One-Pot Reactions

DOI: 10.1002/anie.201102522

A Simple Recipe for Sophisticated Cocktails: Organocatalytic One-Pot Reactions—Concept, Nomenclature, and Future Perspectives

*Łukasz Albrecht, Hao Jiang, and Karl Anker Jørgensen**

asymmetric synthesis · classification · nomenclature · one-pot reactions · organocatalysis

Asymmetric organocatalysis has been successfully incorporated in many multistep one-pot sequences to provide simple access to structurally complex target molecules in a highly stereoselective fashion. The key feature behind this success is the ability of organocatalyzed reactions to proceed efficiently in the presence of large amounts of spectator reagents. Additionally, owing to their organic nature and substoichiometric presence, organocatalysts are also expected to become innocent bystanders in subsequent transformations. In this Minireview, an easy-to-use classification and nomenclatural system that is capable of systematically and informatively describing each one-pot reaction is introduced, and selected important contributions within the field of organocatalytic one-pot reactions are reviewed according to this new system. Finally, future developments and perspectives in the field are discussed.

1. Introduction

Purification processes are probably the most time- and cost-demanding and waste-producing manual operations in modern organic syntheses. However, to avoid various compatibility issues and thus ensure that consecutive reactions proceed smoothly, intermediate purification steps often seem obligatory in synthetic routes (Figure 1, top). As a rival to this traditional "stop-and-go"[1] approach to synthesis with its obvious drawbacks stands the "one-pot" strategy,[2] in which multiple chemical transformations are performed sequentially in a single reaction vessel without intermediary purification steps (Figure 1, bottom). In industrial processes, the one-pot approach has long been adapted as an effective means of reducing time, costs, and waste generation, whereas in small-scale laboratory synthesis the "stop-and-go" tactic still seems to prevail. Especially in the case of asymmetric synthesis, in which reliability and reproducibility with respect to yield and stereoselectivity are key issues, the underlying uncertainties regarding compatibility and outcome often discourage the use of one-pot approaches. Although the economic benefits resulting from the use of fewer purification steps compensate the time and effort devoted to the optimization and fine-tuning of industrial processes, similar advantages are much less predominant in laboratory synthesis.[3] To make it easier and more attractive to replace traditional purification-dependent step-by-step synthesis with much more step- and atom-economical one-pot strategies even on a small scale, two crucial bottlenecks, namely, the issues of compatibility and reliability, must be circumvented.

As one of the major hot topics in organic chemistry throughout the past decade, asymmetric organocatalysis[4] has introduced new perspectives with regard to the design and application of one-pot processes in enantioselective transformations.[5] Marked by its robust nature, organocatalysis is probably the most condition-tolerant method within the modern toolbox of asymmetric catalysis.[6] The fact that organocatalysis is insensitive to air and moisture as well as many metal or organic contaminants is believed to provide a higher degree of compatibility and reliability, hence setting the necessary foundation for successful and facile enantioselective one-pot syntheses. A basic keyword search in SciFinder reveals a clear picture of the historical development of one-pot reactions.[7] The number of scientific reports contain-

[*] Dr. Ł. Albrecht, H. Jiang, Prof. Dr. K. A. Jørgensen
Center for Catalysis, Department of Chemistry
Aarhus University
Langelandsgade 140, DK-8000 Aarhus C (Denmark)
E-mail: kaj@chem.au.dk

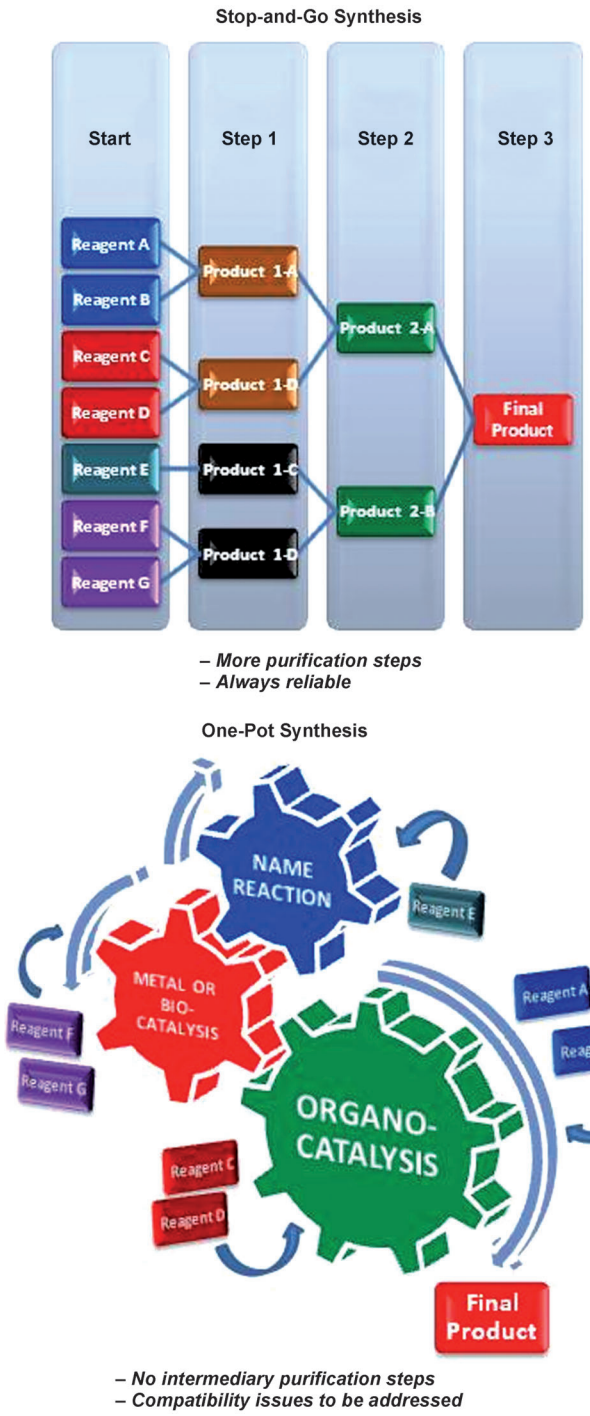
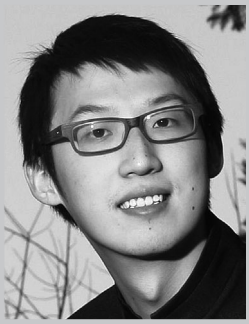


Figure 1. Stop-and-go versus one-pot synthesis.

Łukasz Albrecht, born in Łódź, Poland, received his MSc in chemistry in 2004 from the Technical University of Lodz. In 2008, he spent four months in the research group of Prof. Karl Anker Jørgensen. In 2009, he obtained his PhD from the Technical University of Lodz under the guidance of Professor Henryk Krawczyk. Currently he is a postdoctoral fellow at the Center for Catalysis, Aarhus University, Denmark, where he is investigating new applications of asymmetric organocatalysis under the supervision of Prof. Karl Anker Jørgensen.



Hao Jiang was born in Shanghai, P. R. China in 1984. He studied chemistry at Aarhus University and received his MSc in 2009. He is currently persuing his PhD studies under the supervision of Prof. Karl Anker Jørgensen at the Center for Catalysis, Aarhus University. His research involves the development of new methodologies in asymmetric organocatalysis.

Karl Anker Jørgensen received his PhD from Aarhus University in 1984. He was a postdoctoral student with Prof. Roald Hoffmann, Cornell University in 1985. In the same year, he became an assistant professor at Aarhus University, and in 1992 he was promoted to full professor. His research interests include the development, understanding, and application of asymmetric catalysis.

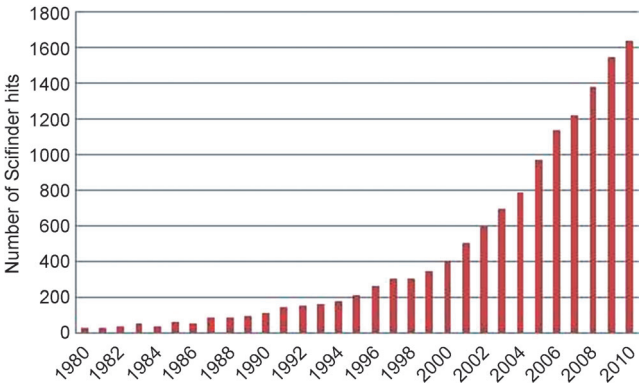


Figure 2. Number of references containing the keyword "one-pot reaction" from 1980 to 2010. (Data were obtained from a keyword search with SciFinder.)

ing the keyword "one-pot reaction" that appeared each year increased significantly during the period 1980–2010 (Figure 2). Prior to 1980, the number of reports on this subject was almost negligible. Although the number of articles containing the concept of a "one-pot reaction" rose steadily from 1980 to the turn of the millennium, it was during the last decade (2000–2010) that the one-pot reaction truly gained its current popularity. Significantly, the articles published in 2010 alone outnumbered the sum of reports published prior to 2000. The renaissance experienced around the year 2000 by organocatalysis, which quickly became a gold mine for organic chemists in the following years, does not necessarily provide a direct link to the escalation of one-pot reactions in the same

period; however, judging from the enormous popularity of organocatalytic one-pot reactions today, a symbiotic interaction between the two hot topics might have occurred.

The compatibility of organocatalysis with various catalytic systems based on bio-, metal, and photoredox catalysts, as well as many name reactions, has enabled facile access to complex and structurally diverse chiral compounds with minimal manual effort.[8] Field-specific readers are referred to several excellent and highly detailed reviews on related topics (e.g. the merging of organo- and metal catalysis).[9] A full overview of the enormous and rapidly expanding topic of organocatalytic one-pot reactions is outside the scope of this Minireview; instead, key success criteria and future perspectives are discussed. Moreover, a new method for the systematic classification and naming of one-pot reactions is introduced.

2. Classification and Nomenclature of One-Pot Reactions: Type, Order, Fingerprint

Traditionally, asymmetric organocatalytic one-pot reactions have been differentiated by their respective mode of activation (e.g. aminocatalysis) and reactivity (e.g. the first reaction step proceeds via enamine or iminium-ion intermediates). Although this approach is highly logical, it occasionally suffers from the drawback that the actual classification of each reaction is made subjectively by the individual author. In most cases, there is universal agreement; however, when dealing with certain special reaction sequences, a "gray zone" may appear. Another disadvantage (which sometimes may be an advantage) may be that the division by reactivity is too specific, and a new subgroup must be introduced each time a new activation mode or reactivity pathway is invented. These concerns led us to attempt to produce a simple yet informative complementary instrument which would enable the systematic classification and description of each specific one-pot reaction on the basis of a set of universal rules. The proposed system relies on three parameters: type, order, and fingerprint (Figure 3). The reason for this division is discussed in the following.

One-pot reactions have the ultimate goal of reducing time demands and waste production, and they have a clear link to industrial processes, for which economic and ecological profitability are the main issues of concern.[3c] Therefore, we propose that instead of focusing on the activation mode, a classification based on "manual operations" (number and position) may be more suitable. The total number of manual operations in a one-pot sequence is easily counted and may provide an indication of the complexity of the overall reaction and the required manual effort. With respect to asymmetric organocatalytic one-pot reactions, which are the main focus of this Minireview, different design plans could be selected depending on the nature of the final target and the availability of the starting materials. On the other hand, because of differences in reaction design, distinct success criteria apply for each specific type of one-pot sequence. A good differentiator for the various "types" of one-pot reaction is the position of the enantiodifferentiating operation in the entire reaction sequence. This operation could occur at the start, at the end, or in the middle of the whole sequence. By combining the "type" (position of enantiodifferentiation) and "order" (total number of manual operations) of the reaction, every organocatalytic one-pot sequence may be categorized in a simple and clear way. The two suggested indicators (type and order) also carry important information regarding the design, purpose, complexity, and success criteria of the overall transformation, and are therefore highly informative.

Besides the two proposed levels of classification (1°: position of the enantiodifferentiating manual operation; 2°: total number of manual operations), it may be desirable to provide each specific reaction sequence with a "fingerprint" parameter (comparable to the nature of a molecular formula of a given structure). However, there are two main criteria that such a "fingerprint" should fulfill. First, it should be informative and capable of summarizing the overall transformation of the reaction sequence. Second, it should be universally applicable to every reaction and as simple as possible to use so as to ensure wide applicability. Among possible fingerprint parameters, we chose to use "bond formation" as the final indicator (*m*C*n*X, in which *m* is the number of C–C bonds formed, and *n* is the number of C–X bonds formed). Finally, by merging the two classification terms (position of the enantiodifferentiating manual operation; total number of manual operations) and the fingerprint, we could establish a general nomenclature that classifies and describes asymmetric one-pot reaction cascades. The three parameters and their purpose are summarized in Figure 3. In this section, each of the parameters is described in detail. We discuss the purpose and success criteria of each "type" of reaction, define a manual operation, and establish a universal set of rules for counting bonds formed.

