl-Ph	82
3	Ph	Me	Ph	*p*-MeO-Ph	80
4	Ph	Me	1-naphthyl	Ph	72
5	Ph	Me	*p*-Br-Ph	Ph	66
6	Ph	Me	*p*-Cl-Ph	Ph	74
7	Ph	Me	*o*-Cl-Ph	Ph	68
8	Ph	Me	*p*-Me-Ph	Ph	84
9	Ph	Me	*m*-MeO-Ph	Ph	75
10	Ph	Me	*p*-MeO-Ph	Ph	77
11	Ph	Me	*p*-OH-Ph	Ph	50
12	*p*-Cl-Ph	Me	Ph	Ph	82
13	*p*-Me-Ph	Me	Ph	Ph	70
14	Ph	Ph	Ph	Ph	61
15	Me	Ph	Ph	Ph	70
16	Cy	Ph	Ph	Ph	63
17	Ph	Me	CO_2Et	OEt	65
18	Ph	Me	H	OEt	72
19	Ph	Me	H	Me	75
20	*p*-Cl-Ph	Me	Ph	Me	63
21	*p*-Cl-Ph	Me	Ph	*t*-Bu	48

A one-pot sequential multicatalytic process, a Pd-catalyzed allylic amination−thiazolium salt-catalyzed Stetter reaction cascade, was developed by Hamada and co-workers.[93] Functionalized racemic dihydroquinolinones **98** were obtained directly in a single-pot reaction starting from 2-aminobenzaldehyde derivatives **96** and γ-acetoxy α,β-unsaturated carbonyl compounds **97** using commercially available thiazolium salt **10a** as catalyst for the second step (Scheme 35).

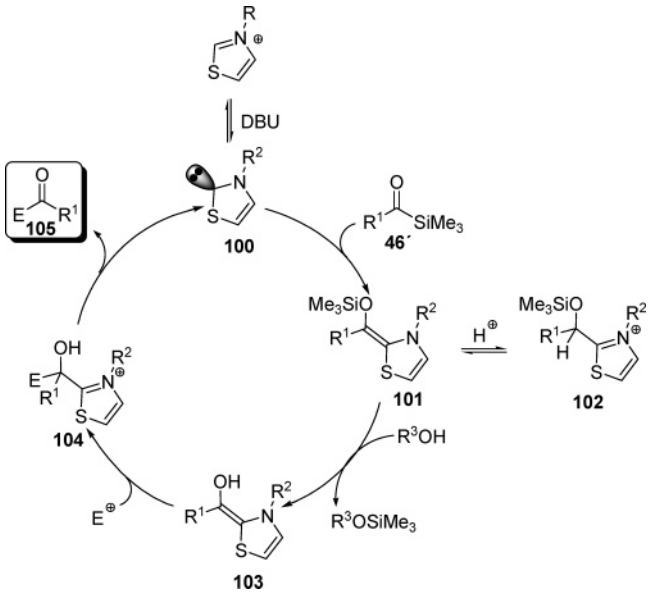
Scheme 35. One-Pot Sequential Multicatalytic Process



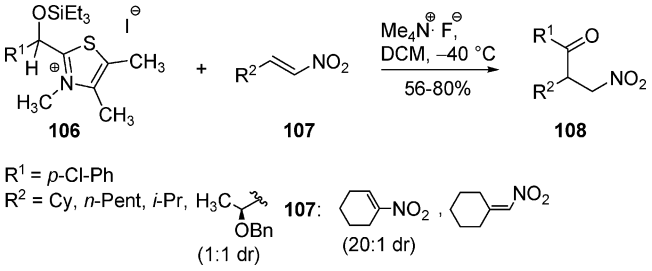
Scheme 36. Sila-Stetter Reaction by Scheidt and Co-workers



Scheme 37. Mechanistic Proposal for the Sila-Stetter Reaction



Scheme 38. Acylation of Nitroalkenes by Scheidt and Co-workers



4.3. Special Intermolecular Stetter Reactions

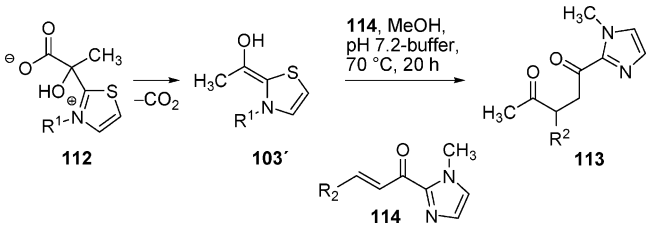
In the intermolecular Stetter reaction, self-condensation of the donor aldehyde can, in principle, take place besides the desired 1,4-addition, leading to benzoins as side products. To circumvent this problem, Scheidt and co-workers[94] devised a strategy that employs acylsilanes as acyl anion precursors.[62] The thiazolium-catalyzed reaction of the acylsilanes **46** and the conjugate acceptors **66** proceeded smoothly to give the corresponding 1,4-dicarbonyl compounds **99** in good yields (Scheme 36, Table 10). Interestingly, electron-donating and electron-withdrawing groups on either side of the α,β-unsaturated system had no significant influence on the reaction outcome. The reaction is tolerant to an unprotected phenol (entry 11) at the acceptor **66** as well as to enolizable groups at the acylsilane (entries 15 and 16).

In the postulated catalytic cycle, the carbene catalyst **100** initially attacks the acylsilane **46′**. Via 1,2-silyl migration (Brook rearrangement), the intermediate **101** is formed, which is in equilibrium with **102** and is presumably desilylated to the Breslow intermediate **103** because of the added alcohol and the present 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reduced electrophilicity of the acylsilane (in comparison with an aldehyde) favors the conjugate addition, and the key carbon−carbon bond is formed (**104**). The catalytic cycle is closed with the collapse of **104** to regenerate the carbene **100** and to produce the product **105** (Scheme 37).

In a further contribution, Scheidt and co-workers could transfer this concept to a direct nucleophilic acylation of nitroalkenes **107** for the preparation of β-nitroketones **108**.[95] Because of the rapid base-induced decomposition of the nitroalkene under these conditions, the Breslow intermediate was generated in situ from the corresponding thiazolium-carbinol **106**. An activation of the nitroalkene by thiourea addition led to higher yields of the β-nitroketones (Scheme 38).

Scheidt and co-workers could also carry out Stetter reactions under neutral aqueous conditions.[97] In a biomimetic fashion, a thiazolium catalyst, when added to the keto group of pyruvate (**112**), led via decarboxylation to the Breslow intermediate **103′**. Reaction with substituted α,β-unsaturated 2-acylimidazoles **114** gave the usual Stetter product **113** (Scheme 40). Stetter and Lorenz were the first who successfully employed α-ketoacids instead of aldehydes in a thiazolium salt-catalyzed Stetter reaction (Scheme 39).[96]

Scheme 40. Stetter Reaction in Aqueous Solution by Scheidt and Co-workers



4.4. Stetter–Paal–Knorr Reactions

The 1,4-dicarbonyl compounds **117** resulting from Stetter reactions are useful precursors for the synthesis of heterocycles.[98] They have been used by Müller and co-workers (Table 11)[99] and Bharadwaj and Scheidt (Table 12)[100] in efficient one-pot Stetter−Paal−Knorr protocols for the synthesis of highly substituted pyrroles **119**.[101] Müller et al. could synthesize tetrasubstituted pyrroles in a one-pot, three-step, four-component process. A coupling−isomerization−Stetter reaction−Paal−Knorr sequence was developed between an aryl halide **115**, a terminal propargyl alcohol **116**, an aldehyde, and a primary amine.[102] In an analogous manner, the pyrroles were synthesized by Scheidt and co-workers as a consecutive reaction of their sila-Stetter

Scheme 39. Thiazolium Catalyzed Reaction of α-ketoacids with Enones by Stetter and Lorenz

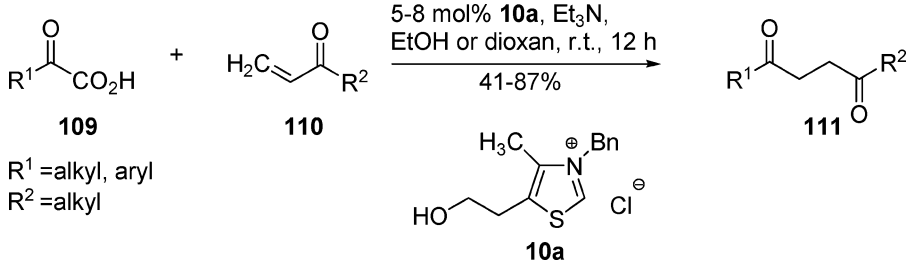


Table 11. Synthesis of Pyrroles 119 by Müller and Co-workers (AcOH, Δ)

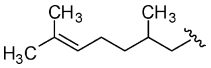
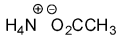
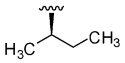
R^1	R^2	R^3NH_2	yield (%)
Ph	*p*-CN-Ph	NH_4Cl	70
p-MeO-Ph	*p*-CN-Ph	NH_4Cl	60
p-F-Ph	4-pyridinyl	NH_4Cl	54
n-pentyl	*p*-CN-Ph	NH_4Cl	59
$(CH_2)_5OH$	*p*-CN-Ph	NH_4Cl	53
Ph	*p*-CN-Ph	$BnNH_2$	60
2-furyl	*p*-CN-Ph	$BnNH_2$	55
Ph	*p*-CN-Ph	$EtCO_2CH_2NH_2$	54
	*p*-CN-Ph	$NH_2COCH_2NH_2$	56
Ph	*p*-CN-Ph	$HOCH_2CH_2NH_2$	57
n-pentyl	*p*-CN-Ph	*i*-$PrNH_2$	59

Table 12. Synthesis of Pyrroles 119 by Scheidt and Co-workers (TsOH, 4 Å MS)

R^1	R^2	R^3	yield (%)
Ph	Ph	Ph	66
p-Me-Ph	Ph	Ph	71
p-Cl-Ph	Ph	Ph	61
Cy	Ph	Ph	69
Me	Ph	Ph	71
Ph	*p*-Me-Ph	Ph	70
Ph	*p*-Cl-Ph	Ph	58
p-Cl-Ph	*p*-MeO-Ph	Ph	69
Ph	Ph	*p*-Cl-Ph	57
Ph	Ph	*p*-Br-Ph	71
Ph	Ph	*p*-OH-Ph	61
Ph	Ph	 [a]	62
Ph	Ph	Me	70
Ph	Ph	$CH_3(CH)_2$	82
Ph	Ph	Bn	65
Ph	Ph	Cy	63
Ph	Ph		54
Ph	Ph		56
Ph	Ph	*p*-NH_2-Ph	70

[a] Used instead of R^3NH_2.

protocol. Simple addition of a primary amine in the presence of an acid after full conversion into the 1,4-dicarbonyl compound **117** gave the pyrroles **119** in good yields. They are important structural motifs in natural products. Upon addition of acid, Müller and co-workers and Scheidt and co-workers could apply this methodology for the synthesis of furans **118** (Table 13, Müller and co-workers; Table 14, Scheidt and co-workers) (Scheme 41).[94b]

Table 13. Synthesis of Furans 118 by Müller and Co-workers (HCl, AcOH, Δ)

R^1	R^2	yield (%)
Ph	*p*-CN-Ph	79
o-furyl	*p*-CN-Ph	74
p-F-Ph	4-pyridinyl	46
Ph		42
2-pentyl	*p*-CN-Ph	64

Table 14. Synthesis of Furans 118 by Scheidt and Co-workers (AcOH)

R^1	R^2	yield (%)
Ph	Ph	81
Et	Ph	82
Et	3,4-dichlorophenyl	81
Et	*p*-Br-Ph	84
Me	Ph	74
Me	*p*-Me-Ph	83

In an analogous fashion, but by employing a crossed azabenzoin condensation as the initial step, Frantz et al. converted their α-ketoamides **45** into the corresponding substituted imidazoles **120** by treatment with a primary amine.[103] Several di- and trisubstituted imidazoles **120** could be synthezised by this one-pot procedure with differing yields. Chiral imidazoles could also be obtained by utilizing chiral amines or amino acids (Scheme 42).

A further extension of this reaction was shown in the synthesis of oxazoles **121** and thiazoles **122** by in situ treatment with triphenylphosphine/iodine or Lawesson's reagent, demonstrating a rapid access to imidazoles, oxazoles, and thiazoles with analogous substitution patterns utilizing the same starting materials (Scheme 43).

The Stetter−Paal−Knorr reaction could also be utilized for the synthesis of extended heterocyclic systems.[104] Poly-1,4-diketones, such as **125**, were obtained from the reaction of diformylarenes, e.g., **123**, and bis-Mannich bases, e.g., **124**. After ring closure, alternating copolymers (**126**) are produced (Scheme 44).

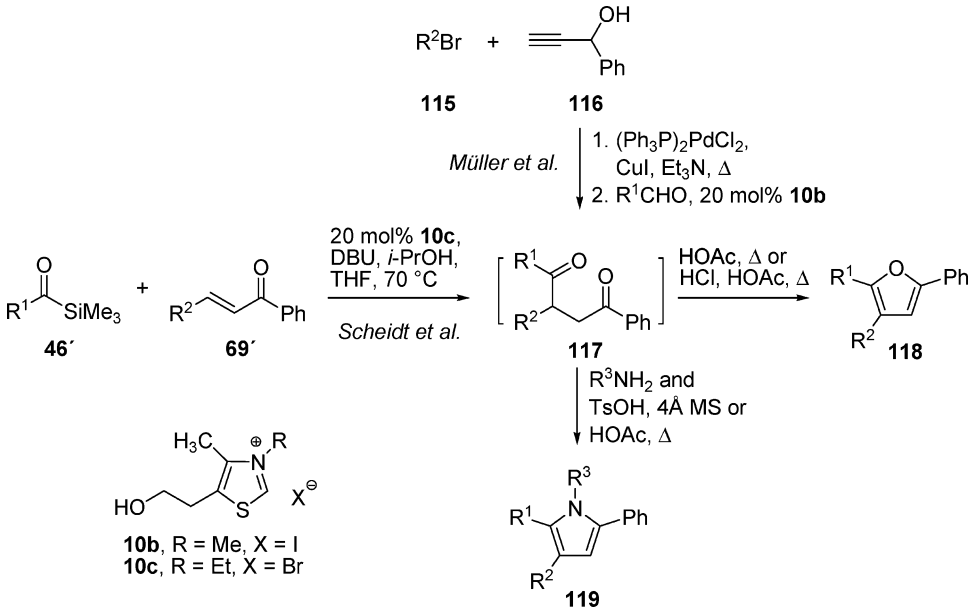
4.5. Polymer-Supported Stetter Reactions

In order to carry out Stetter (and other) reactions in a parallel fashion and with minimal purification, it is necessary to immobilize the NHC catalysts. This strategy should also allow for catalyst recycling and was first adressed by our research group.[105] Yadav et al. reported a microwave-accelerated Stetter reaction of thiazolium salts dispersed onto the surface of alumina.[106] Thus, treatment of aliphatic, aromatic, and heteroaromatic aldehydes with α,β-unsaturated ketones under solvent-free conditions afforded the corresponding 1,4-diketones in high yields.

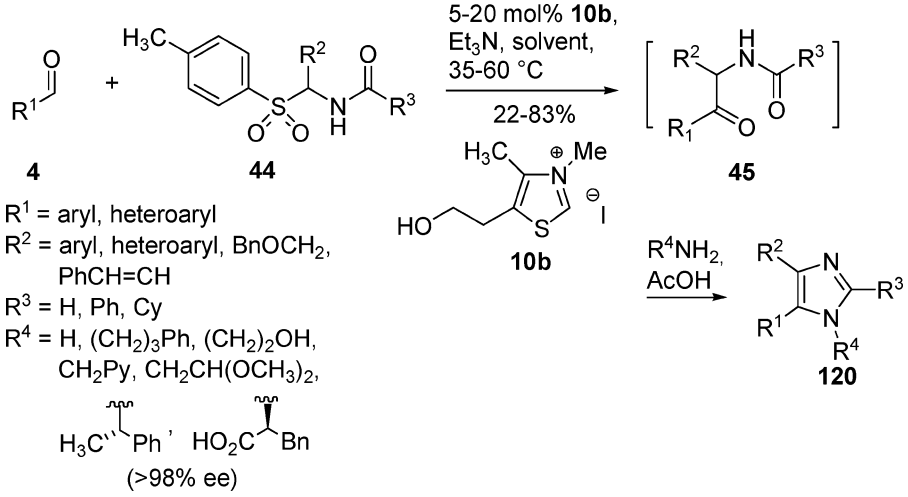
Starting from the thiazole **127**, Barrett and co-workers have synthesized a gel-supported thiazolium iodide **128** via a ring-opening metathesis polymerization (ROMP), which was successfully applied to Stetter reactions and afforded the products in high yields and purity (Scheme 45).[107]

Further investigations with resin-bound (Wang resin) α,β-unsaturated carbonyl compounds **129** in the Stetter reaction were reported by Raghavan and Anuradha[108] and Kobayashi et al.[109] Numerous 1,4-diketones **130** could be obtained after cleavage from the solid phase, demonstrating the broad applicability of this method (Scheme 46).

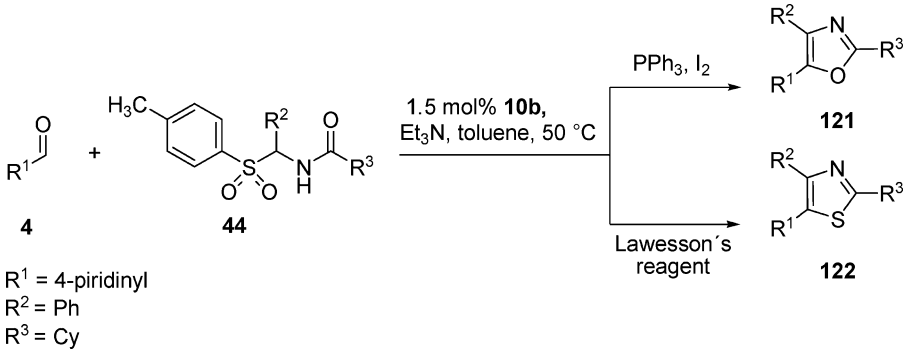
Scheme 41. One-Pot Synthesis of Pyrrols and Furans



Scheme 42. Synthesis of Substituted Imidazoles by Frantz et al.



Scheme 43. One-Pot Synthesis of Oxazoles 121 and Thiazoles 122



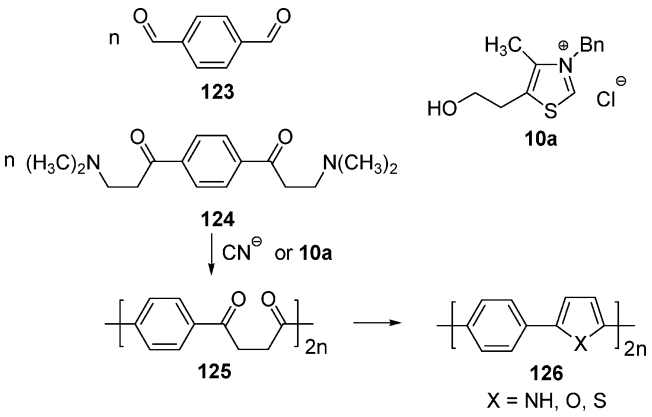
4.6. Natural Product Synthesis

Despite the unrivaled easy access to 1,4-dicarbonyl compounds, only a few examples of the application of Stetter reactions in the synthesis of natural products have been reported so far.[110] In 1975, Stetter and Kuhlmann reported the synthesis of *cis*-jasmon and dihydrojasmon (Scheme 47). After the catalytic nucleophilic acylation, the corresponding 1,4-diketones were cyclized in good overall yields to *cis*-jasmon (**133a**) and dihydrojasmon (**133b**).

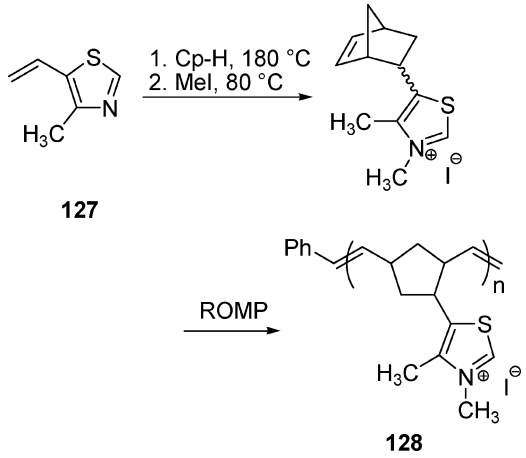
In 1979, Trost et al. reported an intramolecular Stetter reaction with **134** as one of the key steps in their synthesis of (±)-hirsutic acid C (**136**), a tricyclic sesquiterpene.[111] In the tricyclic ketone **135**, four of the seven chiral centers of **136** were formed with the correct relative configuration and allowed to control the formation of the remaining three (Scheme 48).

The research group of Roth could successfully apply the Stetter reaction in the preparation of various 1,4-diketones

Scheme 44. Synthesis of Heterocyclic Polymers with the Stetter Reaction



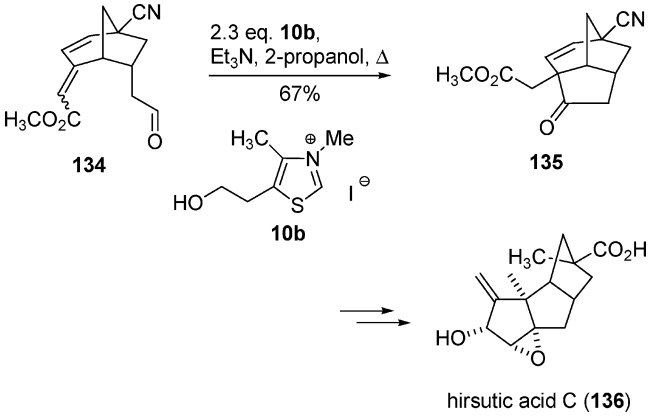
Scheme 45. Synthesis of the ROMP Gel-Supported Thiazolium Iodide 128



138, which served as precursors in the synthesis of a number of HMC-CoA reductase inhibitors **139** and **140** (Scheme 49).[112]

Galopin used an intermolecular Stetter reaction in his synthesis of (±)-*trans*-sabinene hydrate (**141**), a flavor chemical found in essential oils from mint and herbs.[113] The Stetter reaction of isovaleraldehyde (**139**) and methylvinylketone (**132**) furnished the dione **140**, which upon cyclization yields the corresponding cyclopentenone as key intermediate for the synthesis of **141** (Scheme 50).

Scheme 48. Synthesis of Hirsutic Acid C by Trost et al.



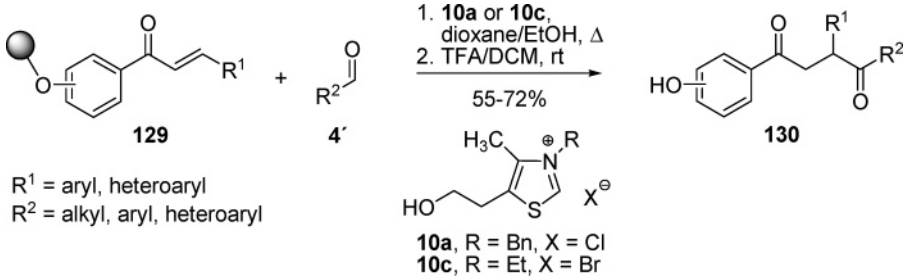
Harrington and Tius employed a diastereoselective intermolecular Stetter reaction and a ring-closing metathesis reaction as key steps in their elegant synthesis of roseophilin (**143**).[114] The 1,4-dicarbonyl functionality in **142** served as a precursor for the central pyrrole unit of the natural product (Scheme 51).

Grée and co-workers developed an interesting application of the intermolecular Stetter reaction for the synthesis of haloperidol **146**.[115] In the key step, room-temperature ionic liquids (RTILs) of the imidazolium type were employed successfully as solvents in the Stetter reaction. However, addition of the thiazolium catalyst **10a** was necessary, because the ionic liquid itself only produced small amounts of the 1,4-addition product **145** (15%) (Scheme 52).

