Organocatalytic asymmetric synthesis of polyfunctionalized 3-(cyclohexenylmethyl)-indoles *via* a quadruple domino Friedel–Crafts-type/Michael/Michael/aldol condensation reaction†

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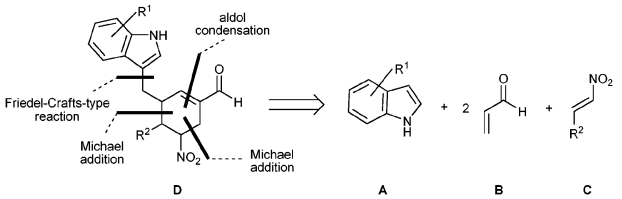
A new organocatalytic quadruple domino Friedel–Crafts-type/Michael/Michael/aldol condensation reaction has been developed. In this one-pot multi-component process acrolein, various indoles and nitroalkenes are used as starting materials. The diphenylprolinol TMS-ether catalysis provides a straightforward and efficient entry to 3-(cyclohexenylmethyl)-indoles bearing three stereogenic centers in moderate to excellent yields (23–82%) and excellent stereoselectivities (dr = 91 : 9 to >95 : 5, ee = 94 to >99%).

In the last decade organocatalysis attracted much attention and became a focal point of asymmetric synthesis.[1] One development is designing new cascade reactions, in which complex molecules are constructed from simple precursors in one single operation, thereby avoiding the isolation of reaction intermediates and time-consuming protecting group manipulations. Furthermore, these domino processes are often accompanied by excellent stereoselectivities. Due to these advantages, organocatalytic domino reactions have been intensively investigated by many research groups in recent years.[2–4]

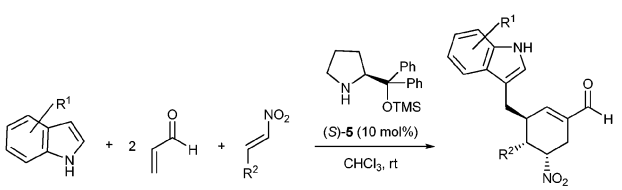
Indole is a ubiquitous subunit present in a large number of alkaloids with biological and pharmacological activities.[5] Employing indole or its derivatives as a component in cascade, tandem or one pot reactions provides direct access to complex indole alkaloids. For example, Franzén and Fisher reported a highly enantioselective one pot synthesis of indolo[2,3*a*]-quinolidines using an organocatalytic Michael addition as the initial step followed by an intramolecular acid-catalyzed Friedel–Crafts-type reaction.[4r] Very recently, our group and Wang *et al*. developed independently a domino aza-Michael/aldol condensation reaction with indole-2-carbaldehydes and enals as starting materials furnishing 3*H*-pyrrolo[1,2-*a*]indoles in a highly enantioselective manner.[4n,w] 3-(Cyclohexylmethyl)-1*H*-indole is a core structure of suaveolindole, which shows activity against Gram-positive and methicillin-resistant bacteria.[6] We envisaged a quadruple cascade using indoles (**A**), acrolein (**B**), and nitroalkenes (**C**) as components to afford polysubstituted functionalized 3-(cyclohexenylmethyl)-1*H*-indoles (**D**) as the domino products (Scheme 1). This cascade is initiated by a Friedel–Crafts reaction after an iminium activation mode,[7] followed sequentially by an enamine- and an iminium-mediated



Scheme 1 Retrosynthetic analysis of the domino Friedel–Crafts-type/Michael/Michael/aldol condensation reaction.

Michael addition.[8] After an intramolecular aldol-condensation, four C–C bonds are formed and the domino product is constructed bearing three stereogenic centers. To the best of our knowledge, only three examples of an organocatalytic quadruple cascade have been published so far.[4o–q] Additionally, 3-(1*H*-indol-3-yl)propanals are not commercially available and are usually synthesized in two steps starting from indole-3-acetic acids[9a,b] or in one step from tryptophans.[9c] Therefore, involving these indolylpropanals as a component in our triple cascade[4e,j] would necessitate additional manual operations.

