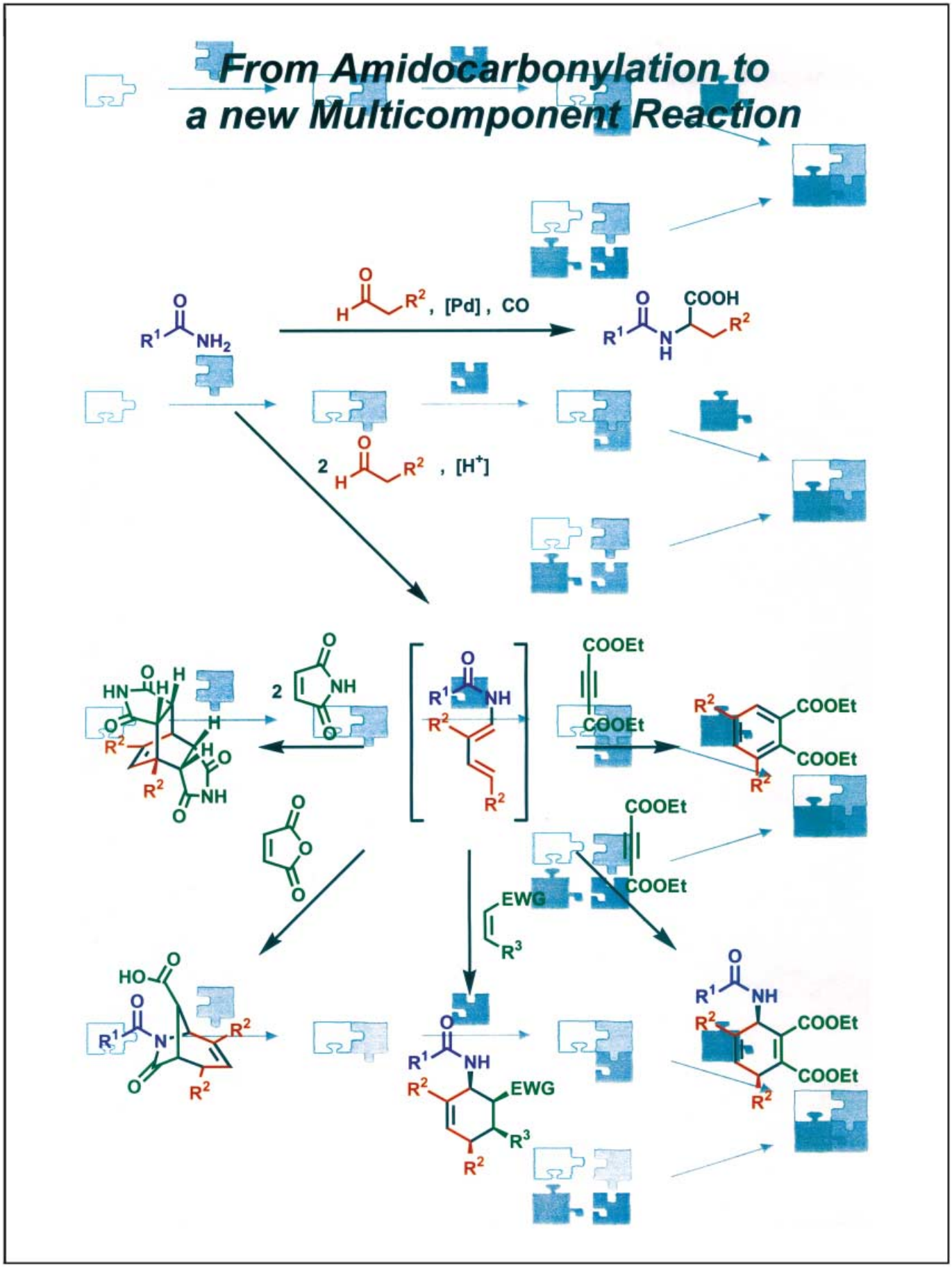

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Multicomponent Coupling Reactions for Organic Synthesis: Chemoselective Reactions with Amide – Aldehyde Mixtures

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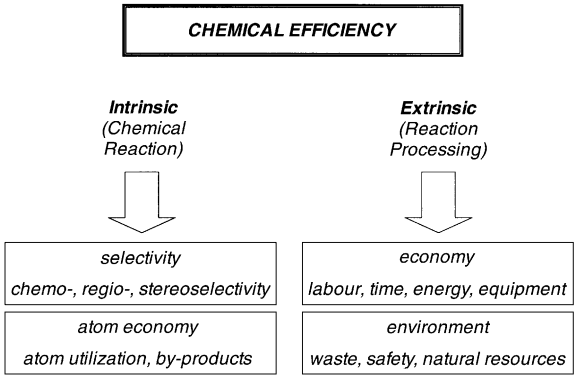
Abstract: The acid-catalyzed condensation chemistry of simple amides and aldehydes provides a highly prolific source of diverse reactants for irreversible follow-up reactions. Amide – aldehyde mixtures have been successfully employed in multicomponent syntheses of *N*-acyl α-amino acids (via palladium-catalyzed amidocarbonylation) and various cyclohexene, cyclohexadiene, and benzene derivatives (via the amide – aldehyde – dienophile (AAD) reaction).