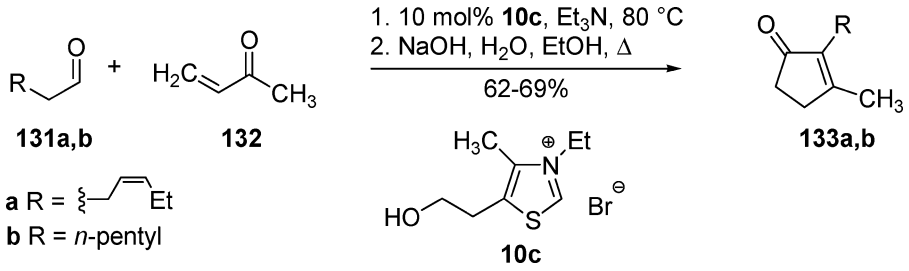
5. a^3 to d^3 Umpolung

The reactions described in the previous chapters belong to the class of a^1-d^1 Umpolung, according to the terminology of Seebach.[116] A classical example for this type of reaction is the Benzoin reaction (reaction of d^1-nucleophiles with aldehydes, section 3) or the Stetter reaction (reaction of d^1-

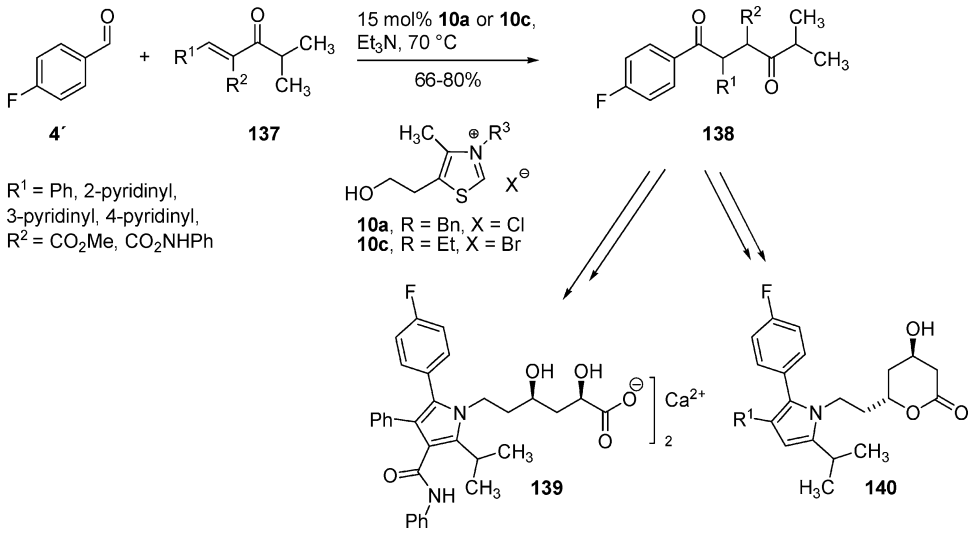
Scheme 46. Solid-Phase Synthesis of 1,4-Diketones by Raghavan and Anuradha



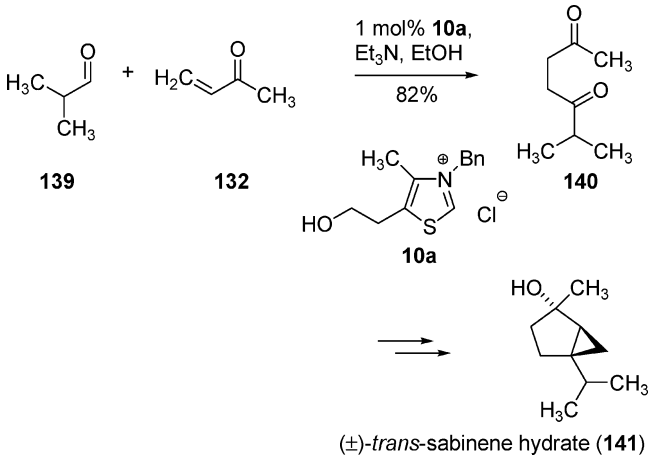
Scheme 47. Synthesis of *cis*-Jasmon (133a) and Dihydrojasmon (133b) by Stetter and Kuhlmann



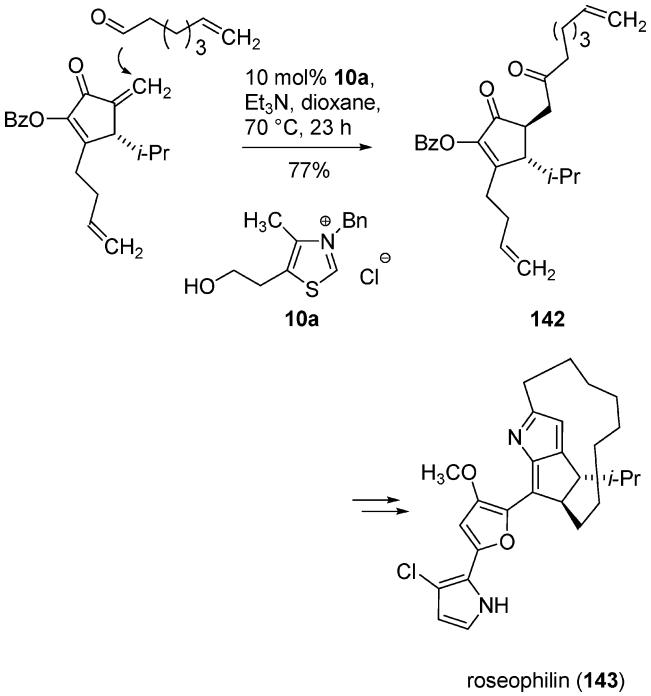
Scheme 49. Synthesis of HMC-CoA Reductor Inhibitors by Roth and Co-workers



Scheme 50. Synthesis of (±)-*trans*-Sabinene Hydrate by Galopin



Scheme 51. Synthesis of Roseophilin by Harrington and Tius



nucleophiles with Michael acceptors, section 4). In carbene-catalyzed reactions, α,β-unsaturated aldehydes, however, do not show a similar reactivity as compared to their saturated aldehyde counterparts because of the favored homoenolate reactivity during the reaction course (Figure 17). The homoenolates **147′** can be considered as d^3-nucleophiles and, thus, constitute an a^3-d^3 Umpolung.

5.1. Cross-Condensation of Enals and Aldehydes or Imines

An application based on the catalytic generation of a homoenolate intermediate is the formation of γ-butyrolactones through the reaction of α,β-unsaturated aldehydes **148** with aldehydes **4** (Scheme 53), which was first published simultaneously by the research groups of Glorius (Table 15)[117] and Bode (Table 16).[118] In both approaches, the commercially available N-heterocyclic bisarylimidazolium salt **19d** was used, emphasizing the need for disubstituted imidazolium-based catalysts, since the use of thiazolium salts as precatalysts only afforded the formation of the benzoin product in poor yields. The resulting disubstituted γ-butyrolactones were generated in moderate-to-good yields, favoring the formation of the *cis*-diastereomers.

In the postulated catalytic cycle, the α,β-unsaturated aldehyde **148** is attacked by the in situ formed carbene **15d**. The resulting zwitterionic intermediate **150** then tautomerized to the conjugated Breslow intermediate **147‴**. This in turn attacks the aldehyde **4** as a d^3-nucleophile under formation of the alcoholate **151**. The tautomerization of **151** to the acylimidazolium intermediate **152** is followed by an intramolecular attack of the alcoholate oxygen atom at the carbonyl function to afford the γ-butyrolactone **159** and the regeneration of the catalyst (Scheme 54).

Glorius and co-workers accentuated that a sterically demanding precatalyst, such as **19d**, is the key to success for the generation of a homoenolate species within this methodology.[119] In the case of the addition of the catalyst to an aromatic aldehyde, a benzoin or Stetter reaction is suppressed by an efficient shielding of the nucleophilic center of the resulting Breslow intermediate **6′**. Moreover, the same effect is responsible for the favored formation of the homoenolate species (Figure 18).

Scheme 52. Synthesis of Haloperidol by Grée and Co-workers

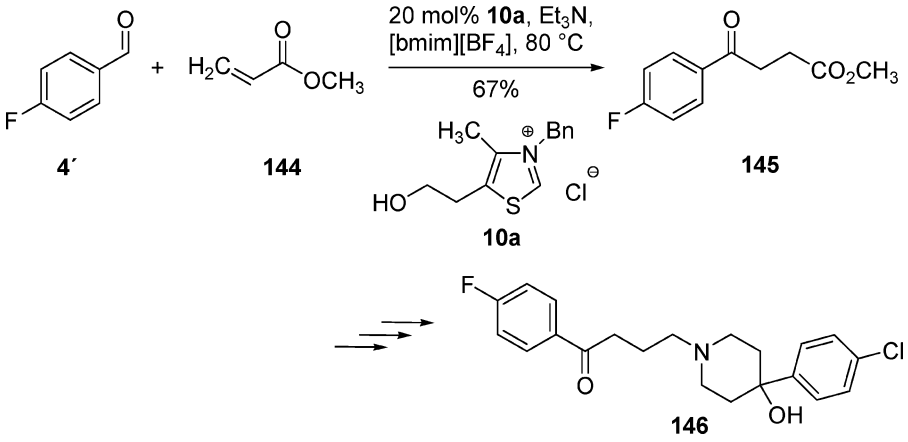


Table 15. Results of Burstein and Glorius: 5 mol % 19d, 10 mol % KO*t*-Bu, THF, 16 h

entry	R^1	R^2	yield (%)	cis/trans
1	*p*-Cl-Ph	Ph	53	81:19
2	*p*-Br-Ph	Ph	49	80:20
3	*p*-CO_2Me-Ph	Ph	70	79:21
4	*p*-F_3C-Ph	Ph	44	77:23
5	*m*-F-Ph	Ph	52	78:22
6	*m*-Cl-Ph	Ph	61	79:21
7	*m*-Br-Ph	Ph	60	79:21

Table 16. Results of Bode and Co-workers: 8 mol % 19d, 7 mol % DBU, THF/*t*-BuOH (10:1), 3−15 h

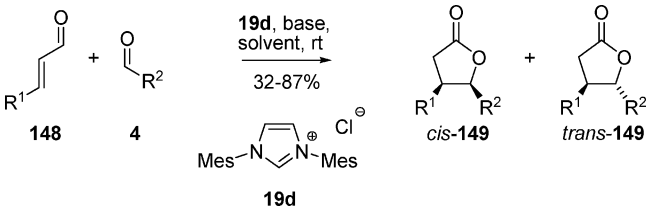
entry	R^1	R^2	yield (%)	cis/trans
1	Ph	*p*-Br-Ph	79	4:1
2[a]	Ph	*p*-CO_2Me-Ph	87	5:1
3	*p*-MeO-Ph	*p*-Br-Ph	76	4:1
4[b]	*p*-MeO-Ph	Ph	65	4:1
5[a,c]	TIPSC≡C	*p*-CO_2Me-Ph	41	3:1
6	TIPSC≡C	TIPSC≡CCH═CH	83	5:1
7[b]	1-naphthyl	1-naphthyl-CH═CH	67	5:1

[a] Concentration = 0.1 M. [b] Performed with 15 mol % **19d**, 14 mol % DBU. [c] The enal was added over a period of 3 h.

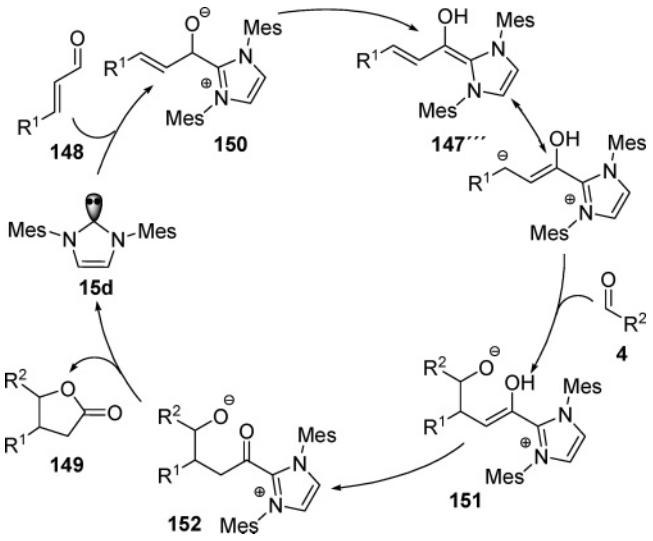
In further investigations, Glorius and co-workers also made use of this concept in order to generate γ-butyrolactones **154** bearing quaternary stereocentres by using several electron-deficient ketones **153** as electrophiles as well as a variety of nonaromatic α,β-unsaturated aldehydes **148** as homoenolate equivalents (Scheme 55 Table 17).[119] It is noteworthy that, in most cases, improved diastereomeric ratios were obtained using nonaromatic α,β-unsaturated aldehydes as compared to the previously utilized cinnamaldehydes.

Further investigations revealed that α-methyl-unsaturated aldehydes **148′** could also be utilized as substrates. A sterically less demanding precatalyst **155** was deployed for this transformation since the previously used precatalyst **19d** did not show any activity, presumably due to steric interactions of the methyl group and the mesityl unit of the catalyst.

Scheme 53. Generation of γ-Butyrolactones by Burstein and Glorius and Bode and Co-workers



Scheme 54. Postulated Catalytic Cycle for the Carbene-Catalyzed Formation of γ-Butyrolactones



Of the four possible diastereomers, mainly the two epimers **154** and **154′** were obtained, in which the methyl group was oriented trans relative to the R^1-group. In addition, Glorius and co-workers focused on the development of an enantioselective version of the latter reaction by using chiral heterazolium salts such as (*S*)-**33**, (*S*,*R*)-**74′**, and (*S*)-**156** as precatalysts.[117,119] The salts (*S*)-**33** and (*S*,*R*)-**74′** showed no catalytic activity, whereas the imidazolium salt (*S*)-**156**

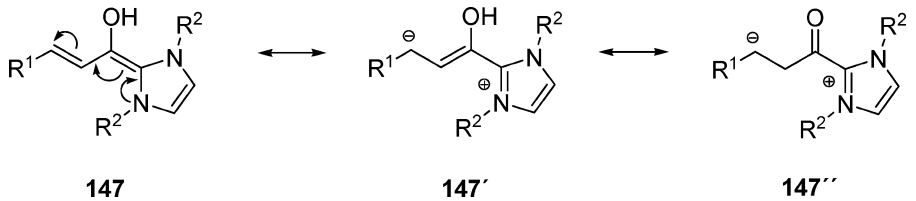


Figure 17. Homoenolate reactivity.

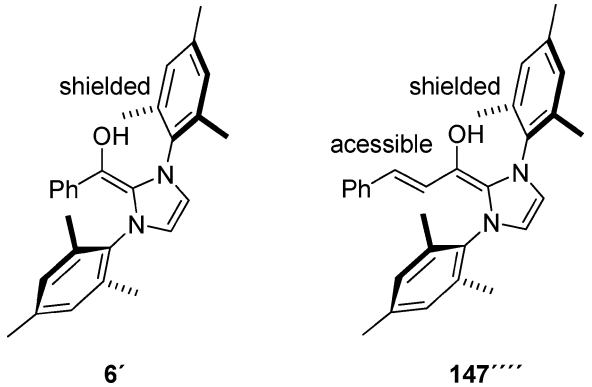
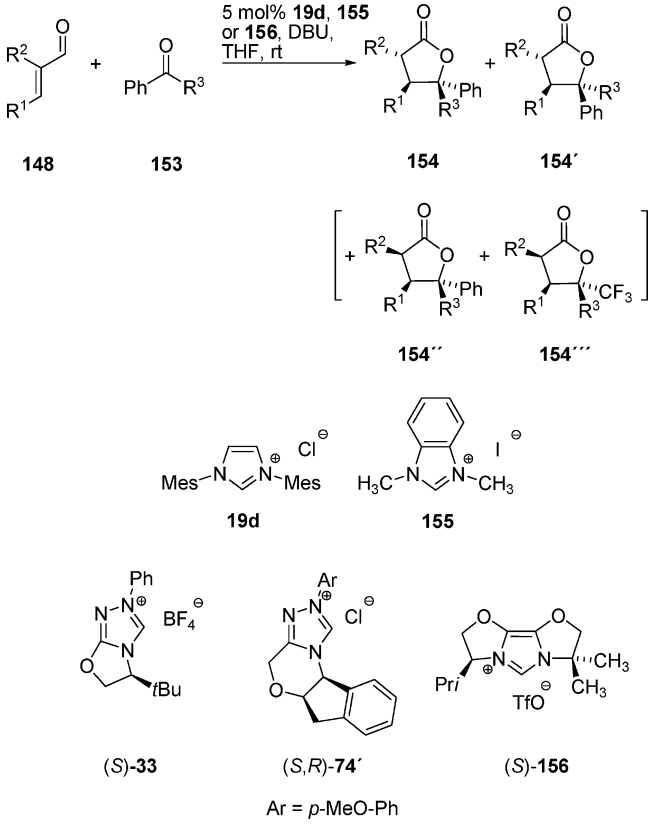


Figure 18. Possible sterical influence of the catalyst on the nucleophilicity.

Scheme 55. Conditions for the Generation of γ-Butyrolactones from Ketones by Glorius and Co-workers



appeared to be an efficient precatalyst for this reaction. By utilizing 5 mol % of (*S*)-**156**, advanced diastereoisomeric ratios for α,β-unsaturated aldehydes as substrates (entry 2) could be obtained with this method. However, the resulting ee values of 12% (**154**) and 25% (**154′**), respectively, were unsatisfyingly low. An enantioselective procedure with better asymmetric inductions for this novel carbon−carbon bond formation has not been reported so far. Furthermore, an intramolecular variant for the generation of γ-butyrolactones was also reported by the same research group. Different bi- and tricyclic γ-lactones **157**/**158** could be synthesized in a straightforward synthetic method in four or less steps (Figure 19).

It was observed by Glorius and co-workers that, under certain reaction conditions, an isomeric side product, the corresponding β-lactone **159**, was formed during the reaction course of the homoenolate condensation with electron-deficient ketones. Further investigations of this

Table 17. Generation of γ-Butyrolactones from Ketones by Glorius and Co-workers

entry[a]	R^1	R^2	R^3	precat.	yield (%)	dr
1[b]	Ph	H	CF_3	**19d**	84	66:34
2[b]	Ph	H	CF_3	(*S*)-**156**	70	74:26
3[b]	*m*-MeO-Ph	H	CF_3	**19d**	92	66:34
4[b]	*m*-Me_2N-Ph	H	CF_3	**19d**	74	70:30
5[c]	Ph	H	COMe	**19d**	55	58:42
6	Ph	H	CO_2Me	**19d**	78	50:50
7	*m*-MeO-Ph	H	CO_2Me	**19d**	94	47:53
8	*m*-Me_2N-Ph	H	CO_2Me	**19d**	98	44:56
9	Me	H	CF_3	**19d**	82	81:19
10	Pr	H	CF_3	**19d**	90	84:16
11	*i*-Pr	H	CF_3	**19d**	66	93:7
12	Me	H	CO_2Me	**19d**	87	68:32
13	Pr	H	CO_2Me	**19d**	71	67:33
14	*i*-Pr	H	CO_2Me	**19d**	72	65:35
15[d]	Ph	Me	CF_3	**156**	83	62:30:6:2
16[d]	*p*-Cl-Ph	Me	CF_3	**156**	71	63:29:6:2
17[d]	PhCH=CH	Me	CF_3	**156**	82	32:66:2:0

[a] General reaction conditions: 5 mol % DBU, THF, rt, 16 h. [b] Reaction conditions: 10 mol % KO*t*-Bu, THF, rt, 16 h. [c] Reaction conditions: 5 mol % DBU, THF, 60 °C, 16 h. [d] Reaction conditions: 5 mol % DBU, DMF, 75 °C, 16 h.

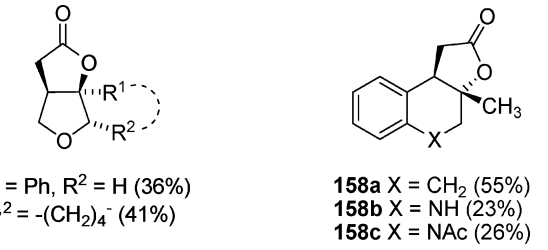


Figure 19. Product scope for the intramolecular homoenolate addition by Glorius and co-workers.

Scheme 56. Synthesis of β-Lactones by Glorius and Co-workers

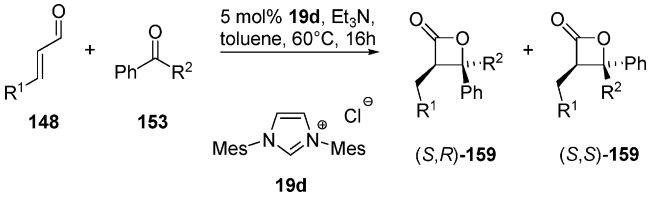


Table 18. Substrate Scope for the Synthesis of β-Lactones by Glorius and Co-workers

R^1	R^2	yield (%)	dr
Me	CF_3	34	60:40
Pr	CF_3	45	55:45
i-Pr	CF_3	48	62:38
Ph	CF_3	30	70:30
i-Pr	CO_2Me	22[a]	71:29

[a] Reaction was performed with 10 mol % **19d** and 10 mol % DBU.

interesting reaction outcome revealed that less polar solvents, higher temperatures, and triethylamine as a base seemed to favor the formation of the β-lactones **159** (Scheme 56, Table 18).

The authors explained the observed formation of the β-lactones via the following mechanistic model (Scheme 57).

The upper mechanism differs as compared to the mechanism for the formation of the γ-lactones in terms that homoenolate **147′′′** tautomerized to enolate **151**, which later on attacks ketone **153′** to generate the zwitterionic species

Scheme 57. Suggested Mechanism for the Formation of β-Lactones

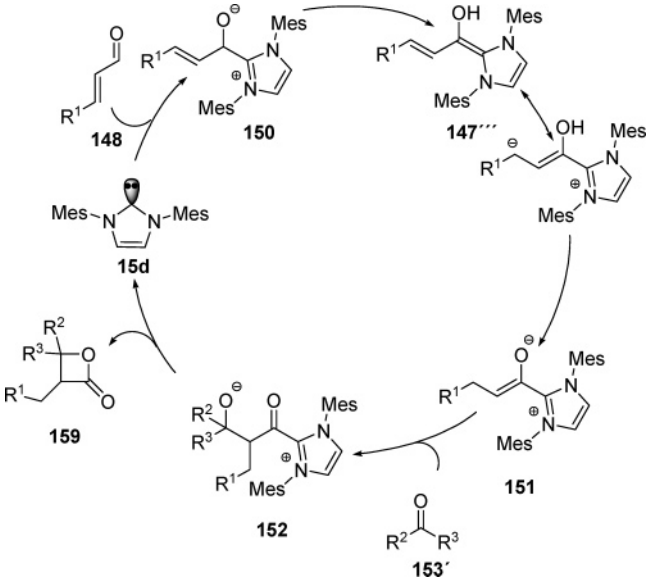


Table 19. Substrate Scope for the Carbene-Catalyzed Generation of γ-Lactams by He and Bode

R^1	R^2	yield **161** (%)	cis/trans
Ph	*p*-Me-Ph	70	4:1
Ph	*m*-Me-Ph	69	3:1
Ph	2-furyl	73[a]	1.7:1
Ph	PhCH=CH	61[b]	8:1
Ph	PhCH=C(Me)	62	5:1
m-CF_3-Ph	*p*-Me-Ph	70	3:2
p-CF_3-Ph	*p*-Me-Ph	70	3.5:1
Me(CO)	*p*-Me-Ph	65	3.5:1
TIPSC≡C	*p*-Me-Ph	51[c]	10:1

[a] Performed with 2 equiv of **160** at 75 °C, 63 h. [b] Reaction at room temperature. [c] Performed with addition of 1 equiv of **148** to 3 equiv of **160** over a period of 3 h.

152. Finally, a cyclization to the β-lactone **159** liberates the catalyst and closes the catalytic cycle. Employing a similar strategy, He and Bode developed a technique for the synthesis of γ-lactams **161** via the condensation of a homoenolate to imine **160** (Scheme 58, Table 19).[120]

In this approach, a variety of functionalized α,β-unsaturated aldehydes **148** were converted with *N*-4-methoxybenzenesulfonyl imines **160** into their corresponding γ-lactams **161** in good yields and in favor of the *cis*-diastereomers. In order to enable the addition of the carbene to the aldehyde, the undesired nucleophilic addition of the catalyst to the imine has to be reversible. To fulfill this task, different imines have been screened, revealing that *N*-alkyl and *N*-aryl imines were unreactive and more electrophilic imines such as *N*-tosyl and *N*-phosphinoyl inhibited the catalyst through the formation of stable catalyst-imine adducts. *N*-4-methoxybenzenesulfonyl imines were found to be the most suitable ones, providing the desired γ-lactams in up to 75% yield.

5.2. Protonation and Nucleophile Trapping

Since N-heterocyclic carbene catalysts are such a powerful tool for generating homoenolate species from α,β-unsaturated aldehydes, further applications for these reactive intermediates have been developed. In 2005, Chan and Scheidt reported the protonation of a nucleophilic homoenolate where the resulting activated carbonyl unit is trapped by a nucleophile (Scheme 59, Table 20).[121] By simply employing an excess of phenol as a Brønsted acid, they succeeded in overcoming the difficulties of decoupling the electrophiles from their corresponding nucleophiles (primary or secondary alcohols), leading to a broad scope of the accordant esters **162** in good-to-excellent yields.