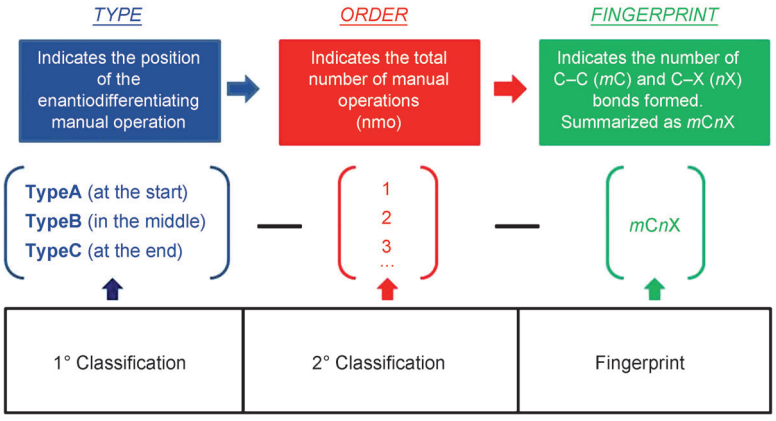


Figure 3. General nomenclature for one-pot reaction cascades.

2.1. Type (1° Classification): Position of the Enantiodifferentiating Manual Operation

Organocatalytic one-pot synthetic strategies may serve many different purposes and have distinct success criteria. With the aim of achieving the highest degree of simplicity and rationality, we proposed to differentiate the different types one-pot reactions by the relative position of the enantiodifferentiating manual operation, which could be at the start (TypeA), in the middle (TypeB), or at the end (TypeC) of the whole sequence. The chemical purposes of the different reaction types are distinct, and as a result of the differences in reaction setup and positioning of the sensitive asymmetric catalytic step, the success criteria of TypeA/B/C reactions are also different. An overview of the chemical purpose and the success criteria of the three types of organocatalytic one-pot approaches is outlined in Table 1.

TypeA reactions (with asymmetric catalysis as the first manual operation) serve the chemical purpose of the rapid assembly of structurally diverse chiral frameworks, which upon in situ modification may lead to highly complex target molecules that are often difficult to obtain by conventional methods. Catalyst deactivation is not an issue of concern owing to the early-stage catalysis step; instead, racemization and decomposition of the assembled chiral framework must be avoided. In contrast, TypeC reactions (with asymmetric catalysis at the end of the sequence) are valuable when complex and difficult-to-handle starting materials are involved. The common issues of concern, such as substrate lability and volatility or purification problems, are elegantly avoided by employing a one-pot strategy. However, as a consequence of the late-stage asymmetric catalytic reaction, relatively large amounts of contaminants and leftover chemicals coexist in the reaction mixture. These compounds could potentially inhibit the catalyst or erode stereoselectivity. Thus, the key success criterion in TypeC sequences is the use of a noninterfering catalytic system that is not sensitive to the reaction conditions. TypeB reactions combine the advantages of both TypeA and TypeC reactions and thereby provide a shortcut to the target molecules with minimal manual effort and waste generation. However, the success criteria of TypeB reactions will also be the sum of all previously mentioned issues, which makes reaction design a highly tedious process.

2.2. Order (2° Classification): Total Number of Manual Operations

A second degree of classification may be provided by the total number of manual operations in the reaction sequence (nmo). This number gives a rough estimation of the complexity of the overall reaction and the manual effort required. However, it should not be used as a way of ranking reactions. For the purpose of simplicity, the number of manual operations (nmo) is counted as the sum of operations prior to the final purification step (which is not included in the factor nmo). A manual operation can be defined as any interruption of the cascade by the addition of reagents or the removal of the solvent. If removal of the solvent is followed by the addition of a reagent, and no time interval occurs between those two operations, solvent removal and reagent addition count as one manual operation. The first manual operation, which initiates the overall cascade, contributes to this parameter as one operation. The factor nmo (2° classification) serves as a parameter for the fine division of reactions within each main type (1° classification) of sequence.

2.3. Fingerprint: Bond Formation (mCnX)

To complete the classification system, each overall one-pot transformation is also given a fingerprint parameter in the form of "number of bonds formed". This parameter summarizes the one-pot reaction cascade by relating it to the number of bonds formed in the overall transformation. To make this parameter more informative, we make a distinction between the formation of C–C and C–X bonds. The fingerprint parameter is defined by the expression *m*C*n*X, in which C refers to C–C bonds, and *m* is the number of C–C bonds created in the one-pot reaction cascade. Similarly, X refers to C–X bonds (in which X is any element other than carbon), and *n* is the number of C–X bonds formed in the one-pot reaction cascade. When calculating the number of bonds, the following rules apply: I) The number of bonds formed in the reaction cascade is defined by simple comparison of the starting materials and the final

Table 1: The three main types of one-pot reaction, as distinguished by the relative position of the enantiodifferentiating operation.

Type	Position of enantiodifferentiation	Purpose	Success criteria
TypeA[a]	first manual operation	construction of chiral frameworks, which are transformed into more valuable motifs through in situ modifications	avoid racemization/decomposition of the chiral framework
TypeB	in the middle of the sequence	assembly of labile starting materials, followed by the in situ construction of chiral frameworks; final modifications transform the crude intermediates into the target motifs in one reaction vessel	avoid racemization/decomposition as well as catalyst inhibition
TypeC	last manual operation	in situ assembly of labile starting materials, followed by asymmetric catalysis	avoid catalyst inhibition by the relatively large amounts of leftover chemicals

[a] "TypeA-1" describes a special class of one-pot reactions commonly known as domino/tandem reactions. The success criteria of these reactions often include the necessity to ensure the "sequence specificity" of the reactions in the whole cascade.

product; it does not depend on bond multiplicities. Newly formed single, double, and triple bonds are therefore treated in the same manner and contribute as one bond to the overall number of bonds formed. II) The formation of X–X bonds (in which X is any element other than carbon) is neglected for simplicity. III) For reasons of simplicity, bond-breaking processes or bonds formed in one of the intermediates but destroyed at a later stage are not taken into consideration. IV) In oxidative (or formally oxidative) transformations, in which a double/triple bond is created from an existing single/double bond, the formation of one bond is noted. V) For the corresponding reduction of unsaturated systems (from triple/double bonds to double/single bonds), the simultaneous formation of a C–X or C–C bond in the reduction reaction (e.g. hydride addition, Grignard addition) is counted. Throughout the manuscript, the formed C–C and C–X bonds are colored **red** and **blue**, respectively, to provide a simpler overview for the reader.

2.4. Nomenclature Flowchart and Manual-Operation Toolbox

To ease the usage of the proposed classification and nomenclature system, we have designed a simple step-by-step flowchart. All important information and the necessary tutorial guidance has been included (see Figure 4). Moreover, since many one-pot processes do not include an enantiodifferentiating step, for example, diastereoselective synthesis or the synthesis of racemic or achiral compounds, we have added three additional types, TypeDia, TypeRac, and TypeAch, to the 1° classification to incorporate these sequences in the present system.

In the same way as this flowchart may ease nomenclatural assignment, it is also desirable to be able to graphically visualize the individual steps in a one-pot sequence to obtain a simple and descriptive overview of an otherwise complex reaction cascade. We have chosen to depict each manual operation as a gear wheel; thus, the overall one-pot process can be represented as a chain of connected gears. The most commonly encountered manual operations, categorized according to their chemical purpose, are listed in Table 2. Each individual one-pot reaction may then be readily depicted schematically on the basis of its composition of manual operations. This method of illustration is used throughout this Minireview.

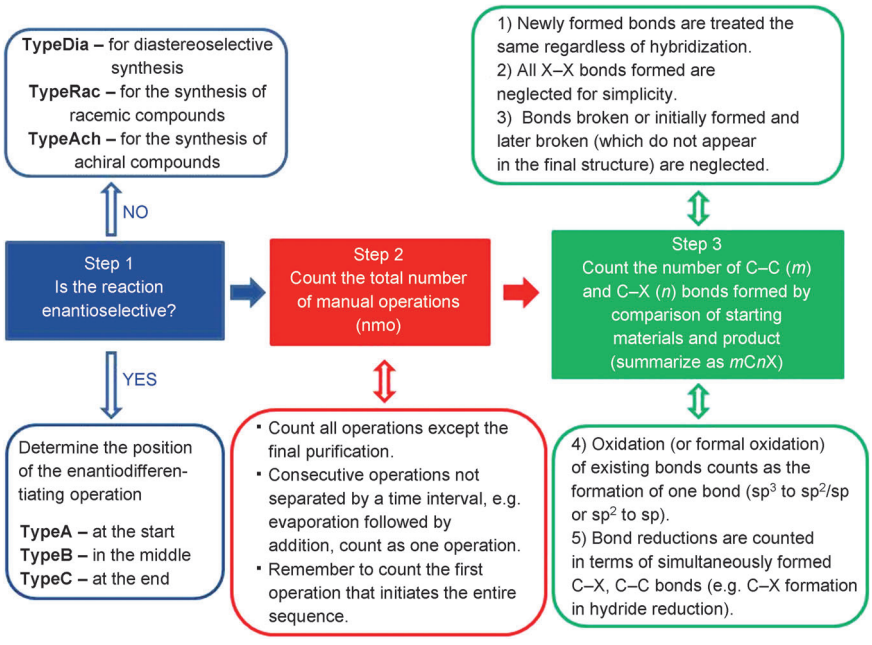


Figure 4. Nomenclature flowchart.

3. Quantification Methods

Besides a classification and nomenclature system, it is also desirable to have measures to quantify the efficiency of the one-pot reaction cascade. The classical yield expression is not very informative or accurate in these instances, since it does not reflect the fact that several bonds are formed and a number of manual operations are performed in a given one-pot reaction cascade. Furthermore, such operations benefit from the omission of all intermediary purification or isolation procedures when the reaction sequence is performed in a one-pot fashion. Therefore, we propose the use of expressions such as yield per bond formed (Y_{PBF}), yield per manual operation (Y_{PMO}), and purification factor (P_f) to improve the overview of the one-pot cascade performed.[10]

3.1. Yield per Bond Formed (Y_{PBF})

The expression Y_{PBF} defines the efficiency of the one-pot reaction by relating its yield to the number of bonds formed (b) in the overall cascade. The b factor is determined by simple comparison of the starting materials and the products. Similarly to the fingerprint parameter used in the nomenclature introduced, only bonds formed that are present in the final product are taken into consideration. However, in this case C–C and C–X bonds are treated the same. Each multiple bond formed contributes as one bond to the b factor. The expression Y_{PBF} is defined by Equation (1):

$$Y_{PBF} = \sqrt[b]{\frac{Y}{100\%}} \times 100\% \qquad (1)$$

in which Y_{PBF} is the yield per bond formed [%], Y is classical yield of the one-pot reaction cascade, and b is the number of bonds formed in the one-pot reaction cascade ($b = m + n$; see Figure 3 and Section 2.3).

Table 2: Manual-operation toolbox.

Manual operation	Abbreviation	Illustration	Details
asymmetric organocatalysis	AOC		describes all asymmetric organocatalytic transformations
addition reaction	ADN		describes various addition reactions, e.g. 1,2- and 1,4-additions
elimination reaction	ELN		describes E1, E2, and E1cb reactions
substitution reaction	SBN		describes all nucleophilic and electrophilic substitution reactions
rearrangement	REA		describes all rearrangement reactions
metal catalysis	MEC		describes all metal-catalyzed reactions
redox reaction	ROX		describes all transformations involving redox manipulations
protection/ deprotection	PDN		describes all protection and deprotection reactions
condensation	CDN		describes all condensation reactions
annulations	ANN		describes all ring-closure reactions
chain elongation	CEN		describes all chain elongations, e.g. Wittig, Corey–Fuchs reactions
inactivation/ neutralization/ isolation	INI		describes all manual operations designed to neutralize or inactivate contaminants or reagents from previous reaction steps or the isolation of the final product by crystallization or precipitation
isomerization	ISM		describes all isomerization reactions
other reactions	OTH		describes all other reactions

3.2. Yield per Manual Operation (Y_{PMO})

In contrast to Y_{PBF}, Y_{PMO} relates the yield of the one-pot cascade to the simple manual operation. In this respect, Y_{PMO} is more similar to classical yield and indicates the average yield of each single manual operation performed in the one-pot reaction cascade (for the definition of a single manual operation, see Section 2.2). The expression Y_{PMO} is an average intended as an alternative way of quantifying the overall process. Therefore, it does not have a "physical meaning" as in the case of the traditional reaction yield. Clearly, manual operations, such as the addition of a reagent, cannot have a yield. Instead, they initiate chemical reactions, which result in a product with a particular yield. However, it is often simpler to count the number of manual operations than to count the number of distinct reaction steps, and given the correlation between the manual operations and the reactions, the term Y_{PMO} should serve as a good indicator of the efficiency of the overall process. The value of Y_{PMO} can be calculated from Equation (2):

$$Y_{PMO} = \sqrt[nmo]{\frac{Y}{100\%}} \times 100\% \qquad (2)$$

in which Y_{PMO} is the yield per manual operation [%], Y is the classical yield of the one-pot reaction cascade, and nmo is the number of manual operations performed in the one-pot reaction cascade.

