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Domino Reactions

N-Heterocyclic Carbene Catalyzed Domino Reactions

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asymmetric catalysis · carbenes · domino reactions · organocatalysis · umpolung

While organocatalyzed domino reactions or "organocascade catalysis" developed into an important tool in synthetic chemistry during the past decade, the utility of N-heterocyclic carbenes (NHCs) as catalysts in domino reactions has only received growing attention in the past three years. Taking into account the unique activation modes of the substrates by NHC catalysts, it is often difficult to distinguish between a single chemical transformation and a sequential one-pot transformation. Therefore, herein we present a critical consideration of domino, cascade, and tandem catalysis in the case of NHC catalysts and highlight recent publications in this area.

1. Introduction

Nature has always fascinated scientists for its intrinsic efficiency. For example, countless numbers of different chemical compounds are transformed in numerous parallel reactions with extraordinary selectivity in a single cell. By learning from nature and adopting its concepts in the laboratory, chemists were able to reduce the purification steps and thereby optimize synthesis time, costs, and minimize chemical waste.[1] Unsurprisingly, the interest of the chemical community towards such bio-inspired "one-pot" reactions increased rapidly over the past two decades. These processes, characterized by their high level of atom,[2] step,[3] redox,[4] and pot economy,[5] were predominantly termed domino, cascade, or tandem reactions (Figure 1).

The sequence of consecutive transformations is of particular importance in organocatalysis.[6] This biomimetic methodology uses small organic molecules as catalysts under mild conditions, where a metal is not actively involved in the catalytic cycle. As a result, these catalysts tolerate a broad range of functional groups and circumvent the application of time-consuming protecting groups. In addition to this significant advantage, organocatalysts allow distinct activation modes of the respective substrates making the combination of different catalysts in the same flask possible. For these reasons, organocatalytic one-pot reactions or "organocascades" gained a lot of attention in recent years.[7] Interestingly, this field is strongly dominated by the secondary amine and Brønsted acid catalysis, with comparatively few applications of thioureas and N-heterocyclic carbenes reported in the literature. The fact that NHC catalysis is a well developed field in organic chemistry,[8] and offers a broad range of unconventional transformations, it is surprising that the publications on NHC organocascades are limited to the last three years. Considering the advantages NHC-catalyzed domino reactions might bring, it is worthwhile to discuss this emerging area.

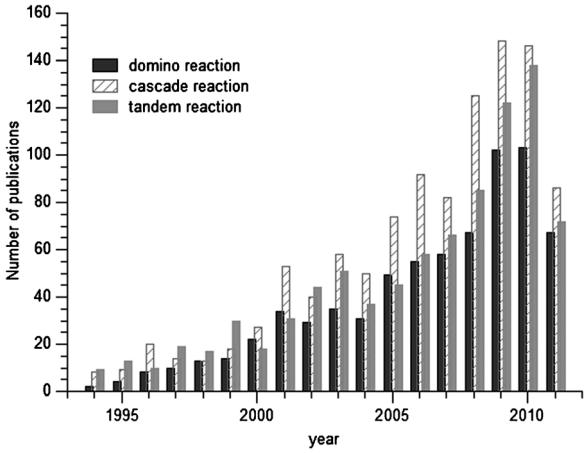

Figure 1. Histogram of publications per annum containing "domino reaction", "cascade reaction" or "tandem reaction" in the title.[9]

Keeping this in mind, we begin with an attempt to define "NHC cascade reaction" followed by an insight into recent publications in this field.

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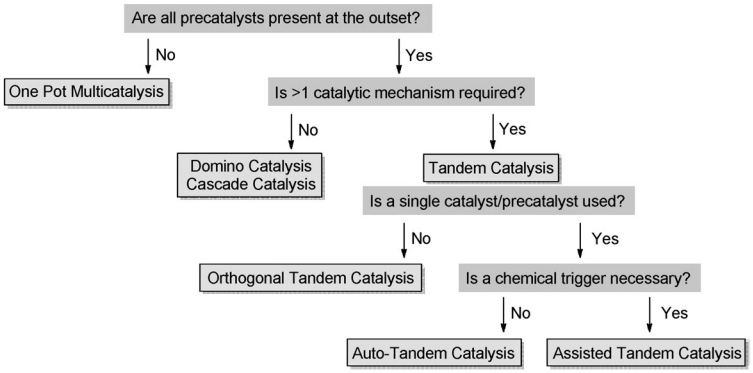


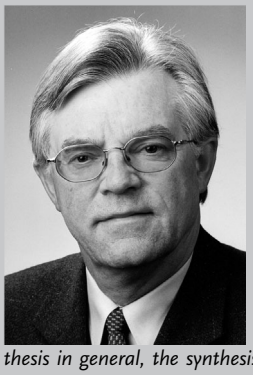
Scheme 1. Taxonomy of one-pot multiple catalytic transformations according to Fogg and dos Santos.[11a]

2. NHC-Catalyzed Transformations

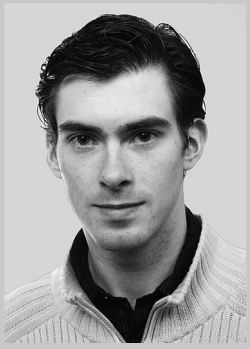
Before the real rush, Tietze and Beifuss first defined a domino reaction as "*a process involving two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step*".[10] In contrast to this time-resolved process, a "tandem reaction" is space-resolved. That's why the term domino reaction is reserved for two independent transformations on the substrate. In the case of the third term, "cascade reaction", Tietze and Beifuss suggest to avoid its further usage because of its wide-spread use in several independent contexts.[1b] A decade later, another classification was suggested by Fogg and dos Santos and followed by Chapman and Frost for the corresponding catalyzed processes ("domino catalysis", "cascade catalysis," and "tandem catalysis").[11] Their taxonomy is based on the number of distinct mechanisms and required catalysts (Scheme 1). In this case "domino catalysis" and the synonymic "cascade catalysis" mean sequences of consecutive transformations which are all described by one kind of mechanism. Sequences of steps with different mechanisms are "tandem reactions". Furthermore, both tandem catalysis and domino catalysis are special cases of one-pot reactions with all the catalysts being present from the beginning.[12] Hence, there are two incongruent classifications in the literature, each having its limitations.

A major handicap of both classifications is that they are based on terms like "chemical reaction", "individual transformation", and "distinct mechanism". The crux is that the application of the proposed classifications is only possible if the sequence of transformations is separable in taxonomically distinct reactions or mechanistically distinct steps. Unfortunately, it is not a trivial question to answer where the boundary between an individual reaction and a sequence of reactions is. Furthermore many chemical transformations have several plausible mechanisms and only few were verified by experimental techniques. Therefore a direct application of Tietze's or Fogg's classifications is difficult. Hence, we suggest appointing a simple synthon classification of NHC-catalyzed reactions to circumvent these problems.

