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Quadruple Domino Organocatalysis: An Asymmetric Aza-Michael/Michael/Michael/Aldol Reaction Sequence Leading to Tetracyclic Indole Structures with Six Stereocenters

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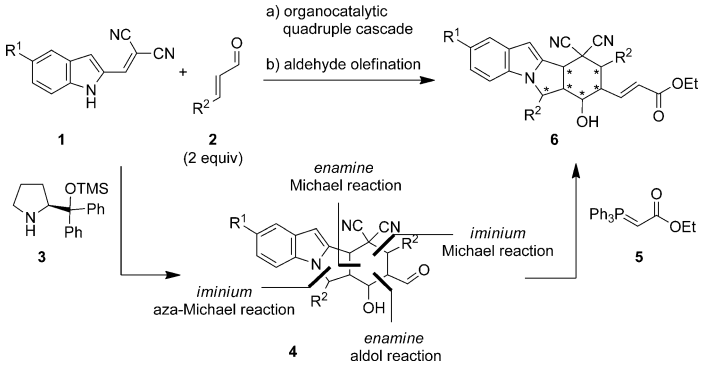
Dedicated to Professor Dieter Seebach on the occasion of his 75th birthday

Organocatalyzed domino reactions by now are widely regarded as powerful tools in contemporary organic chemistry. The progress in the development of new domino reactions has been extremely rapid,[1] and today they are increasingly applied in the synthesis of natural products and other biologically active compounds, such as pharmaceuticals and agrochemicals.[2] Secondary amines, like proline and derivatives thereof, are especially useful organocatalysts, because they are capable of promoting a variety of transformations by their complementary iminium-ion and enamine activation modes, thereby allowing for an efficient activation of both donor- and acceptor-type molecules. In addition, secondary-amine-catalyzed domino reactions are generally compatible with numerous functional groups, avoid protecting groups,[3a] are redox-,[3b] atom-, and step-economic,[3c,d] and can often imitate biosynthetic pathways.[3e,f] Accordingly, a large number of organocatalyzed domino reactions,[4] triple,[5] and even quadruple cascades[6] were developed in the last few years by the suitable combination of the different activation modes.

The indole moiety is arguably the most abundant heterocycle found in nature. Because of the great importance of indole-based structures, a lot of effort has been devoted to gain novel entries into this group of molecules. Indoles are also suitable substrates for organocatalytic transformations,[7] of which most of the publications deal with the enantioselective alkylation at the C-3[8] or C-2[9] position of the pyrrolidine ring. In contrast, enantioselective N-alkylations are rarely reported,[10] most likely owing to the insufficient nucleophilicity of the indole NH group and the fact that amino-based catalysts are unable to deprotonate unsubstituted indoles to obtain a sufficiently nucleophilic species. The introduction of an electron-withdrawing substituent at the C-2 position, however, reduces the pK_A value of the NH position dramatically.[11] Based on this concept, we[10a]—and independently the group of Wang and co-workers[10b]—developed the organocatalytic addition of indole-2-carbaldehydes to α,β-unsaturated aldehydes to give optically pure 3*H*-pyrrolo[1,2-*a*]indoles in high yields. Herein, we extend the chemistry of related acidic 2-substituted indoles and report a new quadruple domino reaction, which employs a sequential iminium–enamine–iminium–enamine activation approach to synthesize the tetracyclic structures shown in Scheme 1.



Scheme 1. Asymmetric one-pot synthesis of polyfunctionalized tetracyclic indole derivatives **6** by an organocatalytic three-component quadruple cascade, followed by aldehyde olefination.

The organocatalytic quadruple cascade, leading to tetracyclic aldehydes **4**, is initiated by the asymmetric aza-Michael-type N-alkylation of indole-2-methylene malononitrile derivatives **1** to different α,β-unsaturated aldehydes **2** under iminium activation. The corresponding enamine derivative of intermediate **A** then reacts in a Michael addition to the methylene malononitrile to give tricyclic malononitrile derivatives **B**, which can again act as nucleophiles to another equivalent of the activated α,β-unsaturated aldehyde. Michael addition leads to intermediates **C**, suitable substrates for an intramolecular aldol reaction to give tetracyclic aldehydes **4** (Scheme 2). This reaction sequence readily gives