Keywords: amidocarbonylation · domino reactions · Diels – Alder reactions · multicomponent reactions



Scheme 1. Key criteria for chemical efficiency.

Introduction

The science of organic synthesis is constantly enriched by the improvement of synthetic methodologies. Driven by the needs to improve our capability to synthesize molecules in more facile and efficient as well as economical ways, the paradigms of organic synthesis have shifted from the traditional concept of efficiency in terms of chemical yield to one that also considers economic and ecological values. The efficiency of a chemical reaction generally means the ability to assemble the target molecule from readily available building blocks in relatively few operations that require only minimal amounts of resources (raw material, energy, labour etc.) and generate minimal amounts of waste. While selectivity and atom economy issues were considered the sole criteria that judge the efficiency of a chemical synthesis in the past, efficiency criteria regarding the reaction processing are being equally emphasized now (Scheme 1).[1]

Multicomponent reactions (MCR) have attracted considerable interest owing to their exceptional synthetic efficiency.[2] The bond forming efficiency (BFE),[3] that is the number of bonds that are formed in one process, is an important measure to determine the quality of a multicomponent reaction. Unlike the usual stepwise formation of individual bonds in the target molecule, the utmost attribute of MCRs is the inherent formation of several bonds in one operation without isolating the intermediates, changing the reaction conditions, or adding further reagents. It is obvious that the adoption of such strategies would allow minimization of both waste production and expenditure of human labour. The products are formed just by pooling their collections of corresponding starting materials (Scheme 2).

Since the products carry portions of all employed reactants in their structure, MCRs with high attendent bond-forming efficiency (BFE) assure a marked increase in molecular complexity and diversity. Upon wide variations of the starting materials, opportunities arise for the synthesis of compound libraries.[2, 4] The transferability to as many available starting materials as possible is an indispensable characteristic for a general application. Multicomponent reactions thus address the requirements for efficient high-throughput synthesis of new drug candidates in a cost and time effective manner.

Reactions that build up carbon–carbon bonds and at the same time introduce nitrogen-containing functionalities into the structural framework are especially attractive for the rapid construction of organic molecules. Consistently, the majority of multicomponent reactions developed to date relate to the α-aminoalkylation of carbonyl compounds,[5] a

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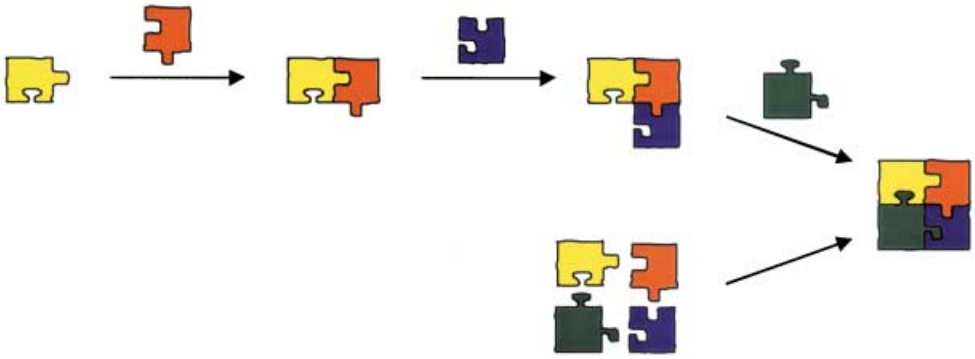


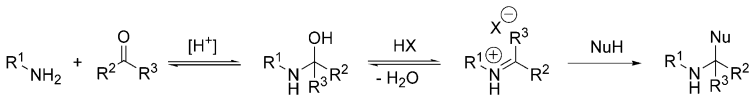
Scheme 2. Chemistry jigsaws: Multi-step (top) vs. multicomponent (bottom) assembly of the same compound.

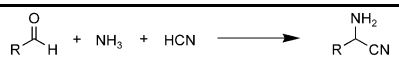
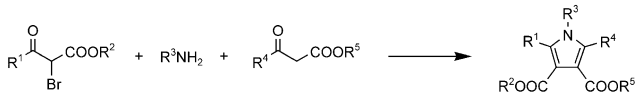
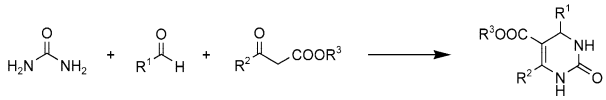
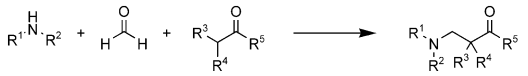
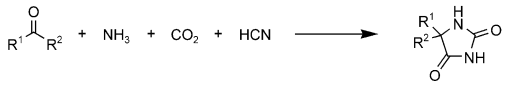
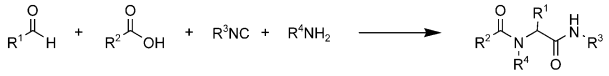
powerful synthetic tool that exploits the paired electrophilic and/or nucleophilic (enolizable α-position) reactivity of imines (or enamines) for the synthesis of amine-bearing compounds (Table 1).