3.3. Purification Factor (P_f)

The parameter P_f indicates how many isolation or purification protocols are omitted when a given reaction sequence is carried out in a one-pot fashion with respect to a classical stop-and-go sequence (assuming that isolation or purification is necessary after each step in the classical sequence). This parameter thus underlines the practical aspects of the developed methodology. It is defined by Equation (3):

$$P_f = \text{nmo} - 1 - n(\text{INI}) + x \qquad (3)$$

in which P_f is the purification factor, nmo is the number of manual operations performed in the one-pot reaction cascade, and n(INI) is the number of inactivation/neutralization/isolation (INI) operations. These operations only serve the purpose of purification and should therefore not account for any contribution to the factor P_f. For sequences that do not require a final purification, $x = 1$; for sequences that require a final purification, $x = 0$. Except for filtration or evaporation, all isolation/purification procedures, such as flash chromatography, distillation, extraction, and combinations of these processes, count as the final purification step.

To illustrate the use of Equation (3), we can consider a one-pot reaction including four manual operations, the last step of which is an INI operation to precipitate the product from solution. Since no final purification (see above definition) is needed (the products just need to be filtered from the liquid), $x = 1$. Therefore, $P_f = 4 - 1 - 1 + 1 = 3$.

In Sections 4–6 important and representative examples of recently developed organocatalytic one-pot reaction cascades are discussed. These cascades are classified according to the proposed nomenclature. The efficiency and practicality of the cascades included are evaluated on the basis of the expressions Y_{PBF}, Y_{PMO}, and P_f. When possible, we compare the developed one-pot cascades with classical "stop-and-go" approaches.

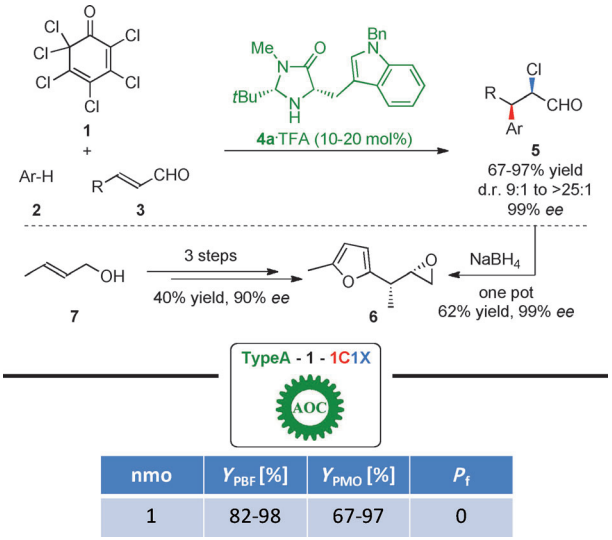
4. TypeA One-Pot Sequences

4.1. TypeA-1 Reactions

Organocatalytic cascades consisting of more than one bond-forming process and involving only one manual operation may be categorized as a "TypeA-1" reactions, in which "TypeA" indicates the position of the enantiodifferentiating manual operation (first manual operation), and the number "1" refers to the total number of manual operations. These reactions, also named domino or tandem reactions,[11] are highly special one-pot reactions, since no additional manual operation (prior to final purification) is required. In "TypeA-1" reactions, compatibility-related problems also prevail owing to the relatively large amounts of reagents present in the mixture from the start. Moreover, it is crucial that the respective steps in the cascade reaction are sequence-specific to minimize the amount of by-products formed. Nevertheless, if successful, domino reactions are effective tools for the rapid synthesis of enantiomerically enriched compound libraries with rich possibilities in terms of structural variation. Multicomponent reactions constitute a specific subgroup of domino reactions in which three or more reagents react in a domino fashion to form a single product.[11c–e] Therefore, catalytic enantioselective versions of such reactions should also be classified as "TypeA-1" sequences. A classification system of well-known multicomponent reactions has been developed previously (e.g. U-4CR for four-component Ugi reactions), and such systems may appear more relevant to some practitioners in certain cases. However, these systems do not take into account the influence of a chiral catalyst. Neither would such systems be universally applicable to any given reaction (beyond the well-established "name reactions"). A different perspective is therefore provided within the current nomenclature, which may complement the existing classification of multicomponent reactions.

In a seminal report in 2005, MacMillan and co-workers described an elegant tandem consecutive α and β functionalization of enals **3** in the presence of the imidazolidinone-based catalyst **4a** (Scheme 1).[12] The conjugate addition of electron-rich aromatic compounds to enals **3** is facilitated by the intermediacy of an iminium-ion species formed by the condensation of aminocatalyst **4a** with **3**. The resulting enamine intermediate acts in the following step as a carbanion equivalent and reacts with the electrophilic chlorination reagent **1**. Subsequent hydrolysis separated the catalyst from the product **5**, which was obtained in 67–97% yield with d.r. 9:1 to >25:1 and 99% *ee*. In the overall reaction, one C–C bond and one C–X bond are formed. Therefore, according to the nomenclature system proposed in Figure 3, it may be categorized as a TypeA-1-1C1X reaction. Moreover, to roughly quantify the efficiency of the reaction sequence, the yield per bond formed (Y_{PBF}) and yield per number of manual operations (Y_{PMO}) were 82–98 and 67–97%, respectively.

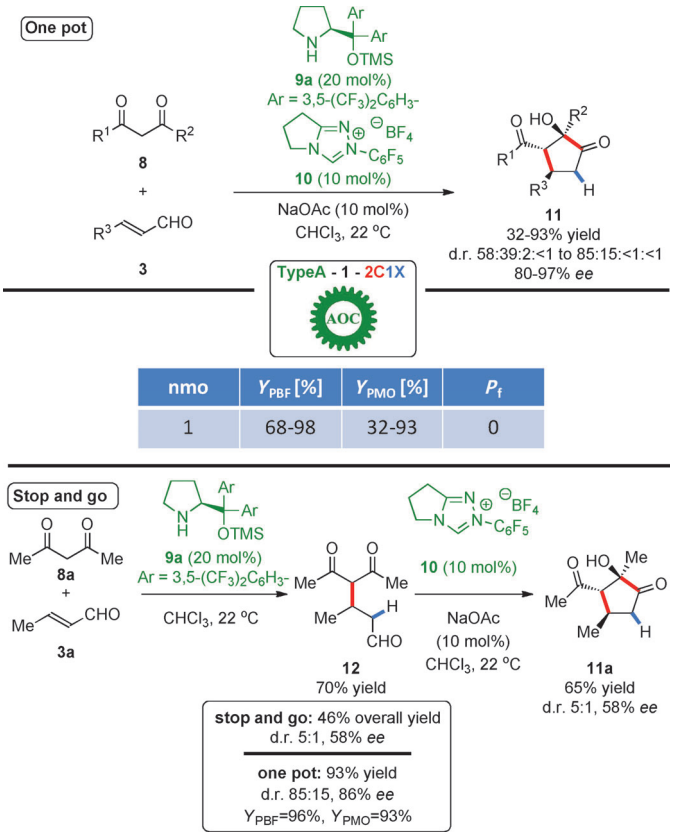
A very interesting TypeA-1-2C1X sequence was developed by Lathrop and Rovis in 2009. In this multicatalytic cascade, cyclopentanones **11** containing three stereogenic centers, including a quaternary stereogenic center, can be accessed efficiently by merging aminocatalysis with catalysis



nmo	Y_{PBF} [%]	Y_{PMO} [%]	P_f
1	82-98	67-97	0

Scheme 1. Organocatalytic domino α,β functionalization of enals. Bn = benzyl, TFA = trifluoroacetic acid.

by N-heterocyclic carbenes (NHCs; Scheme 2).[13] The authors show that the symbiotic cooperation between the amine and NHC catalysts **9a** and **10** is responsible for the excellent enantioselectivity observed for the overall process leading to the cyclopentanone framework. The cascade consists of the iminium-ion-mediated Michael addition of 1,3-dicarbonyl

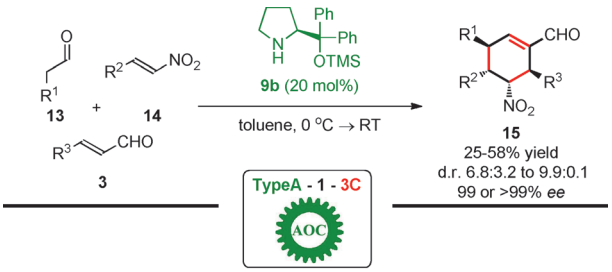


nmo	Y_{PBF} [%]	Y_{PMO} [%]	P_f
1	68-98	32-93	0

Scheme 2. Multicatalytic approach to cyclopentanones. TMS = trimethylsilyl.

compounds **8** to α,β-unsaturated aldehydes **3**, followed by an NHC-catalyzed intramolecular benzoin condensation. The one-pot cascade outperformed the classical "stop-and-go" approach. Cyclopentanone **11a** was obtained in significantly lower yield (46 versus 93%) when synthesized through separate sequential reactions. Furthermore, the *ee* value of **11a** synthesized in a one-pot reaction was superior to that observed for the corresponding sequential approach (86 versus 58% *ee*). These results show that a symbiotic cooperation of the two catalysts **9a** and **10** is crucial for the success of the overall process, whereby the presence of the NHC catalyst **10** enables instant consumption of the initially formed enantiomerically enriched Michael adduct **12**.

In 2006, Enders et al. reported an elegant multicomponent TypeA-1-3C reaction cascade for the formation of pentasubstituted cyclohexenes **15** containing four consecutive stereogenic centers (Scheme 3).[14] This domino reaction proceeds through a sequence consisting of three catalytic steps: enamine-mediated Michael addition/iminium-ion-mediated Michael addition/enamine-mediated aldol condensation. The involvement of the TMS-protected prolinol catalyst **9b** in each step of the cascade ensures particularly high enantioselectivities. However, the yields of this domino one-pot reaction cascade are not spectacular at first glance (the yields given are the yields of the isolated main diastereoisomer). A much more precise evaluation of this one-pot cascade can be made when the complexity of the cascade is taken into consideration with respect to the number of bonds formed throughout the cascade. Thus, the expression Y_{PBF} is very useful in this case. Three new C–C bonds are formed in this domino cascade; therefore, the Y_{PBF} parameter for the reaction sequence is high (Y_{PBF} = 63–83%), which indicates that the efficiency of the one-pot process is much higher than it seems to be when only the classical yield is considered.



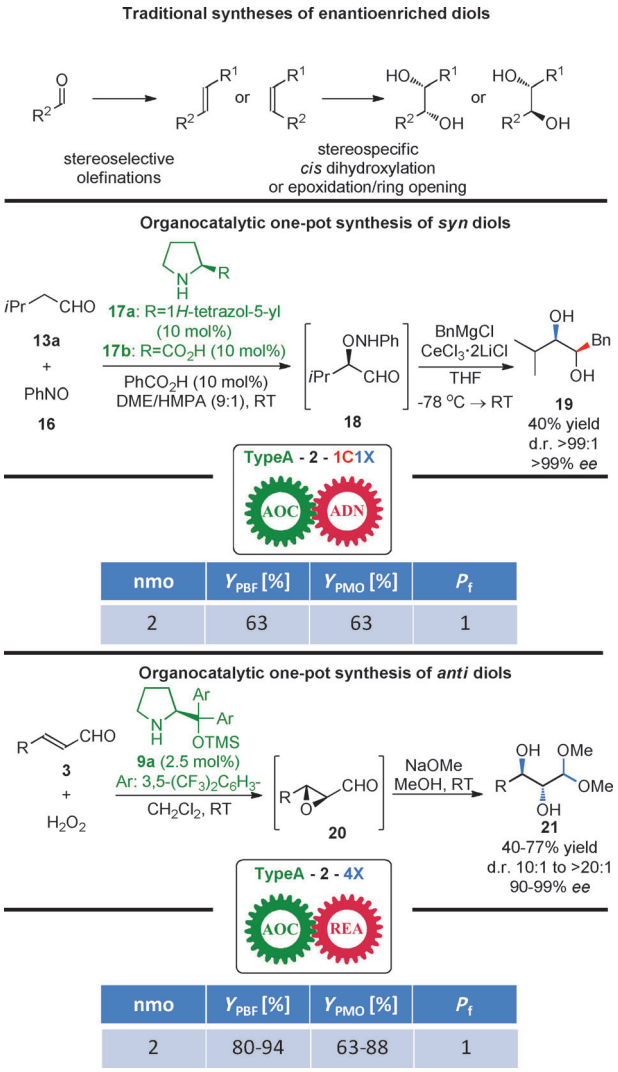
nmo	Y_{PBF} [%]	Y_{PMO} [%]	P_f
1	63-83	25-58	0

Scheme 3. Multicomponent domino synthesis of cyclohexenes.

