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COMMUNICATION

Nature-inspired cascade catalysis: reaction control through substrate concentration—double *vs.* quadruple domino reactions†

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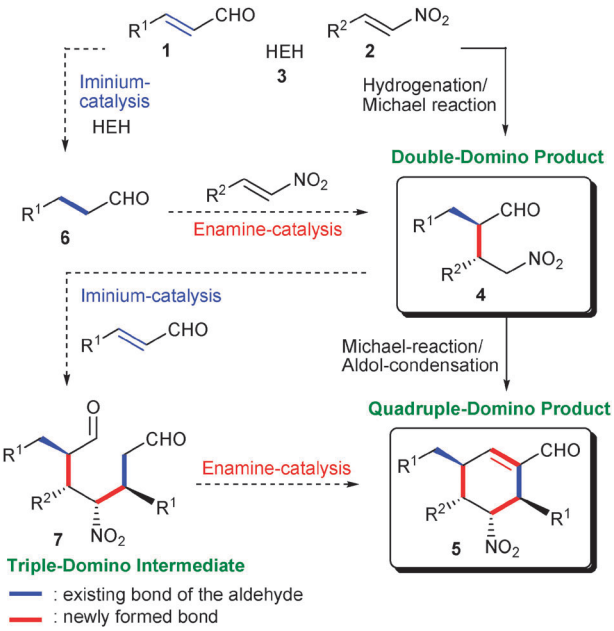
The design of biologically inspired, multi-component cascade reactions enables the targeted synthesis of assorted structurally complex products. Similar to regulation in cells the reaction path is controlled by the substrate concentration and complex enantiopure products with high structural diversity are provided.

The development of reactions with efficiency comparable to that seen in natural biosynthesis has always been the greatest goal of organic synthesis. Enzyme catalyzed reactions are especially atom efficient, as well as being highly chemo-, regio-, and stereoselective. Starting from simple reactants, complex structures with multiple stereocenters are highly selectively created in only a few steps. The enzymatic processes often utilize domino[1] and multi-component reactions[2] and their efficiency makes them increasingly attractive for the organic chemistry community[3] so that recently organocatalytic triple and quadruple domino reactions were developed.[4,5] Furthermore, the biological activity and the complexity of the structures found in nature stimulated chemists to develop methods which provide access to a multitude of skeletally diverse small molecules, essential for biological assays, in an easy and effective manner. Recently introduced concepts, in particular DOS (diversity oriented synthesis)[6] and BIOS (biology oriented synthesis),[6d,e,7] offer the opportunity to accomplish this goal.

In contrast to organic synthesis, enzymatic reactions are highly regulated, often being subject to activation or inhibition by a particular substrate. This ensures that the synthesis of a particular target substance is favored. For example, pyruvate, an important metabolic intermediate, is found in numerous metabolic pathways.[8] If pyruvate is present in low concentrations within yeast cells, it is oxidatively decarboxylated by pyruvate-dehydrogenase to acetyl-CoA but at high concentrations it is decarboxylated to acetaldehyde by pyruvate decarboxylase. Furthermore, even higher intracellular concentrations of pyruvate trigger anaplerotic carboxylation to oxalacetate.

In this communication we describe the development of a biologically inspired, one-pot multi-component domino reaction



Scheme 1 Reaction sequence of the double- and quadruple-domino reaction cascade.

which facilitates the directed synthesis of product **4** or, alternatively, **5** (Scheme 1). The reaction path can be controlled by varying the concentration of the substrates **1**, **2** and **3**. Furthermore, the presence of different functional groups within the products renders them as versatile building blocks for the generation of structurally complex molecules in diversity oriented synthesis.[6,7]

Conversion of α,β-unsaturated aldehyde **1** into the corresponding saturated aldehyde **6** is the key step in both reaction sequences and was achieved *via* biomimetic transfer hydrogenation in the presence of Hantzsch dihydropyridine **3** (HEH).[9] Due to their relatively low activity, α,β-unsaturated aldehydes have to be activated in order to be hydrogenated by the Hantzsch ester.[10] In general the activation of aldehydes and nitroalkenes can be achieved either by Lewis bases or by Brønsted acids at high temperature. In this context it has been shown that the acid catalyzed reduction of nitroolefins **2** in the presence of α,β-unsaturated aldehydes **1** leads selectively to nitroalkanes while the carbonyl compounds can almost

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fully be recovered.[11] The chemoselective reduction of an α,β-unsaturated aldehyde **1**, in the presence of a nitroolefin **2** was not described. Therefore, we decided to examine this reaction as its successful achievement would allow a subsequent 1,4 addition resulting in a first domino-hydrogenation-Michael reaction sequence.