Scheme 59. Carbene-Catalyzed Reaction of α,β-Unsaturated Aldehydes with Alcohols by Chan and Scheidt

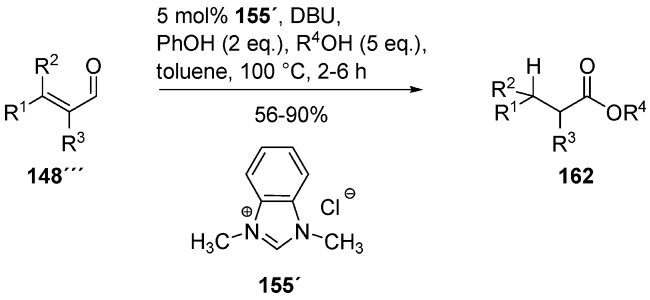


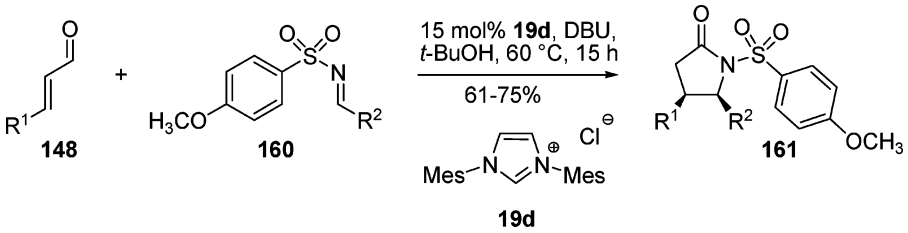
Table 20. Substrate Scope and Yields for the Carbene-Catalyzed Reaction of α,β-Unsaturated Aldehydes with Alcohols

R^1	R^2	R^3	R^4	yield **162** (%)	R^1	R^2	R^3	R^4	yield **162** (%)
Ph	H	H	Et	72	*n*-Pr	H	H	Bn	90
Ph	H	H	Ph	56	*p*-Cl-Ph	Ph	H	Bn	82
Ph	H	H	Cy	57	Ph	Ph	Ph	Bn	86
Ph	H	H	Bn	82					

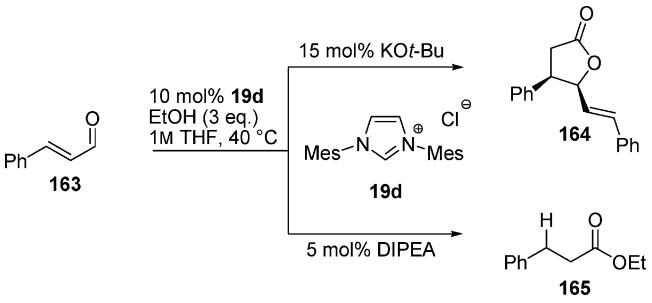
Sohn and Bode showed that the fate of the generated homoenolate correlates with the character of the catalytic base disposed in the reaction.[122] Strong bases such as KO*t*-Bu promote the carbon−carbon bond formation, as observed in enal−aldehyde cross-condensations, while weaker bases such as diisopropylethylamine (DIPEA) allow protonation of the homoenolate and the formation of an activated carbonyl unit (Scheme 60).

It is emphasized that the problem of distinguishing the reaction course mostly occurred when the imidazolium salt IMes-HCl **19d** is used as the precatalyst. In contrast, optimization studies revealed that the combination of the precatalyst **166** and DIPEA in tetrahydrofuran (THF) required no further additives, enabled milder reaction conditions, and avoided the formation of enal−aldehyde cross-condensation products (Figure 20).

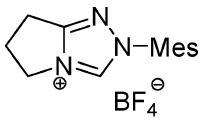
Scheme 58. Carbene-Catalyzed Generation of γ-Lactams by He and Bode



Scheme 60. Effect of the Catalytic Base on the Reaction Course of the Homoenolate



Inspired by the possibility of protonation and nucleophilic trapping of homoenolates, Zeitler developed a method for the stereoselective preparation of (*E*)-configured α,*β*-unsatured esters **168** starting from propargylic-derived aldehydes



166

Figure 20. Tetrazolium precatalyst employed by Sohn and Bode.

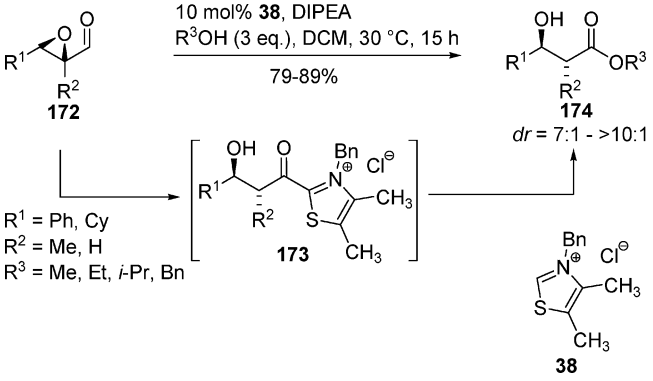
167 (Scheme 61).[123] The method is based on the generation of an activated carboxylate **171**, which results from the tautomerization of the intermediate allenol **170**.

Applying this method, Zeitler could obtain a variety of different alkyl, aryl, and heteroaryl functionalized α,*β*-unsaturated esters in good yields and with preference for the (*E*)-configured isomers. Different carbene catalysts were tested in this reaction with regard to their (*E*/*Z*)-stereoselectivity. The sterically hindered imidazolium salt IMes−HCl **19d** was found to be the most selective catalyst, providing the product in selectivities greater than 95:5 (*E*/*Z*).

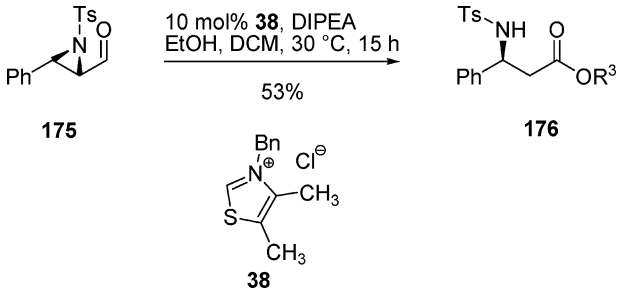
Already in 2004, Chow and Bode had developed a procedure for the diastereoselective formation of *β*-hydroxyesters by employing the thiazolium salt **38** as a precatalyst (Scheme 62).[124] The key step in the catalytic cycle of this reaction is the generation of an activated carboxylate **173**, which can then be converted into the desired *β*-hydroxy ester **174**. In order to obtain the acyl imidazolium intermediate **173**, a nucleophilic attack of the catalyst at the aldehyde unit of the substrate followed by an epoxide opening is required.

It is worth mentioning that the substrate scope in this application is not limited to epoxide aldehydes. Chow and Bode were also able to convert α,*β*-aziridinylaldehydes **175** into their corresponding *N*-tosyl-*β*-aminoester **176** in moderate yields under the same conditions (Scheme 63).

Scheme 62. Diastereoselective Synthesis of *β*-Hydroxyesters by Chow and Bode

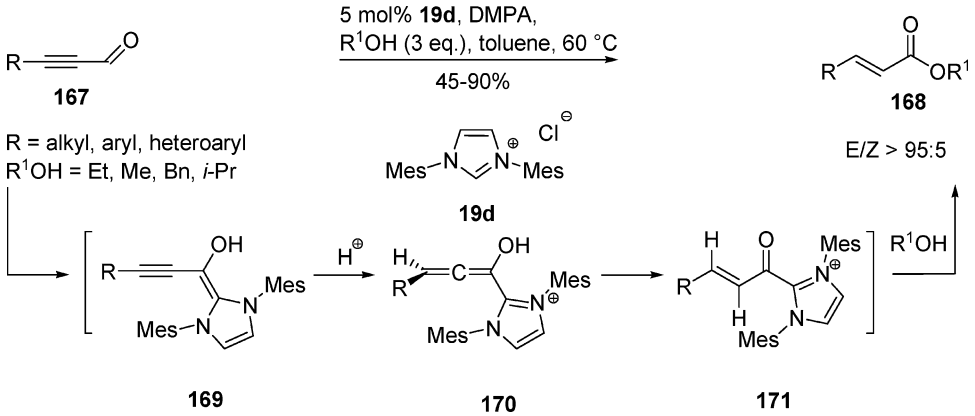


Scheme 63. Diastereoselective Synthesis of *N*-Tosyl-*β*-aminoester by Chow and Bode



Shortly after Chow and Bode had published their method for the carbene-catalyzed formation of *β*-hydroxyesters, Rovis and co-workers presented an alternative way for the generation of saturated esters **162** starting from α-haloaldehydes **177** (Scheme 64, Table 21).[125] The transformation of the α-haloaldehydes **177** into dehalogenated acylation agents was envisioned to proceed via the Breslow intermediate **178**, which contains a *β*-leaving group. After the formation of the enol **179** and tautomerization to the intermediate acyl azolium **180**, reaction with an alcohol afforded the esters **162** and regenerated the catalyst. Secondary and sterically hindered bromides (entry 4) were shown to be suitable substrates. By utilizing the chlorinated analogues as substrates, lower yields were obtained (entry 3). The range of nucleophiles included primary alcohols as well as secondary ones. Phenols and anilines (entry 12) could also be utilized.

Scheme 61. Stereoselective Preparation of (*E*)-Configured α,*β*-Unsaturated Esters by Zeitler



Scheme 64. Method Developed by Rovis and co-workers for the Generation of Saturated Esters

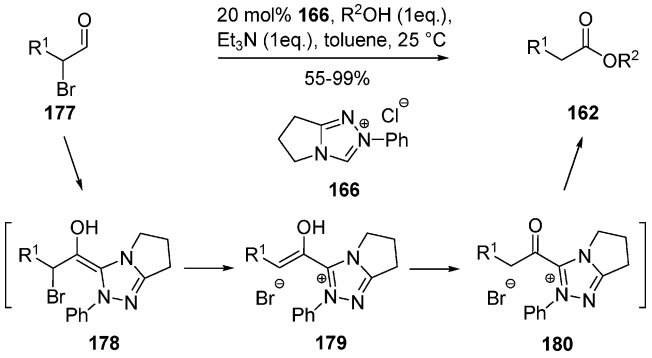
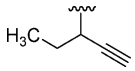


Table 21. Substrate Scope and Yields for the Esterification of α-Haloaldehydes

entry	R^1	R^2	time (h)	yield (%)	entry	R^1	R^2	time (h)	yield (%)
1	H	Bn	4	60	7	Bn	$Ph(CH_2)_4$	4	73
2	Bn	Bn	4	80	8	Bn	*i*-Pr	24	66
3[a]	Bn	Bn	4	65	9	Bn	Cy	24	66
4	Cy	Bn	24	99	10	Bn	Ph	24	55
5	Bn	Me	4	78	11	Bn		24	65
6	Bn	Et	4	78	12[b]	Bn	Ph	24	91

[a] Performed with the corresponding chloride. [b] Performed with R^2NH_2 instead of R^2OH.

Employment of a chiral carbene in this method allowed Rovis and co-workers the successful desymmetrization of *meso*-hydrobenzoin with α-bromocyclohexanecarboxaldehyde. The corresponding monoacylated diol could be obtained in 75% yield and 83% ee.

Table 22. Substrate Scope for the Enantioselective Synthesis of α-Chloroesters

R^1	R^2	yield (%)	ee (%)
Bn	H	79	93
p-MeO-$PhCH_2$	H	76	90
$Ph(CH_2)_3$	H	68	89
$CyCH_2$	H	65	93
Bu	H	65	89
Bn	4-Me	71	89
Bn	4-MeO	71	91
Bn	2-Me	62	90
Bn	2-Cl	75	91
Bn	3,4-dimethyl	80	89

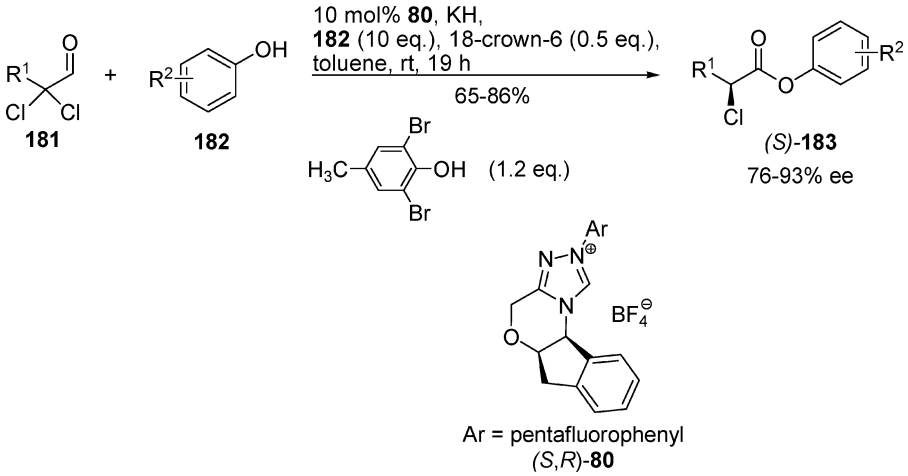
In 2005, the enantioselective synthesis of α-chloroesters **183** was developed by the same group.[126] The desymmetrization of the prochiral α-dichloroaldehydes **181** in the presence of the chiral triazolium salt (*S*,*R*)-**80** provided the corresponding α-haloester (*S*)-**183** in good yields and enantiomeric excesses (Scheme 65, Table 22).

The key step in the catalytic cycle is the enantioselective protonation of the generated chloroenolate **185** (Scheme 66). Important additives for the reaction are **18**-crown-**6** and 2,6-dibromo-4-methyl-phenol to ensure a homogeneous reaction mixture and to suppress an undesired background epimerization. Furthermore, it is noteworthy that the substrate scope of the reaction is limited to aldehydes lacking beta-branching.

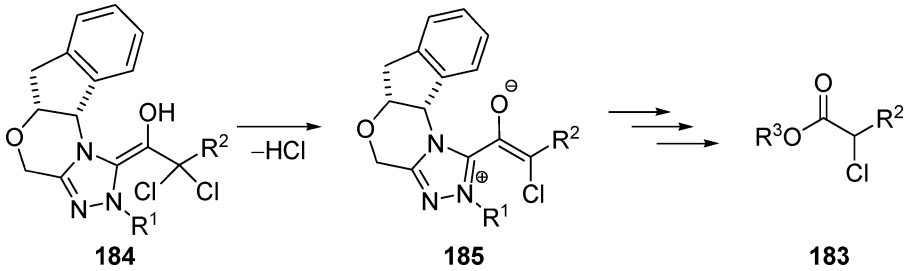
5.3. Diels–Alder Reactions

In 2006, Bode and co-workers applied the carbene-mediated generation of homoenolates in the first NHC-catalyzed Diels−Alder reaction.[127] In this enantioselective azadiene Diels−Alder reaction, a catalytically generated and highly reactive dienophile undergoes a $LUMO_{diene}$-controlled

Scheme 65. Enantioselective Synthesis of α-Chloroesters by Rovis and Co-workers



Scheme 66. Proposed Reaction Course for the Enantioselective Synthesis of α-Chloroesters



Scheme 67. Enantioselective Azadiene Diels−Alder Reaction by Bode and Co-workers

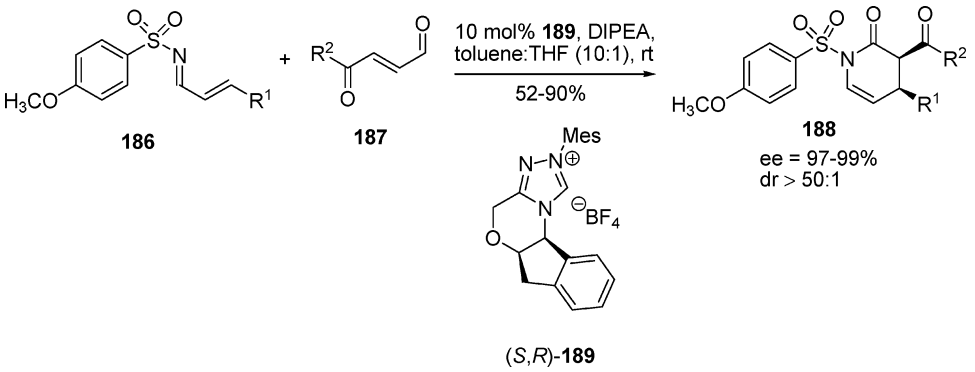
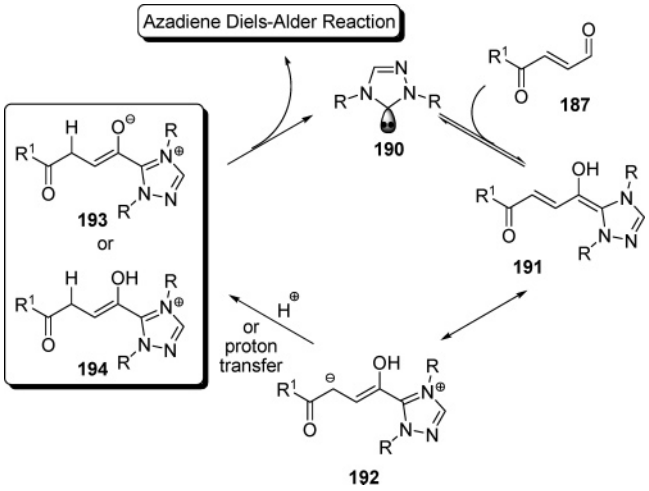


Table 23. Synthesis of 188 by Bode and Co-workers

R^1	R^2	yield (%)	ee (%) (config.)
Ph	OEt	90	99 (*S*,*S*)
Ph	OEt	90	99 (*R*,*R*)[a]
p-MeO-Ph	OEt	81	99 (*S*,*S*)
p-Me(CO)-Ph	OEt	55	99 (*S*,*S*)
2-furyl	OEt	71	99 (*S*,*S*)
n-Pr	OEt	58	99 (*S*,*S*)
Ph	O*t*-Bu	70	97 (*S*,*S*)
Ph	Me	51	99 (*S*,*S*)
n-Pr	Me	71	99 (*S*,*S*)
p-MeO-Ph	Ph	52	98 (*S*,*S*)

[a] 10 mol % of (*S*,*R*)-**189** was used as catalyst.

Scheme 68. Postulated Cascade for the Dienophile Formation



cyclization with N-protected α,*β*-unsaturated imines **186** to form the corresponding Diels−Alder products **188** (Scheme 67, Table 23). The dienophiles mentioned above are generated in situ during the reaction course via the following proposed catalytic cycle (Scheme 68).

The homoenolate **192** can be transformed to the dienophile **193** or **194** via protonation or an intramolecular proton transfer. Efforts to trap the generated dienophile with the imines **186** were only fruitful in the case of an electron-deficient enal, such as (*E*)-4-oxo-2-butenoate. Bode and co-workers underlined the need for a more sterically demanding catalyst, since the tested catalyst **19d** was inactive and the triazolium-derived catalysts **166′** and (*S*,*R*)-**74′** did not provide satisfying results (Figure 21). This obstacle was overcome by the development of the catalysts **166″** and **(***R*,*S*)-**189′**, both bearing a mesityl group as one of the N-substituents at the triazolium unit and, therefore, providing good-to-excellent yields and excellent enantioselectivities favoring the *cis*-stereoisomer.

A variability of the imine protection group is claimed, but so far only examples of *para*-methoxybenzesulfonyl as N-protection have been published. The reaction is tolerant to a variety of electron-deficient and electron-rich unsaturated imine substrates, which all provided enantiomeric excesses of >99%. The observed diastereoselectivity can probably be explained by a prefered formation of an endo transition state, as shown in Scheme 69. This upper transition state model also explains the observed *cis*-stereoselectivity as it arises from the (*Z*)-enolate.

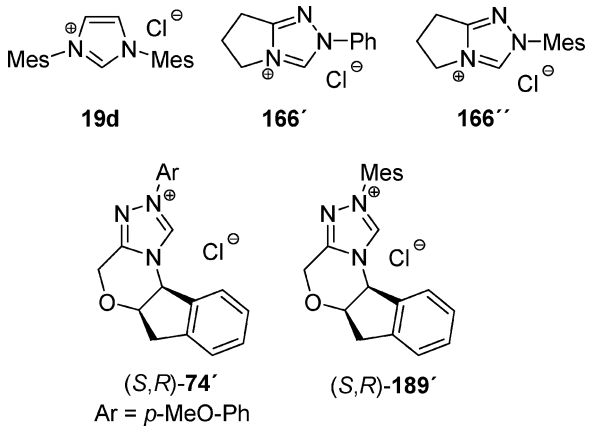
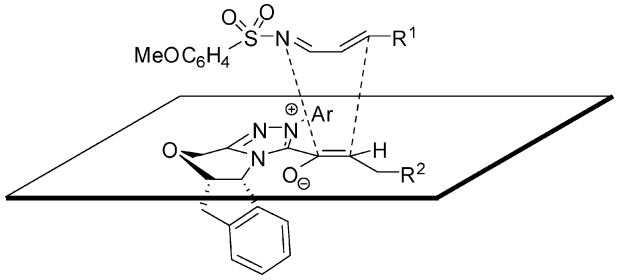


Figure 21. Screened caralysts for the azadiene Diels−Alder reaction.

Scheme 69. Transition State of the Azadiene Diels−Alder Reaction



Very recently, Bode and co-workers published an extension for homoenolate trapping via Hetero−Diels−Alder reactions.[128] In this method, the reactive enolate dienophile results from the racemic α-chloroaldehyde precursor *rac*-**195** and can further react with the heterodiene **196** in the manner of an oxodiene Diels−Alder reaction (Scheme 70, Table 24).

Scheme 70. Oxodiene Diels−Alder Reaction by Bode and Co-workers

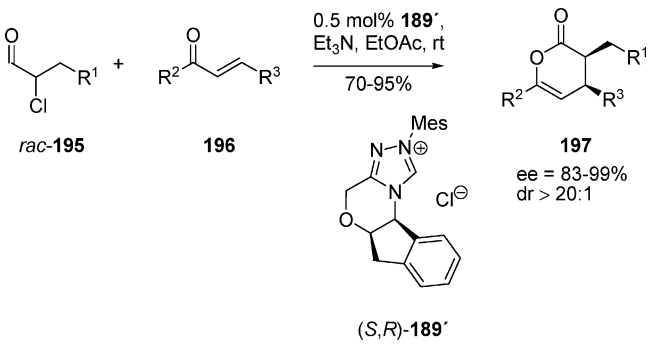


Table 24. Substrate Scope of the Oxodiene Diels−Alder Reaction by Bode and Co-workers

R^1	R^2	R^3	dr	yield (%)	ee (%) (config.)
Ph	Me	CO_2Me	>20:1	88	99 (*S*,*S*)
Ph	Ph	CO_2Me	8:1	91	99 (*S*,*S*)
Ph	*p*-Br-Ph	CO_2Me	6:1	80	99 (*S*,*S*)
Ph	Cy	CO_2Me	>20:1	76	86 (*S*,*S*)
Ph	2-furyl	CO_2Me	8:1	94	99 (*S*,*S*)
n-nonyl	Me	CO_2Me	>20:1	71	99 (*S*,*S*)
n-nonyl	Ph	CO_2Me	>20:1	90	99 (*S*,*S*)
OTBS	Ph	CO_2Me	3:1	80	97 (*R*,*S*)
Ph	CO_2Et	*p*-Me-Ph		74[a]	97 (*S*,*S*)
Ph	CO_2Et	*n*-Pr		84[a]	98 (*S*,*S*)
Ph	CO_2Et	Cy		85[a]	95 (*S*,*S*)
n-nonyl	CO_2Et	*p*-Me-Ph		70[a]	99 (*S*,*S*)
OTBS	CO_2Et	*p*-Me-Ph		83[a]	95 (*R*,*S*)

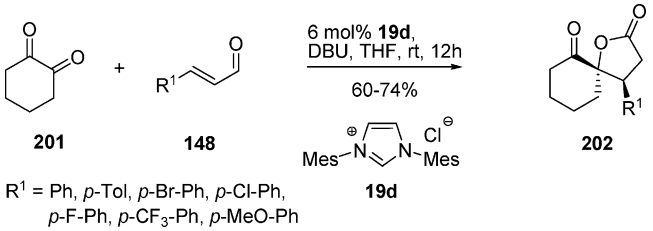
[a] Reactions were performed with 2 mol % of **189′**, the dr value was not determined.

Different enones bearing electron-withdrawing groups as well as aromatic and aliphatic enoates were tested in the reaction, all providing comparable yields and enantioselectivities as obtained in the azadiene Diels−Alder reaction. However, outstanding for the oxodiene reaction is the remarkably low catalyst loading of 0.5 mol %. Furthermore, it is notable that the reverse configured catalyst (*R*,*S*)-**189′** provides the corresponding *cis*-cyclization products **200** with respect to the opposite absolute configuration, therefore making this method highly applicable in asymmetric organic synthesis (Scheme 71).