4.2. TypeA-2 Reactions

Despite their elegance, domino reactions that can be classified as "TypeA-1" are limited to relatively few well-engineered multicomponent systems with fairly restricted applicability in target-directed organic synthesis. In this respect, the development of higher-order sequences involving additional manual operations seems to be a necessity. The "TypeA-2" sequences described and exemplified in this section form the mainstream of advances in recent years in organocatalytic one-pot reactions: highly enantiomerically enriched molecular frameworks initially assembled by asymmetric organocatalysis (AOC) are coupled to a second manual operation (see Table 2).

For example, TypeA-2 sequences have been used to construct highly valuable organic building blocks, such as enantiomerically enriched vicinal diols. These substrates are traditionally synthesized by *cis*-dihydroxylation[15] or an epoxidation/regioselective-ring-opening sequence[16] from stereochemically pure olefins (Scheme 4). Although these methods involve highly efficient catalytic systems, the toxicity of the metal catalysts applied and the requirement of stereochemically defined olefin starting materials may be issues of concern.



nmo	Y_{PBF} [%]	Y_{PMO} [%]	P_f
2	63	63	1

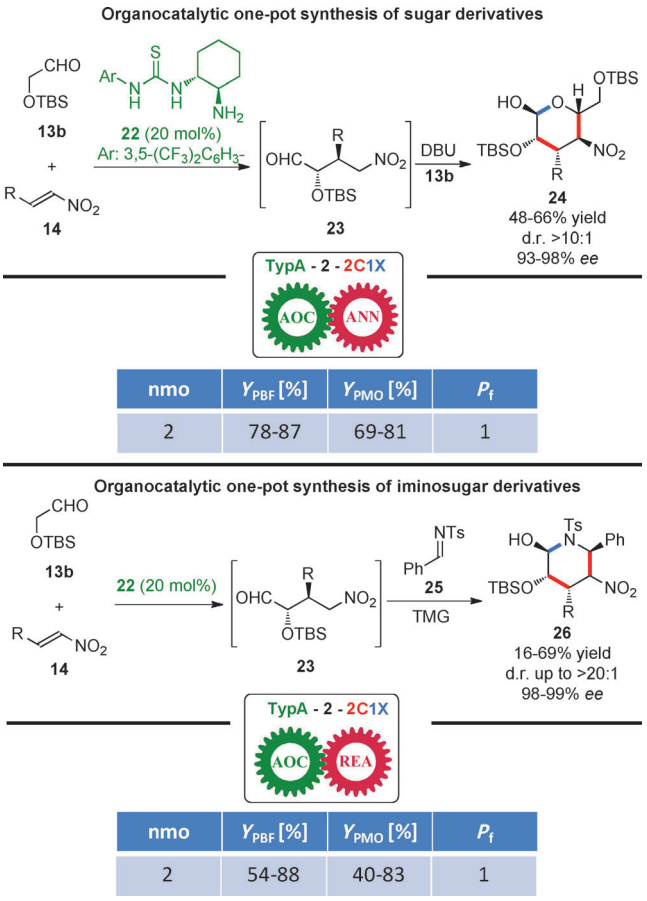
nmo	Y_{PBF} [%]	Y_{PMO} [%]	P_f
2	80-94	63-88	1

Scheme 4. Organocatalytic one-pot synthesis of vicinal diols. DME = dimethoxyethane, HMPA = hexamethylphosphoramide.

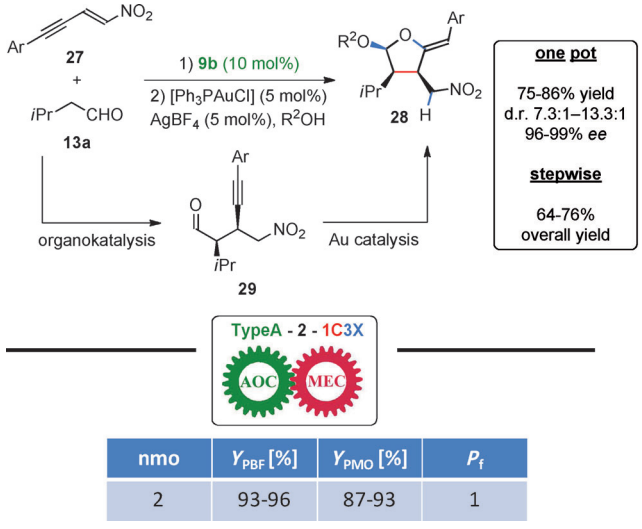
In 2009, Yamamoto et al. reported a facile organocatalytic approach towards *syn* diols **19**[17a] in which they exploited an α-oxyamination reaction of enolizable aldehydes **13** initially developed, independently, by MacMillan and co-workers[17b] and Zhong.[17c] Upon completion of the α-functionalization step with nitrosobenzene (**16**) as the O electrophile and tetrazole **17a** (or proline (**17b**)) as the catalyst, the addition of a Grignard reagent to the reaction vessel afforded the vicinal *syn* diol **19** as the product (Scheme 4). The organometallic reagent not only undergoes the desired 1,2-addition to the aldehyde, but also simultaneously cleaves the labile O–N bond to provide the free alcohol functionality. The formation of one C–C bond and one C–X bond in the reaction sequence results in a TypeA-2-1C1X transformation. The yield per manual operation for this one-pot sequence is 63%, which could be further improved if an additional extraction step was added between the transformations. If instead the *anti*-substituted vicinal diols are the desired products, a different two-manual-operation organocatalytic procedure may be followed.[18] Starting from aliphatic α,β-unsaturated aldehydes **3**, an epoxidation/rearrangement sequence (TypeA-2-4X) enables a formal *trans*-dihydroxylation of the olefin with in situ aldehyde protection. Owing to the volatility of the intermediate 2,3-epoxyaldehydes **20**, a one-pot approach is in this case greatly favored over the stepwise strategy, not only because of the avoided purification step, but also in terms of the yields of the isolated products.

A highly challenging task in asymmetric organic synthesis lies in the development of alternative and de novo syntheses of carbohydrates and derivatives, preferably with the possibility of structural variation and minimal use of protective groups. Recently, Barbas and co-workers reported two closely related TypeA-2-2C1X procedures targeting sugar and iminosugar derivatives (Scheme 5).[19] Both procedures are based on an initial *anti*-selective conjugate addition of the silyl-protected hydroxyacetaldehyde **13b** to nitroalkenes **14** in the presence of a bifunctional amino–thiourea organocatalyst **22**. From the resulting common nitroalkane intermediate **23**, two divergent approaches, a Henry and an aza-Henry reaction, may be applied for the stereoselective formation of 3,4-deoxy sugar **24** and iminosugar **26** derivatives, respectively. Remarkably, the two initial stereogenic centers fully govern the diastereoselectivity of the consecutive Henry/aza-Henry–annulation sequence to enable construction of the five contiguous stereocenters with nearly perfect stereoselectivity.

The merging of organo- and metal catalysis has proven to be one of the most successful strategies for designing new and synthetically useful one-pot reaction cascades.[8a–d,9] This combination has two main advantages: I) the activation modes of metal and organocatalysts are often complementary; II) stoichiometric waste generation is minimized, since both steps are catalytic. In 2009, Krause, Alexakis, and co-workers showed that amino-[4] and gold catalysis,[20] two current hot topics in the field of catalysis, could be combined effectively in a two-step reaction sequence consisting of an initial organocatalyzed *syn*-selective conjugate addition to nitroenynes **27**, followed by a gold-catalyzed acetalization–cyclization of **29** to give highly enantiomerically enriched tetrahydrofuranyl ethers **28** (Scheme 6).[21] When the two



Scheme 5. Organocatalytic one-pot synthesis of sugar and iminosugar derivatives. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBS = *tert*-butyldimethylsilyl, TMG = 1,1,3,3-tetramethylguanidine, Ts = *p*-toluenesulfonyl.



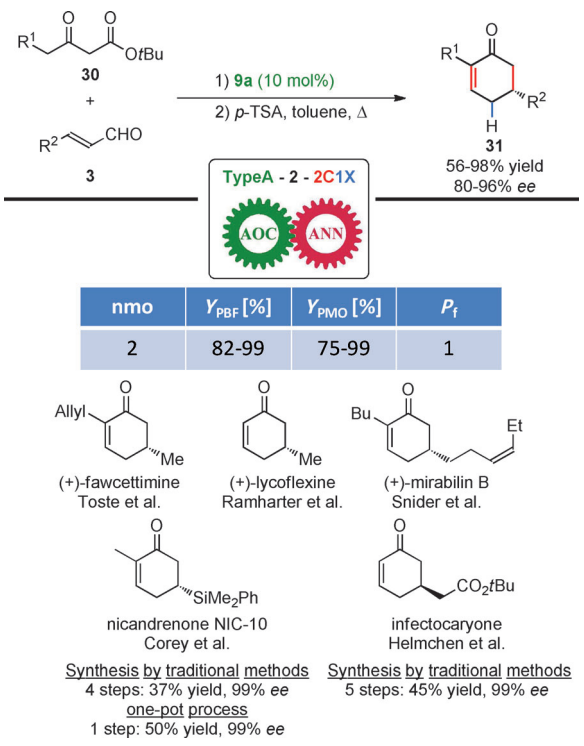
Scheme 6. Reaction sequence combining amino- and gold catalysis.

reactions were performed as separate steps, excellent stereoselectivities were observed, and the yields reached 64–76% for the overall transformation. However, it was later discov-

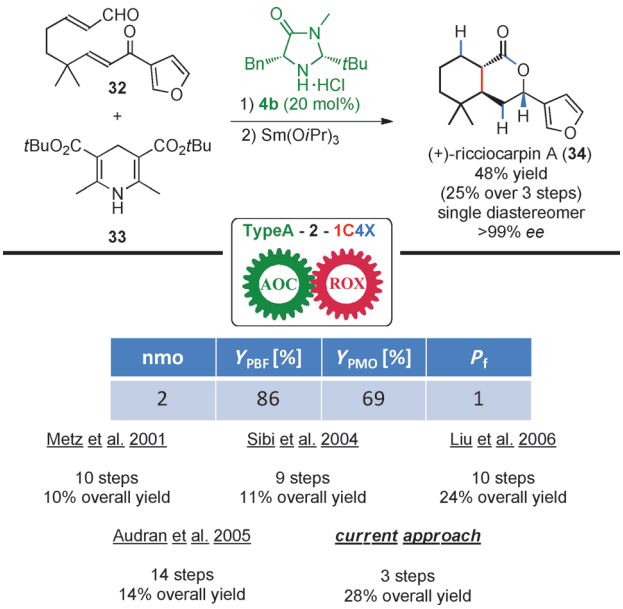
ered that it was not only possible to omit the intermediate purification procedure, but also highly profitable. The yields of purified products were typically more than 10% higher for the one-pot approach (TypeA-2-1C3X) than for the stepwise synthesis. Although stereoselective versions of gold-catalyzed cyclizations have been well explored, the synthesis of the corresponding cyclization precursors is often tedious and complicated. In contrast, this combined organo-/gold-catalyzed approach elegantly circumvents the complex starting-material synthesis through the rapid in situ assembly of the chiral cyclization precursor from readily available substrates by asymmetric aminocatalysis.

The development of new organocatalytic one-pot processes has shortened the synthesis of many valuable chiral building blocks. For example, through a TypeA-2-2C1X sequence involving an aminocatalyzed conjugate addition, decarboxylation, and aldol condensation, highly useful 2,5-disubstituted cyclohexenones **31** can be assembled in a straightforward manner with wide substituent variation from simple enals **3** and β-ketoesters **30** (Scheme 7).[22] This methodology was later implemented as the key enantiodifferentiating step in several total syntheses,[23] for example, of fawcettimine, lycoflexine, and mirabilin B. In comparison with traditional methods, which often require four or five steps from known or commercially available reagents, this procedure effectively shortens the synthetic route to only two manual operations and a single purification step, and hence significantly reduces time demands and waste generation.