By employing a secondary amine catalyst, it should be possible to lower the LUMO of the carbonyl compound to such an extent that, in the presence of nitroolefins, the hydrogenation of the α,β-unsaturated carbonyl compounds is favored. Subsequently, the reduced carbonyl compound **6** can serve as a substrate for the formation of an enamine which in a nucleophilic attack adds to nitroolefin **2**[12] to provide the domino product **4** with the formation of multiple stereocenters. Yet, such an enantio- and chemoselective double addition sequence has not been described.

Initial experiments showed that L-proline is able to selectively catalyze the reduction of aldehyde **1a** (R^1 = Ph) in the presence of β-nitrostyrene **2a** (R^2 = Ph). The previously reported chemoselectivity of the Brønsted acid catalyzed reaction is thereby reversed. Upon screening of different reaction parameters, optimal conditions for the reduction–addition sequence have been identified.[13] The resulting domino product **4a** was subsequently reduced to the δ-nitro alcohol **9a**. The desired product **9a** was obtained in 72% yield and 99% ee when the domino reaction was performed at 10 °C with diphenylprolinol–TMS–ether (**8**)[14] as the catalyst and silica gel as an additive.

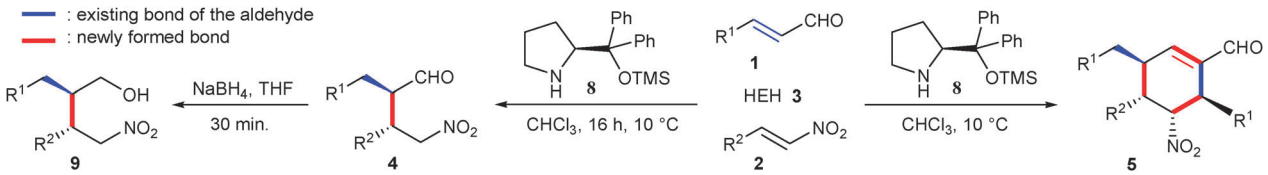
Using the optimized conditions we examined the substrate scope of this new reaction sequence (Table 1, entries 1–12). The substitution pattern of the α,β-unsaturated aldehyde and the nitroolefins used were both varied. The subsequent reduction of the domino-hydrogenation-Michael products with $NaBH_4$ provided the desired alcohols **9a–l** in good yields and with excellent enantioselectivities (up to >99% ee) throughout. Noteworthy, nitroaldehydes **4** are useful synthons for the preparation of biologically relevant and synthetically valuable δ-amino alcohol and γ-amino acid derivatives.[15]

Considering the reaction mechanism, as well as the products and their functional groups, we wondered to what extent the concentration influenced regulation seen in cellular processes could analogously be achieved in these reactions by changing the substrate concentration and thus altering the reaction pathway. The aldehyde and nitro functionalities present in the domino product **4** are available for onward reaction as impressively described by Enders and coworkers.[4a] If the concentration of the α,β-unsaturated aldehyde **1** is now increased, the previously generated domino product **4** should undergo an iminium catalyzed Michael addition to **1**, forming the triple reaction intermediate **7** (Scheme 1). At this stage, under the given reaction conditions, the presence of two aldehyde groups should facilitate an intramolecular aldol condensation to give carbocycle **5**. Cumulatively, by increasing the concentration of the α,β-unsaturated aldehyde **1**, or by reducing the availability of the Hantzsch-ester **3**, a new quadruple reaction in which four stereocenters are formed should occur.

In order to validate our design, we examined various substrate concentrations of the educts in this Lewis base catalyzed reaction. It was shown that the reaction of aldehyde **1**, β-nitrostyrene **2** and dihydropyridine **3** in an equivalent ratio of 4.0 : 1.0 : 2.2 did indeed yield the quadruple reaction product **5** rather than product **4**.