5.4. Cross-Condensation of Enals and 1,2-Diones

In 2005, Nair et al. published the development of a method for the carbene-catalyzed stereoselective synthesis of spiro γ-butyrolactones.[129] The reaction of 1,2-cyclohexanedione **201** with a variety of α,β-unsaturated aldehydes **148** led to a broad range of γ-spirolactones **202 (**Scheme 72**)**.

Scheme 72. Carbene-Catalyzed Reaction of 1,2-Cyclohexanediones with Unsaturated Aldehydes by Nair et al.



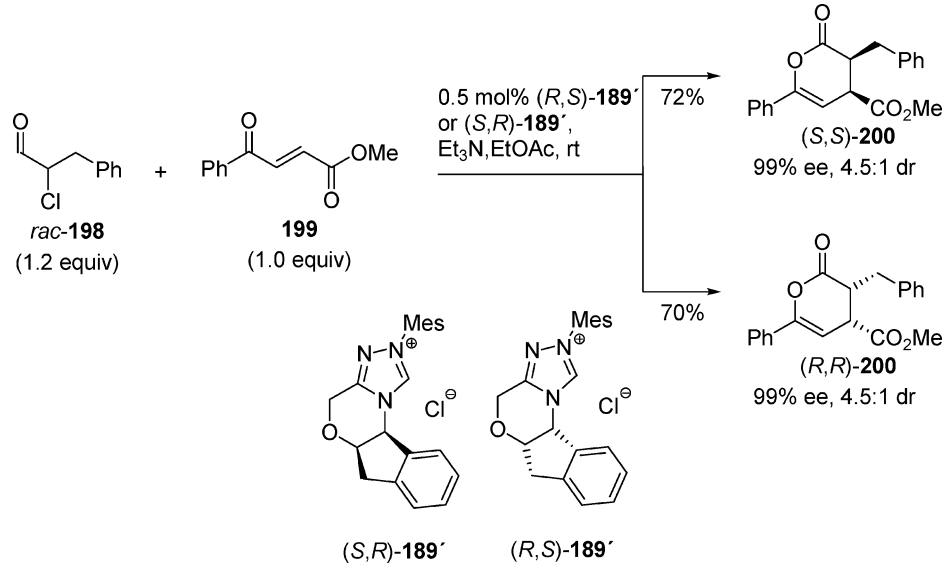
The yields of 60−78% were appropriate, yet the reaction was slow (12 h) but exceptionally selective by forming one diastereoisomer only. Moreover, Nair et al. demonstrated the applicability of this method with different 1,2-diones such as isatin derivatives **203** (Scheme 73). The observed yields of the corresponding spiroannulated oxindoles **205** were higher (85−92%) than the ones obtained with the spirolactones **202**. However, a mixture of both diastereoisomeres was formed.

5.5. Cross-Condensation of Enals and Enones

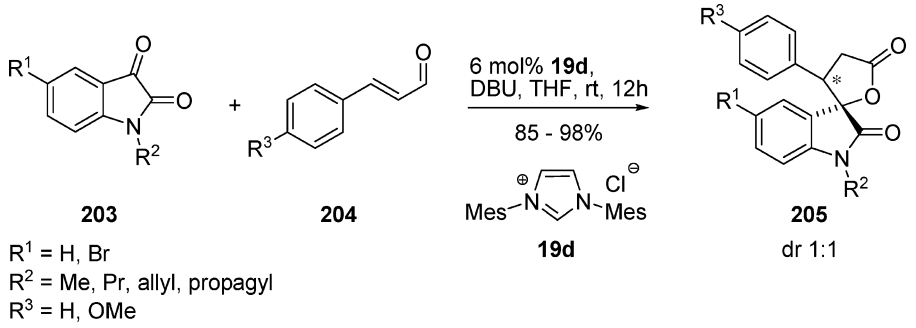
Very recently, another interesting discovery was reported by the Nair research group.[130] The reaction of a homoenolate **147** with an α,β-unsaturated ketone **69** did not lead to the expected β-ketocyclopentanone **206**, but instead to the cyclopentene **207**. This observation was used for the development of a new NHC-catalyzed cyclopentannulation method (Scheme 74).

Nair et al. could apply this novel method for the synthesis of diverse cyclopentenes **207** utilizing different unsaturated aldehydes and ketones (Scheme 75, Table 25). Interestingly, only one diastereomer was formed in all cases, which shows the remarkable diastereoselectivity of this reaction.

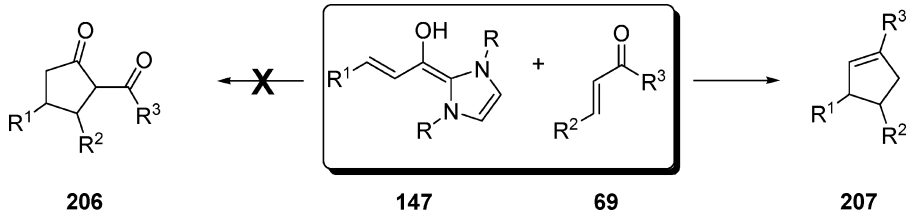
Scheme 71. Oxodiene Diels−Alder Reaction with Both Enantiomers of the Catalyst



Scheme 73. Carbene-Catalyzed Reaction of Isatin Derivatives with Unsaturated Aldehydes by Nair et al.



Scheme 74. Unexpected Outcome of the Reaction of α,β-Unsaturated Ketones with Homoenolates



Scheme 75. Scope and Conditions for the Reaction of α,β-Unsaturated Ketones with Homoenolates by Nair et al.

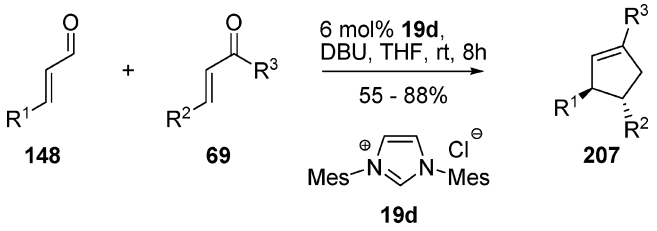


Table 25. Substrate Scope for the Reaction of α,β-Unsaturated Ketones with Homoenolates

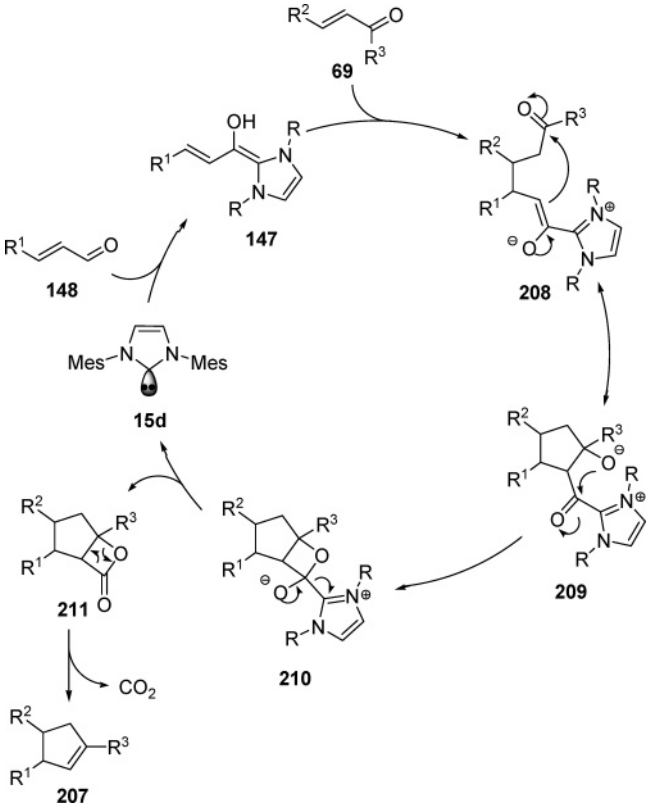
R^1	R^2	R^3	yield (%)
o-MeO-Ph	2-thienyl	*p*-Cl-Ph	88
Ph	1-naphthyl	*p*-Cl-Ph	76
p-MeO-Ph	*p*-CN-Ph	*p*-Me-Ph	85
p-MeO-Ph	Ph	*p*-Cl-Ph	76
p-MeO-Ph	Ph	Ph	88
Ph	Ph	Ph	78
p-MeO-Ph	*p*-F-Ph	*p*-Cl-Ph	78
p-MeO-Ph	*p*-Cl-Ph	*p*-Cl-Ph	76
p-MeO-Ph	2-thienyl	Ph	86
p-MeO-Ph	2-furyl	*p*-Cl-Ph	70
p-MeO-Ph	Me	*p*-Cl-Ph	55
Me	2-thienyl	*p*-Cl-Ph	73

In the postulated catalytic cycle, the generated homoenolate **147** attacks the unsaturated ketone **69** as a d^3-nucleophile in the manner of a Michael addition to form the zwitterionic enolate **208**. After proton transfer, an intramolecular aldol reaction to form **209** and subsequent β-lactonization via **210** regenerates the catalyst and forms the bicyclic lactone **211**, which is then converted into the trisubtituted cyclopentene **207** under the loss of CO_2 (Scheme 76).

Very recently, Bode and co-workers developed an enantioselective extension of Nair et al.'s method for the synthesis of cyclopentenes via the cross-condensation of enals and enones (Scheme 77).[131]

By employing the *N*-mesityl-substituted chiral triazolium precatalyst **189′**, Bode and co-workers were able to achieve high yields and excellent ee's. The substrate scope is limited to enones bearing an aromatic substituent, because only those

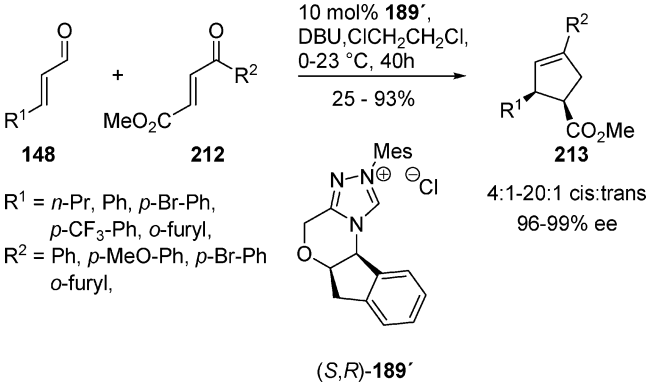
Scheme 76. Postulated Catalytic Cycle for the Reaction of α,β-Unsaturated Ketones with Homoenolates



lead to intermediates that undergo facile transformation. While Nair et al. reported that chalcone substrates gave trans configured products, Bode and co-workers obtained cis products with higher ee's when employing α,β-unsaturated enones like **212**. Mechanistic evidence supports a cascade sequence, which differs in the first steps with the one reported by Nair et al. involving an intramolecular aldehyde−ketone crossed-benzoin condensation and an oxy-Cope rearrangement as shown in Scheme 78.

Nair et al. also investigated the reaction of homoenolates **147** with tropone (**218**).[132] Surprisingly, the reaction took

Scheme 77. Enantioselective Cross Condensation of Enals and Enones by Bode and Co-workers

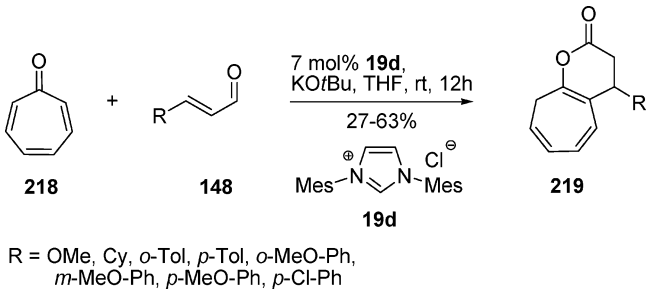


place in the way of an [8+3] annulation, leading to a bicyclic δ-lactone **219** instead of the expected δ-spirolactone **217** (Scheme 79).

Investigations of the scope of the [8+3] annulation revealed that the reaction is tolerant to a broad range of substituted cinnamon aldehydes **148**, providing the bicyclic δ-lactone **219** in moderate-to-good yields (Scheme 80). Interestingly, alkylated allylic substrates (R = Cy) could also be converted into their corresponding δ-lactones **219** by this method.

The postulated mechanism for this reaction is partly similar to the mechanism reported for the reaction of homoenolates with α,β-unsaturated aldehydes. After the conjungate addition of the homoenolate **147** to tropone (**218**), an intramolecular attack of the enolate oxygen at the carbonyl unit regenerates the catalyst and forms the bicyclic lactone **223**. Then, the initially formed lactone **223** undergoes isomerization to its presumably more stable form **219** (Scheme 81).

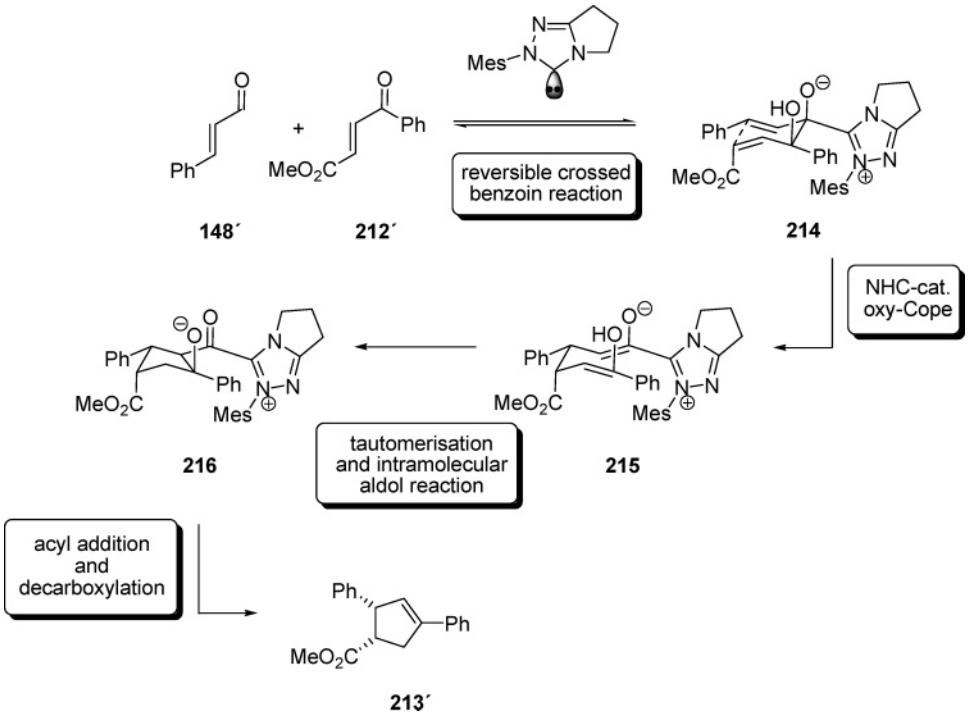
Scheme 80. Carbene-Catalyzed Reaction of Tropone with α,β-Unsaturated Aldehydes by Nair et al.



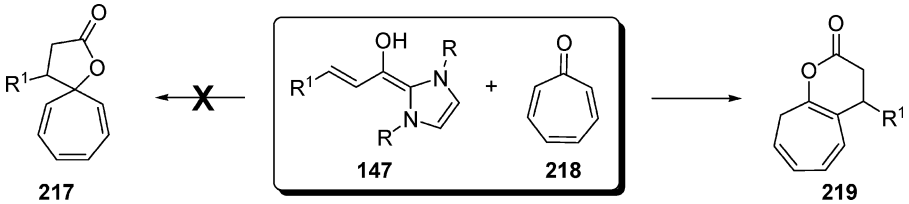
5.6. Miscellaneous

Fu and co-workers have recently found that, besides α,β-unsaturated aldehydes, α,β-unsaturated esters **224** can also act as suitable precursors for the generation of homoenolate intermediates.[133] In a carbene-catalyzed Heck-type cyclization, they were able to implement a broad substrate scope including conjungated esters, amides, and nitriles to convert them into the corresponding cycloalkanes and heterocycles **225** (Scheme 82).

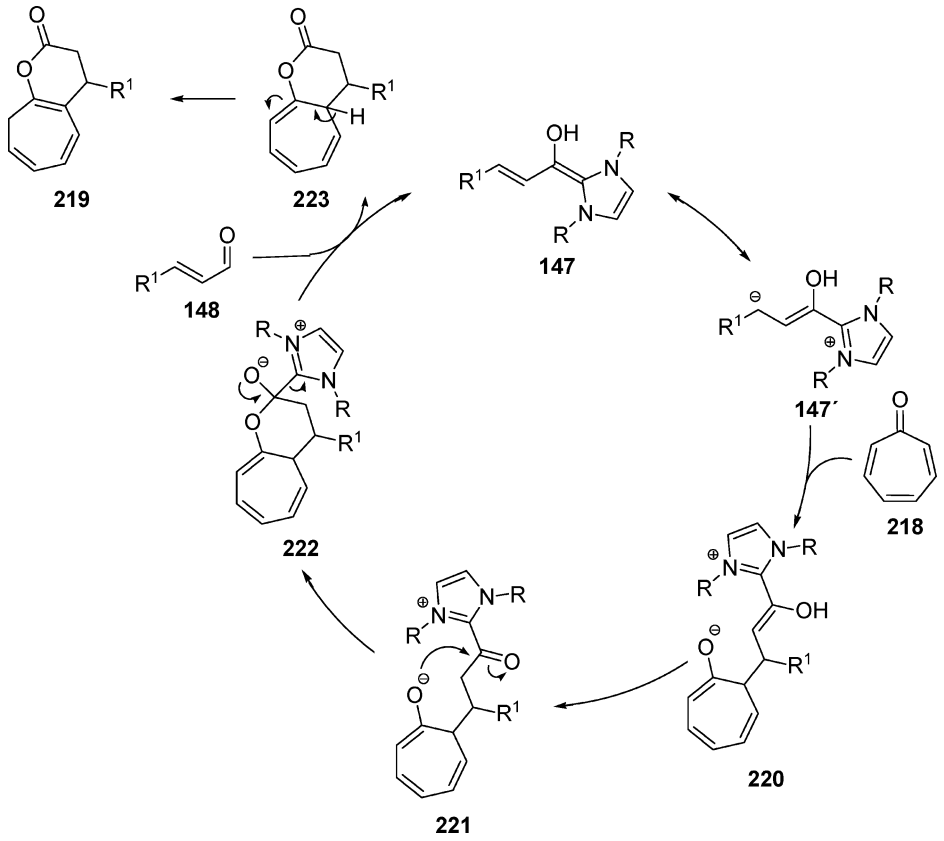
Scheme 78. Catalytic Cycle for the Reaction of α,β-Unsaturated Ketones with Homoenolates by Bode and Co-workers



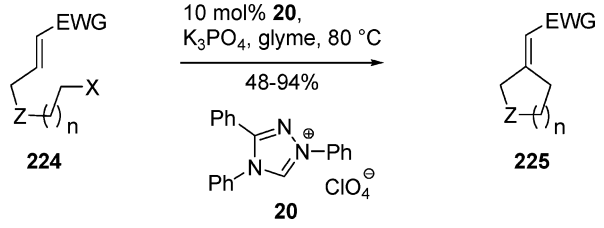
Scheme 79. Unexpected Outcome of the Reaction of Tropone with Homoenolates



Scheme 81. Proposed Catalytic Cycle for the Reaction of Tropone with α,β-Unsaturated Aldehydes

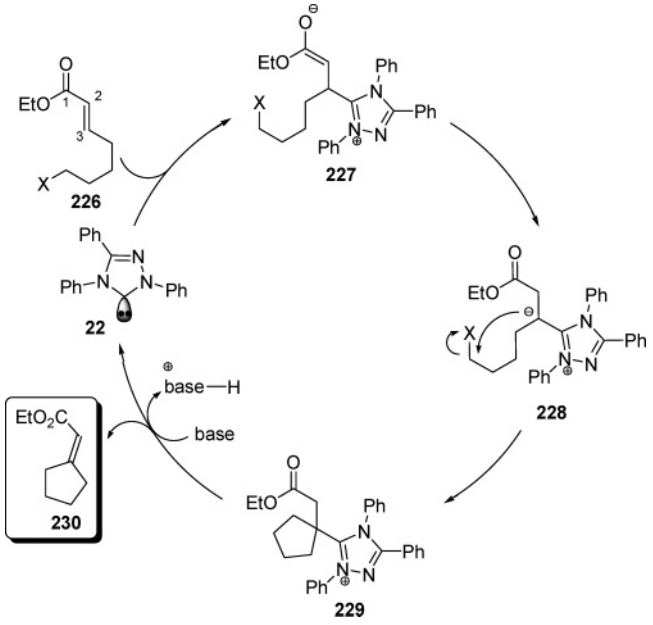


Scheme 82. Carbene-Catalyzed Heck-type Cyclization by Fu and Co-workers



EWG = CO_2Et, CO_2Allyl, $CO_2N(Me)OMe$, CN
Z = CH_2, O
X = Br, Cl, OTs
n = 1, 2

Scheme 83. Proposed Mechanism for the Heck-type Cyclization by Fu and Co-workers



The proposed mechanism for this reaction differs from the already reviewed ones in the way that the addition of the carbene takes place at position 3 of the unsaturated ester **226** (Scheme 83). The Michael adduct **227** undergoes a tautomerization to **228**, which in turn performs an intramolecular nucleophilic substitution to form the cycloalkane **229**. A base-catalyzed β-elimination then regenerates the catalyst and creates the product **230**.

Another interesting approach in applying nucleophilic carbene catalysts for the formation of heterocyclic compounds was reported by Louie and co-workers.[134] Her research group developed a straightforward cyclotrimerization for a variety of isocyanates **231** to convert them into their corresponding isocyanurates **232** in excellent yields and with remarkably low catalyst loadings (0.001−0.1 mol %) (Scheme 84). Different catalysts were tested in the reaction, with the result that **233** was the most suited one because it only generates the trimerization product **232** in high yields with the lowest catalyst loading.

6. Transesterification Reactions

The first contribution to esterifications[135] promoted by N-heterocyclic carbenes was reported by the research group of Smith in 1994.[136] The transfer of an alkoxycarbonyl unit from 2-alkoxycarbonylimidazolium salts **234** to benzyl alcohols was performed in the presence of 1,4-diazabicyclo-[2.2.2]octane (DABCO) at room temperature (Scheme 85).

A drawback of this application is the fact that the alkoxycarbonyl is carried by the imidazolium salt **234**.

Scheme 84. Carbene-Catalyzed Cyclotrimerization by Louie and Co-workers

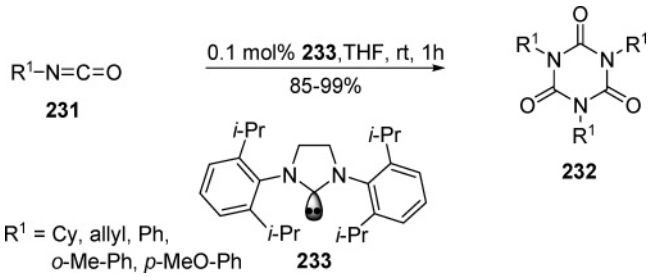


Table 26. Conditions and Substrate Scope for the Transesterification of Primary Alcohols by Nolan and Co-workers; Conditions: 0.5−1.0 mol % 15d or 2.5−5.0 mol % 15e, 4 Å MS

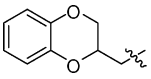
R^1	R^2	R^3	cat. (mol %)	time	yield (%)
$PhOCH_2$	Me	Bn	**15e** (2.5)	30 min	99
PhCH=CH	Me	Bn	**15e** (2.5)	180 min	97
Me	CH_2=CH	geraniol	**15d** (1.0)	60 min	99
Me	CH_2=CH		**15d** (0.5)	15 min	100

Table 27. Conditions and Substrate Scope for the Transesterification of Primary and Secondary Alcohols by Hedrick and Co-workers; Conditions: 3.7−4.4 mol % 15d or 3.7−4.6 mol % 15i

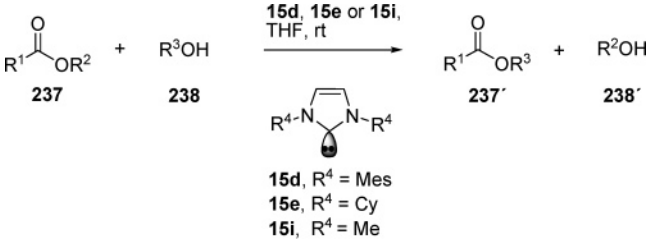
R^1	R^2	R^3	cat. (mol %)	time	yield (%)
Ph	Me	Et	**15d** (4.4)	20 h	85
Ph	Me	*i*-Pr	**15d** (3.7)	20 h	11
Ph	Me	Et	**15i** (4.6)	20 h	79
Ph	Me	*i*-Pr	**15i** (3.7)	20 h	72

Therefore, a stoichiometric amount of the imidazolium salts had to be used and prepared separately for this transformation.