As well as for the synthesis of chiral intermediates, organocatalytic one-pot reactions have also been applied as key reaction steps in synthetic routes toward the assembly of complex natural and pharmaceutical products.[5] By introducing new bond-connectivity possibilities through the use of organocatalytic one-pot reactions, otherwise quite lengthy and "purification-heavy" routes may be replaced by much shorter and simpler alternatives. In 2009, Michrowska and List described an elegant synthesis of (+)-ricciocarpin A (**34**) in three steps from commercially available starting materials (Scheme 8).[24] The crucial and final transformation involved a TypeA-2-1C4X sequence consisting of an aminocatalyzed reductive Michael reaction followed by a $Sm(OiPr)_3$-mediated epimerization/Tischenko reaction to form the enantio- and diastereomerically pure product **34** in 48% yield. This reaction sequence is more step- and atom-economical than existing routes, which typically contain more than nine linear purification-demanding steps, as well as being free from the use of protective groups.[25]



Scheme 7. Synthesis of 2,5-disubstituted cyclohexenones. TSA = toluenesulfonic acid.



Scheme 8. Synthesis of ricciocarpin A.

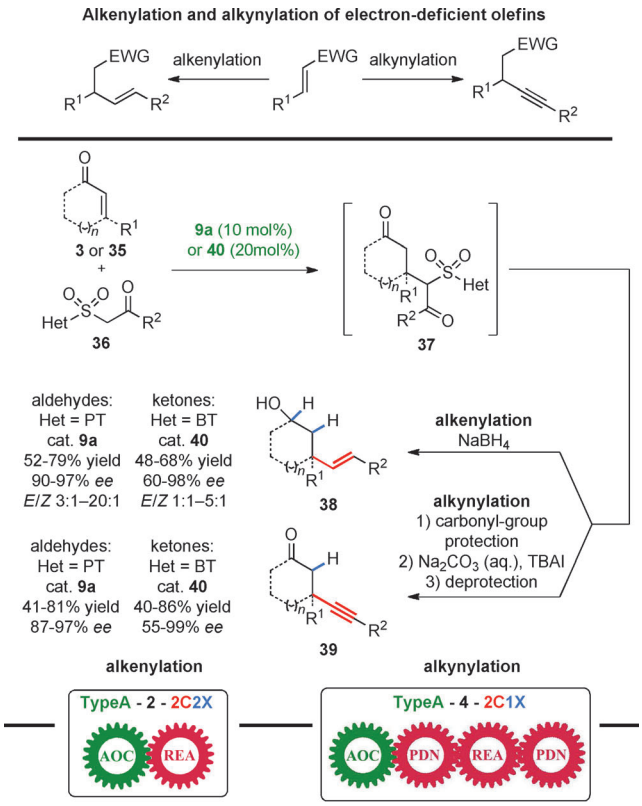
4.3. Higher-Order TypeA Reactions

Several higher-order TypeA sequences were also developed and described in the last few years. Owing to the high complexity of these one-pot protocols and the large amount of reagents that accumulate after each step, the compatibility of the particular processes becomes an important issue. Therefore, the use of additional manual operations to neutralize or inactivate reagents introduced in previous steps is very often inevitable. Moreover, maintaining the enantiomeric purity introduced in the first enantiodifferentiating step throughout a reaction sequence consisting of three or more manual operations is an additional challenge that is very often encountered when dealing with cascades of this type.

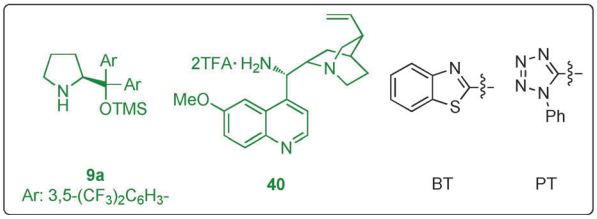
Organocatalytic higher-order TypeA sequences have been successfully applied for the formal alkenylation and alkynylation of electron-deficient olefins. In 2009, two similar procedures for the formal alkenylation and alkynylation of α,β-unsaturated aldehydes **3** and ketones **35** were developed

(Scheme 9).[26] In both reaction sequences, highly enantiomerically enriched Michael adducts **37** were used as common intermediates. These products were generated readily by the organocatalytic Michael addition of β-keto heterocyclic sulfones **36** to α,β-unsaturated aldehydes **3** and ketones **35**. Different aminocatalysts **9a** (for enals) and **40** (for enones) had to be employed to control the stereochemical outcome of the addition reactions. The subsequent treatment of enantiomerically enriched Michael adducts **37** with sodium borohydride initiated a Smiles rearrangement and resulted in the introduction of an alkenyl moiety to give the target molecule **38**. On the other hand, a TypeA-4-2C1X one-pot reaction cascade enabled the formal alkynylation of α,β-unsaturated carbonyl compounds **3** and **35**. In this case, the carbonyl group derived from **3** or **35** was protected as the corresponding acetal or ketal prior to the formation of the enolate, which underwent the desired Smiles rearrangement. Subsequent deprotection of the aldehyde or ketone functionality afforded alkynylated products **39** in good overall yield with excellent enantioselectivity.

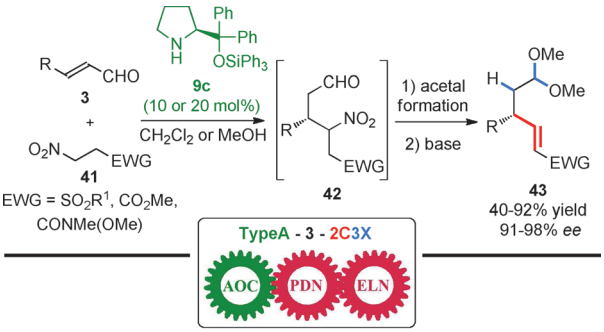
Recently, an alternative strategy for the alkenylation of α,β-unsaturated aldehydes **3** was developed on the basis of an iminium-ion-mediated Michael addition of nitroalkanes **41** containing an electron-withdrawing group in the β position to enals **3** (Scheme 10).[27] The Michael addition was fully



	nmo	Y_{PBF} [%]	Y_{PMO} [%]	P_f
alkenylation - aldehydes	2	85-94	72-89	1
alkynylation - aldehydes	4	74-93	80-95	3
alkenylation - ketones	2	83-91	69-82	1
alkynylation - ketones	4	74-95	80-96	3



Scheme 9. Formal conjugate alkenylation and alkynylation of α,β-unsaturated aldehydes and ketones. EWG = electron-withdrawing group, TBAI = tetrabutylammonium iodide.

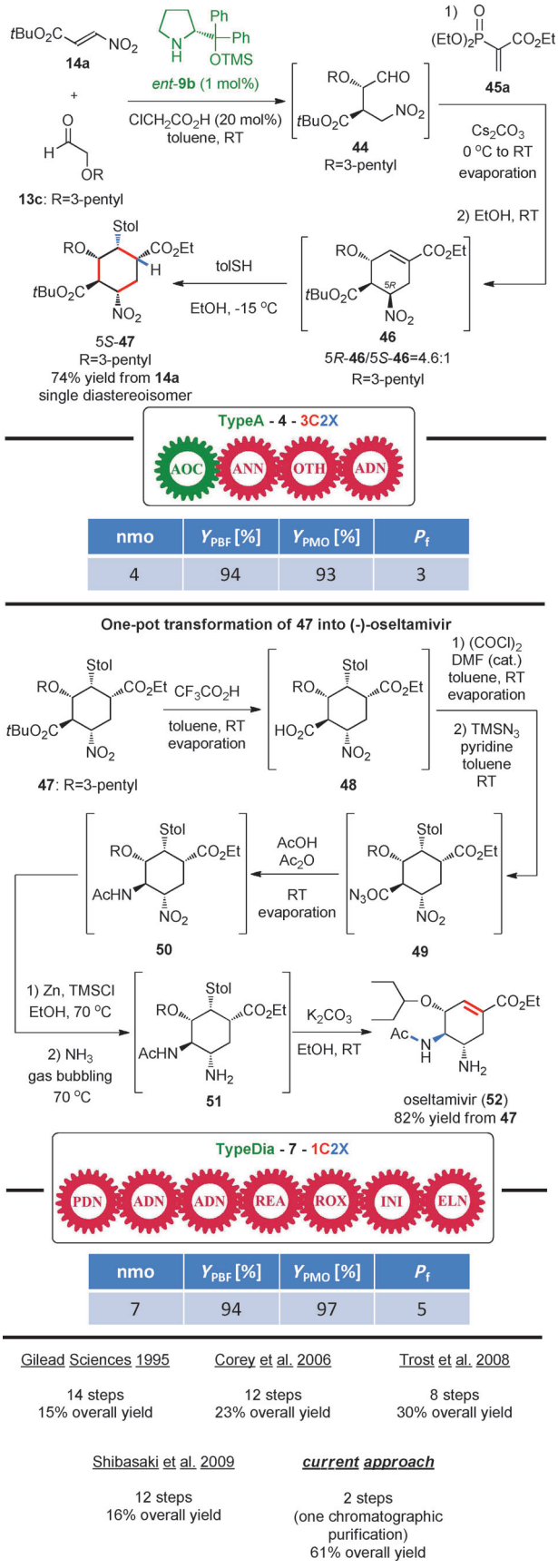


nmo	Y_{PBF} [%]	Y_{PMO} [%]	P_f
3	83-98	74-97	2

Scheme 10. Formal conjugate alkenylation of α,β-unsaturated aldehydes.

chemoselective and occurred at the more acidic methylene position next to the nitro substituent in the donor. Removal of the nitro group was possible under basic, eliminative conditions after protection of the aldehyde functionality as the corresponding dimethyl acetal. Depending on the nature of the substituent at the β position of the starting α,β-unsaturated aldehyde **3**, different bases were employed in the nitrous acid elimination step. For Michael adducts **42** derived from aliphatic enals (R = alkyl) the best results were obtained with DBU as the base. On the other hand, a different base, such as $Mg(OMe)_2$, had to be employed for adducts derived from aromatic enals (R = aryl). In contrast to the TypeA-2-2C2X alkenylation protocol described above, the TypeA-3-2C3X strategy enables the incorporation of electron-deficient double bonds with a stereogenic center in the α position in the product. Furthermore, as a result of the protection of the aldehyde moiety as the corresponding acetal, the oxidation state of the carbonyl carbon atom remains unchanged.

The total synthesis of (−)-oseltamivir phosphate, an antiviral influenza drug (marketed as Tamiflu), has been a subject of thorough investigation.[28] Recently, Hayashi and co-workers reported an elegant and straightforward total synthesis of (−)-oseltamivir (**52**) in two one-pot operations (Scheme 11).[29] The first enantioselective one-pot operation was initiated by the Michael addition of aldehyde **13c** to nitroolefin **14a**. This reaction proceeded in a highly enantioselective fashion, and its stereochemical outcome was controlled by the chirality of the prolinol catalyst *ent*-**9b**.



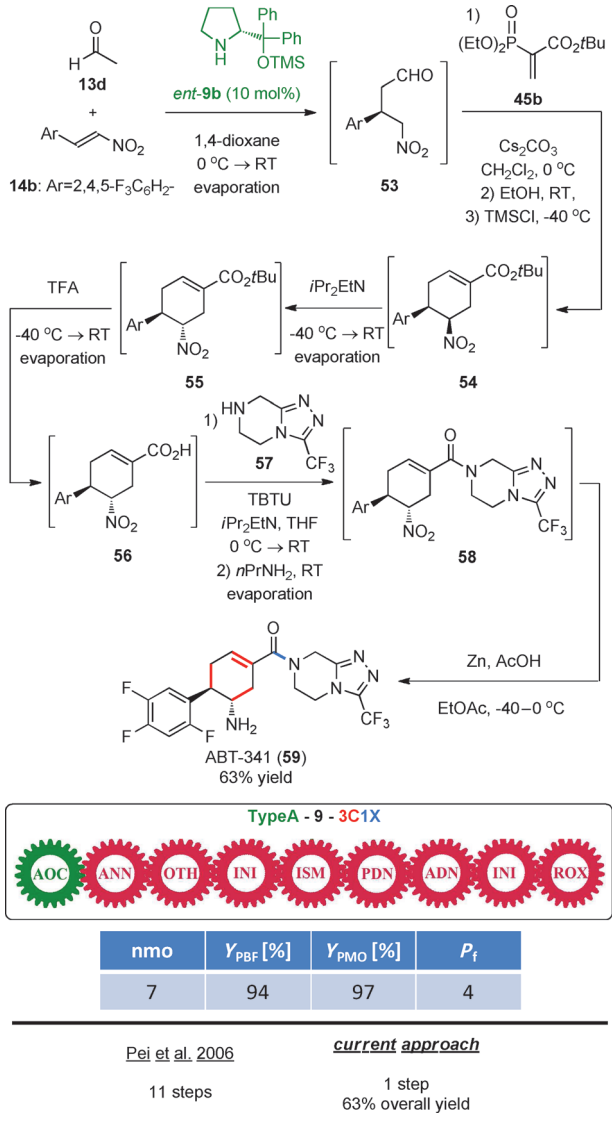
Scheme 11. Total synthesis of (−)-oseltamivir. DMF = *N*,*N*-dimethylformamide, tol = tolyl.