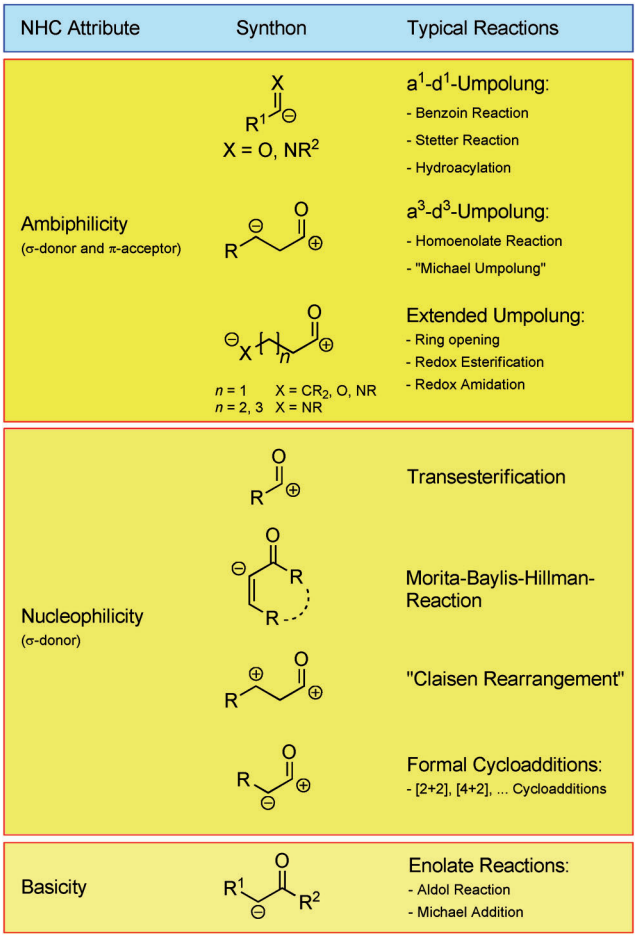
A rational way to classify organocatalytic NHC reactions is based on the catalytic activation modes of the substrates. Since these catalysts undergo a covalent bond formation reaction with the substrate, NHC-substrate adducts are present in all cases. Theoretically, such an intermediate can be traced back to a synthon as was introduced by Corey.[13] According to the present state of NHC organocatalysis we will use eight synthons. Furthermore, these synthons can be divided into three groups according to the three major attributes of N-heterocyclic carbenes (Scheme 2): ambiphilicity, which is the result of the σ-donor and π-acceptor character of N-heterocyclic carbenes (Scheme 3), moderate nucleophilicity, and strong basicity.[14]



Dieter Enders was born in 1946 in Butzbach, Germany, studied chemistry at the Justus Liebig University Giessen and received his PhD under the supervision of Professor D. Seebach in 1974. After postdoctoral research at Harvard University with Professor E. J. Corey, he returned to Giessen and obtained his habilitation in 1979. In 1980 he moved to the University of Bonn as an associate professor, and in 1985 to his present position as Professor of Organic Chemistry at the RWTH Aachen University. His research interests are asymmetric synthesis in general, the synthesis of biologically active compounds, and organocatalysis. He has received many awards and is a member of Leopoldina, The German National Academy of Sciences.

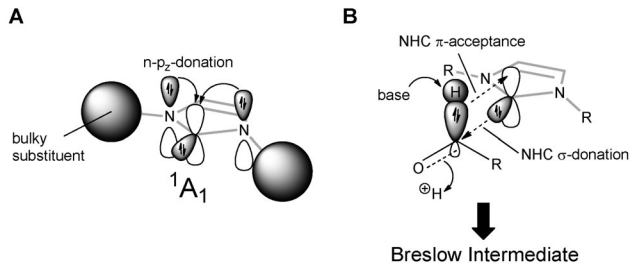


André Grossmann was born in 1984 in Tschutowo, Ukraine. He studied chemistry in Marburg and Edinburgh and received his degree in 2009 at the Philipps University Marburg under the mentorship of Prof. U. Koert. As a scholarship holder of the SeleCa international graduate students training group (RWTH Aachen University and Osaka University), he is working on his PhD thesis under the supervision of Prof. D. Enders. His research focuses on N-heterocyclic carbene catalysis and its application in domino reactions.



Scheme 2. Synthon classification of NHC-catalyzed reactions.

Pioneered by Seebach, the concept of "umpolung" (polarity reversal) triggered a novel way of thinking beyond the traditional reactivity patterns in the retrosynthetic analysis of target molecules.[15] Nowadays three types of umpolung are associated with NHC catalysis: umpolung of aldehydes to acyl nucleophiles (a^1–d^1 umpolung) first reported by Ugai et al. in 1943 in the thiazol-2-ylidene-catalyzed benzoin reaction,[16] the "conjugate umpolung"[17] (a^3–d^3 umpolung) independently developed by Glorius and Burstein[18a] and by Bode and He,[18b] and the extended "umpolung" (sometimes referred as an "internal redox reaction")[19] independently demonstrated



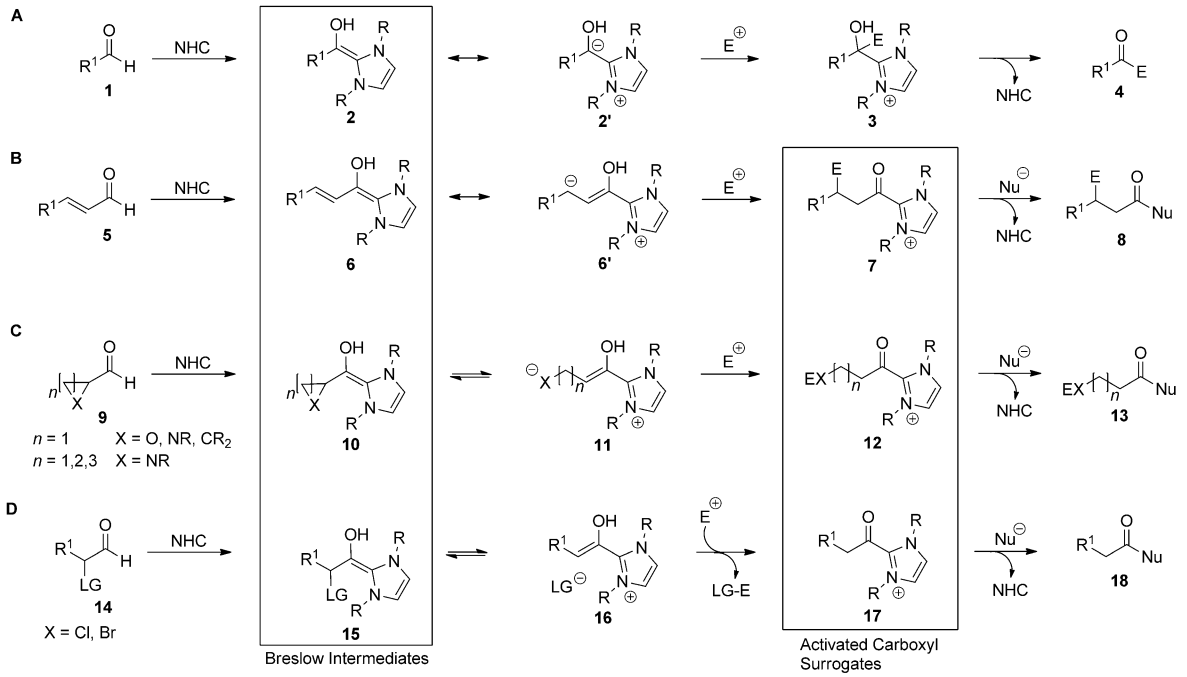
Scheme 3. Electronic ambiphilicity of N-heterocyclic carbenes: A) stabilization of the singlet carbene by n-p_z donation (where n is the lone pair of the nitrogen center) of the N substituents; B) formation of the Breslow intermediate by σ donation and π acceptance.

by Bode and co-workers[20a] and Rovis and co-workers.[20b] Although the mechanisms of these reactions have not been completely verified yet, similar mechanisms can be postulated for all three kinds of umpolung (Scheme 4).[21,22] Clearly the catalytic cycle starts with the nucleophilic attack of the σ-donor lone pair of the carbene on the carbonyl group. For a^1–d^1 umpolung, it is accepted that the adduct leads to the Breslow intermediate **2** through deprotonation of the carbene–aldehyde adduct by the external base and π-back-donation of the former σ_{CH} orbital to the empty p_z orbital of the carbene (Scheme 3B). Subsequently, this intermediate **2** (also drawn as its mesomeric zwitterionic form **2′**) can react with different electrophiles, such as another carbonyl compound as in the benzoin reaction, with Michael acceptors in the Stetter reaction, with activated or unactivated double and triple bonds without electron-withdrawing groups, or with alkyl halides. After the reaction, the carbene is liberated and can re-enter the catalytic cycle (Scheme 4A).