Diphenylprolinol TMS-ether **5**[10,11] shows good catalytic activity and excellent stereocontrol in the triple cascade reactions.[4e,f,j] Thus, we used it as a catalyst again in the new quadruple cascade. Initially, we performed the reaction of indole (**1a**), acrolein (**2**) and β-nitrostyrene (**3a**) using toluene as solvent (Scheme 2). The reaction provided the desired product **4a** only in a very low yield but with high diastereoselectivity (Table 1, entry 1). It was observed that a large mount of polymer was formed during the reaction. In addition, the analytical TLC revealed that the conversion of indole (**1a**) was completed within an hour. Furthermore, we carried out the reaction involving only acrolein (**2**) and indole (**1a**) under the catalysis of **5** or pyrrolidine, which also gave much polymer but only traces of 3-(1*H*-indol-3-yl)propanal. The formation of the polymer may be attributed to a competing Michael addition with acrolein (**2**) as acceptor. To avoid the polymerisation we



Scheme 2 Asymmetric synthesis of 3-(cyclohexenylmethyl)-indole **4** from indoles **1**, acrolein (**2**) and nitroalkenes **3**.

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Table 1 Optimization of reaction conditions for the quadruple cascade[a]

Entry	Solvent	*t*/d	Yield[b] (%)	dr[c]	ee[d] (%)
1	Toluene	1	<5	>95 : 5	n.d.[e]
2	Toluene	3	54	>95 : 5	91
3	THF	3	48	>95 : 5	93
4	$CHCl_3$	1	55	>95 : 5	94

[a] Reactions were performed on a 1 mmol scale of β-nitrostyrene (**3a**) using 1.5 equiv. of indole (**1a**), 3.0 equiv. acrolein (**2**) and 10 mol% catalyst **5** at RT in 4.0 mL solvent. [b] Yield of isolated product. [c] Determined on isolated product by ^{1}H-NMR-spectroscopy. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Not determined.

conducted the reaction in toluene by slowly adding acrolein (**2**) within 12 h with the assistance of syringe pump. Encouragingly, the polymerisation was effectively hampered and the reaction was completed after 3 days affording the domino product **4a** in a yield of 54% and very high stereoselectivity (dr >95 : 5, ee = 91%, Table 1, entry 2).[12] The yield is quite good considering that it is a quadruple cascade with three intermolecular reactions where many side-reactions could compete. Next a brief solvent screening was undertaken. Employing THF as solvent no improved results with respect to yield and stereoselectivity were achieved (Table 1, entry 3). Performing the reaction in chloroform, the reaction time was shortened to one day and the product was obtained with a better yield (55%). Importantly, the stereoselectivity remained excellent (dr >95 : 5, ee = 94%, Table 1, entry 4).

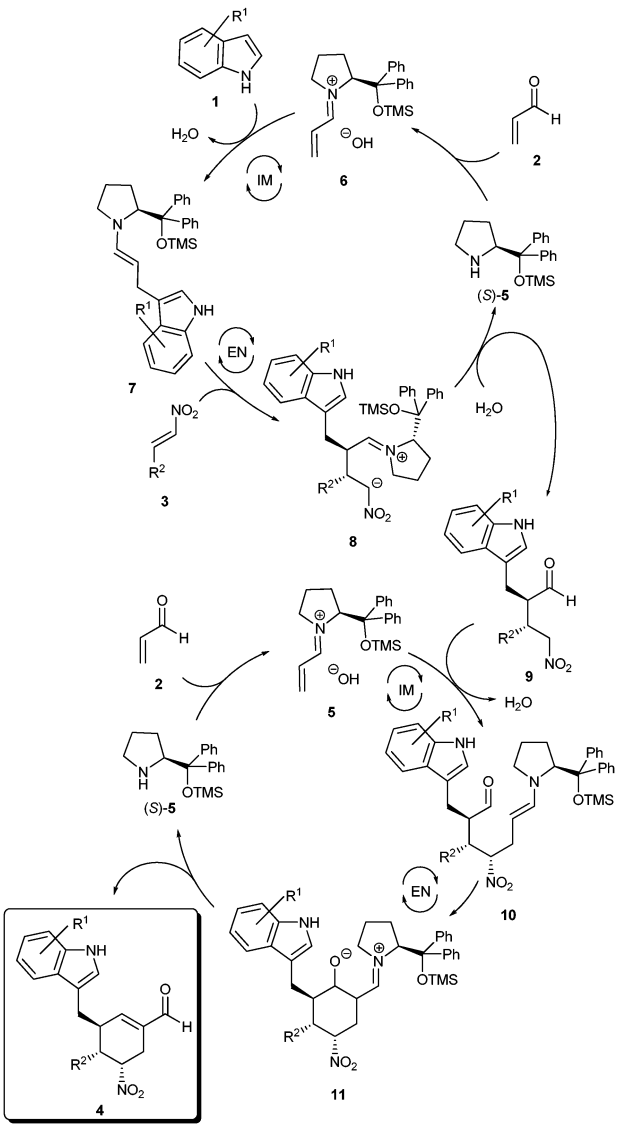
The scope of this domino reaction was evaluated by varying the structure of both indoles **1** and nitroalkenes **3**. Firstly, we reacted indole (**1a**) and acrolein (**2**) with different nitroalkenes **3**. Employing electron-deficient *o*-bromo nitrostyrene (**3b**) as substrate, the product **4b** was obtained in good yield (55%) and excellent stereoselectivity (dr >95 : 5, ee > 99%) (Table 2). In the case of the electron-rich piperonyl nitroalkene (**3c**), the reaction proceeded with an excellent yield (82%) and stereocontrol (dr >95 : 5, ee > 99%). Furthermore, the heteroaromatic nitro-olefin **3d** turned out to be a reactive component for this domino reaction, too, furnishing the product **4d** in a moderate yield (30%) and excellent stereoselectivity (dr >95 : 5, ee > 99%). One limitation of the substrate spectrum was observed in the case of the aliphatic nitroalkene **3e**, which did not lead to the desired product. Next several substituted indoles **1b–f** were examined for the quadruple cascade. In general, the reactions occurred with various indoles bearing electron-withdrawing or donating groups in different positions, yielding the corresponding products **4f–j** in moderate to good yields (23–54%) and excellent stereoselectivities (dr = 91 : 9 to >95 : 5, ee = 97 to >99%). The higher diastereomeric ratios in comparison to our previous triple cascade may be attributed to the more sterically demanding intermediates bearing the indol moiety.