Almost simultaneously, the research groups of Nolan and Hedrick independently reported in 2002 on the first carbene-promoted transesterification that required only catalytic amounts of a carbene.[137] In the case of Nolan and co-workers' work, low catalyst loadings (0.5−5 mol %) of the aryl- or alkyl-substituted imidazolium based salts **15d** or **15e** were utilized accompanied with high yields of the transesterification product **237′** under mild conditions and short reaction times (Scheme 86, Table 26).

Remarkably, this method enabled a selective protection of primary alcohols in the presence of secondary alcohols. This was observed during an experiment where benzyl alcohols was exclusively acetylated with vinyl acetate in the presence of 2-butanol. In the case of Hedrick and co-workers, the yields for the esterification products were slightly lower and the reaction times were significantly longer, but by employing the methyl-substituted imidazolium-based catalyst **15i**, they were able to widen the substrate scope to secondary alcohols (see Table 27). Later on, an extension for the conversion of secondary alcohols into their corresponding esters was developed by the Nolan group.[138] The use of 1,3-

Scheme 86. Transesterification Developed by Nolan and co-workers and Hedrick and Co-workers



dicyclohexylimidazolin-2-ylidene (**15e**) as catalyst made the reaction of a variety of different alcohols possible, including aliphatic, cyclic, and aromatic ones, with diverse esters **239** to the corresponding transesterificated products **241** with moderate-to-excellent yields (Scheme 87, Table 28).

It was found that a sterically more demanding environment at the α-position of the alcohols reduced the reaction rate and required longer reaction times. The conversion of tertiary alcohols was also possible with this method; however, prolonged reaction times and higher catalyst loadings (20 mol %) were needed.

In 2005, an interesting contribution to the field of transesterification reactions was made by Movassaghi and Schmidt, when reporting the amidation of unactivated esters **237** with amino alcohols **242** promoted by N-heterocyclic carbenes (Scheme 88, Table 29).[139]

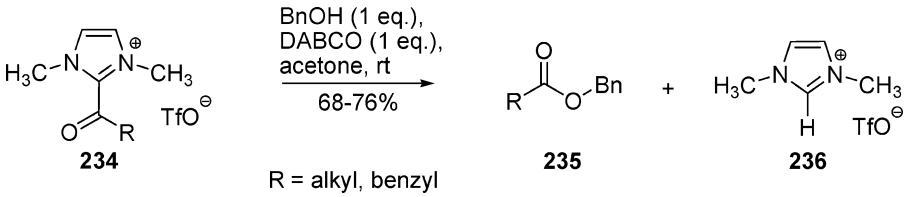
With this method, Movassaghi and Schmidt were able to obtain the amidation product **243** in excellent yields, utilizing different amino alcohols **242** and aliphatic or aromatic esters **237** bearing different functionalities. It is also remarkable that chiral amino alcohols were also suitable for this method since no epimerization was observed during their reaction. The reaction outcome may be explained via the following proposed mechanism (Scheme 89).

In the initial step, a nucleophilic activation of the hydroxyl group of the amino alcohol **242**, promoted by the carbene catalyst **15d**, is followed by the transesterifiction to the ester **244**. The latter is then converted in situ to the amide **243** via a N → O acyl transfer.[140]

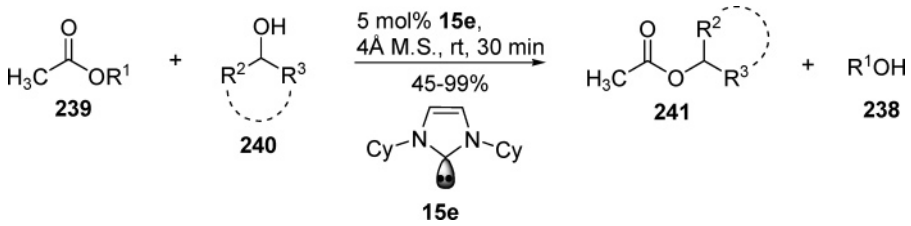
Suzuki et al.[141] and Maruoka and co-workers[142] made further progress in the field of carbene-catalyzed transesterifications by developing enantioselective acylations. By employing the C_2-symmetric chiral imidazolium salts **246** and vinyl acetate **244**, Suzuki et al. were able to report moderate enantiomeric excesses (up to 58% ee) in the first carbene-catalyzed kinetic resolution of secondary alcohols (Scheme 90).

Suzuki et al. also found out that more sterically demanding catalysts do not show better selectivities in this application. Later on, the research group of Maruoka reported about an

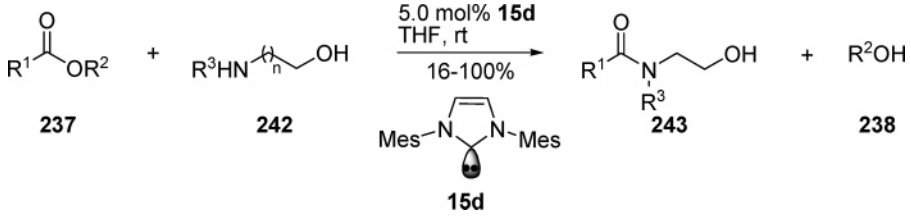
Scheme 85. Carbene-Catalyzed Transesterification Developed by Bakhtiar and Smith



Scheme 87. Transesterification of Secondary Alcohols 240 by Nolan and Co-workers



Scheme 88. Amidation of Unactivated Esters with Amino Alcohols by Movassaghi and Schmidt



Scheme 89. Proposed Mechanism for the Amidation of Unactivated Esters with Amino Alcohols by Movassaghi and Schmidt

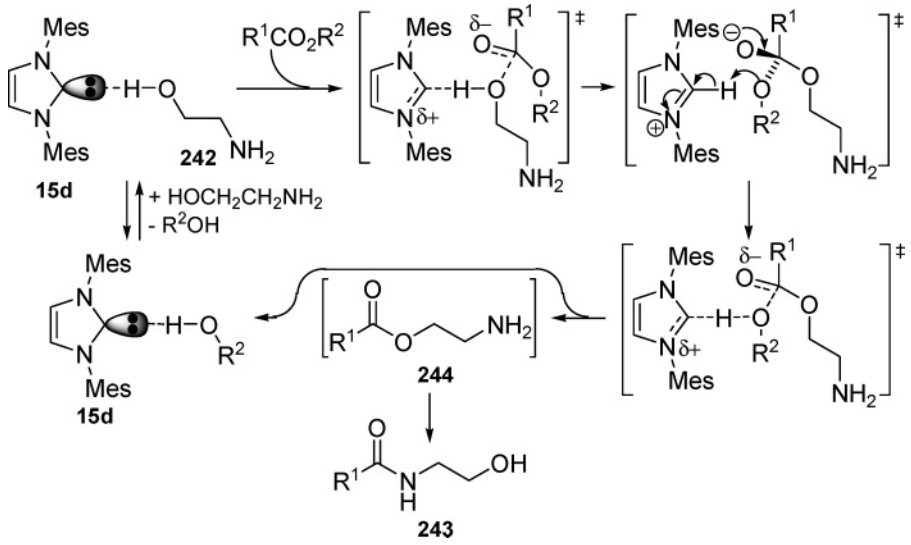


Table 28. Scope of the Transesterification of Secondary Alcohols by Nolan and Co-workers

R^2	R^3	yield (R^1 = Me) (%)	yield (R^1 = Et) (%)
Ph	Me	93	75
Ph	Ph	92	56
cyclopentyl		96	92
2-methylcyclohexyl		67	47

Table 29. Scope of the Carbene-Catalyzed Amidation by Movassaghi and Schmidt

R^1	R^2	R^3	n	yield (%)
Bn	Me	H	1	100
p-CN-Ph	Me	H	1	96
Me	Bn	H	1	95
Bn	Me	(*S*)-prolinol[a]		99

[a] The reaction was performed with (*S*)-prolinol as amino alcohol **242**.

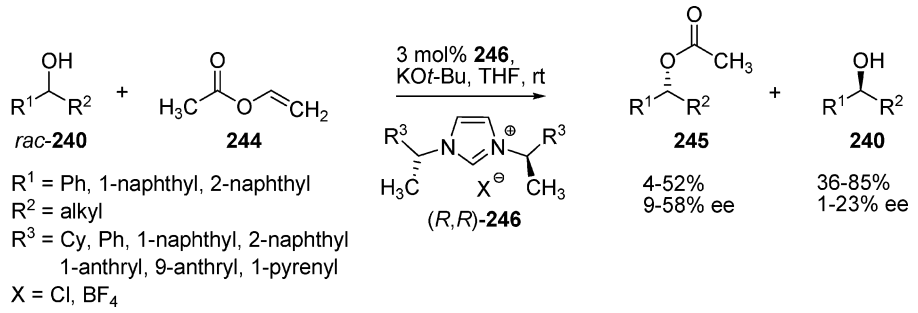
improvement in the carbene-catalyzed kinetic resolution of secondary alcohols. By employing a more sterically demanding acylation agent, such as vinyl diphenyl acetate **247**, Maruoka and co-workers were able to obtain selectivities up to 96% ee (Scheme 91, Table 30).

Recently, Singh and Nolan reported an extension of their protocol for the transesterification of secondary alcohols to phosphorus esters **250** (Scheme 92).[143] The screening of several carbene catalysts in the presence of benzyl alcohol and dimethyl methylphosphonate revealed the alkyl-substituted imidazolium carbene **15e** to be superior in this reaction over their less nucleophilic aryl-substituted imidazolium carbene counterparts. Since the transesterification is an equilibrium process, it is not surprising that product removal from the reaction mixture, which was achieved by applying 4 Å molecular sieves (MS) to remove the generated methanol, has a positive effect on the obtained yields. It was also mentioned that a rise in temperature favors the conversion, although accompanied by a decrease in selectivity since the diester was obtained as well.

Utilizing the N-heterocyclic carbene catalysts **19d** and **254**, Scheidt and co-workers reported a unique conversion of allylic, benzylic, and propargylic alcohols **253** into their unsaturated ester counterparts **237** (Scheme 93).[144] A catalyst screening revealed the sequence to be sensitive to azolium structure-based catalysts, since different imidazolium and thiazolium salts showed either no catalytic activity or incomplete conversion. However, utilizing triazolium salt **254**, the authors obtained high yields in a faster reaction. A possible catalytic cycle for the observed reactivity is shown in Scheme 94.

The catalytic cycle starts with an oxidation of the alcohol **256** to its corresponding aldehyde **148**. The latter is then

Scheme 90. N-Heterocyclic Carbene-Promoted Kinetic Resolution of Secondary Alcohols by Suzuki et al.



Scheme 91. N-Heterocyclic Carbene-Promoted Kinetic Resolution of Secondary Alcohols by Maruoka and Co-workers

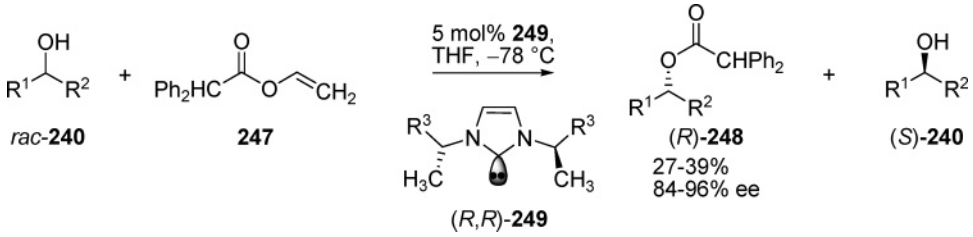
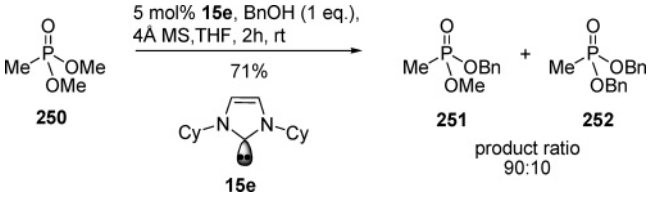


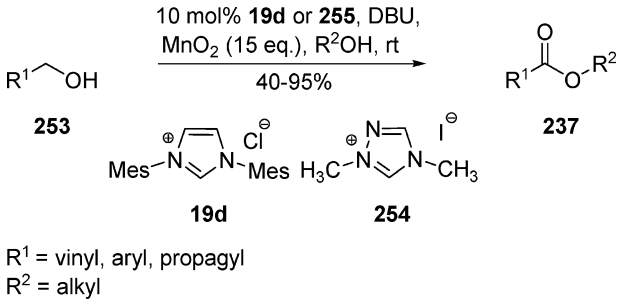
Table 30. Substrate Scope for the Kinetic Resolution of Secondary Alcohols by Maruoka and Co-workers

R^1	R^2	R^3	time (h)	ester (*R*)-**248** (%) (yield (%))
Ph	Me	Ph	3	93 (33)
Ph	Me	1-naphthyl	3	96 (32)
Ph	Et	1-naphthyl	0.5	92 (33)
p-MeO-Ph	Me	1-naphthyl	2	94 (30)
1-naphthyl	Me	Ph	1.5	93 (35)
1-naphthyl	Me	1-naphthyl	6	95 (27)
PhCH=CH	Me	Ph	3.5	84 (27)

Scheme 92. Transesterification of Phosphorus Esters by Singh and Nolan



Scheme 93. Tandem Oxidation of Unsaturated Alcohols to Esters by Scheidt and Co-workers

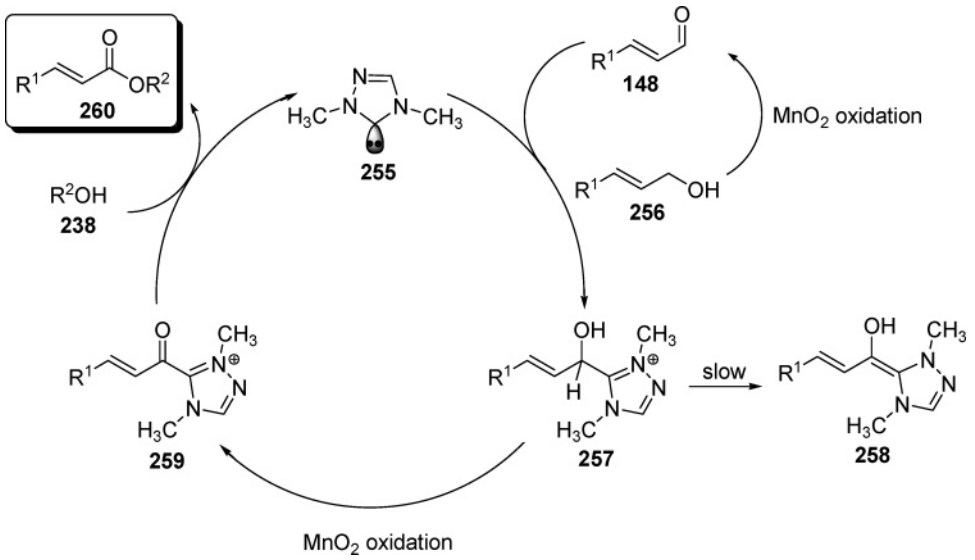


attacked by the carbene **255** to yield the tetrahedral intermediate **257**. A tautomerization of species **257** to the homoenolate equivalent **258** was not observed. Furthermore, the tetrahedral species undergoes a fast oxidation to the activated acyltriazolium species **259**, which is acylated to regenerate the catalyst, and the desired esterification product **260** is formed. With this one-pot tandem oxidation, Scheidt and co-workers were able to convert a variety of different unsaturated alcohols to their corresponding esters by simply oxidizing them in situ with manganese(IV) oxide. The method is not limited to unsaturated esters. Employing the same conditions, Scheidt and co-workers were also able to utilize saturated aldehydes to obtain the corresponding saturated esters in high yields. An enantioselective application of this tandem reaction was also aimed at by the authors. The use of a chiral catalyst, such as the triazolium salt (*R*,*S*)-**189**, allowed the generation of a chiral acyltriazolium intermediate, which could be successfully employed as an acylation agent in the desymmetrization of *meso*-diols **260**. Under optimized reaction conditions, Scheidt and co-workers obtained up to 80% ee with a good yield of 58% (Scheme 95). However, in 2004, Rovis and co-workers reported a similar study regarding the desymmetrization of *meso*-hydrobenzoin with α-bromocyclohexanecarboxaldehyde (see section 5.2).[125]

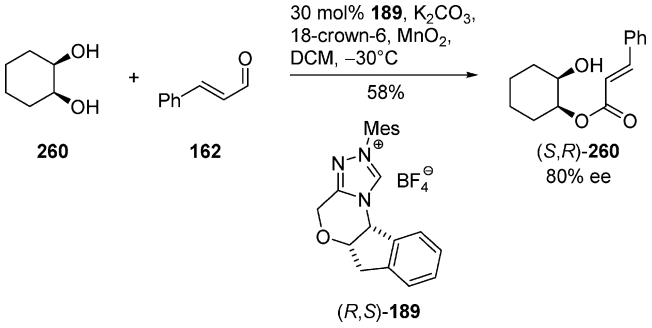
7. Polymerization Reactions

The concept of transesterifications was used for polymerizations by Hedrick and colleagues. Much effort has gone into the development of biodegradable polymers in order to synthesize resorbable biomaterials and commodity thermoplastics from renewable resources. Until now, the synthesis of poly(lactide) by ring-opening polymerization (ROP) of lactide was induced by a variety of metal catalysts through a coordination−insertion mechanism. In 2001, Hedrick and co-workers reported the first organocatalytic approach to the living ROP of lactide using strong basic amines such as 4-(dimethylamino)pyridine (DMAP) or 4-pyrrolidinopyridine (PPY) as transesterification catalyst.[145] Another metal-free approach was published shortly afterward by the use of nucleophilic phosphines, e.g., $P(Bu)_3$, $PhPMe_2$, Ph_2PMe, or PPh_3, as transesterification catalysts.[146] They could also accomplish the ring-opening polymerization of lactide with Bredereck-type reagents in the presence or absence of alcohol initiators[147] and guanidine and amidine organocatalysts.[148] When screening other potential nucleophilic catalysts, they discovered N-heterocyclic carbenes to be very active catalysts.[149] The imidazole-based catalysts showed much higher activities toward ROP than the thiazolium-based analogues. Less sterically demanding carbenes were found to be more

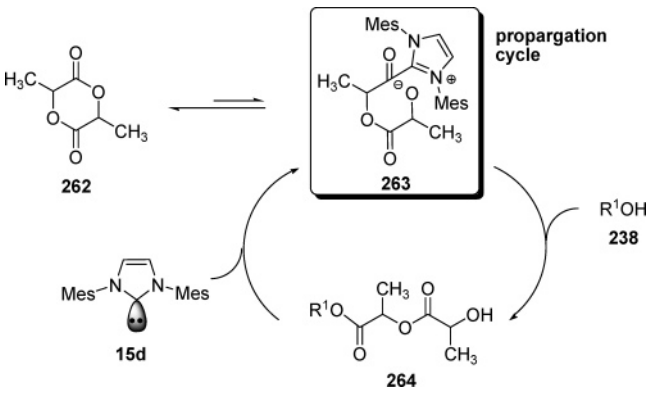
Scheme 94. Possible Catalytic Cycle for the Tandem Oxidation of Allylic Alcohols to Esters by Scheidt and Co-workers



Scheme 95. Desymmetrization of *meso*-Diols by Scheidt and Co-workers



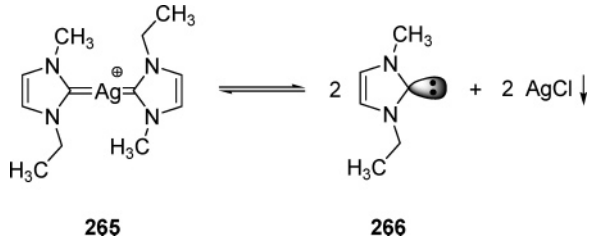
Scheme 96. Proposed Mechanism of the Organocatalytic ROP of L-lactide



active for lactone polymerization than their sterically demanding analogues.[150] Various biodegradable polyesters were synthesized with the 1,3-dimethylimidazol-2-yliden carbene **15d** in THF at 25 °C. Polymers such as poly(L-lactide), poly(ϵ-caprolactone), or poly(β-butyrolactone) could be synthesized (Scheme 96).[151] The same group demonstrated a further alternative to generate N-heterocyclic carbenes for ROP with the thermal decomposition of the silver carbene complexes **265** at 90 °C to compound **266** (Scheme 97).[152]

Poly(ethylene terephthalate) (PET) (**271**) was synthesized in the ionic liquid **272**, which functioned as the reaction medium and, at the same time, as a precatalyst that was activated (**273**) with KO*t*-Bu. Dimethyl terephthalate (DMT)

Scheme 97. Thermal Decomposition of Silver Carbene Complexes by Hedrick and Co-workers



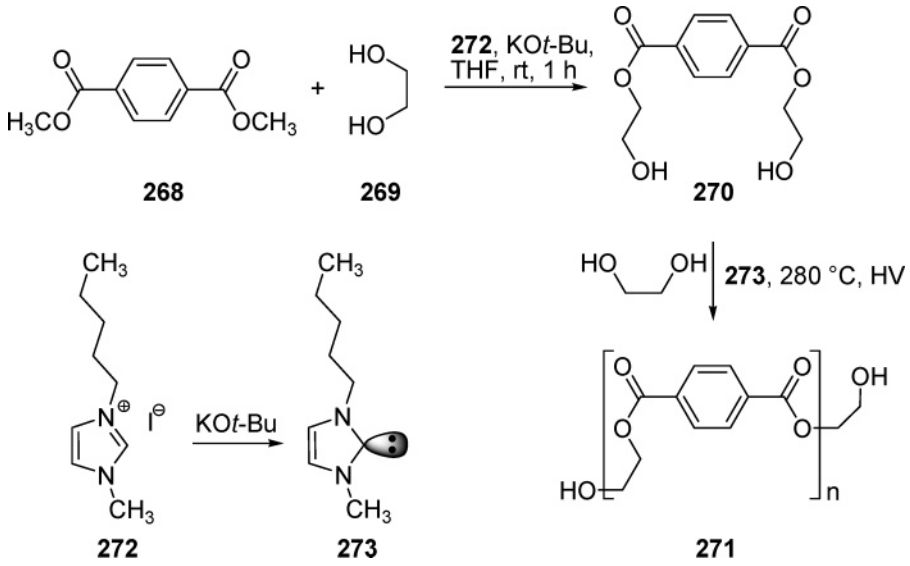
(**268**) was condensed with an excess of ethylene glycol (**269**) to generate **270**. The melt condensation of **270** was performed under vacuum using a heating ramp to 280 °C (Scheme 98).

A protocol for repetitive ROPs was developed by using an ionic liquid (1-ethyl-3-methylimidazolium tetrafluoroborate, [emim][BF_4]) as a precatalyst reservoir in a phase-transfer polymerization with an immiscible THF solution of monomer and initiator. The living ROP was started by the in situ activation of the carbene in the ionic liquid which migrates to the organic phase. Addition of [R_3NH][BF_4] terminated the polymerization due to the regeneration of the precatalyst. Separation of the polymer from the ionic liquid phase enabled the reuse in further ROPs.[150]

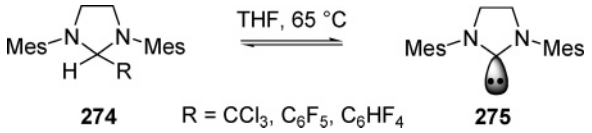
Because NHCs are sensitive to air and moisture, an in situ generation of the active species is advantageous. Besides the established deprotonation of the heterazolium salt, another approach was established by Hedrick and co-workers with the thermal generation of N-heterocyclic carbenes (Scheme 99).[153] The ROP of L-lactide was performed in the presence of benzyl alcohol as initiator at a temperature of 65 °C.