Theoretically, similar reactions can take place for the conjugate umpolung and internal redox reactions (Scheme 4B–D). The difference is that after the formation of the Breslow intermediates **6**, **10**, and **15** the position of the formal negative charge can be transferred by the double bond or the ring opening and therefore the electrophile is trapped in a different place. Furthermore, in contrast to the a^1–d^1 umpolung, where the carbene is liberated spontaneously, the conjugate umpolung and the internal redox reactions are followed by the formation of the activated carboxyl surrogates **7**, **12**, and **17**. To close the catalytic cycle a stoichiometric amount of another nucleophile, that is, an alcohol or an amine, is necessary. Hence the simple acyl umpolung is a one step process in which one bond is formed, whereas the conjugate umpolung and internal redox reactions are a two step reactions.

Unfortunately, this two-step mechanism diminishes the border between the individual reaction and the domino reaction. Using Tietze's definition, a single catalytic cycle of the conjugate umpolung or the internal redox reaction should also be called a domino process because the activated carboxyl surrogate is a consequence of the preliminary nucleophilic addition step. In contrast, according to Fogg's definition this would be either a single, individual reaction because both steps belong to the same cycle, or a domino process if this catalytic cycle can be split in subsequent reactions. Herein, we will avoid this contradiction and follow the widely accepted view considering this process as a single reaction as long as the electrophile is simply a proton. For all other electrophiles, we will use the term domino reaction. Furthermore all processes containing an additional bond forming step after or in between these two steps will also be described as domino reaction.

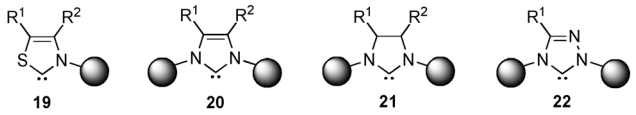
The second major attribute of NHCs is their nucleophilicity. Starting with the seminal work of Wanzlick[23] and Arduengo[24] a large number of different nucleophilic carbenes have been published over the last decades. On the other hand, the carbenes used in Lewis base organocatalysis are mainly limited to the four general structures: thiazol-2-ylidene (**19**), imidazol-2-ylidene (**20**), imidazolin-2-ylidene (**21**), and triazol-5-ylidene (**22**; Scheme 5). The nucleophilic-



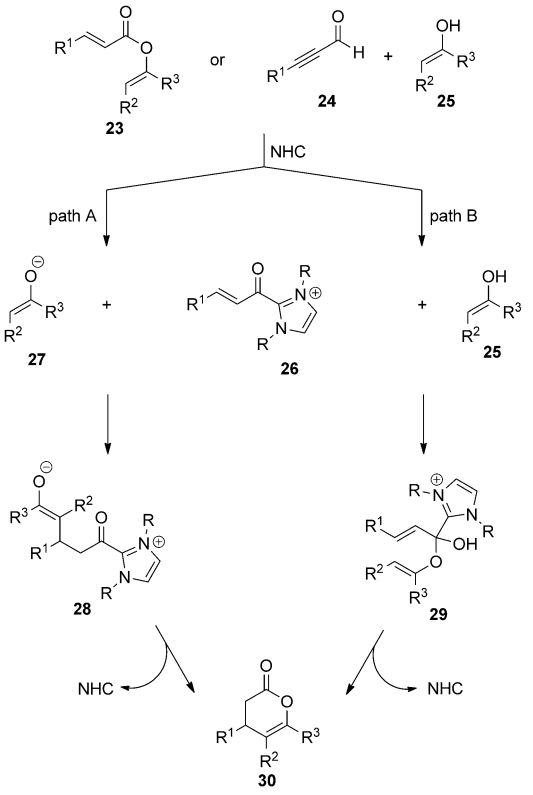
Scheme 4. Comparison of formal mechanisms of NHC reactions attributed to the ambiphilicity of the catalyst: A) a^1–d^1 umpolung, B) a^3–d^3 umpolung, C) extended "umpolung" by ring opening, or D) by elimination of the leaving group.

ity of these carbenes is due to the high population in the singlet state ($^1A_1$) of the divalent carbon atom. In addition, the nitrogen or sulfur atoms in the α-position stabilize these compounds by electron donation from their lone pair to the empty p_z orbital (Scheme 3 A).[25] A further advantage of nitrogen-containing carbenes is the possibility of tuning the electronic and steric properties of the carbenes by substituents at the N atom.

Four types of NHC catalyzed reactions are based solely on the nucleophilicity of the carbene: transesterification, Morita–Baylis–Hillman reaction, "Claisen-type" rearrangement, and formal cycloaddition. While transesterification and the Morita–Baylis–Hillman reaction can be unambiguously considered as individual reactions, it is worthwhile to take a closer look at the "Claisen-type" rearrangement and the formal cycloadditions. First reports on the "Claisen type" NHC-catalyzed reaction came only recently from Lupton and co-workers[26] and independently Bode and co-workers.[27] Interestingly, these groups postulated different mechanisms for their reactions. Lupton et al. discussed a mechanism complementary to the one used for "conjugate umpolung" (Scheme 6, path A). The carbene attacks the ester carbonyl group liberating the enolate **27** which undergoes an 1,4-addition with **26** forming the activated carboxylate **28**. The subsequent lactonization finally releases the carbene catalyst.



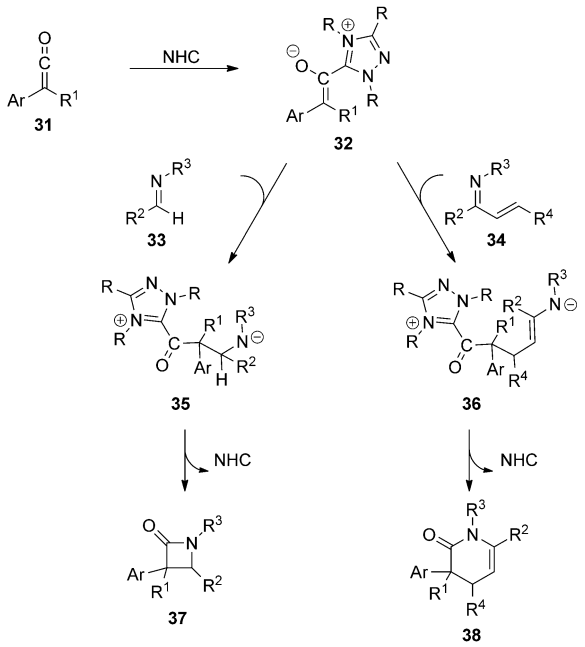
Scheme 5. General structures of N-heterocyclic carbenes used in organocatalysis.