Table 2 Yields and stereoselectivities of the organocatalytic quadruple cascade[a]

4	R^1	R^2	Yield[b] (%)	dr[c]	ee[d] (%)
a	H (**1a**)	Ph (**3a**)	55	>95 : 5	94
b	H (**1a**)	2-BrC_6H_4 (**3b**)	48	>95 : 5	>99
c	H (**1a**)	Piperonyl (**3c**)	82	>95 : 5	>99
d	H (**1a**)	2-Furyl (**3d**)	30	>95 : 5	>99
e	H (**1a**)	Br–$(CH_2)_4$– (**3e**)	0	—	—
f	1-Me (**1b**)	Ph (**3a**)	54	>95 : 5	97
g	5-Br (**1c**)	Ph (**3a**)	50	>95 : 5	>99
h	4-Br (**1d**)	Ph (**3a**)	23	>95 : 5	>99
i	6-F (**1e**)	Ph (**3a**)	54	>95 : 5	97
j	5-OMe (**1f**)	Ph (**3a**)	32	91 : 9[e]	99

[a] Reactions were performed on a 1 mmol scale of nitroalkene **3** using 1.5 equiv. of indole **1**, 3.0 equiv. acrolein (**2**) and 10 mol% catalyst **5** at RT in 4.0 mL solvent. [b] Yields of isolated product. [c] Determined on isolated product by ^{1}H-NMR-spectroscopy. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Determined on isolated product by ^{13}C-NMR-spectroscopy.

A plausible catalytic cycle for the domino reaction is described in Scheme 3. In the first step acrolein (**2**) is activated by the chiral amine catalyst (*S*)-**5** through the formation of the vinylogous iminium ion **6**, with which the indoles (**1**) perform an intermolecular Friedel–Crafts-type reaction. The resulting enamines **7** subsequently undergo an intermolecular Michael addition to the nitroalkenes **3** affording the intermediates **8**. Next hydrolysis of **8** leads to aldehydes **9**, which react with the iminium ion **6** to give the enamine intermediates **10**. After an



Scheme 3 Proposed catalytic cycle of the quadruple organo-cascade.

intramolecular enamine-mediated aldol reaction, intermediates **11** are formed, which undergo dehydration and hydrolysis to afford the title indoles **4** as products, while the catalyst is regenerated for the next catalytic cycle.

In summary, we have developed a novel organocatalytic quadruple cascade reaction of indoles, acrolein and nitroalkenes under diphenylprolinol TMS-ether catalysis following an iminium/enamine/iminium/enamine activation sequence. This multi-component domino process provides an efficient and direct asymmetric synthesis of polysubstituted functionalized 3-(cyclohexenylmethyl)-indoles controlling three stereogenic centers in moderate to high yields (23–82%) and excellent stereoselectivities (dr = 91 : 9 to >95 : 5, ee = 94 to >99%).

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