Importantly, only 1 mol % of *ent*-**9b** was required to promote this transformation. Subsequent Michael addition to **45a**, followed by an intramolecular Horner–Wadsworth–Emmons olefination and the Michael addition of a thiol to the Michael acceptor **46**, furnished the key intermediate **47**, which was purified by flash chromatography. An additional manual operation had to be performed within the Horner–Wadsworth–Emmons reaction step. Detailed optimization studies on that reaction revealed that the addition of ethanol is crucial for the efficiency of this particular step. It was found that in this reaction the desired product **46** is formed in only 30 % yield and is accompanied by two main by-products, which were identified as: 1) the adduct resulting from a Michael reaction between **46** (at the α position to the nitro group) and the vinyl phosphonate **45a** and 2) the cyclic β-hydroxy phosphonate initially formed in the Horner–Wadsworth–Emmons reaction (most likely, the *anti* arrangement of the diethoxyphosphoryl and hydroxy substituents prevents this compound from collapsing to the final product). Ethanol was found to promote both the retro-Michael and retro-Horner–Wadsworth–Emmons reaction and thus enabled the smooth conversion of these unwanted by-products into **46**.

The stereoselectivity of this process is another important issue. Enantioselectivity is induced in the first Michael addition step, and the use of the *R*-configured catalyst *ent*-**9b** ensures the correct absolute configuration of the final product. Notably, the undesired 5*R* diastereoisomer **46** was formed as the major product of the Horner–Wadsworth–Emmons reaction. Fortunately, it epimerized to the thermodynamically stable 5*S* isomer during the Michael reaction with the thiol nucleophile in the last step of the cascade. In this manner, the cyclohexane framework of (−)-oseltamivir with correctly configured C3, C4, and C5 stereogenic centers was constructed in a TypeA-4-3C2X one-pot reaction sequence.

A second one-pot cascade, a diastereoselective TypeDia-7-1C2X sequence to afford the target (−)-oseltamivir (**52**), started out with the conversion of *tert*-butyl ester **47** into the corresponding azide **49** in a three-step sequence involving cleavage of the *tert*-butyl ester, transformation of the acid **48** into its acid chloride, and the reaction of this intermediate with $TMSN_3$ to give azide **49**. A subsequent Curtius rearrangement of **49** proceeded with concomitant protection of the amino group as the acetamide **50**. The second amino moiety was created by reduction of the nitro group with Zn/TMSCl/EtOH. Importantly, quenching of the interfering Zn^{II} species with NH_3 was necessary prior to the base-promoted retro-Michael reaction performed in the last step to afford target product **52** in 82 % overall yield. Both one-pot reaction cascades are characterized by their high efficiency. Despite the complexity of the reaction sequence, the final product **52** was obtained in high yield by fine-tuning of the reaction conditions applied in each step. Thus, the total synthesis of (−)-oseltamivir (**52**) was performed in two reaction vessels in excellent overall yield (61 %). This result stands in marked contrast to classical approaches to (−)-oseltamivir (**52**). For comparison, summaries of selected total syntheses of **52** are also given in Scheme 11.[28]

A similar methodology was applied by the same research group for the synthesis of structurally related ABT-341 (Scheme 12).[30a] This TypeA-9-3C1X one-pot reaction sequence was initiated by a highly enantioselective enamine-mediated Michael addition of acetaldehyde (**13d**) to nitroolefin **14b**. A subsequent nitro-Michael addition of **53** to vinyl phosphonate **45b**, followed by an intramolecular Horner–Wadsworth–Emmons reaction, led to the assembly of the cyclohexene framework. Notably, this initial three-reaction sequence involved five manual operations. As in the synthesis of oseltamivir, ethanol was added in an extra manual operation as part of the Horner–Wadsworth–Emmons reaction step. Furthermore, the addition of TMSCl prior to the following isomerization step to inactivate Cs_2CO_3 present in the reaction mixture turned out to be of importance for the success of the one-pot strategy. The iPr$_2$EtN-induced isomerization of **54** to thermodynamically stable **55** and TFA-mediated hydrolysis of the *tert*-butyl ester group afforded the free carboxylic acid **56**. Coupling of **56** with the secondary amine **57** to give **58** was followed by the reduction of the nitro group to form the target ABT-341 (**59**) in 63% overall yield. The most striking feature of the overall one-pot cascade is the fact that it consists of six consecutive reactions and nine manual operations. Furthermore, exceptionally high values of Y_{PBF} and Y_{PMO} indicate that each step in this synthesis proceeded in nearly quantitative yield. The very high value of the purification factor is also remarkable. For comparison, enantiomerically enriched ABT-341 was synthesized previously in 11 steps from **14b**.[30b] This huge difference in the number of steps required underlines the extraordinary efficiency and simplicity offered by asymmetric organocatalytic one-pot cascades.



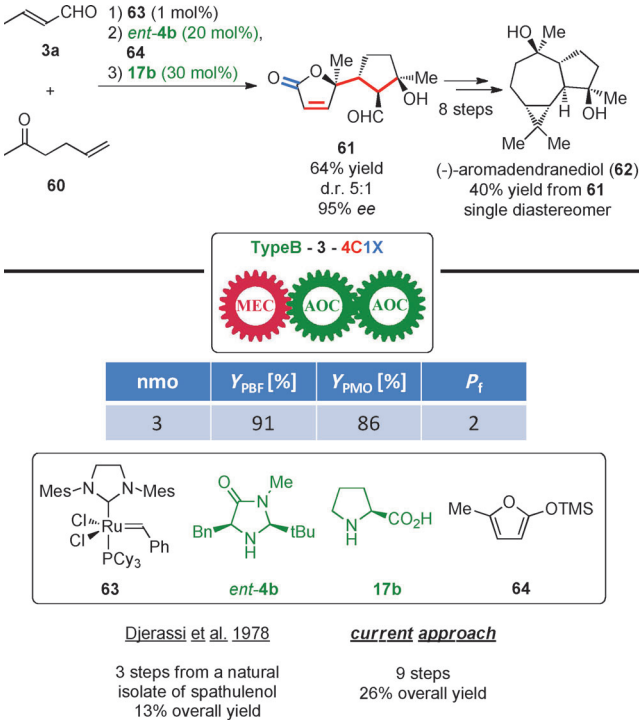
Scheme 12. Total synthesis of ABT-341. TBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate.

5. TypeB and TypeC One-Pot Sequences

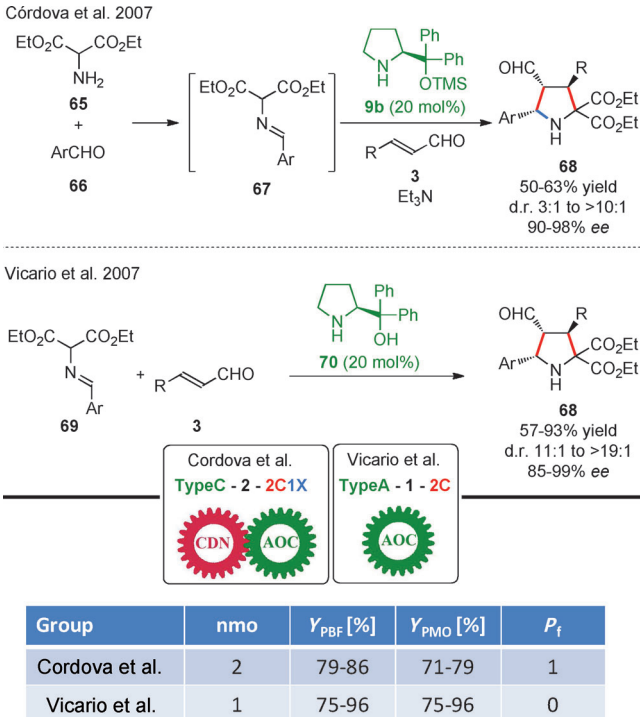
One-pot sequences categorized as "TypeB" and "TypeC" reactions serve the purpose of assembling one or more of the reactants in situ; a late-stage asymmetric organocatalytic functionalization step follows. As a result, one purification step may be omitted, which effectively reduces time demands and waste production and improves the step economy of the overall process. These methods have especially proven useful in scenarios in which the initial reactants are not readily isolable owing to stability or volatility issues. In fact, in rare cases, these one-pot approaches become the only possible solution.

An excellent example of a TypeB reaction (enantiodifferentiating step in the middle of the sequence) was provided by MacMillan and co-workers, who generated a labile polyfunctionalized α,β-unsaturated aldehyde in situ through cross-metathesis with the Grubbs second-generation catalyst **63** (Scheme 13).[31a] To the assembled enal was then added catalyst *ent*-**4b**, which promoted the enantioselective conjugate addition of the furanyl nucleophile **64** to the enal through activation of the enal as an iminium ion. In a third and final manual operation, a second aminocatalyst, proline (**17b**), was added to activate the resulting intermediate as an enamine and thus promote the final annulation through a diastereoselective intramolecular aldol reaction. The TypeB-3-4C1X one-pot sequence consisting of three catalytic reactions furnished the aromadendranediol precursor **61** in 64% overall yield with d.r. 5:1 and 95% *ee*. Subsequently, eight linear (purification-requiring) steps completed the total synthesis of the natural product **62** as a single isomer in 40% overall yield (for the eight steps from **61**). In comparison, a previous synthetic route based on transformations of an enantiomerically pure natural isolate of spathulenol provided aromadendranediol (**62**) in 13% yield in three steps.[31b]

In 2007, Córdova and co-workers reported an aminocatalyzed TypeC-2-2C1X one-pot transformation for the synthesis of fully substituted pyrrolidines through a 1,3-dipolar cycloaddition of an azomethine ylide (Scheme 14).[32] The azomethine ylide, generated by the in situ condensation of diethyl aminomalonate (**65**) and aromatic aldehydes **66** in the presence of Et$_3$N, smoothly reacted with an activated, electron-deficient olefin **3** to furnish the desired products **68** in moderate to high yields and with excellent enantioselec-



Scheme 13. Synthesis of (−)-aromadendranediol. Cy = cyclohexyl, Mes = mesityl (2,4,6-trimethylphenyl).

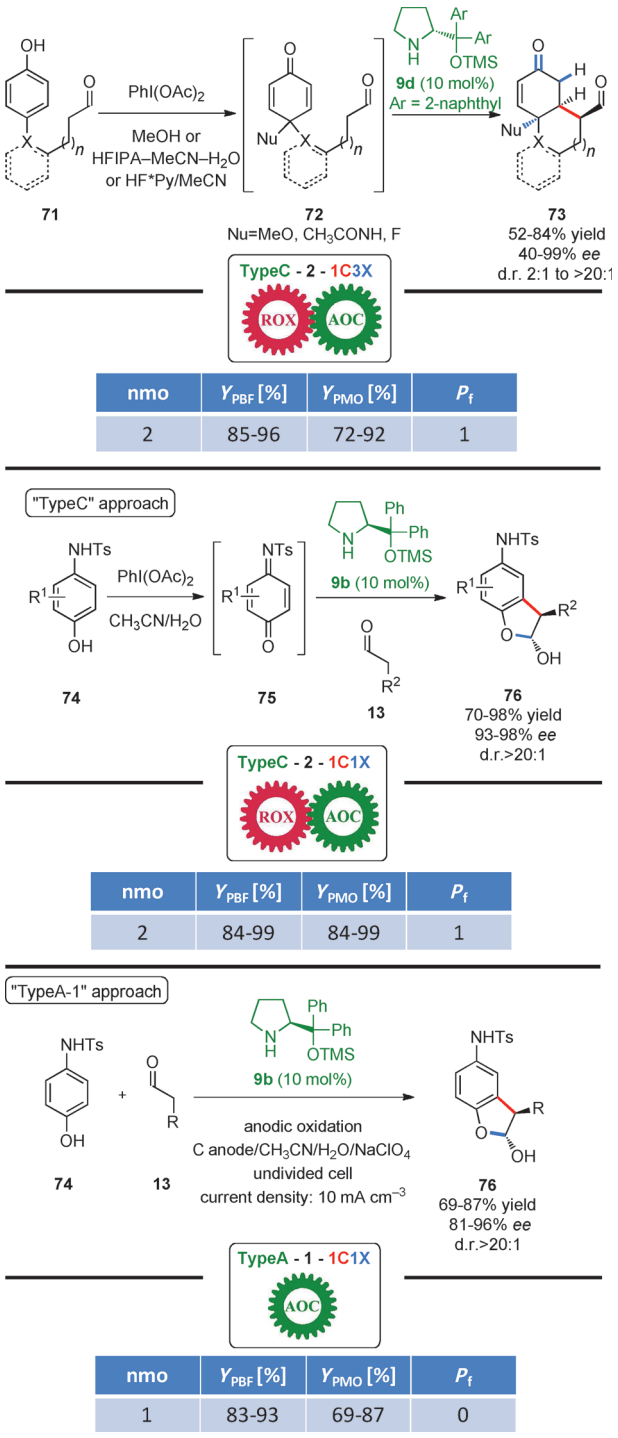


Scheme 14. Access to fully substituted pyrrolidines.

tivity. Independently, Vicario et al. developed a similar reaction with a preformed imine reactant **69** by using the diaryl prolinol catalyst **70**.[33] The yields and diastereoselectivities were slightly improved in this TypeA-1-2C sequence relative to those observed by Córdova and co-workers; however, when the yields per bond formed and the yields per manual operation are compared, the differences between these strategies are relatively small.