Scheme 6. NHC-catalyzed dihydropyranone synthesis, stepwise (path A) versus Claisen-type rearrangement (path B).

Bode et al. used ynals **24** and enolic compounds **25** as substrates for this reaction. Based on kinetic studies they suggested that instead of the 1,4-addition the enol undergoes an 1,2-addition forming a hemiacetal **29** (Scheme 6, path B). After the Coates–Claisen rearrangement the catalyst is regenerated resulting in the dihydropyranones **30**. It should be mentioned that in spite of their kinetic results, they could not exclude the alternative mechanism completely. Comparing these two mechanisms, we have again the problem of a multistep reaction. While Lupton's mechanism is a two-step process, 1,4-addition and esterification, Bode's version is clearly an individual reaction by its simultaneous bond-forming character. Herein we will consider this process as an individual reaction.

Formal cycloadditions are the third type of reactions made possible by the nucleophilicity of the carbene (Scheme 7). Ye et al. were the first to observe the reaction of ketenes **31** with aldimines **33**[28] in the presence of triazol-5-ylidenes and the



Scheme 7. Formal cycloadditions.

vinologous reaction utilizing the ketimine **34**.[29] Both reactions start with the nucleophilic attack of the carbene on the ketene forming zwitterionic enolate **32**. This enolate undergoes a nucleophilic attack on the aldimine **33** or ketimine **34** yielding the activated carboxylates **35** and **36**. As described for other reactions above, these compounds cyclize by intramolecular amidation. As in the "Claisen type" rearrangement, both are two-step processes and hence these reactions cause the same problem in the application of the domino concept as discussed for the "Claisen rearrangement", conjugate umpolung, and internal redox reaction. Since in all these cases the mechanism is not solved completely, we will use the same argument as above counting such processes as individual reactions.

The third attribute of N-heterocyclic carbenes is their basicity. There are several theoretical and experimental reports on this topic where a pK_a value between 21–25 was reported for the corresponding conjugate acids in DMSO and water.[30] Only imidazolium salts with aromatic substituents of one of the two nitrogen atoms were calculated as being less basic, with pK_a values between 16–19 in DMSO.[30b] As expected, due to their strong basicity, there are some reports on aldol[31] and Michael reactions[32] catalyzed by NHCs. All these reactions can be clearly divided into single and domino reactions. Therefore the application of the definitions above can be used without any further limitations.

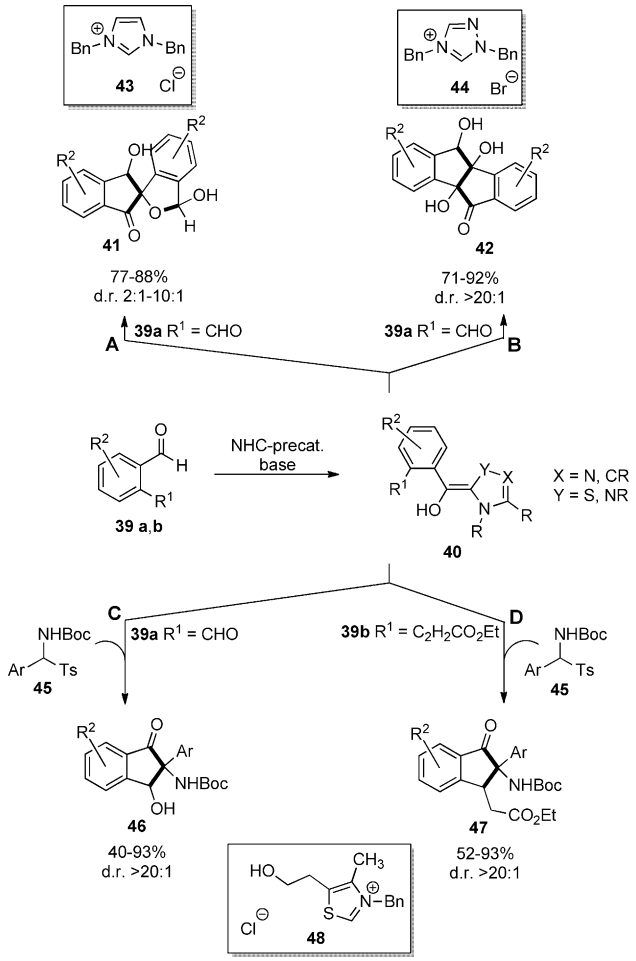
It is common practice to generate the carbene catalyst by deprotonation of the corresponding azolium salt. For this purpose, another base is added in sub-stoichiometric amounts. Unfortunately, the exact role of carbenes in the catalytic reactions is unknown to date although a range of control experiments is usually performed. Therefore the application of Fogg's taxonomy in one-pot processes with reaction steps based on NHC basicity is difficult, as the precise number of catalysts is not known.

In summary, there are arguments to consider some of the NHC-catalyzed reactions as domino processes because of their multistep mechanism, in contrast to the literature precedent where they are usually named individual reactions. Based on the eight synthons given in Scheme 2, we can now proceed to reactions which can be identified as domino processes. We should mention that there are some publications dealing with new reaction pathways involving oxidation of the substrate–carbene adduct.[33] Such reactions can also be called domino processes but are excluded for clarity.

3. NHC Domino Reactions

From the set of the eight reaction types classified by synthons (Scheme 2), the combination of an umpolung step and reactions based on the carbene basicity are most common in NHC-catalyzed domino reactions. Recently, several research groups demonstrated that an a^1–d^1 umpolung can be followed by aldol or Michael reactions. Since the nucleophile for the second step is generated by the previous umpolung, all these examples should be called domino processes according to Tietze. Likewise, using Fogg's taxonomy, all of them are auto-tandem processes if the carbene is responsible for all steps. They are called orthogonal tandem processes if the added base, which has generated the carbene, catalyzes the subsequent aldol or Michael reactions. As stated above, it is hard to verify the role of the catalyst. Therefore, the application of Tietze's definition seems more appropriate in such cases.

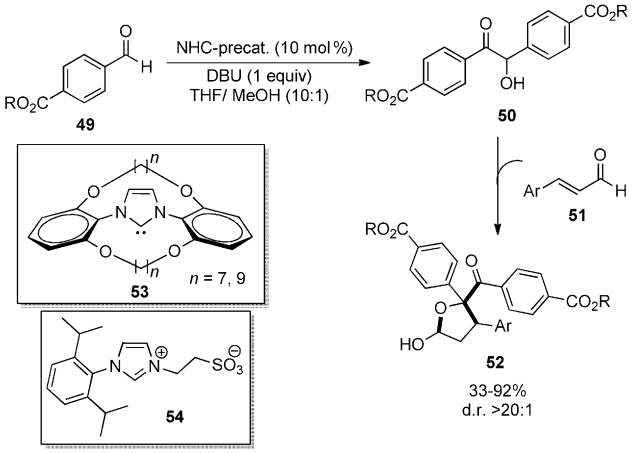
The first example presented herein was disclosed by Cheng et al. in the dimerization reaction of phthalaldehyde **39a** towards polyhydroxylated spiro-indanones **41** (Scheme 8A).[34] Mechanistically this reaction represents a benzoin–aldol–hemiacetalization sequence. The carbene catalyst generated from the imidazolium salt **43** led to the desired products in good yields (77–88%). This methodology is applicable for neutral or electron-poor arenes but was



Scheme 8. Sequences: A) Benzoin–aldol–hemiacetalization, B) benzoin–aldol–benzoin, C) *aza*-benzoin–aldol, D) *aza*-benzoin–Michael; bonds formed by the domino sequences are marked bold. Bn = benzyl, Boc = *tert*-butyloxycarbonyl, Ts = tosyl (4-methylphenylsulfonyl).

configured *cis* to the carbamate group. Independently, You et al. used *ortho*-formyl ethyl cinnamate **39b** instead of phthalaldehyde **39a** in a similar *aza*-benzoin–Michael reaction (Scheme 8D).[36] Utilizing the same catalyst precursor **48** as Ye and Sun, the products were obtained in moderate to good yields (52–93%) and excellent diastereoselectivity for a broad range of aldimines and differently substituted enoates **39b**. Again, only single diastereomers were observed with a *cis* configuration between the carbamate and the alkyl residue. The products could further be transferred to pharmaceutically interesting tricyclic pyrrolidinones.

