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Diastereoselective Synthesis of Functionalized Angularly-Fused Tetracycles *via* an Organocatalytic Quadruple Reaction Sequence

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Abstract: An efficient diastereoselective strategy to access complex structural tetracycles was described through an organocascade quadruple reaction sequence between (*E*)-2-(3-arylallylidene)-1*H*-indene-1,3(2*H*)-diones and β-keto esters. The reaction proceeded through remote 1,6-addition followed by sequential 1,4-addition and aldol/aldol reactions to generate angularly-fused carbocyclic motifs with favourable to excellent yields (up to 94%) and diastereoselectivities (up to >20:1 *dr*). An enantioselective organocascade approach was attempted to yield densely functionalized tetracycles containing seven chiral centres including a quaternary centre.

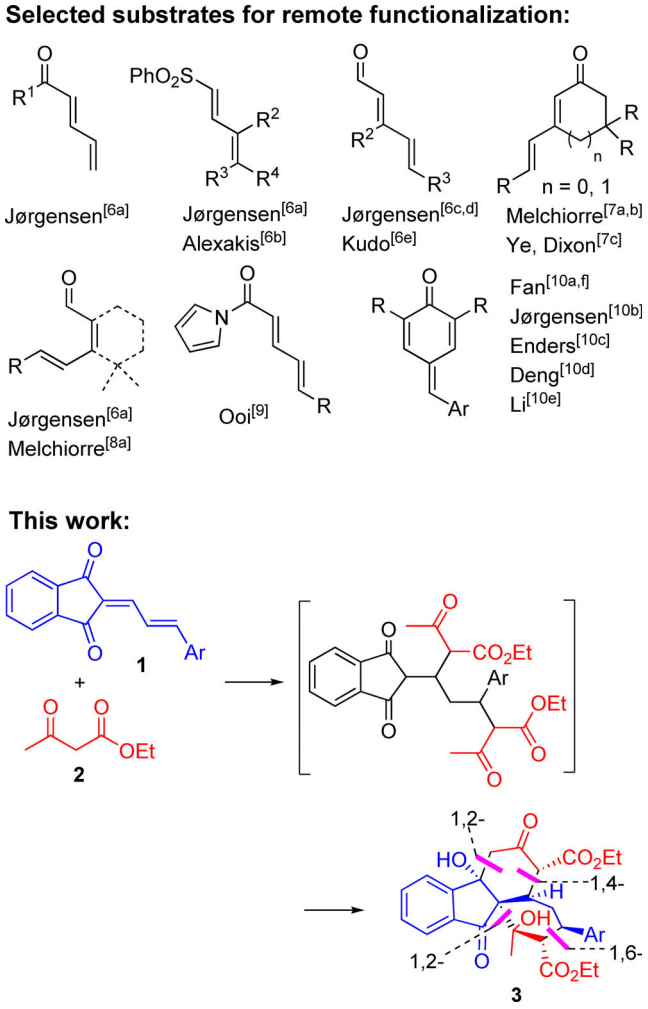
Keywords: indane-1,3-diones; Michael reaction; organocatalysis; quadruple reaction sequence

Asymmetric amino organocatalysis has advanced to enable the generation of remote stereogenic centres with optimal regio- and stereoselectivities by raising the highest occupied molecular orbital (HOMO) of the nucleophile through dienamine,[1] trienamine,[2] cross-conjugated trienamine,[3] and tetraenamine[4] activation modes. The principle of vinylogy[5] can also be applied for the lowering of the lowest unoccupied molecular orbital (LUMO) strategy of conjugated carbonyl electrophiles (iminium ion catalysis).[6–10] This vinylogy-based strategy is implemented for linear dienals, diene sulfones, and extended cyclic dienones to achieve structurally diverse motifs.[11] The recent development of organocascade reactions has become an economical and powerful synthetic tool for producing highly complex structural motifs in a sustainable manner.[12] In addition to metal-mediated protocols,[13] the remote asymmetric 1,6-addition was developed under metal-free conditions to afford enantioenriched structural skeletons. However, the merging of the 1,6-addition in triple/quadruple cascade sequences remains elusive.[14] This approach is synthetically significant as it can avail more reactive sites that are available either in the substrates or in key intermediates.