An interesting advance in the area of organocatalytic TypeC one-pot sequences was reported in 2008 by Gaunt and co-workers, who developed an elegant TypeC-2-1C3X cascade consisting of the oxidative dearomatization of phenols, followed by organocatalytic desymmetrization (Scheme 15).[34] Crucial to the success of this late-stage organocatalytic one-pot protocol was the careful choice of the oxidant. The ideal reagent should promote the oxidative dearomatization of phenols and not interfere with the organocatalytic desymmetrization process performed afterwards. The appropriate choice of an aminocatalyst was another important issue. The chiral amine employed should ensure high levels of enantioselectivity without being very susceptible to N-oxidation by leftover oxidant, which could lead to its deactivation by possible hydroxylamine formation. These two criteria were successfully fulfilled by the use of $PhI(OAc)_2$ as the oxidant and the bulky TMS-protected prolinol **9d** as the aminocatalyst. Phenols **71** underwent oxidative dearomatization in the presence of methanol as a cosolvent, which acted as a nucleophile and enabled the generation of a quaternary oxygenated carbon atom. Subsequent desymmetrization of **72** by an enamine-mediated intramolecular Michael addition efficiently assembled the decaline framework **73** with three new stereogenic centers in a highly enantio- and diastereoselective manner. Nitrogen- and oxygen-containing heterocycles could also be prepared by this one-pot approach. Furthermore, when the oxidation was carried out in the presence of other nucleophilic species, such as the HFIPA–MeCN system (with CN^- acting as the nucleophile in a Ritter-type reaction) or the pyridine–HF complex (with F^- acting as the nucleophile), nitrogen- or fluorine-containing quaternary stereogenic centers could be introduced.

A similar oxidative dearomatization/Michael addition strategy was recently used for the synthesis of enantiomerically enriched *meta*-substituted aniline derivatives.[35] Iodobenzene diacetate was again applied as the oxidant. The oxidation of *N*-tosyl-4-aminophenols and naphthols **74** led to the formation of electrophilic intermediates **75**, which in turn acted as Michael acceptors. The intermolecular Michael addition of various enamines generated catalytically from enolizable aldehydes **13** and the prolinol catalyst **9b**, followed by aromatization, afforded *meta*-substituted aniline derivatives in a highly enantioselective manner. Importantly, the overall TypeC-2-1C1X reaction sequence could be efficiently performed in a one-pot, domino fashion (TypeA-1-1C1X sequence) by the use of electrochemical oxidation. These reactions again demonstrate the very high tolerance of asymmetric organocatalysis towards a range of reaction conditions.

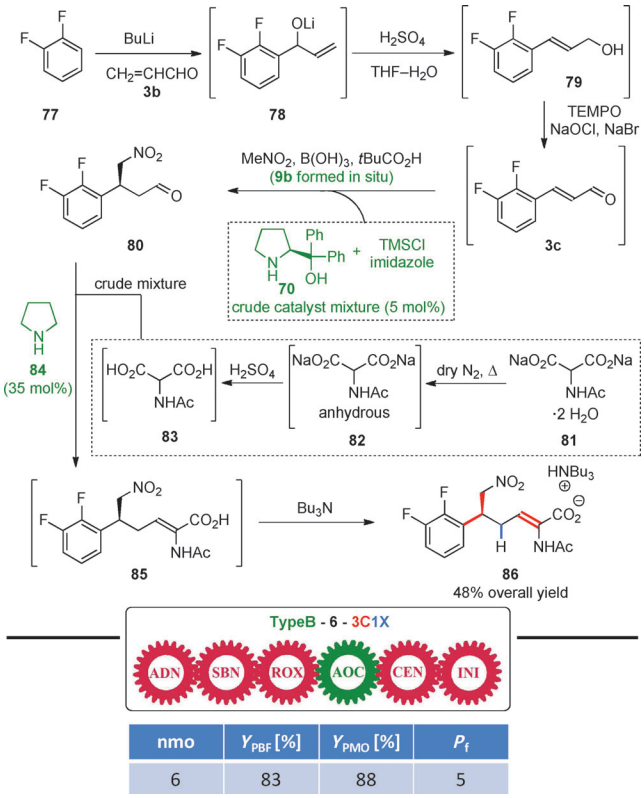


Scheme 15. Sequences involving oxidative dearomatization as the key step. HFIPA = 1,1,1,3,3,3-hexafluoro-2-propanol, Py = pyridine.

6. Future Perspectives: Higher-Order Reactions and Industrial Organocatalysis

To date, by far the majority of organocatalytic one-pot reactions are sequences involving two or three manual operations, whereas the number of higher-order and "very late stage" (in which the enantiodifferentiating step is performed in a late manual operation: the fourth or higher) one-pot reactions remain relatively few and elusive. The short time span of development is undeniably one of the main reasons for this tendency, as initial investigations are often curiosity-driven and serve only as a proof of concept. However, given the current rate of progress, the concept of organocatalytic one-pot reactions is rapidly transitioning from a hot topic to a reliable strategy in contemporary organic synthesis. As the field approaches maturity, it is believed that "target-directed" organocatalytic one-pot reactions involving higher-order and "very late-stage" strategies will play a much more dominant role in future developments.

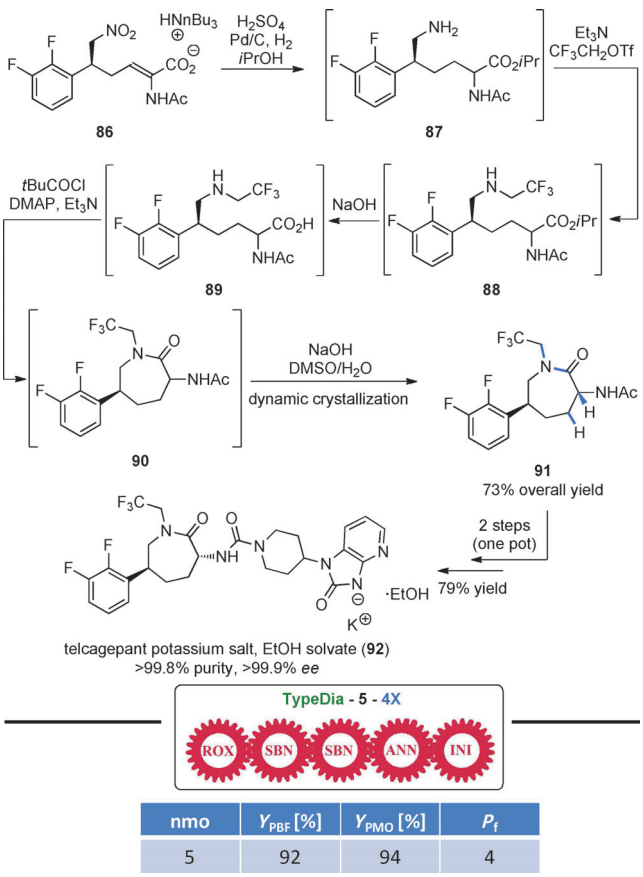
In this respect, seminal studies were reported by researchers at Merck Research Laboratories, who presented an impressive TypeB-6-3C1X reaction sequence to furnish a crucial intermediate **86** in their synthesis of telcagepant, a CGRP-receptor antagonist for the treatment of migraine (Scheme 16).[36a] The overall yield of this transformation reached 48%, which corresponds to 88% yield per manual operation. In three steps from 1,2-difluorobenzene (**77**), the reaction sequence afforded an α,β-unsaturated aldehyde **3c** that reacted with nitromethane in the presence of the aminocatalyst **9b**. The optically active Michael adduct **80** was subsequently homologated and isolated as the corresponding tributylammonium salt **86**. To make the synthesis cost-effective, only cheap and readily available reagents were used. More impressively, in this "very late stage" reaction sequence, even the crucial aminocatalyst **9b** was prepared in situ from **70** and added to the reaction vessel as a crude



Scheme 16. Industrial organocatalysis. TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.

solution, without affecting the yield and stereoselectivity of the asymmetric conjugate addition.

Upon the successful assembly of the core chiral framework **86**, a diastereoselective TypeDia-5-4X one-pot sequence was applied to form the ε-lactam ring structure **91** containing two stereogenic centers in 73% overall yield (Scheme 17).



nmo	Y_{PBF} [%]	Y_{PMO} [%]	P_f
5	92	94	4

Scheme 17. Final stages of the synthesis of telcagepant. DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, Tf = trifluoromethanesulfonyl.

The diastereoselectivity of the generation of the new stereogenic center is controlled by a dynamic epimerization/crystallization process. Finally, the synthesis of the therapeutic agent **92** was completed in a one-pot two-step reaction sequence in 79% yield according to known procedures. Remarkably, throughout the entire synthetic route, only three intermediates were isolated, and no chromatographic purification was necessary. By this environmentally friendly process, telcagepant could be prepared on an industrial scale with the high quality demanded in pharmaceutical production.

The prediction of future developments is highly challenging, if not impossible. In 1990, Seebach wrote a highly insightful review article entitled *"Organic Synthesis—Where Now?"*, in which he sketched the past developments in organic synthesis and projected these into future perspectives.[37] Two of the subjects outlined were the future challenges within the synthesis of enantiomerically enriched compounds by catalytic methods and "stereoselective reaction sequences in which a few steps suffice to generate surprisingly complex molecules". Standing where we are today, 20 years later, we are delighted as organic chemists to have witnessed the great advances made within these research areas over the past two decades. Arguably, the topic of this Minireview, asymmetric organocatalytic one-pot reactions, has also been a positive contributor to these developments. It is not within our capacity to follow in Seebach's footsteps and take on the impossible challenge of predicting future developments, even in a relatively small subarea of research in organic chemistry, such as organocatalytic one-pot reactions. However, on the basis of historical analogies and current progress, some developing tendencies may be summarized. Organocatalytic one-pot reactions may serve two main purposes: the synthesis of chiral building blocks and intermediates, and industrial applications. A common feature is that the future development of these reactions will be more target-oriented and mainly focus on compounds or compound libraries with high synthetic value. Moreover, we believe that different types of one-pot sequences will serve complementary purposes: I) one-pot sequences (TypeA–C) of lower order (typically, nmo = 2 or 3) may primarily be used as effective methods for the construction of chiral building blocks or intermediates in total synthesis that are difficult to obtain by conventional methods; II) higher-order (nmo ≥ 4) and "very late stage" sequences may serve as an important link between academic developments and industrial applications. Despite the popularity of organocatalysis, industrial processes based on organocatalysis beyond the Hajos–Parrish reaction[38] are, as yet, almost non-existent. Higher-order and "very late stage" sequences, in which readily available starting materials can be used, make organocatalysis a more affordable and attractive choice for the design of industrial syntheses. The environmentally friendly and nontoxic nature of these reaction sequences should also contribute to their expected popularity within the industrial community.

7. Limitations and Pitfalls

Clearly, each system that aims to comprehensively evaluate or categorize a given problem has its limitations and pitfalls, as in the case of the introduced classification and nomenclature of one-pot reactions. For example, the number of stereocenters introduced, the number of reactants, and the type of catalysis are important issues that are not reflected in this relatively simple system. During the preparation of the manuscript, the discussion of many possibilities led to the final choice of parameters, which, we believe at the present time, provide the best balance between simplicity (easy to remember and use) and generality (fewer pitfalls and "gray zones"). Many other parameters that could have been chosen as indicators might seem more informative; however, such parameters might also require more effort to learn and use.