The Strecker reaction (1850),[6] a reaction of central importance to the life sciences, has traditionally been viewed as the earliest recognized multicomponent reaction. This one-pot reaction denominates the three-component coupling of an amine and an aldehyde with hydrogen cyanide to give α-aminonitriles which constitute important precursors for α-amino acids. Over the years, safer, milder, and even asymmetric[7] reaction conditions have been developed and inspired new interest in this reaction. The best known classical multicomponent reaction clearly is the Mannich reaction.[5, 8] This α-aminoalkylation of ketones has proven an extremely valuable transformation as evidenced by the numerous natural product syntheses that involve Mannich-type chemistry. Based upon sequential aminoalkylation of succinaldehyde, Robinsons 1917 synthesis of tropinone is generally recognized as the first multicomponent synthesis of a natural product.[9] Other historically significant MCRs that are based on the reactivity of carbonyl and amine functionalities include the Hantzsch pyrrole synthesis,[10] the Biginelli synthesis of dihydropyrimidines,[11] and the four-component Bucherer–Bergs reaction,[12] an extension of the Strecker reaction for the synthesis of amino acids and hydantoins. In the Ugi-4CR, the four reactants aldehyde, amine, isonitrile, and carboxylic acid combine to give a peptidoic α-acylamino carboxamide.[13] The key in this transformation lies in the unique property of the isocyanide function to undergo a formal α-addition.

These and other prominent reactions bear witness to the incredibly rich multicomponent chemistry that has been established upon the versatile imine (or iminium ion) moiety. Nucleophilic attack onto an intermediate imine or iminium ion is central to all of the aforementioned reactions. Upon

Table 1. Historically significant multicomponent reactions based on the α-aminoalkylation of carbonyl compounds.

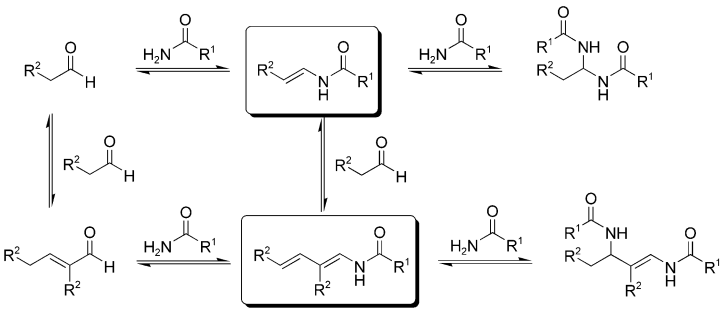


name (year)	reaction
Strecker (1850)	
Hantzsch (1890)	
Biginelli (1891)	
Mannich (1912)	
Bucherer-Bergs (1941)	
Ugi (1959)	

Abstract in German: *Die säurekatalysierte Kondensationschemie von einfachen Amiden und Aldehyden generiert einen reichhaltigen Pool an diversen Reaktanden für irreversible Folgereaktionen. Amid-Aldehyd-Mischungen wurden erfolgreich in Multikomponentenreaktionen zur Synthese von N-Acyl-α-aminosäuren (Palladiumkatalysierte Amidocarbonylierung) sowie vielfältiger Cyclohexen-, Cyclohexadien- und Benzol-Derivate (Amid-Aldehyd-Dienophil-Reaktion, AAD) eingesetzt.*

introduction of a carbonyl group adjacent to the nitrogen atom, the electrophilic reactivity of an imine (or iminium ion) can be greatly increased. This enhanced reactivity of *N*-acylimines (or *N*-acyliminium ions) significantly broadens the range of nucleophiles that can be used in carbon–carbon bond forming reactions.[14]

Simple one-pot reaction of a carboxamide and an aldehyde usually affords a mixture of equilibrating amide–aldehyde adducts (Scheme 3). Apart from the corresponding *N*-acylimine (or *N*-acylenamine) species, the acid-catalyzed condensation of amide and aldehyde in NMP solution also affords