The use of indane-1,3-dione and 2-arylideneindane-1,3-dione derivatives in organocascade/domino reactions has been extensively studied.[15] Similarly, the exquisitely explored remote 1,6-addition on activated 2,4-diene systems has also been demonstrated. However, to the best of our knowledge, no examples of a 1,6-addition employing arylallylideneindane-1,3-diones have been reported, although this skeleton is abundant in numerous biologically active motifs.[16] Building angularly-fused tetracyclic core skeletons is a laborious process, that typically involves various synthetic transformations and these skeletons prevail in a myriad of biologically active molecules.[17] Herein, we report an unprecedented organocascade quadruple reaction sequence to produce highly complex structural motifs containing malleable functional groups *via* a 1,6-/1,4-/aldol/aldol sequence (Scheme 1).

We optimized the conditions of the reaction between phenylallylideneindane-1,3-dione **1a** and ethyl acetoacetate **2a** by employing various hydrogen bonding (HB) catalysts (**I–IV**, 20 mol%) in combination with 1,4-diazabicyclo[2.2.2]octane (DABCO, 20 mol%) as additive in toluene. After the preliminary examination, the HB catalyst **III** was found to be superior among the HB catalysts **I–IV** affording the desired product with a favourable yield (84% yield) and diastereoselectivity (20:1 *dr*) (Table 1, entries 1–4). We also observed that only DABCO as additive was effective for the cascade process, and inferior results were obtained for other additives, namely DMAP, Et_3N and DBU (Table 1, entries 5–7). Furthermore, the diastereoselectivity of the cascade product **3a** improved when the reaction was conducted in $CHCl_3$ (>20:1 *dr*) (Table 1, entries 8–10).

The optimized conditions were generalized by using various arylallylideneindan-1,3-dione derivatives (**1b–1g**) containing different aryls with electron-releasing and electron-withdrawing groups, heteroaryls and dif-

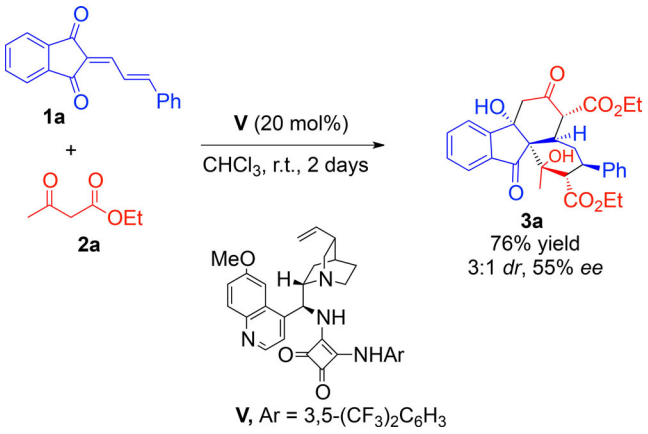


Scheme 1. Previous activated dienes utilized for organocatalytic 1,6-additions and indane-1,3-dione-derived diene for the organocascade quadruple reaction.

ferent β-keto esters. The organocascade reaction between electron-rich diene (**1b**) and ethyl acetoacetate generated the corresponding angularly-fused carbocycle (**3b**) with a favourable yield (88%) and diastereoselectivity (12:1 *dr*) (Table 2, entry 1). Subsequently, the optimized conditions were examined using moderate to strong electron-withdrawing groups on the aryl group of the arylallylideneindane-1,3-diones (**1d**–**1f**), and the reaction generated the corresponding cascade products (**3d**–**3f**) with moderate to favourable yields (53–85%) and diastereoselectivities (up to 14:1 *dr*) (Table 2, entries 3–5). The use of 2-furylallylideneindane-1,3-dione (**1g**) generated the cascade product (**3g**) with a favourable yield (76%) and excellent diastereoselectivity (>20:1 *dr*) (Table 2, entry 6). The substrate scope was further extended using varying β-keto esters with *O*-alkyl groups of different sizes. All esters (**2b**–**2g**) afforded the corresponding cascade products (**3h**–**3m**) with favourable yields (up to 94%) and excellent diastereoselectivities (>20:1 *dr*) (Table 2, entries 7–12). However, as expected, sterically more hindered *tert*-butyl 3-oxobutanoate (**2e**) generated the desired product **3k** with a moderate yield and diastereoselectivity after 7 days (55% yield, 12:1 *dr*) (Table 2, entry 10). The organocascade process was compatible even with the more reactive pentane-2,4-dione (**2h**), because it afforded the spirofused product **3n** with a favourable yield (81%) and excellent diastereoselectivity (>20:1 *dr*) (Table 2, entry 13).