Although we have attempted to provide a system that is universal and can be applied to any given reaction sequence, some disadvantages still exist. One of the most debatable issues is the counting of bonds formed. The fact that only C–C

and C–X bonds are counted will presumably result in the undercounting of some bonds (e.g. X–X, C/X–metal, and metal–metal bonds). Important bond formations may also be neglected, for example, if a particular bond is broken at a later stage of the reaction sequence. On the other hand, in some cases the number of bonds formed may be overestimated. A good example is the protonation step following a 1,4-addition step (see, for example, Schemes 2, 6, 8, and 10). According to the general set of rules given in Figure 4, this protonation is regarded as the formation of one C–X bond, which clearly overestimates the synthetic relevance of this elemental step. One solution to this problem would be to ignore C–H bonds (as in the case of X–X bonds); however, in this case, important transformations, such as reduction processes, would also be neglected. Although another specialized rule could certainly be added to avoid this "pitfall", we decided to keep the set of rules as simple and "memorable" as possible.

Another issue relates to systems in which two different chiral catalysts are employed to generate stereochemical complexity in the molecule. In such instances, the first enantiodifferentiating step should be taken into consideration when the type of cascade is assigned. Furthermore, not all synthetic protocols are compatible and can be merged into a one-pot procedure. Therefore, the development of one-pot cascades should not become the preeminent goal of the synthetic chemist. The design and development of new one-pot reactions serve the sole purpose of simplifying organic synthesis. It should therefore not be a competition to develop the longest linear one-pot sequence or to form the highest number of bonds. Instead, the usefulness of the reaction should be the most crucial parameter for the comparison of different approaches. In this light, we believe that the aforementioned pitfalls in the over- and undercounting of bonds are bearable, especially since the aim of this system is to name and classify reactions, not to rank them! We are grateful to the specialized referees for their comments, which have helped to improve the quality of this Minireview. Furthermore, we welcome any suggestions from readers for the further development of the applicability and usefulness of the current classification system.

8. Conclusion

In conclusion, we have presented a classification and nomenclatural system that is capable of systematically and informatively describing any one-pot reaction. Reaction sequences were differentiated on the basis of the relative position of the enantiodifferentiating step, the total number of manual operations, and the overall number of bonds formed. We have reviewed selected important contributions within the field of organocatalytic one-pot reactions according to this classification system and discussed possible future developments and perspectives in this field.

We are truly grateful to Professor Dieter Seebach for careful proof-reading of the manuscript and for providing many insightful comments, which have certainly improved the quality of this manuscript. We acknowledge financial support from the Carlsberg Foundation, the FNU, and OChem Graduate School. Ł.A. thanks the Foundation for Polish Science (Kolumb Program) for financial support.

Received: April 12, 2011
Published online: August 8, 2011

[1] a) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477; b) T. Hudlický, J. W. Reed, *The Way of Synthesis*, Wiley-VCH, Weinheim, **2007**.
[2] a) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831; b) P. A. Dalby, G. J. Lye, J. M. Woodley in *Handbook of Chiral Chemicals* (Ed.: D. Ager), CRC, Boca Raton, **2005**, pp. 419–428.
[3] a) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2010**; b) M. M. Green, H. A. Wittcoff, *Organic Chemistry Principles and Industrial Practice*, Wiley-VCH, Weinheim, **2003**; for a semiquantitative tool for the selection of organic syntheses on the basis of economic and ecological factors, see: c) K. Van Aken, L. Strekowski, L. Patiny, *Beilstein J. Org. Chem.* **2006**, DOI: 10.1186/1860-5397-2-3.
[4] For reviews on organocatalysis, see, for example: a) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8; b) *Chem. Rev.* **2007**, *107*, 5413–5883 (special issue on organocatalysis); c) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; d) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; e) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178; f) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632; g) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2004**; h) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; i) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; j) B. List, J.-W. Yang, *Science* **2006**, *313*, 1584; k) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; l) *Asymmetric Phase Transfer Catalysis* (Ed.: K. Maruoka), Wiley-VCH, Weinheim, **2008**; m) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744.
[5] For recent reviews on one-pot cascades in the synthesis of natural and pharmaceutical products, see: a) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167; b) C. Vaxelaire, P. Winter, M. Christmann, *Angew. Chem.* **2011**, *123*, 3685; *Angew. Chem. Int. Ed.* **2011**, *50*, 3605.
[6] a) *Comprehensive Asymmetric Catalysis III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**; b) *New Frontiers in Asymmetric Catalysis* (Eds.: K. Mikami, M. Lautens), Wiley-Interscience, New York, **2007**.
[7] Scifinder available at: https://scifinder.cas.org.
[8] For selected examples of combined metal, bio-, or photoredox catalysis with asymmetric organocatalysis, see: a) T. Yang, A. Ferrali, L. Campbell, D. J. Dixon, *Chem. Commun.* **2008**, 2923; b) J. T. Binder, B. Crone, T. T. Haug, H. Menz, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 1025; c) G.-L. Zhao, F. Ullah, L. Deiana, S. Lin, Q. Zhang, J. Sun, I. Ibrahem, P. Dziedzic, A. Córdova, *Chem. Eur. J.* **2010**, *16*, 1585; d) K. L. Jensen, P. T. Franke, C. Arróniz, S. Kobbelgaard K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16*, 1750; e) D. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77; f) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875; g) E. Wingstrand, A. Laurell, L. Fransson, K. Hult, C. Moberg, *Chem. Eur. J.* **2009**, *15*, 12107; h) M. Edin, J.-E. Bäckvall, A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 7697.
[9] a) Z.-H. Shao, H.-B. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745; b) C. Zhong, X.-D. Shi, *Eur. J. Org. Chem.* **2010**, 2999; c) M. Rueping, R. M. Koenigs, L. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350.

[10] a) P. L. Fuchs, *Tetrahedron* **2001**, *57*, 6855; b) M. Wernerova, T. Hudlicky, *Synlett* **2010**, 2701; for the use of the expression "yield per bond formed", see, for example: c) S. Rendler, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 5027.

[11] a) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471; *Angew. Chem. Int. Ed.* **2007**, *46*, 467; for a classification and definition of domino reactions, see: b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; for a review on organocatalytic multicomponent reactions, see: c) G. Guillena, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693; d) J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; e) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

[12] a) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; for an alternative synthesis of **6**, see: b) J. Raczko, *Tetrahedron* **2003**, *59*, 10181.

[13] S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628.

[14] D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861.

[15] H. C. Kolb, M. S. Vannieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

[16] E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421.

[17] a) P. Jiao, M. Kawasaki, H. Yamamoto, *Angew. Chem.* **2009**, *121*, 3383; *Angew. Chem. Int. Ed.* **2009**, *48*, 3333; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; c) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247.

[18] Ł. Albrecht, H. Jiang, G. Dickmeiss, B. Gschwend, S. G. Hansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 9188.

[19] a) H. Uehara, R. Imashiro, G. Hernández-Torres, C. F. Barbas III, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20672; b) R. Imashiro, H. Uehara, C. F. Barbas III, *Org. Lett.* **2010**, *12*, 5250; for related studies, see: c) T. Urushima, D. Sakamoto, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 4588; d) H. Ishikawa, S. Sawano, Y. Yasui, Y. Shibata, Y. Hayashi, *Angew. Chem.* **2011**, *123*, 3858; *Angew. Chem. Int. Ed.* **2011**, *50*, 3774.

[20] a) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766; b) T. C. Boorman, I. Larrosa, *Chem. Soc. Rev.* **2011**, *40*, 1910.

[21] S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem.* **2009**, *121*, 9085; *Angew. Chem. Int. Ed.* **2009**, *48*, 8923.

[22] A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928.

[23] a) X. Linghu, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem.* **2007**, *119*, 7815; *Angew. Chem. Int. Ed.* **2007**, *46*, 7671; b) J. Ramharter, H. Weinstabl, J. Mulzer, *J. Am. Chem. Soc.* **2010**, *132*, 14338; c) M. Yu, S. S. Pochapsky, B. B. Snider, *J. Org. Chem.* **2008**, *73*, 9065; d) B. M. Stoltz, T. Kano, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 9044; e) P. Bolze, G. Dickmeiss, K. A. Jørgensen, *Org. Lett.* **2008**, *10*, 3753; f) G. Franck, K. Brödner, G. Helmchen, *Org. Lett.* **2010**, *12*, 3886.

[24] A. Michrowska, B. List, *Nat. Chem.* **2009**, *1*, 225.

[25] a) C. Held, R. Fröhlich, P. Metz, *Angew. Chem.* **2001**, *113*, 1091; *Angew. Chem. Int. Ed.* **2001**, *40*, 1058; b) M. P. Sibi, L. He, *Org. Lett.* **2004**, *6*, 1749; c) N.-W. Jan, H.-J. Liu, *Org. Lett.* **2006**, *8*, 151; d) E. Palombo, G. Audran, H. Monti, *Synlett* **2005**, 2104.

[26] a) M. Nielsen, C. B. Jacobsen, M. W. Paixão, N. Holub, K. A. Jørgensen, *J. Am. Chem. Soc.* **2009**, *131*, 10581; b) M. W. Paixão, N. Holub, C. Vila, M. Nielsen, K. A. Jørgensen, *Angew. Chem.* **2009**, *121*, 7474; *Angew. Chem. Int. Ed.* **2009**, *48*, 7338.

[27] R. López, M. Zalacain, C. Palomo, *Chem. Eur. J.* **2011**, *17*, 2450.

[28] For reviews on the total synthesis of Tamiflu, see: a) M. Shibasaki, M. Kanai, *Eur. J. Org. Chem.* **2008**, 1839; b) J. Magano, *Chem. Rev.* **2009**, *109*, 4398; for selected examples, see: c) C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver, R. C. Stevens, *J. Am. Chem. Soc.* **1997**, *119*, 681; d) Y.-Y. Yeung, S. Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 6310; e) B. M. Trost, T. Zhang, *Angew. Chem.* **2008**, *120*, 3819; *Angew. Chem. Int. Ed.* **2008**, *47*, 3759; f) K. Yamatsugu, L. Yin, S. Kamijo, Y. Kimura, M. Kanai, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 1090; *Angew. Chem. Int. Ed.* **2009**, *48*, 1070.

[29] a) H. Ishikawa, T. Suzuki, H. Orita, T. Uchimaru, Y. Hayashi, *Chem. Eur. J.* **2010**, *16*, 12616; b) H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem.* **2009**, *121*, 1330; *Angew. Chem. Int. Ed.* **2009**, *48*, 1304.

[30] a) H. Ishikawa, M. Honma, Y. Hayashi, *Angew. Chem.* **2011**, *123*, 2876; *Angew. Chem. Int. Ed.* **2011**, *50*, 2824; b) Z. Pei, X. Li, T. W. von Geldern, D. J. Madar, K. Longenecker, H. Yong, T. H. Lubben, K. D. Stewart, B. A. Zinker, B. J. Backes, A. S. Judd, M. Mulhern, S. J. Ballaron, M. A. Stashko, A. M. Mika, D. W. A. Beno, G. A. Reinhart, R. M. Fryer, L. C. Preusser, A. J. Kempf-Grote, H. L. Sham, J. M. Trevillyan, *J. Med. Chem.* **2006**, *49*, 6439.

[31] a) B. Simmons, A. Walji, D. W. C. MacMillan, *Angew. Chem.* **2009**, *121*, 4413; *Angew. Chem. Int. Ed.* **2009**, *48*, 4349; b) C. M. Beechan, C. Djerassi, H. Eggert, *Tetrahedron* **1978**, *34*, 2503.

[32] R. Rios, I. Ibrahem, J. Vesely, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 8695.

[33] J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem.* **2007**, *119*, 5260; *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.

[34] N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404.

[35] K. L. Jensen, P. T. Franke, L. T. Nielsen, K. Daasbjerg, K. A. Jørgensen, *Angew. Chem.* **2010**, *122*, 133; *Angew. Chem. Int. Ed.* **2010**, *49*, 129.

[36] a) F. Xu, M. Zacuto, N. Yoshikawa, R. Desmond, S. Hoerrner, T. Itoh, M. Journet, G. R. Humphrey, C. Cowden, N. Strotman, P. Devine, *J. Org. Chem.* **2010**, *75*, 7829. For this industrial process, simple purification processes, such as extractions, were performed within each "one-pot" sequence to meet the high quality standards demanded in pharmaceutical production. For a review discussing different factors important for industrial processes, see: b) M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem.* **2002**, *114*, 402; *Angew. Chem. Int. Ed.* **2002**, *41*, 414.

[37] D. Seebach, *Angew. Chem.* **1990**, *102*, 1363; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320.

[38] a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615; b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496.