Another method to generate active NHC catalysts is the reversible formation of alcohol adducts.[154] In the on-demand living polymerization of lactide, the alkoxytriazolines **276** were shown to reversibly dissociate at 90 °C to generate an intiating/propagating alcohol.[155] The ring-opening polymerization, a monomer-activated mechanism, can be activated/deactivated with temperature on demand, making it ideally suited for the preparation of block copolymers and complex macromolecular architectures (Scheme 100).[156]

Scheme 98. Synthesis of PET by Hedrick and Co-workers



Scheme 99. Thermal Generation of N-Heterocyclic Carbenes

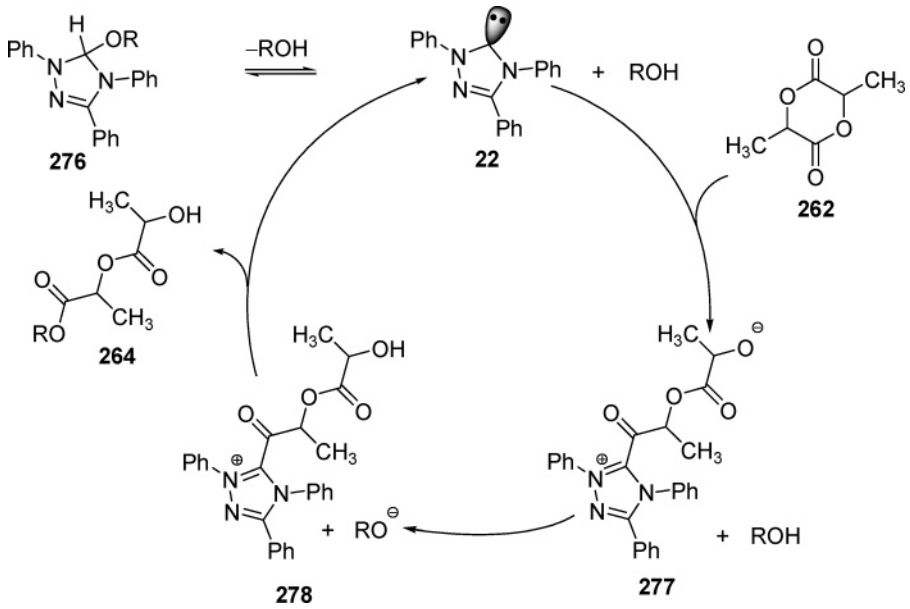


Utilizing a three-step strategy, Hedrick and co-workers could further demonstrate the usefulness of carbene-catalyzed ROP with the ring-opening polymerization of β-lactones for the synthesis of an amphiphilic triblock copolymer with a central hydrophilic sequence.[157] In the first step, an ROP of the benzyl ester lactone **280** and β-lactone **281** with ethylene glycol (**269**) as initiator and the triazolcarbene **22** as catalyst was used. The resulting malolactonate chains can further initiate as difunctional macroinitiators the ROP of L-lactide (**262**) in a second step. In the last step, the benzyl ester functions of **282** are cleaved by catalytic hydrogenation to yield the symmetric triblock copolyester **283** (Scheme 101). Some of the unique properties of **283** are a "flower"-type micelle formation at 4 °C and a reversible gel−sol transition at higher temperatures. Future applications are, e.g., injectable hydrogels in drug-delivery systems.[158]

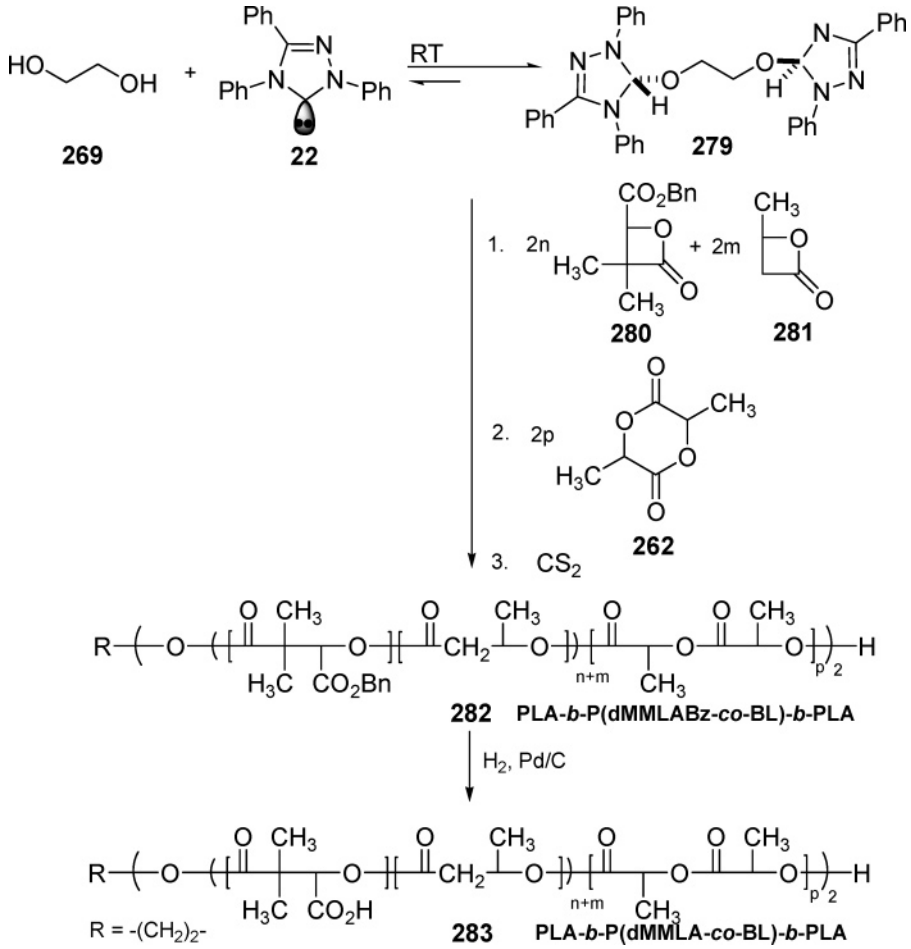
Recently, the same group could further extend the substrate scope for the living ROP to new classes of monomers such as cyclic carbosiloxanes **284**[159] and trimethylene carbonate **285** (Figure 22).[160] Polysiloxanes are commonly used in a variety of applications such as in medicine, microelectronics, or coatings. In further investigations, Hedrick and co-workers reported the stereoselective polymerization of *rac*- and *meso*-lactide catalyzed by sterically encumbered N-heterocyclic carbenes **286a** and **286b** (Figure 23).[161]

Highly isotactic polylactide was obtained from the *rac*-lactide monomer at low temperatures, and the formation of heterotactic polylactide was preferred with the *meso*-lactide monomer. Once again, a monomer-activated mechanism was postulated. In the case of *rac-l*actide (**262**), D- and L-lactide are equally activated. A stereoselective attack by the terminal alkoxide of the last inserted monomer led to an isotactic enchainment of the polymer chain (Scheme 102).

Scheme 100. Postulated Mechanism of the On-Demand Living Polymerization by Hedrick and Co-workers



Scheme 101. Application to the Synthesis of a Triblock Copolymer by Hedrick and Co-workers



Heterotactic polylactide (Figure 24) is formed from *meso*-lactide because of a preferred attack of the oxygen of the polymer chain end to the monomer with the same stereogenic configuration adjacent to it as the last stereogenic center of the polymer chain.

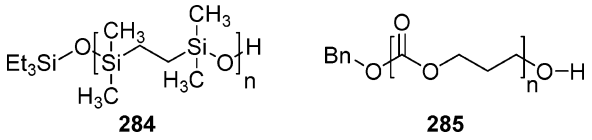


Figure 22. Further products of the carbene-catalyzed ROP by Hedrick and co-workers.

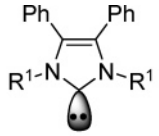


Figure 23. New sterically encumbered NHCs by Hedrick and co-workers.

8. Ring-Opening Reactions

The scope of the electrophiles used in reactions catalyzed by nucleophilic carbenes are not necessarily limited to carbonyl compounds or Michael acceptors. Recently, few examples were reported with the transformation of epoxides, aziridines, or cyclopropanes in ring-opening reactions promoted by carbene catalysts.

8.1. Ring-Opening Reactions of Three-Membered Rings

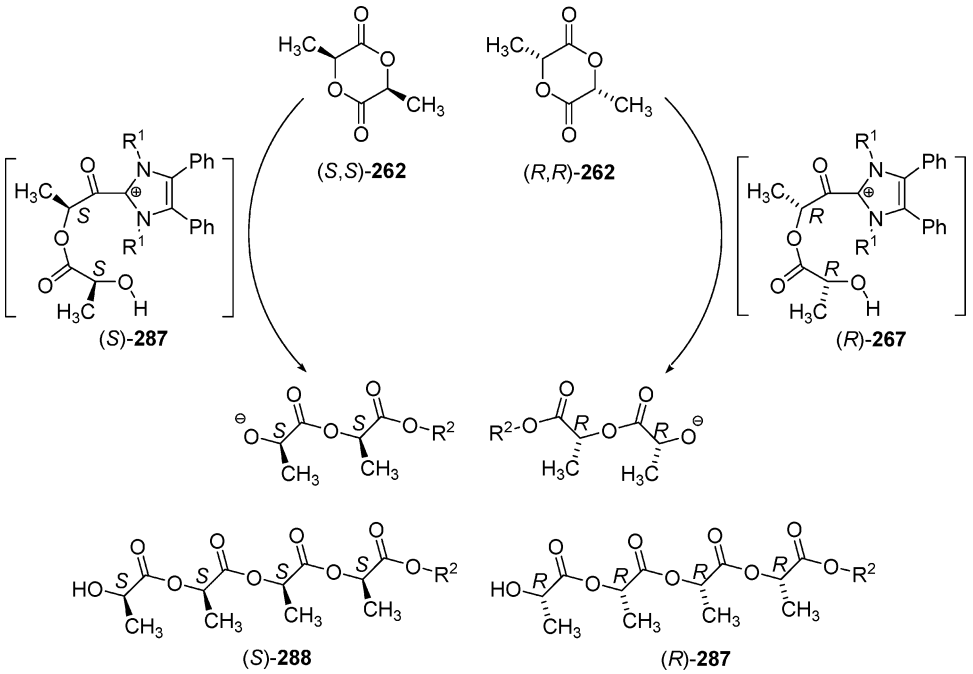
An early contribution to the field of ring-opening reactions was reported by Nguyen and co-workers.[162] In 2001, they reported the ring-opening alkylation of *meso*-epoxides **290** with trialkylaluminium catalyzed by imidazolidine-derived carbenes **233**, a trialkylaluminum imidazolidine complex **292**, and the Wanzlick-type olefins **293** (Scheme 103).

An unexpected observation was made, namely, besides the employed carbenes, a catalytic activity was also observed when utilizing the corresponding imidazolium salt precursor **294** in the absence of a base. A reasonable mechanism for this reaction was not proposed, and because of the above-mentioned catalytic activity of the imidazolium salts, the role of the carbene catalysts still remains unclear.

Recently, Wu and co-workers reported two different methods for the carbene-catalyzed ring-opening of aziridines **295** to the corresponding 1,2-difunctionalized compounds **296**.[163] In their first protocol, the aziridine ring was opened by silylated nucleophiles such as $TMSN_3$, TMSCl, and TMSI in the presence of the catalyst **15d** (Scheme 104, Table 31). Unsymmetrically substituted aziridines (entries 4 and 6) are regioselectively attacked by the nucleophile on the less-substituted aziridine carbon, and **297** was not formed.

A catalyst loading as little as 1 mol % turned out to be sufficient to obtain the desired product **296** in excellent yields and in the expected trans configuration. However, efforts for the application of $TMSCF_3$ as a nucleophile for the ring-opening were less fruitful. A mechanism for this reaction

Scheme 102. Proposed Chain-End Control Mechanism for *rac*-Lactide



was not proposed, but the authors assumed that the observed reactivity originates from an activation of the TMSX (X = N_3, Cl, I) via the formation of a pentavalent silicon−carbene complex (Scheme 105).

In the second method reported by Wu et al., the ring-opening of aziridines **299** was made possible with anhydrides as nucleophiles and the imidazolium-based carbene **15d** as catalyst (Scheme 106, Table 32). The desired products were obtained in their anti configuration. Asymmetrically substituted aziridines were mostly converted by a regioselective attack of the nucleophile at the less-hindered aziridine carbon. By utilizing the phenyl-substituted aziridine **299** (entries 2 and 4), a less-regioselective attack was observed. The formation of product **301** was thought to be caused by electronic effects. Further investigations by the authors revealed that an electron-withdrawing group, such as the employed *N*-tosyl group, is crucial for the reaction outcome since nonactivated aziridines, such as *N*-benzylaziridines, did not show any activity. A mechanistic model for the reported reaction was also proposed by the authors (Scheme 107).

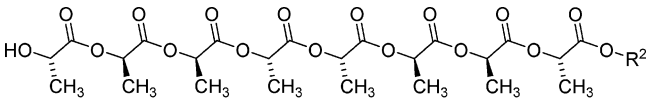


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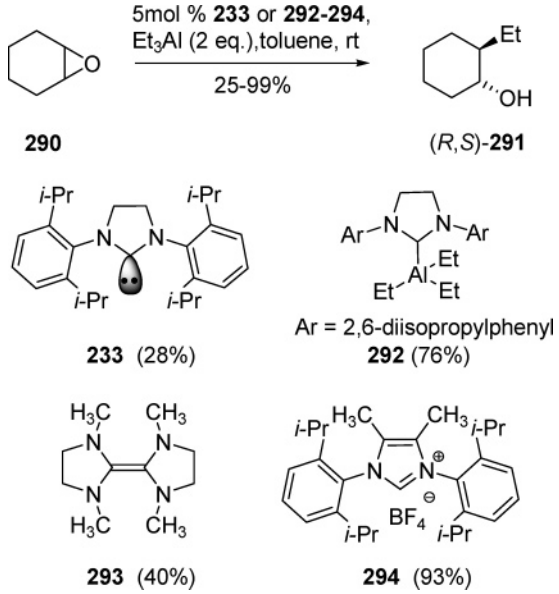
Figure 24. Synthesis of heterotactic polylactide by Hedrick and co-workers.

Scheme 103. Alkylation of *meso*-Epoxides with Trialkylaluminium by Nguyen and Co-workers



Scheme 104. Carbene-Catalyzed Ring-Opening of Aziridines by Wu et al.

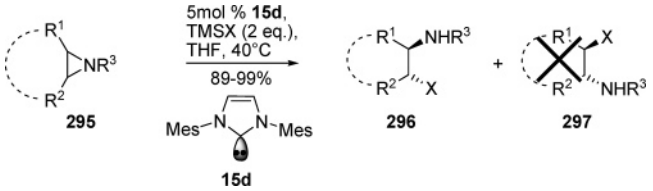
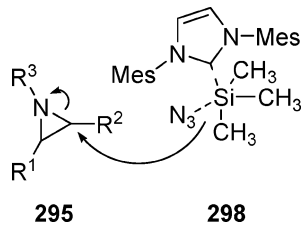


Table 31. Substrate Scope for the Ring-Opening of Aziridines by Wu et al.

entry	R^1	R^2	R^3	X	time	yield **296** (%)
1	cyclohexyl		Ts	N_3	15 h	99
2	cyclohexyl		Bn	N_3	15 h	96
3	cyclopentyl		Ts	Cl	2.5 h	98
4	Bn	H	Ts	Cl	1.5 h	89
5	cyclohexyl		Ts	I	0.5 h	95
6	*n*-Bu	H	Ts	I	0.3 h	98

Scheme 105. Pentavalent Silicon−Carbene Complex



Scheme 106. Carbene-Catalyzed Ring-Opening of Aziridines by Wu et al.

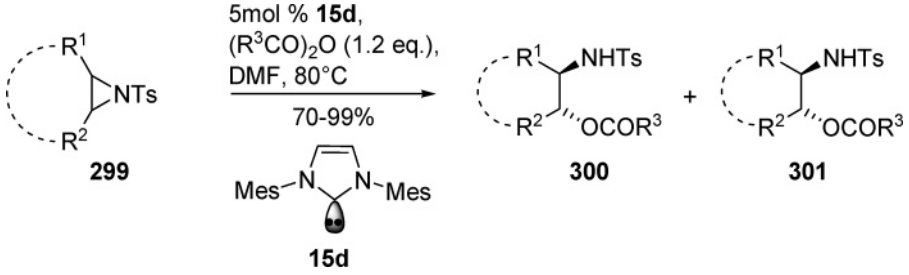
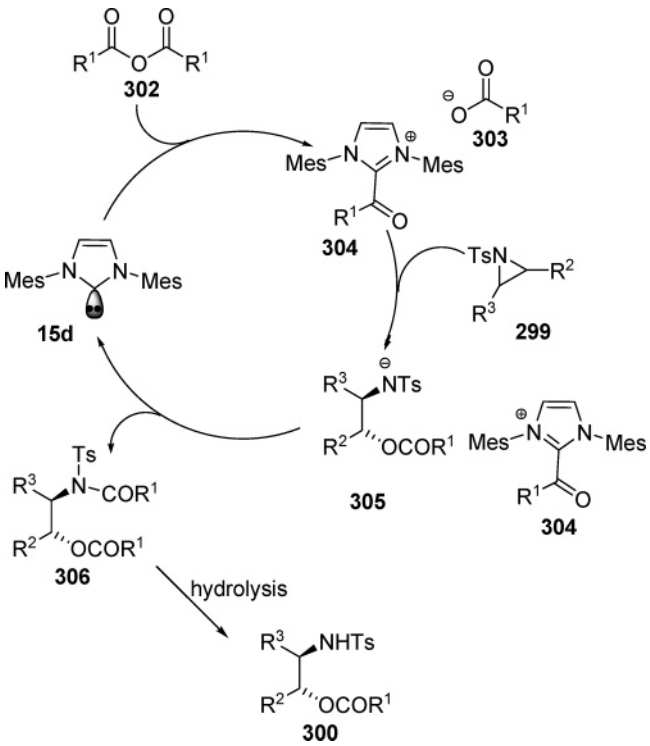


Table 32. Substrate Scope of the Carbene-Catalyzed Ring-Opening of Aziridines

entry	R^1	R^2	R^3	time (h)	yield **300** (%)
1	cyclohexyl		Me	8	96
2	Ph	H	Me	8	70 (**300**/**301** (9:1))[a]
3	*n*-hexyl	H	Me	8	80
4	Ph	H	Ph	3	70 (**300**/**301** (10:1))[a]
5	*n*-Bu	H	Ph	3	99
6	*n*-hexyl	H	Ph	3	98

[a] Ratio of the products.

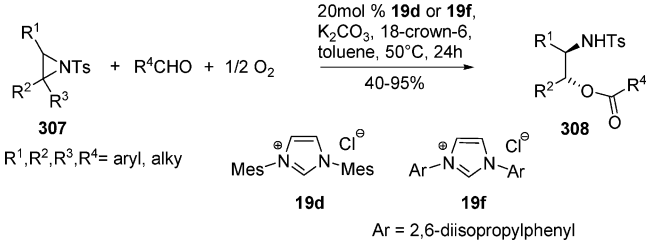
Scheme 107. Proposed Mechanism for the Ring-Opening Reaction of Aziridines with Anhydrides Promoted by N-Heterocyclic Carbenes



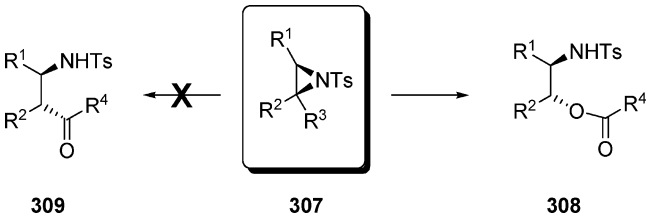
The catalytic cycle starts with a nucleophilic attack of the carbene at the anhydride resulting in the generation of the carboxylate **303**. In the next step, the aziridine ring **299** is opened via a nucelophilic attack of the carboxylate anion **303**. Then an attack of the nitrogen anion of the species **305** at the carbonyl function of the acylimidazolium intermediate **304** regenerates the catalyst and results in the formation of the bis-acylated product **306**.The latter can then be converted into **300** via hydrolysis.

Another interesting approach to the ring-opening of aziridines was developed by Chen and co-workers.[164] His research group reported a method for the chemoselective ring-opening of aziridines with aldehydes promoted by

Scheme 108. Method for the Ring-Opening of Aziridines under Aerobic Conditions by Chen and Co-workers



Scheme 109. Observed Formation of the Carboxylated 1,2-Aminoalcohols 309



N-heterocyclic carbenes under aerobic conditions (Scheme 108). Unexpectedly, the authors observed the formation of the carboxylated 1,2-amino alcohols **308** instead of the β-aminoketones **309**, which would result from the ring-opening via an acyl anion generated during the reaction course (Scheme 109).

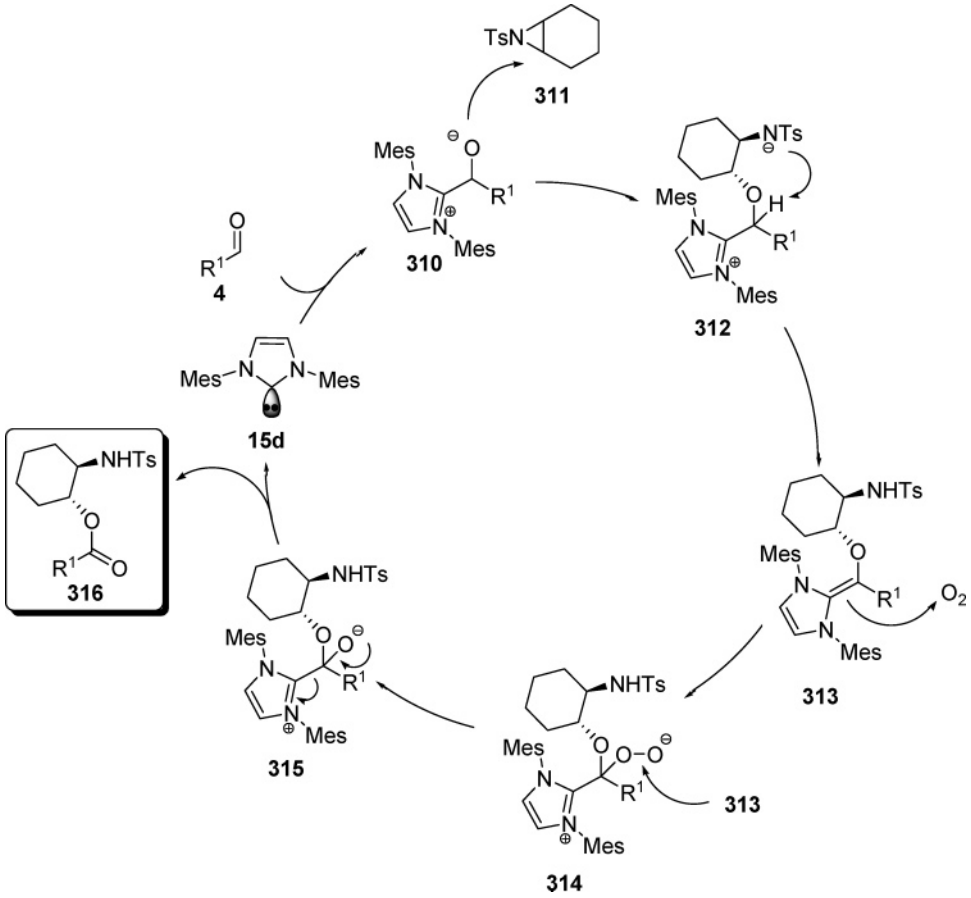
It was emphasized that the reported aerobic conditions are crucial for the reaction outcome since the performance under inert conditions mainly resulted in the benzoin product. Using asymmetric aziridines, a high regioselectivity was observed due to the preferential attack of the zwitterinonic alcoholate **300** at the sterically less demanding aziridine carbon atom. The authors suggested the following mechanism for the observed reactivity (Scheme 110).

In the initial step, the aldehyde **4** is attacked by the nucleophilic carbene catalyst **15d**, resulting in the zwitterinonic alcoholate **310**, which promotes the ring-opening via an attack at the less-hindered aziridine carbon atom. Afterward, the species **312** tautomerized to the enaminol ether **313**, which might be oxidized by dioxygen to afford the hydroperoxide anion **314**. The anion **314** is then reduced by another equivalent of the enamiol ether **313**, affording two molecules of the zwitterionic species **315**. The latter then closes the catalytic cycle by eliminating the carbene unit and generating the observed product **316**.

Very recently, Sohn and Bode developed a method for the carbon−carbon bond cleavage of conformationally strained formyl cyclopropyl units **317** catalyzed by N-heterocyclic carbenes, leading to esters and thioesters **318** (Scheme 111, Table 33).[165]

A broad range of substitution pattern at the trisubstituted cyclopropanes **318** was suitable for the N-heterocyclic

Scheme 110. Proposed Catalytic Cycle for the Carbene-Catalyzed Ring-Opening of Aziridines by Chen and Co-workers



Scheme 111. Ring-Opening of Formyl Cyclopropanes 318 by Sohn and Bode

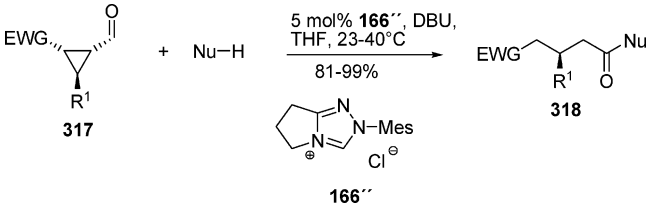


Table 33. Substrate Scope for the Ring-Opening of Formyl Cyclopropanes

R^1	EWG	NuH	*T* (°C)	ee (%)	yield (%)
Ph	PhCO	MeOH	23	89	90
n-Pr	*t*-BuCO	MeOH	40	93	95
Ph	PhCO	*n*-$CH_3(CH_2)_{11}SH$	23	88	99
Ph	PhCO	H_2O	23	88	92

carbene-catalyzed ring-opening reaction. Beside alcohols as nucleophiles, thiols were also highly reactive, leading to the corresponding thioesters. Interestingly, the synthesis of the corresponding acid was also possible in high yields and good enantioselectivities when employing water as the nucleophile. The proposed catalytic cycle for this transformation is shown in Scheme 112.