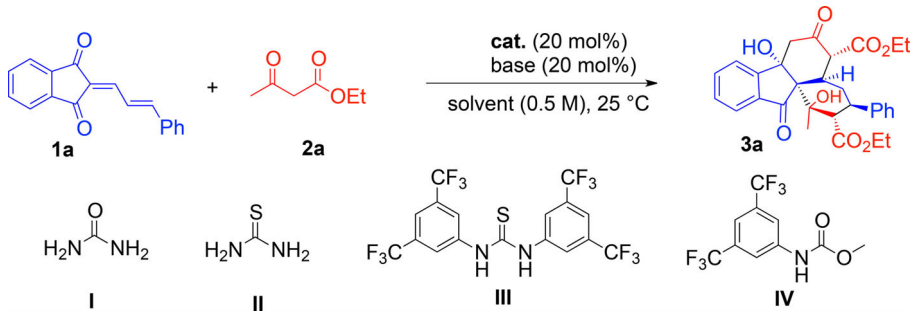
We also adopted an enantioselective organocascade approach to synthesize enantioenriched, functionalized tetracyclic skeletons with seven chiral centres. The organocascade process should address the following issues: (i) delivering one enantiomer out of 128 possible stereoisomers, (ii) generating the chiral angularly-fused tetracyclic core, (iii) building seven chiral centres with absolute control over enantioselectivity, and (iv) the reactive site in the initial 1,6-addition is distal to the chiral environment and hence traversing the chiral information might be practically challenging. In this scenario, to the best of our efforts, the enantioenriched angularly-fused tetracycle (**3a**) was obtained in favourable chemical yield (76%) with moderate enantio- and diastereoselectivity (3:1 *dr*, 55% *ee*) under quinine-derived bifunctional squaramide catalysis (Scheme 2).[18]

A plausible mechanism for the organocascade quadruple reaction sequence was proposed in Scheme 3. The reaction was initiated by the 1,6-addition between ethyl acetoacetate and arylallylideneindane-1,3-dione through HB catalysis to lead to the formation of zwitterion intermediate **4**. The protonation and double-bond isomerization in **4** would generate alkylideneindane-1,3-dione derivative **5** which would readily react with the second equivalent of ethyl acetoacetate **2a** through 1,4-addition to yield **6**. Consequently, the intermediate **6** underwent annulation through a facile intramolecular aldol reaction to



Scheme 2. Enantioselective approach for the organocatalytic process.

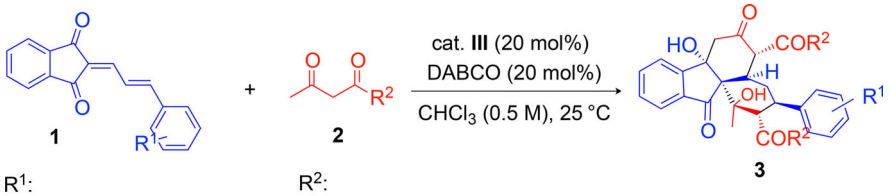
Table 1. Optimization for the organocascade reaction.[a]



Entry	Catalyst	Additive	Solvent	Time [days]	Yield [%][b]	*dr*[c]
1	**I**	DABCO	toluene	4	82	>20:4:1
2	**II**	DABCO	toluene	4	87	4:1
3	**III**	DABCO	toluene	3	84	20:1
4	**IV**	DABCO	toluene	4	87	>20:3:1
5	**III**	DMAP	toluene	3	51	19:1
6	**III**	Et_3N	toluene	2	89	14:1
7	**III**	DBU	toluene	2	33	1:3
8	**III**	DABCO	CH_2Cl_2	3	67	3:1
9	**III**	DABCO	$CHCl_3$	4	82	>20:1
10	**III**	DABCO	THF	3	80	9:1

[a] The reactions were carried out with **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.22 mmol, 2.2 equiv.) using organocatalyst **I–IV** (20 mol%) at 25 °C in the given solvent (0.5 M).
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the crude material.