Another example of d^1–a^1 umpolung together with enolate chemistry was published by Lüning et al. and later Yoshida et al. (Scheme 9).[37,38] In this case, aromatic aldehydes **49** first underwent an intermolecular benzoin reaction. Then, the resulting α-hydroxy ketones **50** performed a

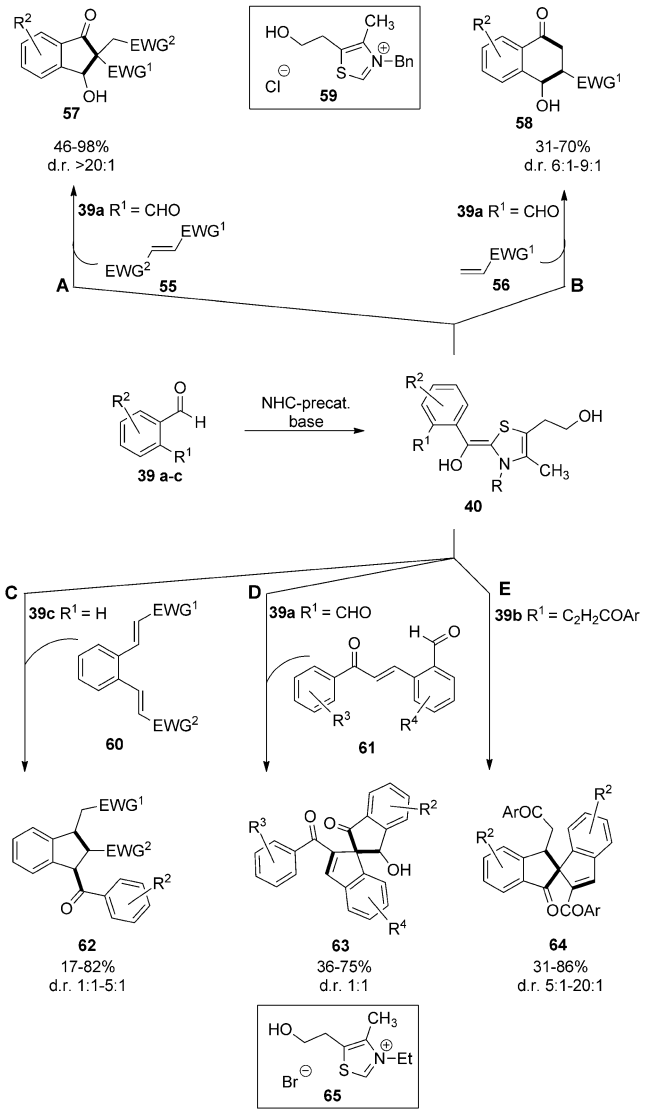


Scheme 9. A sequence consisting of benzoin addition, Michael addition and hemiacetalization; bonds formed by the domino sequence are marked bold. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

completely unsuccessful for electron-rich substrates. All the products had *cis* configuration between the hydroxy group of the indanone ring and the oxygen of the tetrahydrofurane ring, indicating good stereocontrol of the carbene-catalyzed steps. The acetalization was thermodynamically controlled and therefore two diastereomers were observed in a ratio of 2:1 up to 10:1. Interestingly, Cheng et al. also noticed that the change of the catalyst precursor from imidazolium salt **43** to the triazolium salt **44** modified the reaction path (Scheme 8B). Hence, a second benzoin reaction took place before the acetalization producing the fused indanones **42**. The reaction proceeded with very good yields (71–92%) for all examples presented. The configuration of the three hydroxy groups in the product was *all-cis*.

Likewise Ye and Sun reported the *aza*-benzoin–aldol domino reaction of phthalaldehyde **39a** with imines (Scheme 8C).[35] The imine was generated from the tosylcarbamate **45** in situ. The deprotonation of the thiazolium salt **48** resulted in a suitable catalyst yielding the aminohydroxyindanones **46** in moderate to good yields (40–93%) for a broad range of aromatic and heteroaromatic aldimines. Remarkably, only a single diastereomer was observed with the hydroxy group Michael reaction with cinnamic aldehyde derivatives **51**. Finally, the Michael adducts cyclized to the hemiacetals **52**. Lüning et al. proposed the macrocyclic catalyst **53** for this reaction while Yoshida et al. used imidazolium salt **54** as catalyst precursor. The imidazolium salt precursor turned out to be more reactive and the yields of the tetrahydrofuranes **52** increased from up to 42% to up to 92%. Yoshida et al. attributed the improved reactivity to the sulfonate group in the catalyst which was assumed to interact with the benzoin product **50**. The diastereoselectivity of this process is extremely high and only one diastereomer was isolated. Under the reaction conditions the formation of the hemiacetal should be under thermodynamic control. Thus, the high selectivity is unusual but is most likely due to a special substituent pattern. The scope of the reaction is broad with the cinnamic aldehydes **51** but is limited to alkyl *para*-formyl benzoates **49**.

It is well established that the choice of the carbene catalyst determines the reaction path. Therefore, just by changing the catalyst, the benzoin reaction could be suppressed and the same substrates undergo the Stetter reaction. There are already several examples of domino process composed from



Scheme 10. Sequences: A) Stetter–aldol, B) Stetter–aldol, C) Stetter–Michael, D) Stetter–aldol–aldol, E) Stetter–aldol–Michael; bonds formed by the domino sequences are marked bold. EWG = electron-withdrawing group.

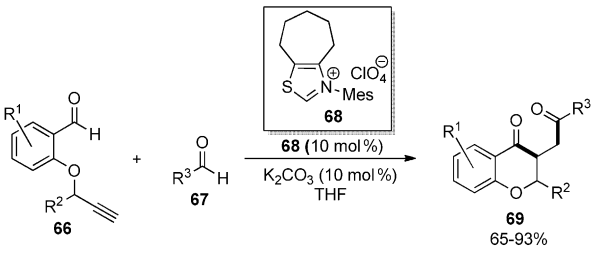
Stetter, aldol, and Michael reactions (Scheme 10). Recently Ye et al. have prepared the hydroxyindanone **57** by the reaction of the phthalaldehyde **39a** with the Michael acceptor **55** bearing two electron-withdrawing groups (Scheme 10A).[39] The reaction proceeded smoothly utilizing the thiazolium catalyst precursor **59**. As in the cases of the other indanones described above, the formation of **57** was strongly stereocontrolled with only one diastereomer observed. The configuration of the product was again *cis* between the hydroxy group and the electron-withdrawing group attached to the ring. High diastereoselectivity combined with high yields (46–98%) make this a useful method for the preparation of these pharmaceutically interesting compounds. Worth mentioning is that only the indanone **57** and no tetralone **58** was observed.