The reaction starts with a nucleophilic attack of the catalyst **319** at the aldehyde function of the substrate **320** to form the adduct **321**, which is converted to the corresponding Breslow intermediate **322**. The following ring-opening leads to the enolate **323**, which then reacts to the more stable catalyst-bound enolate **324** via a rapid proton transfer. Further protonation gives the activated carboxylate **325**, which can be attacked by a nucleophile to furnish the desired ester **326**. This mechanism was proposed on the basis of a reaction performed in the presence of an excess of deuterated methanol. The obtained mixture of diastereomeric products contained a single deuterium in the α-position of the benzoyl function, as would be expected if the reaction proceeded under the proposed mechanism. However, if the reaction was quenched at partial conversion, the observed recovered deuterated aldehyde unit indicates the existence of an alternative pathway including a reversible attack of the catalyst and a hydride shift, which would lead to the same result.

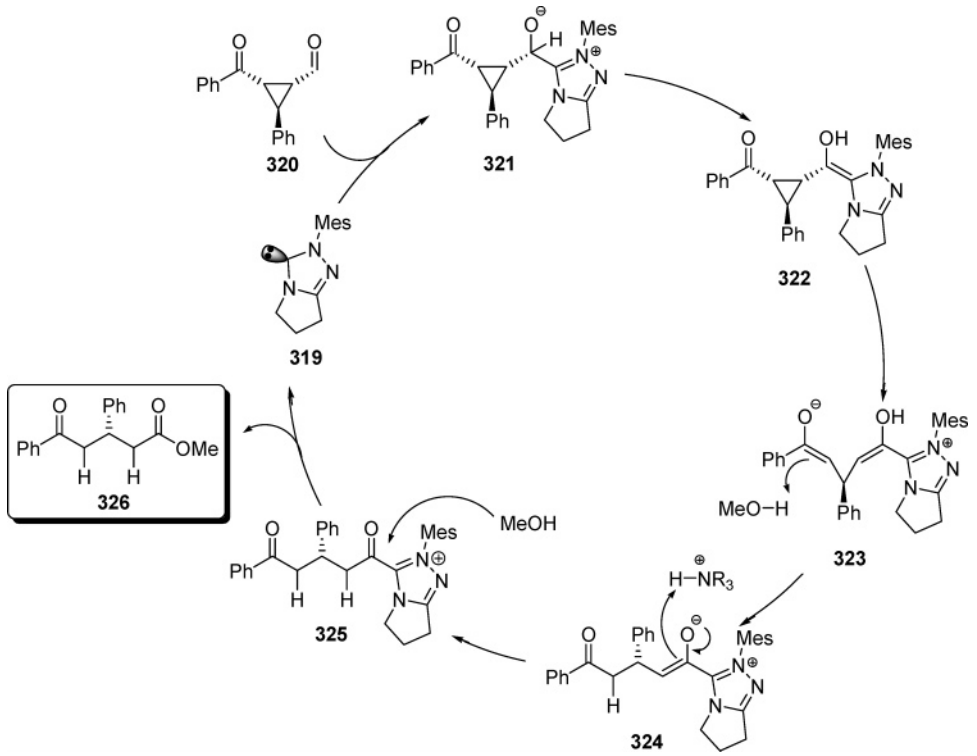
9. 1,2-Additions

A reaction type not covered so far in this review is the carbene-catalyzed 1,2-addition of nucleophiles to carbonyl compounds such as aldehydes, ketones, aldimines, or ketimines. This reaction type stands out from the carbene reactions described so far, because the reaction course is not dependent on the generation of a d^1- or a d^3-nucleophile. In contrast to the reactions reviewed up to this point, the original reactivity/polarity of the carbonyl function stays untouched, whereas the carbene catalyst accelerates the generation and/or the attack of the nucleophile.

9.1. 1,2-Additions to Aldehydes and Ketones

In 2004, Blanrue and Wilhelm were the first to contribute to the field of carbene-catalyzed 1,2-additions.[166] The successful cyanosilylation of the aldehydes **4** to the nitriles **327** was achieved by using the imidazolium carbodithioates **328**−**330** as carbene precursors in dichloromethane (DCM) as solvent at room temperature (Scheme 113).

Scheme 112. Plausible Catalytic Cycle for the Carbene-Catalyzed Ring-Opening of Formyl Cyclopropanes by Sohn and Bode



Scheme 113. Cyanosilylation of Aldehydes by Blanrue and Wilhelm

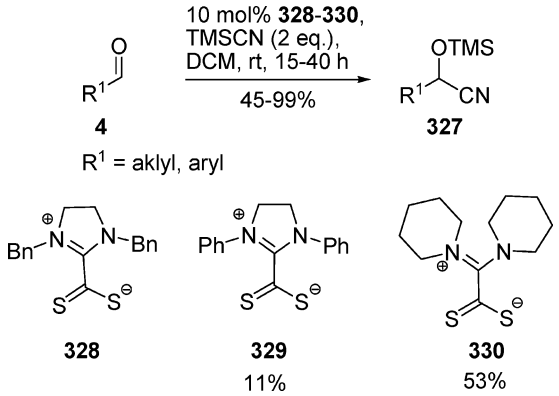


Table 34. Conditions for the Cyanosilylation of Aldehydes 4 by Aoyama and Co-workers: 10 mol % 19d, 9 mol % KO*t*-Bu, TMSCN (1.2 equiv)

R^1	*T*	time	yield (%)
$BnCH_2$	rt	<5 min	90
Cy	rt	<5 min	93
t-Bu	rt	20 h	98
t-$BuCH_2$	rt	20 h	96
Ph	reflux	3 h	95
p-F-Ph	rt	30 min	83
p-MeO-Ph	reflux	3 h	90

Table 35. Conditions for the Cyanosilylation of Aldehydes 4 by Maruoka and Co-workers: 1 mol % 15e, TMSCN (1.2 equiv)

R^1	*T*	time (h)	yield (%)
Ph	0 °C	0.5	89
PhCH═CH	0 °C	0.5	99
$BnCH_2$	0 °C	0.5	99

Catalyst **328** was found to be the most efficient one. A broad range of alkyl- and aryl-substituted aldehydes could be converted to the cyanosilylated products **327** in moderate-to-excellent yields and under mild conditions.

Table 36. Conditions for the Cyanosilylation of Aldehydes 4 by Song et al.: 0.5 mol % 15g, TMSCN (1 equiv), 10 min

R^1	*T*	time (min)	yield (%)	R^1	*T*	time (min)	yield (%)
Ph	rt	10	91	$BnCH_2$	rt	10	93
n-Pr	rt	10	95	*t*-Bu	rt	10	87

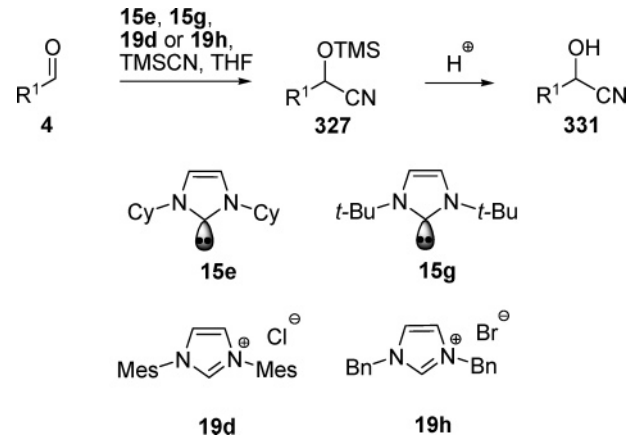
Table 37. Conditions for the Cyanosilylation of Aldehydes by Suzuki et al.: 20 mol % 19h, 20 mol % KO*t*-Bu, TMSCN (1.1 equiv)

R^1	*T*	time (h)	yield (%)	R^1	*T*	time (h)	yield (%)
p-MeO-Ph	rt	0.5	69	*n*-Pr	rt	0.5	81
o-MeO-Ph	rt	0.5	93	Cy	rt	0.5	81
2-naphtyl	rt	0.5	94	*t*-Bu	rt	0.5	65
PhCH═CH	rt	0.5	75				

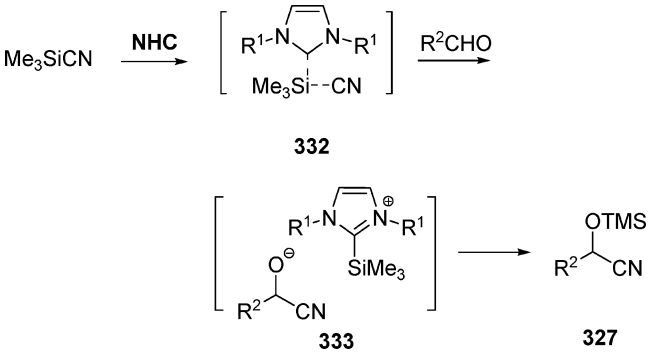
Although the yields obtained in the application described above were exceptionally high in some cases, a drawback of this approach is its slow reactivity. Almost simultaneously, several research groups reported independently their solutions for overcoming this problem. The applications developed by the research groups of Aoyama (Table 34),[167] Maruoka (Table 35),[168] Song (Table 36)[169] and Suzuki (Table 37)[170] all focused on the employment of different imidazolium-based precatalysts. The reaction conditions differed in terms of the employed catalyst and its loading as well as the reaction temperature and the tested substrates (Scheme 114). However, beside these differences, nearly all reactions progressed to completion within <1 h, and the observed yields were all in the same range.

Although all of the employed catalysts turned out to be suited for this cyanosilylation, the catalyst **15g** used by Song et al. was found be the most active one, affording high yields with the lowest catalyst loading (0.5 mol %) and the fastest

Scheme 114. Different Conditions for the Cyanosilylation of Aldehydes



Scheme 115. Proposed Mechanism (1) by Aoyama and Co-workers



conversions (10 min), even with sterically demanding substrates. An interesting synthetic aspect of this application is the straightforward conversion of the generated silylether into its corresponding alcohol by simply adding acid to the reaction mixture.

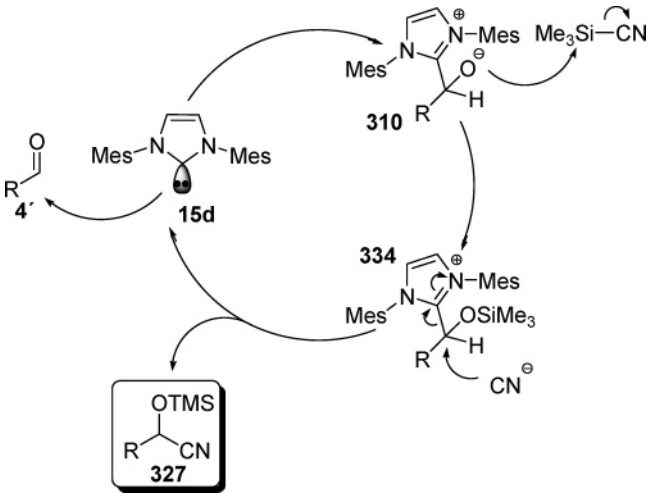
Two plausible mechanisms were suggested for the observed reactions.[167] In the first one, the active intermediate is a postulated hypervalent silicate **332** resulting from the addition of the carbene catalyst to the trimethylsilylcyanide (TMSCN). This active intermediate then enables the nucleophilic attack of the cyanide to the aldehyde (Scheme 115).

The second mechanism is based on the supposition that a zwitterionic alcoholate **311** is generated via an attack of the carbene catalyst at the aldehyde. This active intermediate then reacts with TMSCN to form the silylether **334** under the formation of a cyanide nucleophile. Next, an attack of the cyanide anion at the silylether **334** regenerates the catalyst, and the desired product **327** is formed (Scheme 116).

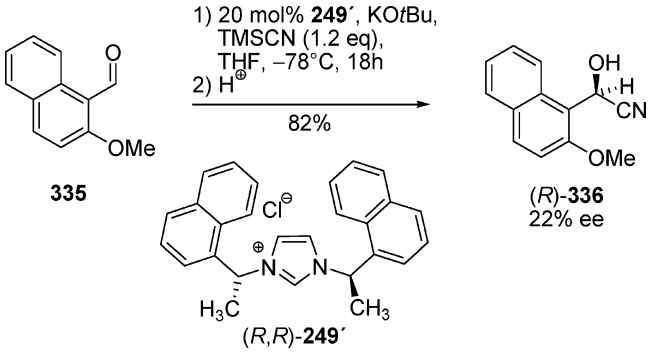
Moreover, Suzuki et al. reported an enantioselective application of this method.[170] By using the sterically demanding imidazolium salt **249′**, the substrate **335** could only be converted to the cyanoalcohol **336** with a low enantiomeric excess of 22% (Scheme 117). However, to the best of our knowledge, this is the only literature precedence where an enantiomeric excess was obtained in a carbene-catalyzed cyanosilylation reaction so far.

In 2005, Aoyama and co-workers reported the first cyanophosphorylation reaction of aldehydes catalyzed by N-heterocyclic carbenes.[171] By applying the precatalyst **19d** and diethyl cyanophosphonate (DEPC) as a cyanide source and phosphorylation agent, a variety of different aromatic

Scheme 116. Proposed Mechanism (2) by Aoyama and Co-workers



Scheme 117. Enantioselective Attempt for the Carbene-Catalyzed Cyanosilylation of Aldehydes by Suzuki et al.



Scheme 118. Cyanophosphorylation Reaction of Aldehydes by Aoyama and Co-workers

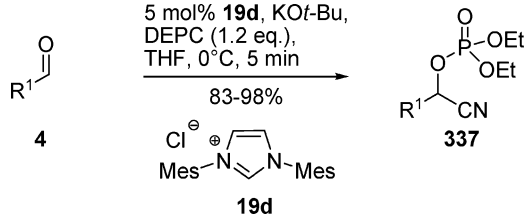


Table 38. Substrate Scope For the Cyanophosphorylation of Aldehydes

entry	R^1	yield (%)	entry	R^1	yield (%)
1	*t*-Bu	98	5	PhCH=CH	19
2	Cy	94	6	Ph	94
3	vinyl	90	7	*p*-MeO-Ph	90
4	$BnCH_2$	91	8	*p*-Cl-Ph	92

and aliphatic cyanohydrine-*O*-phosphonates **337** could be synthesized (Scheme 118). This new transformation was accomplished with a low catalyst loading of 5 mol % with mostly excellent yields (Table 38). Utilizing ketones such as acetophenone or methyl vinyl ketone as substrates afforded little or none of the desired products.

Song et al. described a novel method for the trifluoromethylation of carbonyl compounds **338** by employing N-heterocyclic carbenes as a catalyst and $TMSCF_3$ as a trifluoromethylation agent.[172] The employment of the adamantyl-substituted imidazolium carbene **15a** led to a broad

Scheme 119. N-Heterocyclic Carbene-Catalyzed Trifluoromethylation of Aldehydes and Ketones by Song et al.

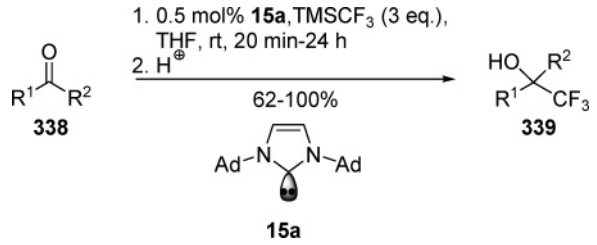


Table 39. Scope of the Trifluoromethylation by Song et al.

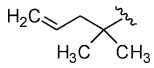
entry	R^1	R^2	yield (%)	entry	R^1	R^2	yield (%)
1	*n*-heptyl	H	90	9	*p*-NO_2-Ph	H	75
2	Cy	H	81	10	*p*-COMe-Ph	H	85
3		H	71	11	*p*-CN-Ph	H	87
4	$BnCH_2$	H	80	12	*p*-CO_2H-Ph	H	84
5	PhCH=CH	H	89	13	*p*-NO_2-Ph	Me	75
6	Ph	H	73	14	COOEt	CH_2Bn	54
7	*p*-MeO-Ph	H	81	15	COOEt	Me	62
8	*p*-Cl-Ph	H	86				

Table 40. Scope of the Cyanosilylation of Ketones by Aoyama and Co-workers (5 mol % 19d, 4 mol % KO*t*-Bu, TMSCN (1.5 equiv), DMF, rt)

R^1	R^2	time	yield (%)
p-Cl-Ph	Me	10 min	91
p-MeO-Ph	Me	1 h	90
Bn	Me	5 min	94
Ph	*i*-Pr	1 h	89
PhCH=CH	Me	20 min	87
2-dihydronaphthyl		5 min	90

range of substituted trifuoromethylation products **339** in good-to-excellent yields (Scheme 119, Table 39).

This application was shown to be suitable for the trifluoromethylation of aldehydes as well as ketones and β-keto esters. Moreover, this reaction is outstanding for trifluoromethylation reactions, because the conditions are mild and, therefore, tolerant to a variety of functional groups. More importantly, it displays a greater catalytic efficiency compared to the reported protocols for Lewis base-catalyzed trifluoromethylation, as only 0.5−1.0 mol % of the commercially available catalyst **15a** is sufficient.

Since the nucleophilic 1,2-addition to aldehydes promoted by carbene catalysts turned out to be such a sophisticated reaction, efforts were made to broaden the scope of this method. Several research groups independently published their contributions to the field of 1,2-addition of TMSCN to ketones **338**. The results obtained by the groups of Aoyama (Table 40),[173] Maruoka (Table 41)[168] and Song (Table 42)[169] are summarized in Scheme 120.

All research groups utilized the imidazolium-based catalysts **15e**, **15g**, and **19d** since these showed the best activities during the course of their investigations of the cyanosilylation of aldehydes. The reported reaction conditions differ slightly in terms of the used catalyst loading, the temperature, and the solvent. The described methods show different advantages that can be ascribed mainly to the different types of the employed catalysts. In the version of Aoyama and coworkers, the reaction rate was the fastest, whereas Maruoka and co-workers' resulted in the highest yields and Song et al.'s required the lowest catalyst loading.

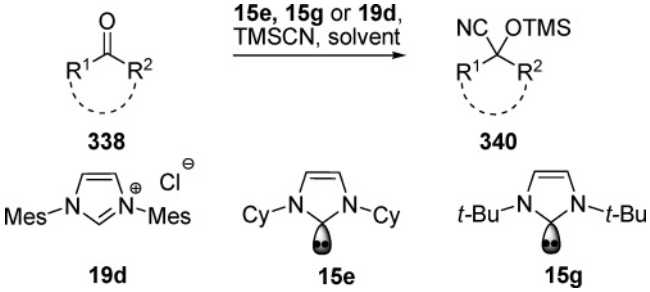
Table 41. Scope of the Cyanosilylation of Ketones by Maruoka and Co-workers (1 mol % 15e, TMSCN (1.2 equiv), THF, 0 °C)

R^1	R^2	time (h)	yield (%)
Ph	Me	0.5	99
Ph	*t*-Bu	1	87
PhCH=CH	Me	1	93
n-heptyl	Me	1	90
CO_2Et	Me	1	89
cyclohexyl		2	99
2-dimethylcyclohexyl		0.5	99

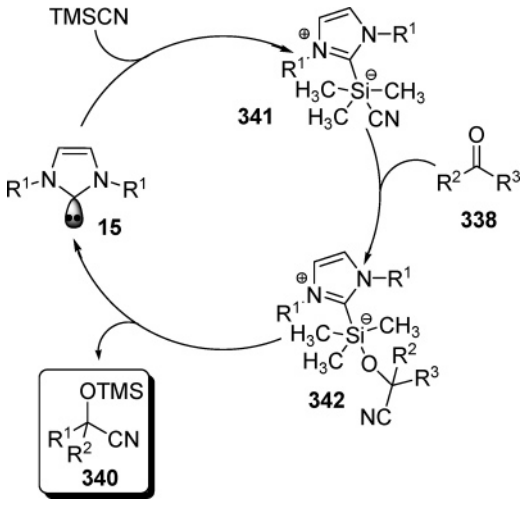
Table 42. Scope of the Cyanosilylation of Ketones by Song et al. (0.5 mol % 15g, TMSCN (1.1 equiv), DMF, rt)

R^1	R^2	time (h)	yield (%)
CO_2Et	Ph	0.5 h	79
Ph	Me	1 h	80
p-NO_2-Ph	Me	2 h	81
Bn	Me	2 h	84
Ph	*t*-Bu	0.5 h	81
Ph	Ph	2 h	83
$BrCH_2$	Ph	2.5 h	86
cyclohexyl		2.5 h	79
2-dihydronaphthyl		2 h	83

Scheme 120. Different Conditions for the Cyanosilylation of Ketones



Scheme 121. Proposed Mechanism for the Cyanosilylation of Ketones



The observed reactivity can be explained via the following proposed mechanism (Scheme 121).[169] It was proposed that the active intermediate is a pentavalent silicate **341**, generated by the addition of the carbene **15** to the TMSCN. The zwitterionic species **341** then reacts with the ketone **348** under the formation of the adduct **342**. By elimination of the catalyst, the desired product is obtained.

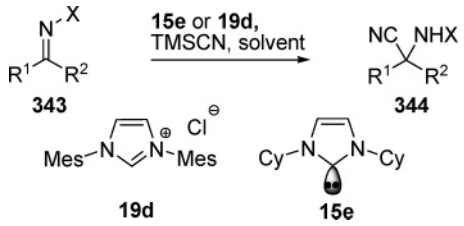
Table 43. Scope of the Cyanosilylation by Aoyama et al. (a) Aldimines: 5 mol % 19d, 4 mol % KO*t*-Bu, TMSCN (1.2 equiv), THF, rt; (b) Ketimines: 5 mol % 19d, 4 mol % KO*t*-Bu, TMSCN (1.5 equiv), DMF, rt, then H_2O

R^1	R^2	X	time	yield (%)
Ph	H	Ts	45 min	97
p-Cl-Ph	H	Ts	30 min	84
p-MeO-Ph	H	Ts	5 h	98
Cy	H	Ts	1h	87
1-naphthyl	H	Ts	30 min	87
1-phenethyl	H	Ts	6 h	82
t-BuCH2	H	Ts	5 h	86
Ph	H	Boc	30 min	80
Ph	Me	Ts	30 min	93
p-Me−Ph	Me	Ts	3 h	99
p-MeO-Ph	Me	Ts	1 h	59
Ph	Ph	Ts	4 h	88
i-Pr	*i*Pr	Ts	5 min	84
PhCH=CH	Ph	Ts	2 h	98

Table 44. Scope of the Cyanosilylation of Aldimines and Ketimines by Maruoka et al. (1 mol % 15e, TMSCN (1.2 equiv), THF, rt)

R^1	R^2	X	time (h)	yield (%)	R^1	R^2	X	time (h)	yield (%)
Ph	H	Ts	4	92	1-naphthyl	H	Ts	2	92
Ph	H	Bn	6	25	Ph	Me	Ts	1.5	49
PhCHCH	H	Ts	3.5	83	Ph	Me	Bn	4	76
Cy	H	Ts	5	82	Et	Et	Bn	2	69

Scheme 122. Strecker Reaction of Aldimines and Ketimines



9.2 1,2-Additions to Aldimines and Ketimines

Encouraged by the good results achieved with the carbene-catalyzed 1,2-additions of TMSCN to aldehydes and ketones, the research groups of Aoyama[173,174] (Table 43) and Maruoka[168] (Table 44) have recently reported the successful transfer of this concept to the cyanosilylation of aldimines and ketimines **343**. The reaction conditions were analogous to their former reported contributions, and the use of their 1,2-addition approved precatalysts provided the addition products **344** in high yields (Scheme 122).

Other imine protection groups such as benzyl, *tert*-butoxycarbonyl, and 2,4,6-triisopropylbenzenesulfonyl were tested as well, but *N*-tosyl was found to be the best protection group, providing the highest yields.

10. Miscellaneous

In 2006, Chan and Scheidt reported a further interesting application of N-heterocyclic carbenes with the hydroacylation of activated ketones **345**.[175] This new reaction is enabled by a chemoselective reduction and acylation of α-keto esters **345** to their corresponding α-acylhydroxyesters **347 (**Scheme 123**)**.

The process is tolerant to a variety of electron-rich and electron-deficient aromatic aldehydes **4**. The observed yields were generally lower if electron-deficient aldehydes were employed. However, no conversion was observed if non-aromatic aldehydes were used. The substrate scope was also examined with regard to the activated ketones **345**. Different aromatic and heteroaromatic esters were screened and provided high yields in all investigated cases. Furthermore, it was reported that changing the reaction media to protic solvents affected the outcome, since only the α-hydroxyesters **346** were obtained. The unusual reactivity was explained via the proposed catalytic cycle shown in Scheme 124.