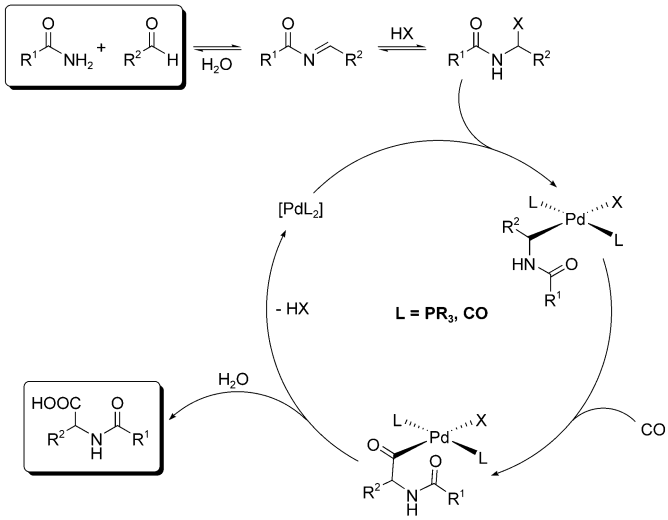


Scheme 3. Major equilibrating species in amide–aldehyde condensation reactions (only *trans*-isomers shown).

aldol and amidal species, and, especially at elevated temperatures, higher order adducts such as 1,3-bis(amido)alkenes and 1-amidobutadienes.[15] On account of the presence of several equilibrating species, the yield of each of the formed adducts is generally low. Nevertheless, this pool of diverse adducts constitutes a highly prolific source of reactants when rendering possible an irreversible, chemoselective trapping of a single component of the mixture. The resultant unbalanced equilibrium (in favor of the consumed compound) could, in principle, lead to quantitative conversion. Two orthogonal strategies for the selective one-pot consumption of amide–aldehyde condensation adducts in irreversible, highly efficient reactions will be discussed in the following.

The palladium-catalyzed amidocarbonylation of aldehydes: A few years ago, we became interested in the palladium-catalyzed three-component coupling reaction of aldehydes, amides, and carbon monoxide.[16] This so-called amidocarbonylation of aldehydes takes advantage of the irreversible carbonylation of amide–aldehyde mixtures and affords *N*-acyl α-amino acids in a one-pot reaction. The cobalt-catalyzed amidocarbonylation was discovered by Japanese corporate chemist Wakamatsu in 1970.[17] Later on, palladium complexes were proven to be more effective catalysts and supplied an optimized procedure for the amidocarbonylation of aldehydes (Scheme 4).

The reaction is assumed to commence with the condensation of amide and aldehyde in the presence of halide ions to give an α-haloamine which is in equilibrium with different *N*-acylimine and enamine species.[18] Subsequent palladium-centered carbonylation and hydrolysis affords the *N*-acyl α-amino acid.[19] Relying upon cheap starting materials, this 100% atom economical one-pot combination of sequential



Scheme 4. Palladium-catalyzed amidocarbonylation of aldehydes.

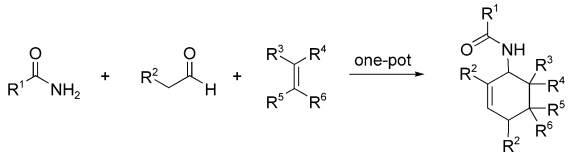
acid- and transition metal-catalyzed processes offers a considerable economical benefit as it is of particularly high value from an ecological point of view.[20] Important synthetic applications of the palladium-catalyzed amidocarbonylation of amide aldehyde mixtures include the synthesis of a wide range of aliphatic and aromatic *N*-acyl amino acids, arylglycines, and hydantoins.[21]

Multicomponent reactions involving 1-amidobutadienes: Another interesting component of the aforementioned condensation equilibrium of amide–aldehyde adducts is the 1-amidobutadiene species (Scheme 3). While studying the palladium-catalyzed amidocarbonylation of aldehydes with carboxamides, we observed the formation of 1-*N*-acylamino-2,4-dialkyl-1,3-butadienes in small amounts ($<5\%$) under amidocarbonylation conditions when employing low catalyst concentrations ([Pd] $<$ 0.1 mol%).[22] These 1-amidobutadienes were not formed via a palladium-catalyzed reaction path but upon simple acid-catalyzed condensation of two molecules of aldehydes with one molecule amide. Obviously, the *N*-acylamino-1,3-butadienes derived from acid-catalyzed condensation of amide and aldehyde bear a conceptual relationship to the established Oppolzer–Overman dienes.