In contrast the corresponding hydroxytetralone **58** can be prepared by using a Michael acceptor with only one electron-withdrawing group (Scheme 10B).[40] Utilizing the precatalyst **59**, the hydroxytetralones **58** were obtained in moderate yields (31–70%) and moderate diastereomeric ratios (d.r. 6:1—9:1). The major diastereomers were assigned the *trans* configuration. Remarkably, if the reaction was performed stepwise instead of in one pot, the major product had the *cis* configuration. It has been speculated that this could be evidence that the carbene catalyst is responsible for both steps.

In 2009 Sánchez-Larios and Gravel published a Stetter–Michael domino sequence producing indanes **62** (Scheme 10C).[41] In this case substituted benzaldehydes **39c** reacted with double Michael acceptors **60**. When comparing several imidazolium, triazolium, and thiazolium salts as catalyst precursors only **65** showed reasonable reactivity in this process. The yields of the reaction are strongly dependent on the substituents and varied between 17–82% with electron-poor Michael acceptors performing best. Aliphatic aldehydes lead to significantly lower yields (15–32%). In contrast to other methods mentioned for the synthesis of indanes and described above, the diastereoselectivity was moderate (up to 5:1). The major diastereomer had a *trans* configuration of the benzoyl group and the electron-withdrawing group attached to the ring. Experiments under basic conditions identified epimerization to be responsible for the moderate diastereoselectivity. Thus the reaction is under kinetic control.

In addition, the Gravel group reported a Stetter–aldol–aldol domino reaction of phthalaldehyde **39a** with *ortho*-formyl chalcone **61** employing the thiazolium precatalyst **65** (Scheme 10D).[42,43] Pharmaceutically important spiro bis-indanes **63** were accessed by this method in moderate yields (36–75%). The product was isolated as a 1:1 mixture of two diastereomers with a different configuration in the α-position of the hydroxy group. Nevertheless, the construction of the quaternary stereogenic center and the formation of three C–C bonds in one pot mark it as an important new method in organic chemistry, as was shown in the synthesis of the spiro core of fredericamycin A.[42] Gravel et al. also demonstrated that the *ortho*-formyl chalcones **39b** dimerized in a Stetter–aldol–Michael reaction to spiro bis-indanes **64** (Scheme 10E).[42,43] In this case better yields (31–86%) and diastereoselectivities (up to 20:1) were achieved than with the other method. The same reaction also worked for alkyl thiocinnamates but failed completely when esters, sulfones, or nitriles were used instead.

Very recently Glorius and co-workers have demonstrated that beside the Stetter reaction, unactivated double and triple bonds can be hydroacylated using N-heterocyclic carbenes.[44] They have also demonstrated the integration of the hydroacylation in a hydroacylation–Stetter sequence (Scheme 11).[44b] Such a process can be considered a domino (Tietze et al.) or auto-tandem (Fogg et al.) since both steps are unambiguously catalyzed by the same compound. The reaction works well for differently substituted salicylaldehyde derivatives **66** and a broad range of aromatic and aliphatic aldehydes **67**, with the aliphatic aldehydes performing worse than the aromatic ones. The thiazolium precatalyst **68** turned

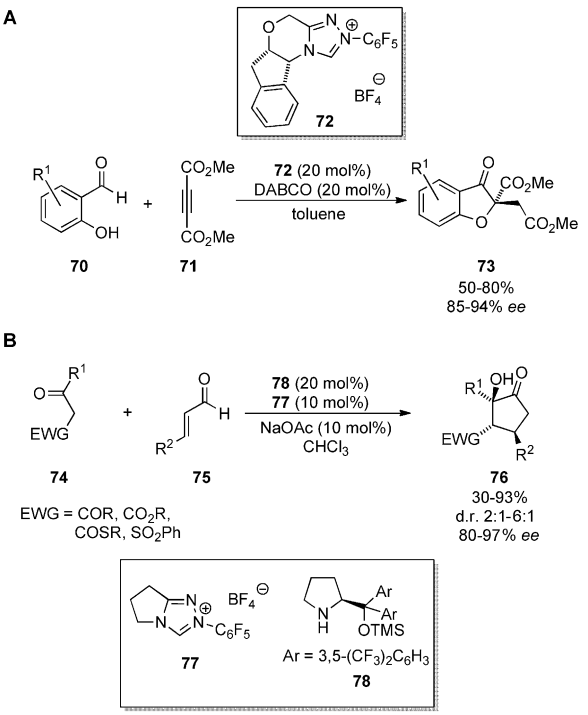


Scheme 11. Hydroacylation–Stetter sequence; bonds formed by the domino sequences are marked bold. Mes = 2,4,6-trimethylphenyl.

out to be the best choice for this domino process by suppressing different benzoin and Stetter side reactions.

By increasing the range of possible combinations of reactions in one-pot processes or triggering unusual selectivity, multicatalysis is an important development in synthetic chemistry. Two main branches can be differentiated for bicatalytic reactions: dual catalysis,[45] where the two catalysts independently work in two distinct catalytic cycles, and cooperative catalysis,[46,47] where the catalysts interact either with each other or both simultaneously with the substrate. Dual catalysis was applied in Michael–Stetter and Michael–benzoin one-pot reactions which can be classified as domino or orthogonal tandem reactions owing to the presence of several catalysts (Scheme 1). Salicylaldehydes **70** react well with activated alkynes **71** in the presence of DABCO shown by Rovis and co-workers (Scheme 12 A).[45d] After the amine-mediated Michael addition the carbene generated from **72** catalyzed the asymmetric Stetter reaction resulting in the benzofuranones **73**. This reaction proceeded well for various substituted salicylaldehydes **70** with symmetrical alkynes **71** to give rise to the benzofuranones **73** in moderate yields (50–80%) and good enantioselectivities (85–94%). Furthermore this selectivity could be increased significantly by the addition of catechol to the reaction. For unsymmetrical alkynes both yields (26–60%) and enantioselectivities (12–86%) dropped considerably. It is worth mentioning that this reaction led to a higher enantioselectivity but lower yields when performed in one pot as compared to the stepwise method. It was speculated that traces of side products formed during the Michael addition are responsible for this.

Rovis and co-workers also envisaged that activated ketones **74** would undergo a Michael–benzoin reaction with enals **75** by a secondary amine (**78**)/NHC (precursor **77**) dual catalytic system (Scheme 12 B).[45a] This time the chiral amine **78** is responsible for the enantioselectivity and the formation of the polysubstituted cyclopentanones **76** took place with moderate to good yields (30–93%) and very good enantioselectivities (80–97). Both aliphatic and aromatic aldehydes **75** were used successfully, while only branched aliphatic aldehydes gave low yields. Furthermore, the reaction tolerated a broad range of aliphatic, cyclic, and acyclic ketones **74**, which were activated by a second keto-, or an α- ester, or thioester group. Interestingly, the reaction progress could be monitored by gas chromatography (GC) and it could be determined that both catalysts worked simultaneously and only a low concentration of the intermediately formed Michael adduct is present. This steady state is an additional