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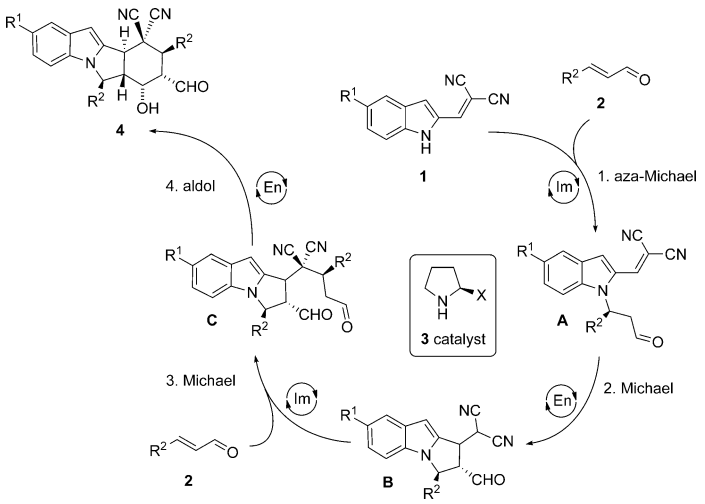


Scheme 2. Proposed mechanism for the organocatalytic asymmetric quadruple domino reaction. Only the putative catalyst-free intermediates **A**–**C** are shown for clarity. Im = iminium activation; En = enamine activation.

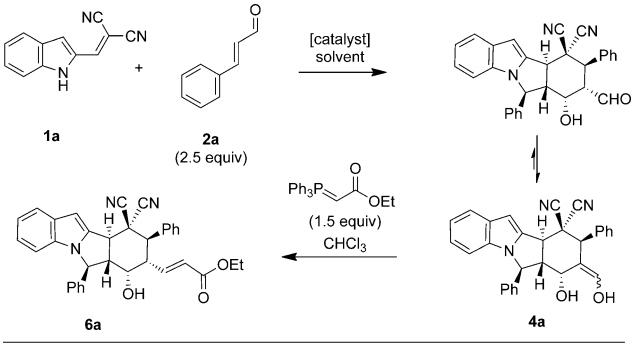
access to tetracyclic indole skeletons with N-fused 5-membered rings annulated to cyclohexanes, a structural motif that is also found in some bisindole alkaloids, namely the borreverines.[12]

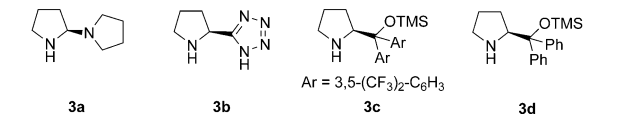
We started our investigation of this sequence with the reaction between cinnamaldehyde (**2a**) and 2-((1*H*-indol-2-yl)-methylene) malononitrile (**1a**), which is easily obtained from indole-2-carbaldehyde and malonitrile in a Knoevenagel reaction (Table 1).[13]

By using dichloromethane as solvent, the (*S*)-TMS-diphenylprolinol catalyst (**3d**) gave a clean conversion of the starting materials (Table 1, entry 4), while all other tested catalysts **3a–c** were ineffective in this reaction (Table 1, entries 1–3). The isolation of the desired quadruple domino product **4a** by flash chromatography revealed that the product aldehyde mainly exists in its corresponding enol form. After due consideration, we decided to trap product **4a** with the stabilized Wittig reagent **5** and convert it into the well-defined ester **6a**. With the diastereo- and enantiomerically pure product **6a** in hand, we performed a short solvent screening. The best results were obtained by using 2.5 equivalents of cinnamaldehyde and 15 mol% of (*S*)-TMS-diphenylprolinolether in chloroform (0.5 M; Table 1, entry 9). With lower catalyst loadings (5 mol% of **3d**), the yield decreased dramatically, while higher catalyst loadings (25 mol% of **3d**) gave no significant improvement of the yield and stereoselectivity of the reaction. In addition, the organocatalytic cascade and subsequent aldehyde olefination could be conveniently performed in a one-pot fashion with no detrimental impact on the reaction outcome (Table 1, entry 10).

Having established the optimum reaction conditions, we started to screen the scope of the quadruple domino reaction (Table 2). Different aromatic α,β-unsaturated aldehydes (electron rich and electron poor) were tested, and the products **6a–k** could be isolated in moderate to excellent yields

Table 1. Optimization of the reaction conditions for the quadruple cascade of indole derivative **1a** and cinnamaldehyde (**2a**).