Although several syntheses of 1-*N*-acylaminodienes have been reported by Oppolzer,[23] Overman,[24] and others,[25] our one-pot procedure is unique in that it merely involves mixing of ubiquitous available amides and aldehydes at elevated temperature.[26] The inherent selective telomerization of two aldehydes with one amide molecule is especially remarkable when considering the numerous side reactions which are likely to proceed under the acidic reaction conditions (further aldol condensations, oligomerizations etc.). Several groups have elegantly demonstrated the synthetic versatility of Diels–Alder chemistry with related 1-*N*-acylamino-1,3-dienes.[27] Much of the research activities revolved around their exploitation for the synthesis of amino functionalized organic molecules with special emphasis on natural products. Prominent examples in which the pivotal aminodiene-based Diels–Alder reactions constitute particularly attractive solutions for

the construction of six-membered carbocyclic subunits with high regio- and stereoselectivity include the total syntheses of pumiliotoxin C,[28, 29] gephyrotoxin,[30] dendrobine,[31] and tabersonine.[32]

One-pot synthesis of 4-amino-1,3-dioxohexahydro-1*H*-isoindoles: As multicomponent reactions involving at least one Diels–Alder step have gained a strong foothold among highly efficient one-pot methodologies during the last decades,[2, 3, 33] we also investigated three-component reactions of amides, aldehydes, and dienophiles in a novel one-pot manner. Indeed, addition of an electron-deficient dienophile to the amide-aldehyde mixture entailed the chemoselective Diels–Alder reaction with the intermediate 1-amidodiene species in a multicomponent reaction sequence (Scheme 5). The high efficiency of such one-pot multicomponent methodology



Scheme 5. One-pot reaction of an amide–aldehyde–dienophile (AAD) mixture.

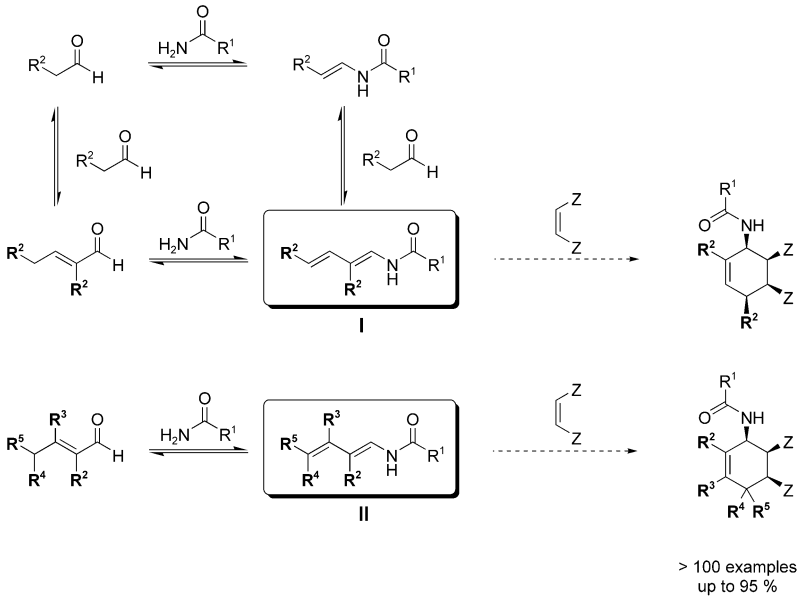
(*a*mide, *a*ldehyde, *d*ienophile = **AAD**) becomes evident upon comparison with an analogous multi-step procedure that involves isolation of the aminodiene intermediate in moderate to low yields. The consumption of in situ prepared 1-*N*-acylamino-2,4-dialkyl-1,3-butadienes in the presence of dienophiles was shown to drive the condensation equilibria well to the amidodiene side, thereby providing a high-yield one-pot access to substituted 1-acylamino-2-cyclohexenes possessing high degrees of diversity and complexity.[34]

Access to intermediate amidodienes of type **I** (Scheme 6, top) was accomplished upon sequential condensations of two α-CH_2 containing aldehydes with an amide. Owing to the incorporation of two identical aldehyde molecules, substitution of the diene backbone in **I** is limited to the 2- and 4-position only. Obviously, the use of α,β-unsaturated aldehydes, which presumably constitute an integral component of the overall reaction mechanism (see Scheme 3), affords 1-*N*-acylamino-1,3-butadiene building blocks **II** (Scheme 6, bottom) with four potential substitution centers along the 1,3-butadiene backbone and hence significantly increases the substrate diversity.[35]

It is important to note that the AAD reaction tolerates a large variety of amides. Not only simple or substituted acetamides and benzamides can be employed in this one-pot reaction, but also ureas, sulfonamides, and carbamates. Upon combination of various amides, aldehydes (simple, unsaturated, linear, branched, arylalkyl, heterocyclic), and maleimide, a series of 1,3-dioxohexahydro-1*H*-isoindoles with diversified substitution patterns has been prepared in a one-pot reaction (Table 2).[34, 35] The straightforward isolation of the products with high purity by simple precipitation from ethyl acetate or ethanol adds to the general simplicity of the methodology described with special regard to high-throughput experimentations.