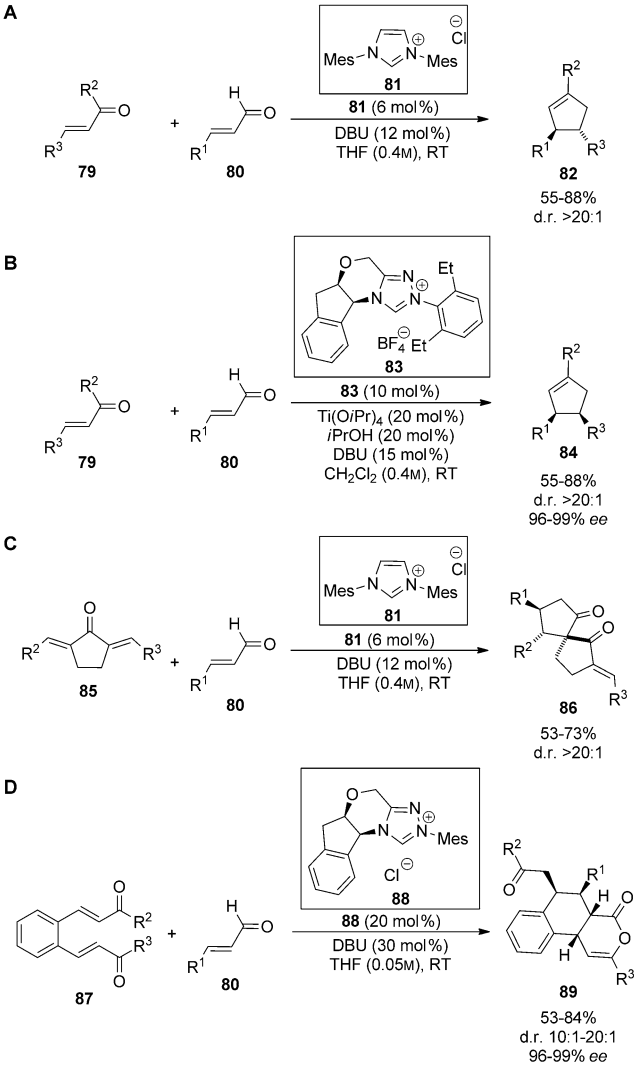
Scheme 12. Sequences A) oxa-Michael–Stetter, B) Michael–benzoin. DABCO = 1,4-diazabicyclo[2.2.2]octane, TMS = trimethylsilyl.

argument for calling this reaction domino as was suggested by Tietze.[1] The only drawback of this method is that the diastereomeric ratio between the major diastereomer and the sum of the minor diastereomers was only modest (d.r. 2:1-6:1). The structure of **76** determined by X-ray analysis indicated that this domino process proceeded by a *trans*-selective Michael addition and a *trans*-selective benzoin condensation. Recently we have extended this methodology to β-oxo sulfones **74** (electron-withdrawing group (EWG) = SO_2Ph).[48] These substrates led to synthetically useful cyclopentanones in yields and enantioselectivities comparable to those achieved by Rovis and co-workers. Surprisingly, only one diastereomer was isolated when acetophenone derivatives **74** with R^1 being an aromatic moiety were used in this reaction. Furthermore, the configuration of this group of products has changed because the benzoin reaction proceeded with *cis* selectivity. Intrigued by this result, we performed the reaction in the NMR tube and monitored the formation and the configuration of the Michael adduct. In this way the epimerization of the Michael adduct could be detected under the reaction conditions. Control experiments indicated that the epimerization is a simple base-promoted protonation–deprotonation process. So the high diastereoselectivity was due to the carbene catalyst, which favored one of the diastereomers of the Michael adducts and the epimerization of the residual isomer. This result is relevant for developing similar reactions in the future, since the variation of the NHC catalyst could further improve the selectivity or maybe other diastereomers could be accessed by choosing the appropriate catalyst.

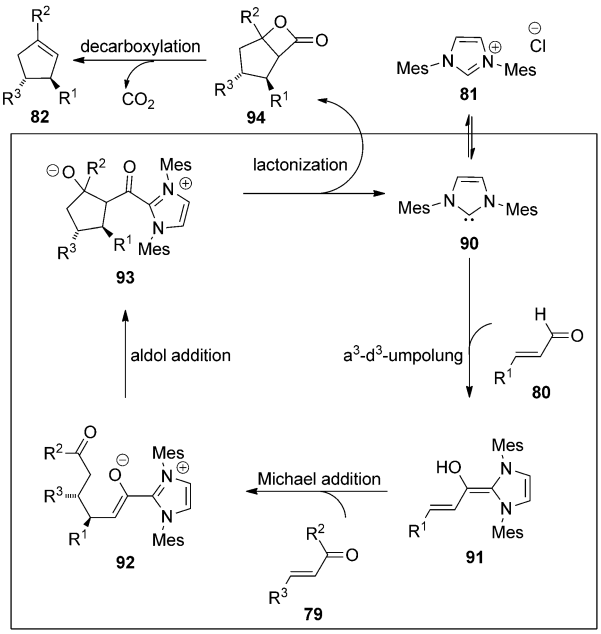
According to the definition made in the previous Section, conjugate umpolung in combination with an additional C–C

bond forming reaction should be considered as a domino process. Over the past decade there were a lot of publications dealing with the conjugate umpolung fulfilling this requirement.[17] Therefore we will limit the discussion of this topic to domino reactions with two or more C–C bonds formed. One of the first examples of such domino processes was reported by Nair et al. in 2006 (Scheme 13 A).[49] This group observed that cinnamic aldehydes **80** can react with chalcones **79** in the presence of the carbene catalyst derived from the imidazolium salt **81**. The bulky substituents on the nitrogen atoms of the catalyst suppressed benzoin and Stetter side reactions, while the conjugate umpolung occurred forming cyclopentenes **82** in moderate to good yields (55–88 %) for a broad range of aromatic substrates. The moieties R^1 and R^3 were *trans* configured with only one diastereomer observed.

This unexpected reaction was described by the mechanism shown in Scheme 14. After the a^3–d^3 umpolung of the enal **80**



Scheme 13. A) Synthesis of cyclopentenes **82** by a^3–d^3 umpolung/Michael/aldol/lactonization/decarboxylation sequence; B) asymmetric synthesis of **84**; C) spiro-annulation to form **86** through an a^3–d^3 umpolung/Claisen sequence; D) synthesis of **89** through an a^3–d^3 umpolung/Michael/Michael/lactonization.



Scheme 14. Mechanism of the domino a^3–d^3 umpolung/Michael/aldol/lactonization/decarboxylation sequence.

by the catalyst **90** the Breslow intermediate **91** attacks *trans*-selectively the chalcone **79**. Then the adduct **92** undergoes an intramolecular aldol reaction to the activated carboxyl surrogate **93**, which lactonizes to the bicyclic β-lactone **94**. The ring strain in **94** is most likely responsible for the final decarboxylation leading to the observed cyclopentene **82**. Therefore this domino process consists of an a^3–d^3 umpolung/Michael/aldol/lactonization/decarboxylation sequence. Bode's group developed the enantioselective version of this reaction using a tetracyclic NHC catalyst derived from **88**, which was limited to 4-oxo-2-butenoates (**79**: $R^3 = CO_2Me$) as substrates.[50] Although the enantioselectivity was excellent (96–99 %) the diastereoselectivity was rather moderate for some examples (4:1–20:1) favoring the *cis* product and the diastereomers were difficult to separate by chromatography. Later, Scheidt and co-workers improved this methodology further (Scheme 13 B).[46a] Best results with yields similar to those obtained by Nair et al. were achieved utilizing a catalyst derived from **83** for a broad range of aromatic substrates without the substrate limitations reported by Bode's group. The enantiomeric excesses were excellent (98–99 %) for the major diastereomer of all examples shown. Interestingly, the diastereoselectivity could be successfully optimized to a level, where none of the minor *trans* diastereomer was observed anymore. This was possible by adding a chelating titanium catalyst. This is an impressive example of cooperative catalysis utilizing a N-heterocyclic carbene simultaneously with a Lewis acid.