After the inital attack of the carbene **255** at the aldehyde **4**, the resulting tetrahedral intermediate **348** acts as a reducing agent by promoting a hydrid transfer to the α-keto function of the ester **345**. The generated α-hydroxyesters **346** are then acylated by the acyltetrazolium species **350**, revealing the desired product **347** and regenerating the catalyst **255**.

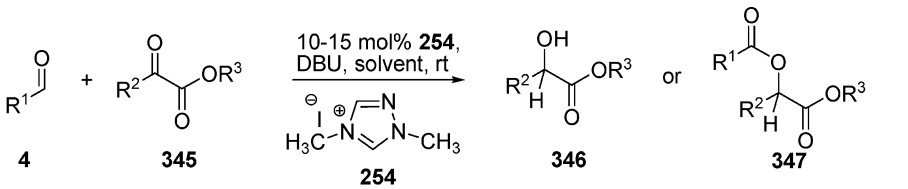
Recently, the research group of Smith widened the scope of reaction pathways utilizing N-heteroclyclic carbenes by employing them as catalysts in the Steglich rearrangement of *O*-acylcarbonates **351** to their corresponding *C*-acylazlactones **352** (Scheme 125).[176]

By developing this new reaction, Smith and co-workers were able to obtain the formation of a new C−C bond and a quaternary stereogenic center under ambient reaction conditions and low catalyst loadings (<1 mol %). In control experiments, no conversion was observed if the *O*-acylcarbonate **351** was treated with either a base or the triazolium salt **166‴**, which indicates the need of an in situ generated carbene species during the reaction. A postulated catalytic cycle that explains the observed reactivity was also reported (Scheme 126).

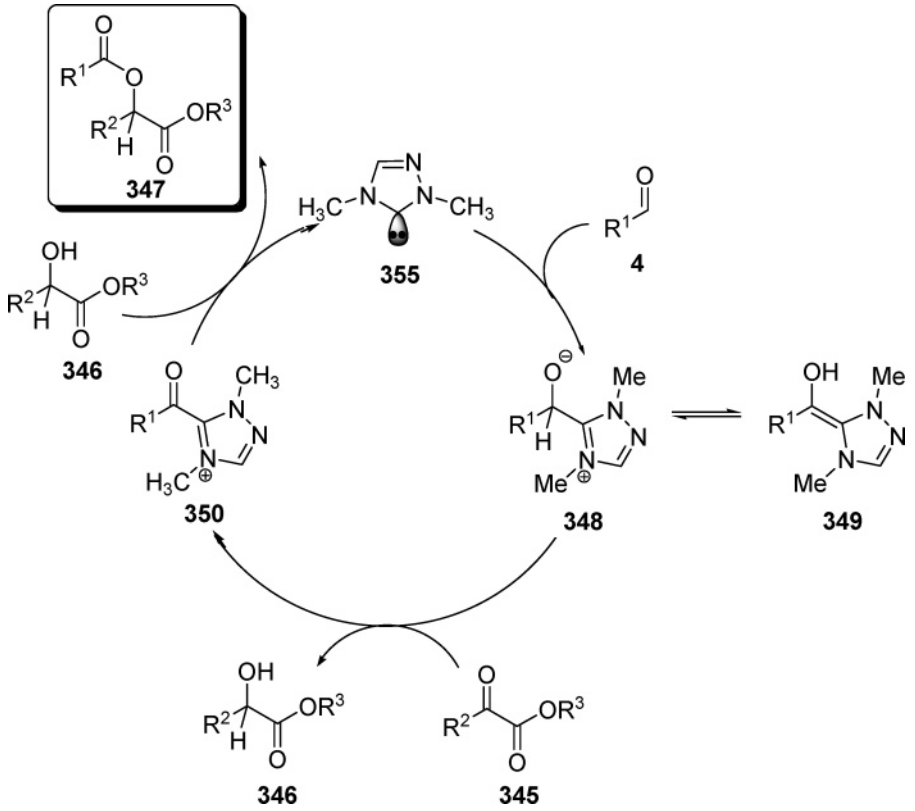
The cycle involves an initial nucleophilic attack of the carbene **353** at the carbonyl moiety of the substrate **351**, resulting in the acyl transfer intermediate **355** and the corresponding enolate **354**. Then *C*-acylation at the α-position of the enolate **354** forms a new C−C bond and closes the catalytic cycle by regenerating the catalyst **353**.

Very recently, Pan and co-workers reported the development of a novel intramolecular nucleophilic substitution reaction promoted by N-heterocyclic carbenes.[177] Pan and co-workers could apply this methodology for the facile construction of benzopyrones **357** and benzofuranones **358**.

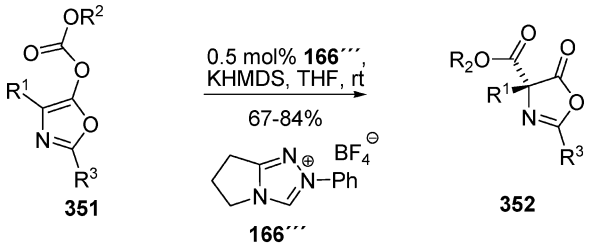
Scheme 123. Hydroacylation of Activated Ketones by Chan and Scheidt



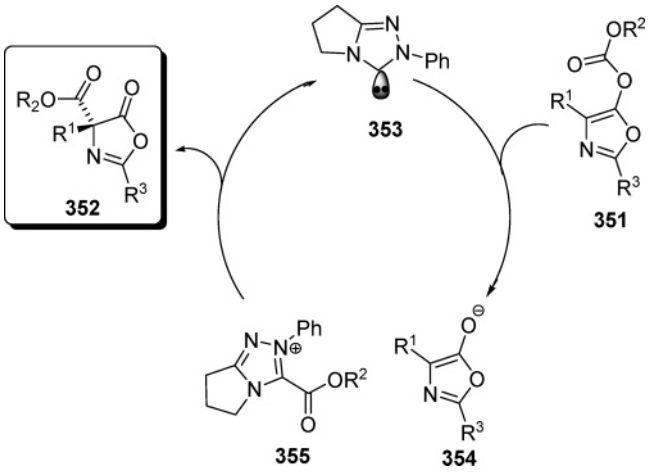
Scheme 124. Proposed Mechanism for the Hydroacylation of Activated Ketones



Scheme 125. Carbene-Catalyzed O- to C-Acyl Transfer by Smith and Co-workers



Scheme 126. Proposed Mechanism for the Carbene-Catalyzed O- to C-Acyl Transfer



The process is based on an intramolecular reaction of a carbonyl anion equivalent (Breslow intermediate), generated by the carbene catalyst, with a suitable leaving group (Scheme 127).

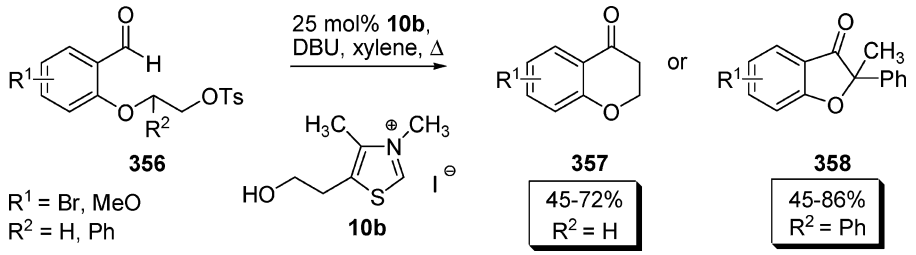
This application is special because of the dependence of the formed products on the utilized substrate. If R^2 is a phenyl group, the observed product was not the expected benzopyrone **357**, but an unexpected formation of the benzofuranone product **358** was observed (Scheme 128). For this unusual reactivity, the authors proposed the following reaction mechanism (Scheme 129).

Under the reaction conditions, an ion pair **359** may be formed, which rearranges to the more stable cation **360**. A nucleophilic attack of the carbene catalyst at the aldehyde function of the cation **360** is followed by the conversion to the Breslow intermediate **362**. The latter undergoes an intramolecular attack at the carbon cation, leading to the intermediate **363** and closing the catalytic cycle by generating the observed product **358** and the catalyst **3′**.

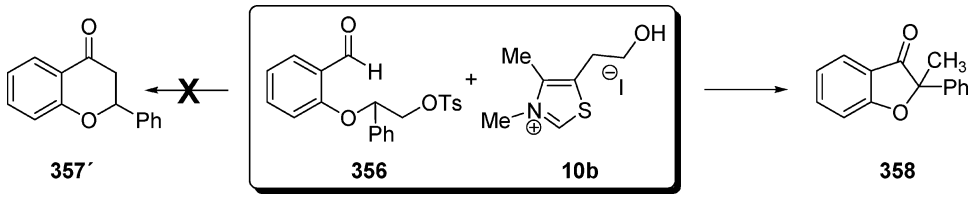
In 2005, Zhai and co-workers reported a one-step assembly of functionalized γ-butyrolactones **365** from benzoins **8** or benzaldehydes **4** via a N-heterocyclic carbene-mediated tandem reaction.[178] The cyclization reaction could alternatively be run starting from the benzoins **8** or by a direct conversion from the aldehydes **4**. The formal [3+2] cyclization product **365** was the only product to be formed instead of the corresponding 1,4-ketoester via a tandem retrobenzoin condensation/Stetter reaction starting from **8**. The Michael acceptor proved to be the decisive factor. No formation of the corresponding γ-butyrolactone was observed when utilizing acceptors other than methyl acrylate like methyl methacrylate, crotonate, or cinnamate (Scheme 130).

The precise reaction mechanism could not be clarified yet. The γ-butyrolactone formation can either result from a tandem transesterification/intramolecular Michael addition via **367** (path **A**) or from a tandem Michael addition/lactonization via the intermediate **368** (path **B**) (Scheme 131).

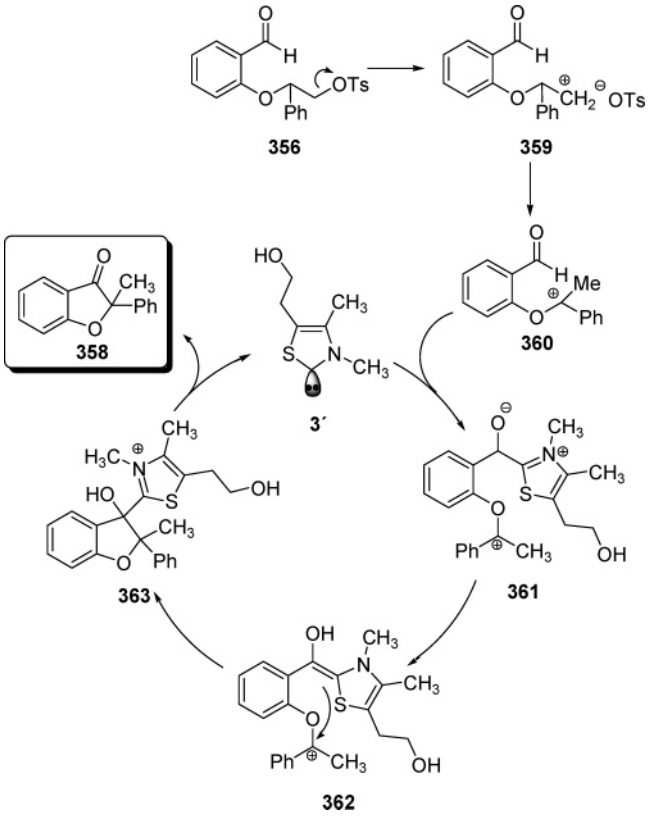
Scheme 127. Carbene-Catalyzed Nucleophilic Substitution Reaction by Pan and Co-workers



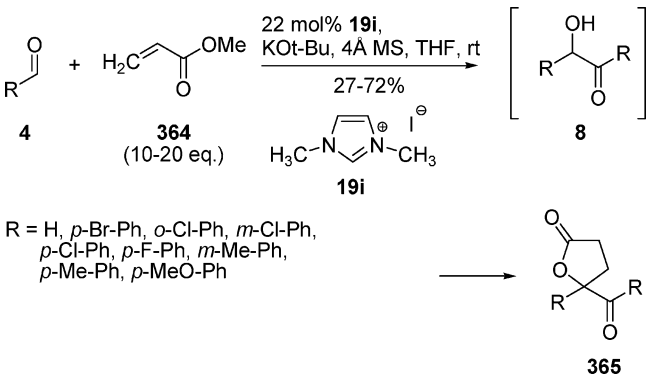
Scheme 128. Observed Formation of the Benzofuranone Product



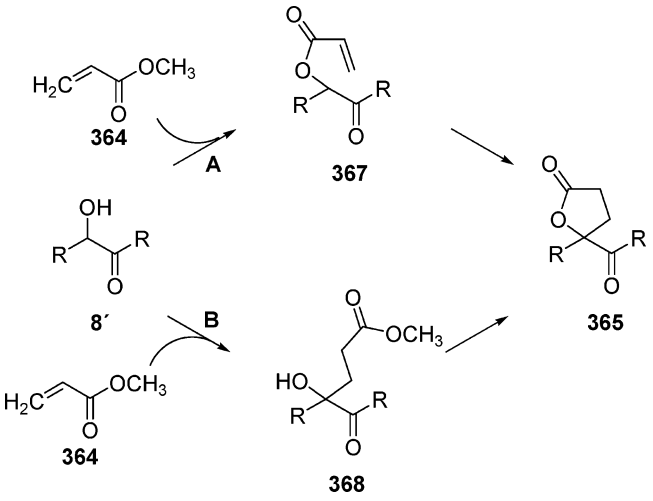
Scheme 129. Postulated Mechanism for Benzofuranone Formation



Scheme 130. One-Step Assembly of Functionalized γ-Butyrolactones by Zhai and Co-workers



Scheme 131. Proposed Mechanism for the Synthesis of γ-Butyrolactones by Zhai and Co-workers

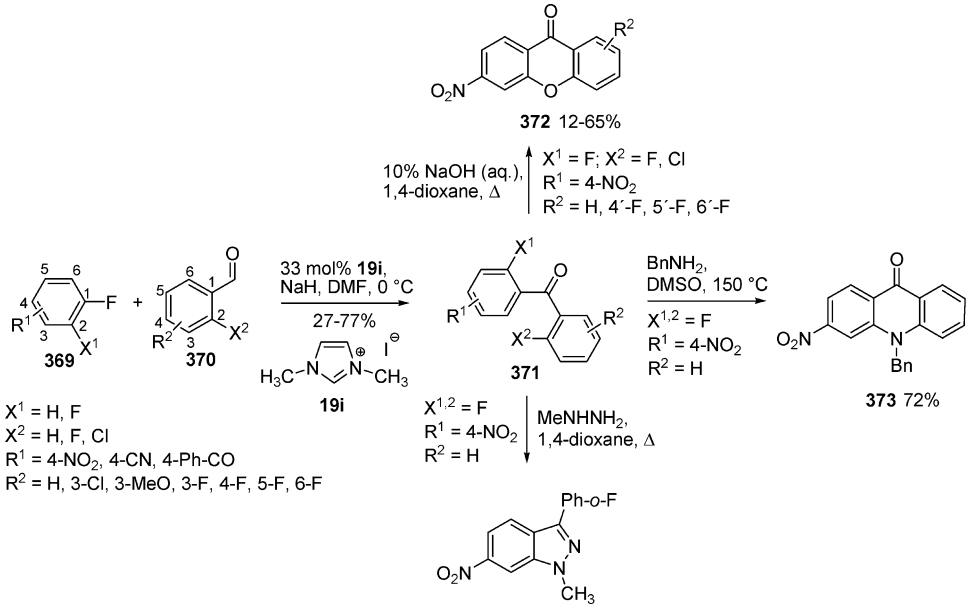


A nucleophilic acylation of arylfluorides **369** with aromatic aldehydes **370** by imidazolin-2-ylidene catalysis to yield the benzophenone derivatives **371** was reported by Suzuki et al.[179] Nitrobenzenes and other fluoroarenes with electron-withdrawing groups were shown to be suitable for this reaction. An application of this new synthetic route was demonstrated for the synthesis of heterocycles.[180] The cyclization of difluorobenzophenones **371** with an aqueous solution of sodium hydroxide by replacement of the two fluorine atoms ortho to the carbonyl group of **371** yielded xanthones **372**. An analogous replacement of a chlorine atom (X^2 = Cl) caused much lower yields. Furthermore, the broad applicability of this methodology was demonstrated in the synthesis of the acridone **373** and the imidazol derivative **374** starting from **371** (Scheme 132).

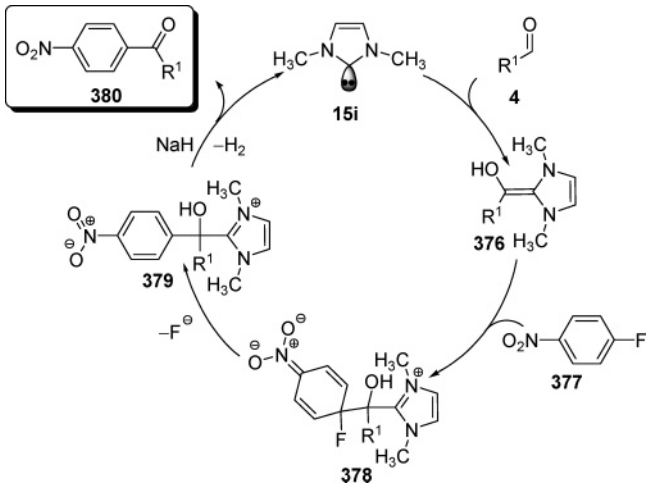
In the proposed reaction mechanism, the imidazolin-2-ylidene **15i** forms the Breslow intermediate **376** with an aromatic aldehyde **4**. The activated aldehyde attacks the heteroarene **377** at the fluorine-bearing carbon to form the adduct **378**. A re-aromatization occurs by the loss of a fluoride anion to yield the tetrahedral intermediate **379**, which is then deprotonated to recycle the catalyst **15i** and to form the product **380**. (Scheme 133).

Miyashita and co-workers developed a general method for the carbene-catalyzed aroylation of 4-chloropyrimidine de-

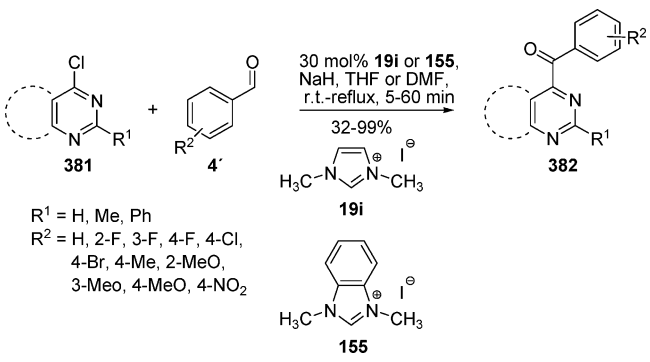
Scheme 132. Carbene-Catalyzed Nucleophilic Acylation of Arylfluorides by Suzuki et al.



Scheme 133. Proposed Catalytic Cycle for the Acylation of 4-Fluoronitrobenzene (377)



Scheme 134. Carbene-Catalyzed Aroylation of 4-Chloropyrimidine Derivatives by Miyashita and Co-workers



rivatives (Scheme 134).[181] By the employment of the two imidazolium based precatalysts **19i** and **155**, they were able to generate a broad number of different *N*-phenyl-4-aroylpyrazolopyrimidines, *N*-phenyl-4-aroyltriazolopyrimidines, *N*-phenyl-4-aroylpurines, and 4-aroylquinazoles, which are important motifs in many pharmaceutical compounds because of their biological activities. Miyashita et al. could also establish a method for the generation of *N*-(α-aroylbenzylidene)anilines **384** by the reaction of the *N*-phenylbenzimidoyl chlorides **383** with aromatic aldehydes **4′** (Scheme 135).[182] By employing the catalytic system NaH and **19i**, the desired *N*-(α-aroylbenzylidene)anilines **384** could be obtained in excellent yields, and afterward, they could be easily converted into their corresponding 1,2-diketo analogues **385**.

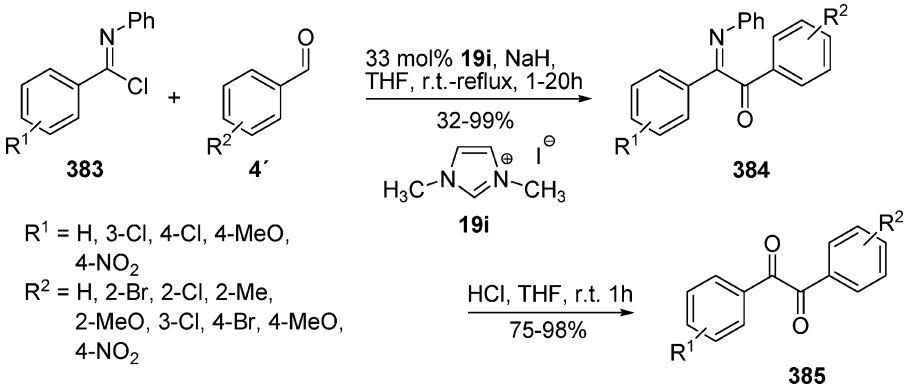
11. Conclusions

More than 20 years ago, when one of us discussed with his predecessor on the chair at RWTH Aachen, the late Professor Hermann Stetter, the possibility to develop an asymmetric version of his name reaction, we did not foresee the breathtaking development of the chemistry of N-heterocyclic carbenes and its implications for organometallic chemistry and a rapidly growing new field, which is now called organocatalysis. We did not foresee that, after a first false report from Aachen in the 1960s (dichlorocarbene), Arduengo would isolate a stable N-heterocyclic carbene in 1991 and the dreams of Wanzlick would come true. We did not foresee that our research group would indeed bottle a carbene and even make it commercially available (Figure 25).

Organocatalysis and this chapter on the catalysis with N-heterocyclic carbenes has its roots back in the early days of organic chemistry, when Liebig and Wöhler investigated the benzoin reaction. From its very beginning, the field was highly competitive. In a letter of May 30, 1832, to Berezelius, Liebig wrote:

"Mit Wöhler bin ich im Begriff, in Feindschaft zu geraten; ich sehe, dass das Schicksal es uns versagt, etwas zu tun, was der andere nicht schon getan hätte oder zu tun im Begriffe ist; alle Originalität geht dabei zum Teufel. So schlägt er mir neuerdings eine gemeinschaftliche Arbeit über das Öl der bitteren Mandel vor, und noch ehe ich seinen Brief erhielt, hatte ich allen Apothekern meiner Bekanntschaft Auftrag gegeben, mir Bittermandelöl zu verschaffen."

Scheme 135. Carbene-Catalyzed Aroylation of *N*-Phenylbenzimidoyl Chlorides by Miyashita et al.



"Wöhler is about to become an enemy, I realized that fate has refused us to do something the other wouldn't have done already or was about to do; all one's originality gets ruined. Thus, he has recently proposed a cooperation on the bitter almond oil, and prior to receiving his letter I had already ordered all the chemists I know to procure me bitter almond oil."

Liebig and Wöhler became good friends, and the result was the seminal joint paper on the benzoyl compounds,[15] which became a milestone of our science and the development of aromatic compounds. Besides this classical benzoin condensation, the development of asymmetric inter- and intramolecular benzoin reactions as well as intramolecular Stetter reactions became the first benchmarks in the rapidly growing field of NHC organocatalysis. In the last few years, the enormous catalytic potential of N-heterocyclic carbenes has enabled a great variety of organic reactions, such as nucleophilic acylations, transesterifications, polymerizations, β-alkylations, hydroacylations, 1,2-additions, ring-opening reactions, and sila-Stetter reactions. The clarification of the underlying reaction mechanisms has enabled a deep understanding of the catalytic role of the carbenes and led to further asymmetric carbene-catalyzed reactions, such as intramolecular aldehyde−imine cross-couplings and Diels−Alder reactions. It can be foreseen that new reaction partners for the NHCs and low catalyst loadings will broaden the remarkable potential of N-heterocyclic carbene-catalyzed reactions and will generate polyfunctionalized molecules of great synthetic importance.

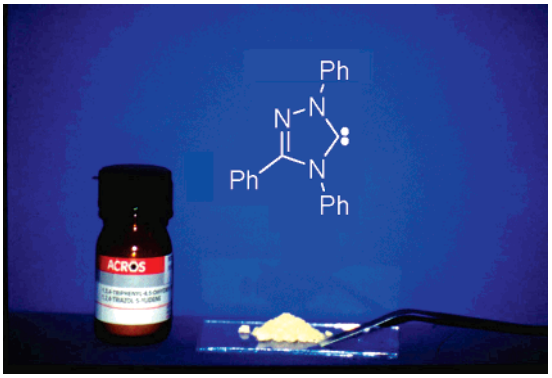


Figure 25. 1,3,4-Triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene, a commercially available carbene.

12. Acknowledgments

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13. Note Added after ASAP Publication

This paper was published on the Web on October 23, 2007, with errors in Table 23. The corrected paper was posted on the Web on October 30, 2007.

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