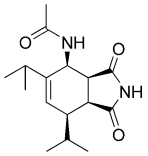
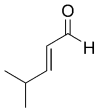
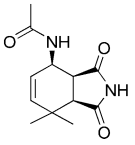
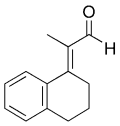
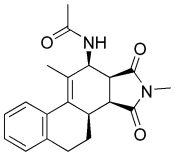
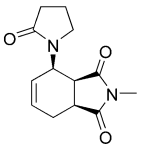
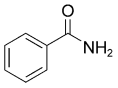
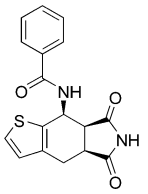
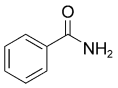
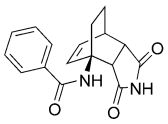
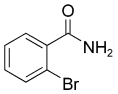
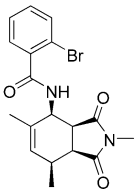
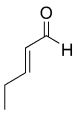
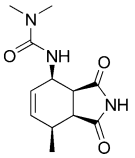
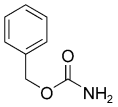
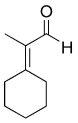
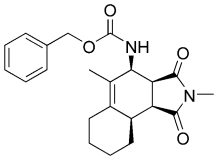
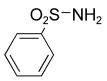
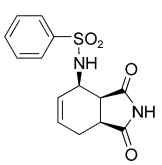
Apart from the common aminocyclohexene motif, the choice of reactants governs the introduction of further structural design elements. Anellated ring systems can be accessed upon employment of cyclic α,β-unsaturated aldehydes (entries 3, 5, 9). Arylhalide-bearing three-component adducts (entry 7) allow for subsequent C–C coupling reactions. O-Substituted carbamates cleanly afforded the desired three-component adducts (entry 9) which provide the opportunity to access the corresponding free aminocyclohexenes via Cbz cleavage.[36] Entry 6 illustrates an extension of the general procedure to α,β-unsaturated ketones, though under drastic conditions (160 °C, 24 h).

The three-component reactions investigated feature the formation of up to three carbon–carbon bonds and one carbon–nitrogen bond. Although up to four stereogenic centers are created in the course of the reaction sequence, only one diastereomer (as a racemic mixture) was isolated in most cases. Although the acid-catalyzed condensation of amide and aldehyde entails—among several other adducts—the concomitant formation of *cis* and *trans* amidodiene isomers,[37] exclusive consumption of the all-*trans*(1*E*,3*E*)-amidodiene in the terminating Diels–Alder reaction was observed in most cases. Furthermore, the Diels–Alder



Scheme 6. In situ formation of *N*-acylaminodienes from simple aldehydes (type **I**, top) or α,β-unsaturated aldehydes (type **II**, bottom) and follow-up Diels–Alder products.

Table 2. Three-component adducts of carboxamides, aldehydes, and maleimides.

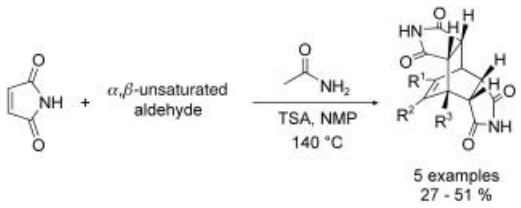
	Amide	Aldehyde	Maleimide	3-CR Product	Yield [%]
1			-H		73
2			-H		71
3			-Me		53
4			-Me		85
5			-H		53
6			-H		70
7			-Me		64
8			-H		65
9			-Me		53
10			-H		79

adducts were found to contain the fused rings in an *endo* configuration. Owing to the *endo* addition of the dienophile to the all-*trans*(1*E*,3*E*)-amidodiene, all substituents on the cyclohexene ring adopt a *syn* position.

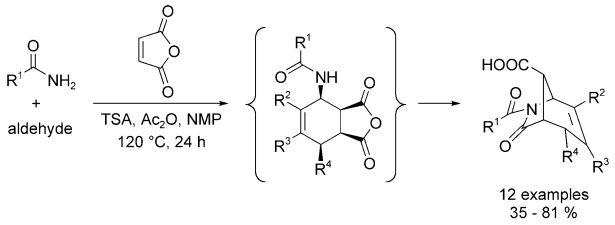
Tetracyclic adducts: Very recently, we found that one-pot reactions at elevated temperatures in the presence of excess maleimide afforded the tetracyclic adducts as predominantly *meso* isomers via repetitive *endo* cycloadditions (Scheme 7). Several derivatives of the structurally related mitindomide, the 1:2 photoadduct of benzene and maleimide, were proven to exhibit high anti-tumor activity.[38]

Maleic anhydride: Upon use of dienophilic maleic anhydride, azabicyclooctene derivatives can easily be accessed via a domino condensation–cycloaddition skeletal rearrangement reaction sequence (Scheme 8).[39] Given the various proffering postsynthesis modifications including reduction of the keto moiety or decarboxylation, the target compounds constitute versatile precursor compounds paving the way for further elaboration to a variety of cyclic compounds ranging from simple phthalic acid derivatives and highly substituted arenes to more complex cage molecules.[27d, 40] $LiAlH_4$ reduction affords 6-azabicyclo[3.2.1]octane derivatives, which constitutes a structural motif central to various polycyclic alkaloids such as the securinega,[41] aristotelia,[42] and other[43] families.