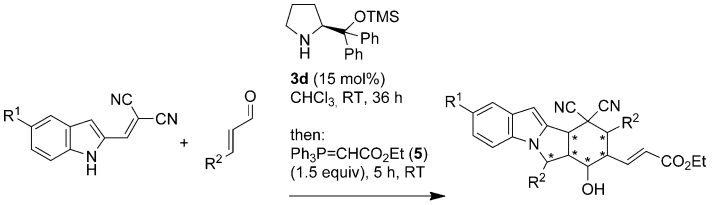


3a 3b 3c 3d

Entry[a]	Cat.	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**3a**	CH_2Cl_2	traces	n.d.	n.d.
2	**3b**	CH_2Cl_2	traces	n.d.	n.d.
3	**3c**	CH_2Cl_2	5	n.d.	n.d.
4	**3d**	CH_2Cl_2	49	>20:1	93
5	**3d**	PhMe	33	>20:1	94
6	**3d**	THF	15	>20:1	85
7	**3d**	EtOH	12	>20:1	89
8	**3d**	MTBE	41	>20:1	41
9	**3d**	$CHCl_3$	67	>20:1	97
10[e]	**3d**	$CHCl_3$	70	>20:1	96

[a] All reactions were performed on a 0.75 mmol scale with catalyst **3** (15 mol%) and solvent (1.5 mL) for 48 h. [b] Yield of isolated product after flash chromatography. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined by HPLC on a chiral stationary phase. [e] The organocatalytic quadruple cascade and aldehyde olefination were performed in a one-pot procedure. MTBE = methyl *tert*-butyl ether; n.d. = not determined.

Table 2. Scope of the organocatalytic reaction sequence.

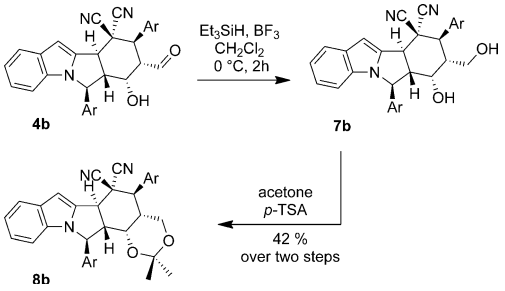


Entry	Product	R^1	R^2	Yield [%][a]	*ee* [%][b]
1	**6a**	H	Ph	70	97
2[d]	*ent*-**6b**	H	*p*-OMe-C_6H_4	70	96
3	**6c**	H	*p*-Cl-C_6H_4	60	99
4	**6d**	H	*p*-F-C_6H_4	63	92
5	**6e**	H	*p*-NMe_2-C_6H_4	25	92
6	**6f**	H	*p*-biphenyl	43	99
7	**6g**	H	3,4-OCH_2O-C_6H_3	45	94
8	**6h**	H	2-furyl	33	78
9	**6i**	Me	Ph	54	98
10	**6j**	OMe	Ph	63	98
11[c]	*ent*-**6k**	Br	Ph	60	91

[a] Yield of isolated, diastereomerically pure (d.r. > 20:1) product after flash chromatography. [b] Determined by HPLC on a chiral stationary phase. [c] The reaction was performed with the opposite enantiomer of the catalyst *ent*-**3d**.

(25–70%), good to excellent enantioselectivities (91–99% *ee*), and as just a single diastereomer (>20:1 d.r.). Heteroaromatic groups, such as furyl, were also suitable substituents, but the yield and the enantioselectivity decreased. Substitution at the 5 position of the indole had no big influence on either yield and/or selectivity. The 3-methyl-substituted analogue of **1** was unreactive and also aliphatic aldehydes did not give any clean conversion. A one-pot combination of the organocatalytic domino reaction and aldehyde olefination was performed for entries 1–3 and 9–11 of Table 2 and further increased the efficiency and simplicity of the overall sequence. Since the quadruple cascade could not be initiated by achiral amine catalysts, like pyrrolidine, all reactions were performed equally successful with both enantiomers of the catalyst to obtain racemic standards of the products.