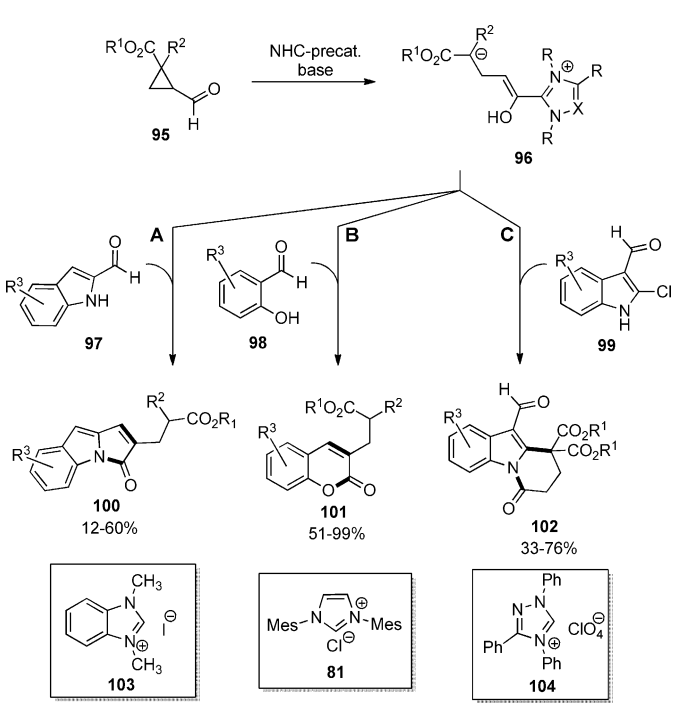
The mechanism shown in Scheme 14 is not necessarily followed if the chalcone derivative **79** has an additional Michael acceptor. Nair et al. could demonstrate that the steps of the domino sequence after the a^3–d^3 umpolung/Michael addition could be suppressed by an intramolecular Claisen-type reaction between the keto-group and the activated

carboxyl surrogate **92**.[51] Hence instead of the cyclopentenes **82** the spiro-annulated compounds **86** were built, although the same catalyst and reaction conditions were used (Scheme 13C). While the reaction proceeded with moderate to good yields (53–73%) the formation of a quaternary stereogenic center with complete stereocontrol is noteworthy.

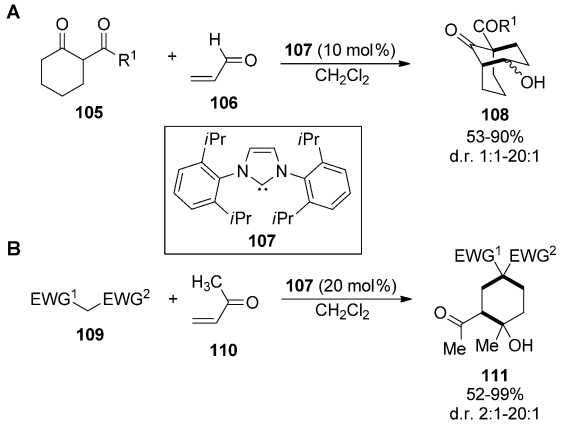
Very recently Chi et al. have shown the application of the benzodienones **87** in an a^3–d^3 Umpolung/Michael/Michael/esterification domino sequence (Scheme 13D).[52] These compounds reacted well with cinnamic aldehydes **80** in the presence of the aminoindanol-derived catalyst precursor **88** yielding **89** in moderate to good yields (53–84%) with a broad scope of differently substituted aromatic substrates. Furthermore, good diastereoselectivities (10:1–20:1) and excellent enantioselectivities (up to 99%) were achieved. For unsymmetrical benzodienones **87** the regioselectivity was excellent as long as the substituents had different electronic properties but dropped to 2:1 for similar ones. Nevertheless, the formation of four contiguous stereogenic centers demonstrates the usefulness of this synthetic method.

Whereas the conjugate umpolung generates a nucleophile in β-position to the carbonyl group, a nucleophile can be generated in the γ-, δ-, and ε-positions by ring opening of cyclopropanes,[53d] oxiranes,[53a,20a] aziridins,[53a] azetidines,[53b,c] and azolidines.[53e] Wang and co-workers reported that nucleophiles generated by ring opening of formyl cyclopropane **95** can undergo an aldol condensation with indol-2-carbaldehyde **97** (Scheme 15A)[54] or salicylaldehyde **98** (Scheme 15B).[55] The catalytic cycle was closed by the intramolecular redox amidation or redox esterification. The annulated products **100** were produced in moderate yields (12–60%) while **101** was formed in good to excellent yields (up to 99%). Although sub-stoichiometric amounts of the imidazolium salts **103** and **81** are necessary for this reaction, the formation of the pharmaceutically relevant pyrrolo-[1,2-*a*]-indoles **100** and coumarins **101** makes these methods worth mentioning. Wang and co-workers also achieved the reaction of **95** with 2-chloro indole-3-carbaldehydes **99** (Scheme 15C).[56] Instead of undergoing an aldol reaction, the intermediate **96** generated by the ring opening of **95** attacked the chloro-substituent in a nucleophilic aromatic substitution. After intramolecular redox amidation hydropyrido-[1,2-*a*]-indoles **102** were produced in moderate yields (33–76%) utilizing a carbene catalyst derived from triazolium salt **104**. Hence, the skeleton of biologically important indole alkaloids can be accessed by a ring-opening/nucleophilic aromatic substitution/redox amidation domino sequence.

The last domino reactions we want to highlight are those where the carbene acts solely as a base. Rodriguez et al. have serendipitously demonstrated that carbene **107** can catalyze the Michael addition of 1,3-dicarbonyl compounds to α-β-unsaturated nitriles.[57] Later they used this methodology in the Michael/aldol (Scheme 16A) and Michael/Michael/aldol domino reactions (Scheme 16B).[58] Good to excellent yields (52–99%) were achieved in both processes although the diastereoselectivity varied strongly (1:1–20:1) depending on the substitution pattern. Testing a range of bases, which were all unsuitable to catalyze this reaction, they suggest that besides carbene basicity, some Lewis acid properties of the conjugate imidazolium salt could be responsible for the unexpectedly good reactivity.



Scheme 15. Sequences: A) ring-opening/aldol condensation/redox amidation, B) ring-opening/aldol condensation/redox esterification, C) ring-opening/nucleophilic aromatic substitution/redox amidation; bonds formed by the domino sequences are marked bold.



Scheme 16. Sequences: A) Michael/aldol, B) Michael/Michael/aldol; bonds formed by the domino sequences are marked bold.

4. Conclusions

Herein we have tried to demonstrate that N-heterocyclic carbene catalyzed domino reactions have developed into a fast-growing subfield in asymmetric catalysis. Although terms such as domino, cascade, and tandem reaction are often used in the literature, their proper application for NHC-catalyzed reactions is somewhat difficult. A set of NHC-catalyzed transformations was used herein to differentiate between a

single reaction and a domino process. While highlighting recent publications, classifications of "organocascades" proposed by Tietze and Fogg were applied. For clarity's sake one-pot processes with only one C–C bond forming step are not part of this article.

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