Acrylonitrile: Reactions with acrylonitrile as an unsymmetric dienophile preferentially afforded the "*ortho*" adduct featuring adjacent amino and cyano substituents (Scheme 9). Again, the investigated one-pot reactions follow an *endo*

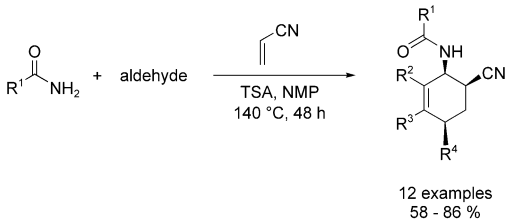


Scheme 7. One-pot synthesis of 4,10-diazatetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradec-13-ene-3,5,9,11-tetraone derivatives from acetamide, α,β-unsaturated aldehyde, and maleimide.



Scheme 8. One-pot approach to 7-oxo-6-aza-bicyclo[3.2.1]oct-2-ene-8-carboxylic acids.

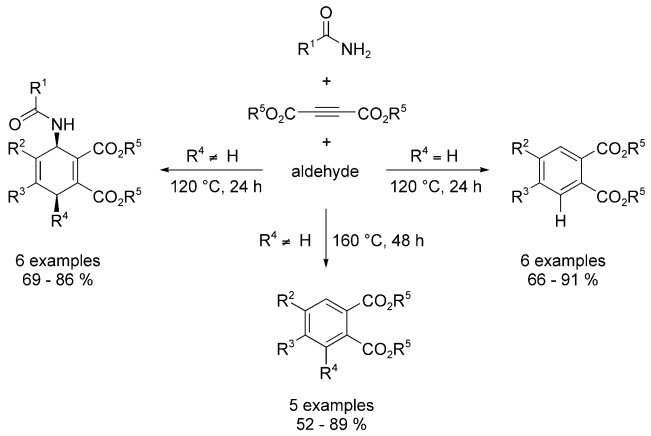
pathway resulting in the typical all-*syn* substitution along the cyclohexene ring.[44] A large excess of acrylonitrile (>300 mol%) was used to counter polymerization of acrylonitrile which occurs under the reaction conditions. Generally, the obtained nitriles are interesting building blocks that can be further elaborated to carboxylic acids,[45] pyridines,[46] or other heterocyclic compounds such as triazines and oxazoles.[47]



Scheme 9. Reactions with dienophilic acrylonitrile.

Alkynes: Reactions with dienophilic acetylenedicarboxylates exhibited two different reactivity patterns dependent on the structure of the aldehyde. Employment of aldehydes that entail the introduction of a substituent (≠H) on C4 of the cycloadduct afforded 1-*N*-acylaminocyclohexadiene derivatives which are subject to double bond isomerization in some cases (Scheme 10, left). Consistently, simple aldehydes (>C_2) and α,β-unsaturated aldehydes (>C_4) gave the expected three-component adducts in good yields. Surprisingly, one-pot reactions employing acetaldehyde or crotonaldehyde derivatives bearing no substituents in γ-position gave rise to the formation of phthalic acid derivatives (Scheme 10, right). This reaction is assumed to proceed via the known aminodiene and cyclohexadiene intermediates with the latter undergoing facile acylamine elimination under the reaction conditions.[48]

The role of the rather distant substituent on C4 becomes evident when considering the operation of a concerted 1,4-elimination. On the basis of the Woodward-Hoffmann rules for sigmatropic reactions, this 1,4-conjugate elimination of allylic leaving groups can be viewed as a thermally allowed σ^2s π^2s σ^2s process,[49] which is in full accord with literature precedents.[50]