Further functionalization of the casade products, besides the Wittig reaction, was achieved by reduction and acetalization. While $NaBH_4$ was ineffective in reducing the strongly enolized aldehyde **4b**, the reduction succeeded with the Et_3SiH/BF_3 system. Transformation of the obtained 1,3-diol **7b** by stirring in acetone with a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) gave acetal **8b** as a single diastereomer (Scheme 3).



Scheme 3. Derivatization of the cascade product **4b** by reduction and acetalization. Ar = *p*-MeO-C_6H_4.

The relative and absolute configuration of the products was elucidated by NOESY experiments and X-ray crystal-structure analysis of compound *ent*-**6k** (Figure 1). Surprisingly, crystallization from 1,4-dioxane exclusively gave racemic crystals, despite an initial enantiomeric excess of 91% *ee*. Crystallization from benzene/*n*-hexane finally resulted in a suitable, enantiomerically pure single crystal. The observed stereochemical outcome of the N-alkylation is in accordance with our results previously obtained in the Michael addition of indole-2-carbaldehyde.[10a,b] The addition of the malonitrile group to the second equivalent of cinnamaldehyde showed the same sense of asymmetric induction as described previously by Jørgensen,[14] which indicates a decisive role of catalyst-controlled asymmetric induction by the Jørgensen/Hayashi catalyst.

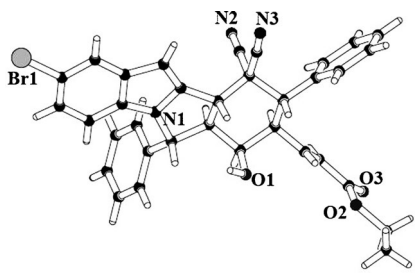


Figure 1. Molecular structure of one of the two independent molecules in crystals of **6k**.[15]

In conclusion, we have developed an organocatalytic three-component quadruple cascade reaction between indole-2-methylene malononitriles and α,β-unsaturated aromatic aldehydes, giving rise to tetracyclic double-annulated indole derivatives. The highly enolized aldehydes obtained were further derivatized in a one-pot fashion, thus producing six novel stereogenic centers, four newly formed C,C-bonds, and one C,N-bond in both a diastereo- and enantiomerically highly selective fashion. The very high degree of molecular complexity, obtained from simple starting materials and with minimal synthetic effort, and the excellent stereoselectivity demonstrates again the enormous synthetic utility of the young and rapidly growing field of organocatalytic domino reactions.

Experimental Section

Organocatalytic three-component quadruple cascade and aldehyde olefination (product 6a as an example): A solution of 2-((1*H*-indol-2-yl)methylene)malononitrile (0.75 mmol), cinnamaldehyde (1.875 mmol, 2.5 equiv), and (*S*)-TMS-diphenylprolinol catalyst (15 mol%) in chloroform (1.5 mL) was stirred for 36 h at RT. Phosphorane $Ph_3P=CHCO_2Et$ (1.5 equiv) was then added and the reaction mixture was stirred for 5 h at RT. The solvent was removed under reduced pressure and the crude product was directly purified by flash column chromatography on silica gel (eluent: pentane/diethyl ether 1:3) to give the product **6a** (277 mg, 0.53 mmol, 70%) as a yellow solid.

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Keywords: asymmetric synthesis · domino reactions · one-pot reactions · organocatalysis · quadruple cascade

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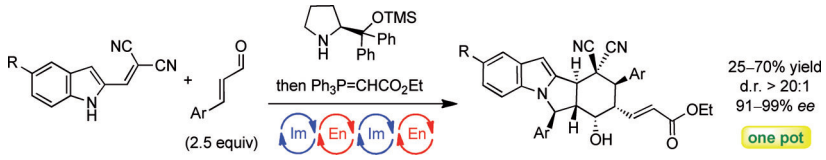

Quadruple domino/Wittig–one pot: An organocatalytic, asymmetric, three-component quadruple cascade, which leads to tetracyclic double-annulated indole derivatives, is described. The domino products were further derivatized by aldehyde olefination under one-pot conditions to obtain complex isoindolo[2,1-*a*]indole derivatives bearing six stereogenic centers in a highly stereoselective fashion.

Domino Organocatalysis

D. Enders, A. Greb, K. Deckers, P. Selig, C. Merkens* ..... ▮▮▮▮–▮▮▮▮

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