In subsequent studies regarding the substrate scope, the carbocyclic aldehydes **5a–j** could all be isolated in almost an enantiomerically pure form (Table 1, entries 13–22) albeit with slightly lower yields than in the simple domino reaction. However, if it is considered that four reaction steps occur in a multi-component, one-pot reaction in order to build these

Table 1 Scope of the double and quadruple-domino reactions



Entry	R^1	R^2	**9**[a]	Yield[b]	dr[c]	ee[d,e]	Entry	**5**[f]	Yield[b]	ee[d,g]
1	Ph	Ph	**a**	72	5 : 1	99	13	**a**	43	>99
2	Ph	*o*-OMe-Ph	**b**	91	5 : 1	>99	14	**b**	35	>99
3	Ph	*m*-OMe-Ph	**c**	80	17 : 1	>99	15	**c**	53	>99
4	Ph	*p*-OMe-Ph	**d**	92	6 : 1	99	16	**d**	50	>99
5	Ph	*o*-F-Ph	**e**	78	6 : 1	>99	17	**e**	50	>99
6	Ph	*p*-F-Ph	**f**	92	4 : 1	>99	18	**f**	46	>99
7	Ph	*p*-Me-Ph	**g**	95	7 : 1	84	19	**g**	49	>99
8	Ph	*m*,*p*-di-Cl-Ph	**h**	77	26 : 1	>99	20	**h**	44	98
9[h]	*o*-Br-Ph	Ph	**i**	81	>50 : 1	96	21	**i**	60	99
10	*p*-OMe-Ph	Ph	**j**	89	10 : 1	>99	22	**j**	61	>99
11	C_4H_9	Ph	**k**	66	>50 : 1	>99				
12	C_7H_{15}	Ph	**l**	80	>50 : 1	>99				

[a] Reaction conditions: (i) **1** (2.0 eq.), **2** (1.0 eq.), HEH **3** (2.2 eq.), silica gel and **8** (20 mol%). (ii) $NaBH_4$, THF, 30 min. [b] Yield after chromatography. [c] Diastereomeric ratio before chromatography. [d] Enantiomeric excess was determined by HPLC using Chiralpak AD–H, AS–H or Chiralcel OD–H. [e] The assignment of the absolute configuration was made based on the absolute configuration of compound **5i**. [f] Reaction conditions: **1** (4.0 eq.), **2** (1.0 eq.), HEH **3** (2.2 eq.), silica gel and **8** (20 mol%). [g] The absolute configuration was determined by X-ray crystal structure analysis of compound **5i**.[13] [h] Reaction was performed at rt.

complex products, the yields of the final products are acceptable. The absolute configuration of the products was determined by X-ray crystal structure analysis of compound **5i**.[13] Furthermore **5a–j** can be used as scaffolds for the synthesis of a broad range of structurally complex molecules.

To the best of our knowledge, the quadruple reaction cascade that we have developed is the first example of a complex asymmetric cascade reaction in which the course of the reaction can be controlled by merely changing the substrate concentration. Similar to enzymatic processes in the metabolism, it is possible to selectively synthesize the quadruple product **5** or the domino product **4** by simply increasing or decreasing the aldehyde concentration. With regard to the mechanism, the quadruple reaction introduced here is an example of a Lewis base catalyzed iminium–enamine–iminium–enamine activation sequence.

In summary, we have developed a substrate regulated, asymmetric, metal-free reaction in which the reaction pathway can be controlled *via* the concentration. Depending on the concentration of the individual substrates, targeted selection between a double and a quadruple reaction can be made. The products of both reaction cascades were isolated for a wide range of substrates in good to very good yields and with excellent enantioselection.

With the aid of this first example of chemoselective reaction control through substrate concentration it is possible, with resourceful reaction planning, to access numerous complex products with high functional diversity and good stereoselectivity, using simple educts in only a few reaction steps as is often seen in nature. This is an example of synthetic chemistry mimicking nature in its precise reaction control. Therefore, the reaction presented above is bound to serve as a template for further studies of efficient reaction control through the substrate concentration.

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