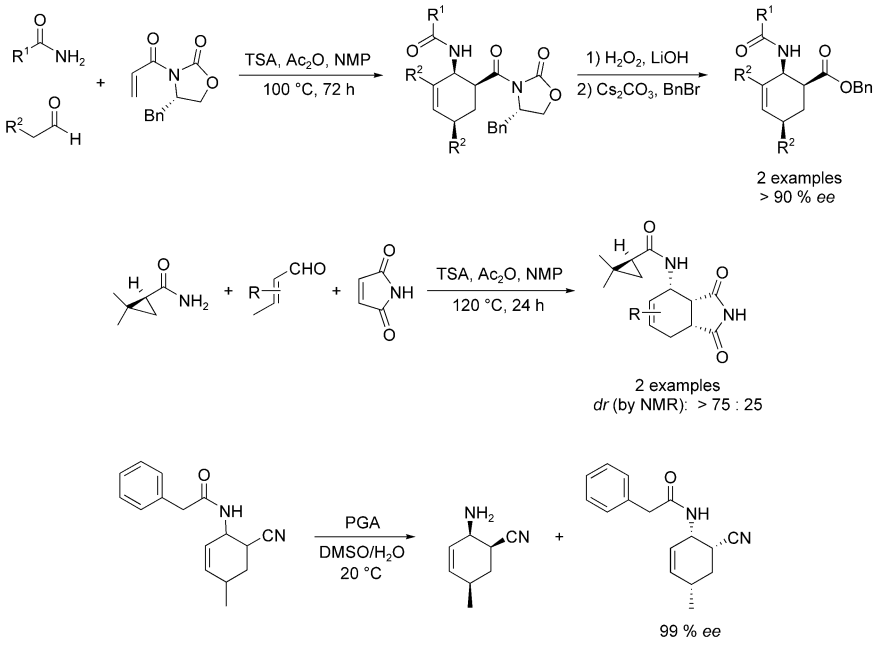


Scheme 10. One-pot reactions of amides, aldehydes, and dialkyl acetylenedicarboxylates.

Although an identical stereochemical result would be the consequence of an initial suprafacial 3,3-sigmatropic rearrangement of the allylic amide followed by 1,2-*syn*-elimination, the relatively low reaction temperature (120°C) make the sigmatropic process unlikely. At higher temperatures, orbital control might become less decisive rendering other mechanisms of elimination competitive. Indeed, all isolated aminocyclohexadiene compounds (with substituents in 4-position) that withstood elimination at standard conditions (120°C, 24 h) were cleanly converted to the corresponding phthalic acid esters in good yields after 48 h at 160°C (Scheme 10, bottom). For the first time, efficient in situ preparation of dienes has been implemented in the syntheses of arenes via domino Diels–Alder elimination reactions.[51]

Stereoselective reactions: Although the investigated multicomponent AAD coupling reactions exhibited high levels of regio- and diastereoselectivity, the importance of Diels–Alder chemistry to natural product synthesis has stimulated our interest in the development of stereoselective variants (Scheme 11). One-pot reactions with chiral dienophilic α,β-unsaturated *N*-acyl oxazolidinones[52] followed by cleavage[53] of the auxiliary afforded the desired 1-*N*-acylaminocyclohexene-2-carboxylates with moderate yields but excellent stereoselectivities (> 90% *ee*).

With chiral amides such as (1*S*)-(+)-2,2-dimethylcyclopropanecarboxamide, one-pot reactions afforded the target molecules in high yields, whereas the attained diastereoselectivities (*de*) were moderately. Penicillin G amidase (PGA, penicillin G acylase, EC3.5.1.11) from *E. coli*, a powerful biocatalyst for the hydrolysis and synthesis of phenylacetyl-protected derivatives, is also used for racemic resolution of



Scheme 11. Different approaches for stereoselective synthesis of AAD products.

amino functions.[54] We recently embarked on such an enzymatic kinetic resolution step for the racemic resolution of phenylacetamide-bearing three-component adducts and obtained perfect resolution.[55]

Conclusion and Outlook

The acid-catalyzed condensation of amide–aldehyde mixtures provides a prolific pool of equilibrating reactants which were shown to undergo highly selective follow-up reactions when rendering possible an irreversible, chemoselective trapping of a single component of the mixture. Three-component coupling reactions based on amides and aldehydes as starting materials allow for the efficient preparation of *N*-acyl α-amino acids in the presence of carbon monoxide (amidocarbonylation reaction) or various cyclohexene, cyclohexadiene, and benzene derivatives with diverse substitution patterns using suitable dienophiles (AAD reaction). Both multicomponent methodologies provide one-pot access to interesting organic target molecules which otherwise would require technically demanding multi-step syntheses. The AAD reaction constitutes the most simple and direct high-yield approach to a variety of amino functionalized cyclohexene and cyclohexadiene derivatives to date. The key of this transformation lies in the intermediacy of substituted 1-amidobutadienes which easily undergo cycloaddition reactions to various dienophiles. The ubiquitous, off-shelf starting materials readily react even in the presence of air or water. It is still surprising to us that even highly reactive aldehydes react to the targeted multicomponent adducts with high yields despite the elevated reaction temperatures (80–120 °C) and the presence of acid catalyst.

AAD adducts are interesting organic building blocks with several functionalities that can be subjected to a wide range of diversity-generating postsynthesis modifications. For example, we demonstrated the synthesis of polysubstituted anilines by sequential combination of a three-component coupling reaction with *O*-benzyl carbamate and a new transition metal-catalyzed aromatization step.[56] Further catalytic refinement reactions, for example intramolecular Heck and Pauson–Khand reactions of suitably substituted AAD products are currently being investigated. We believe that these reaction sequences allow the unique preparation of several interesting analogues of natural products such as the amaryllidaceae alkaloids or dendrobine.

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