Table 2. Substrate scope for the organocascade quadruple reaction.[a]

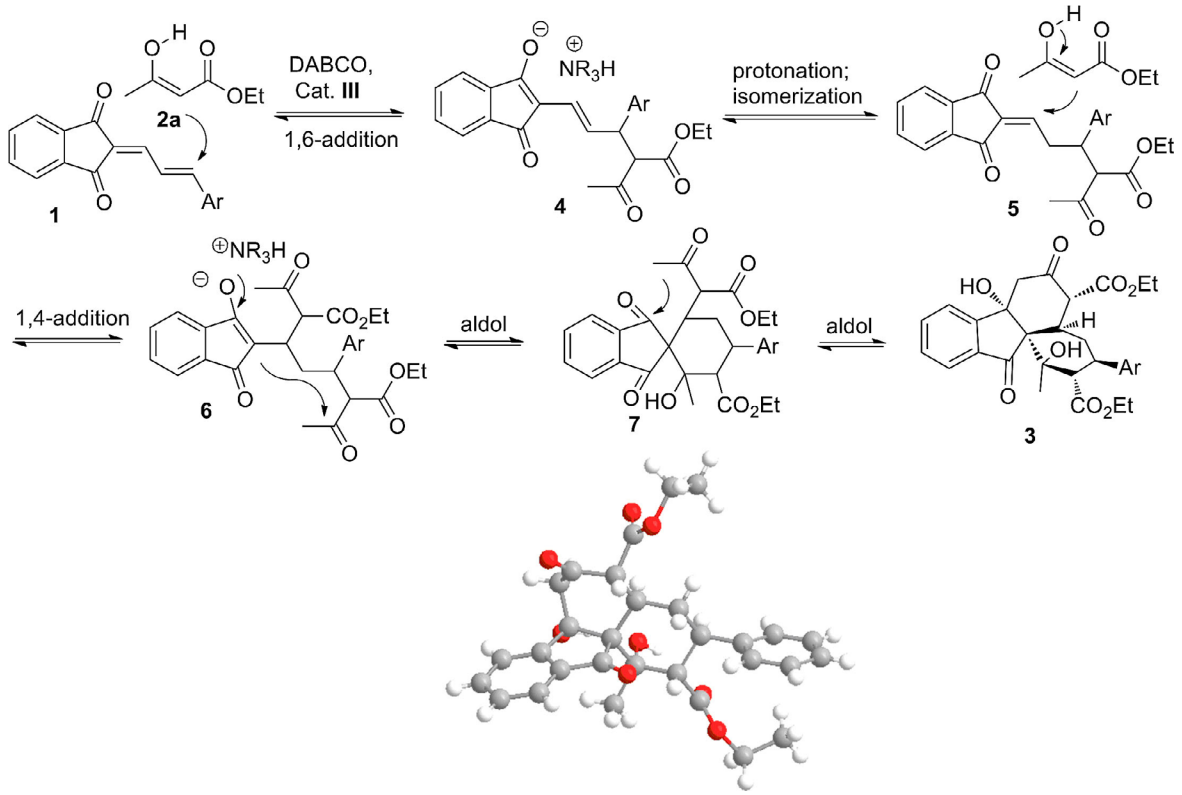


R^1:
1b = 4-OMe **1e** = 4-NO_2
1c = 4-Cl **1f** = 2-NO_2
1d = 4-Br **1g** = 2-furyl

R^2:
2a = OEt **2e** = O-*t*-Bu
2b = OMe **2f** = O-(4-pentenyl)
2c = O-*n*-Pr **2g** = OBn
2d = O-*i*-Pr **2h** = Me

Entry	R^1	R^2	Time [days]	**3**	Yield [%][b]	*dr*[c]
1	4-OMe	OEt	6	**3b**	88	12:1
2	4-Cl	OEt	5	**3c**	53	10:1
3	4-Br	OEt	6	**3d**	68	8:1
4	4-NO_2	OEt	4	**3e**	67	9:1
5	2-NO_2	OEt	6	**3f**	85	14:1
6	2-furyl	OEt	6	**3g**	76	>20:1
7	H	OMe	6	**3h**	58	>20:1
8	H	O-*n*-Pr	6	**3i**	94	>20:1
9	H	O-*i*-Pr	7	**3j**	75	>20:1
10	H	O-*t*-Bu	7	**3k**	55	12:1
11	H	O-(4-pentenyl)	6	**3l**	78	>20:1
12	H	OBn	6	**3m**	84	>20:1
13	H	Me	6	**3n**	81	>20:1

[a] All reactions were carried out with **1** (0.1 mmol, 1.0 equiv.), **2** (0.22 mmol, 2.2 equiv.) using organocatalyst **III** (20 mol%) at 25 °C in $CHCl_3$ (0.5 M).
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the crude material.



Scheme 3. Tentative mechanism for the organocatalytic process.

afford the spiro keto ester **7**, which would proceed through an aldol reaction to produce angularly-fused carbocycles **3**. The relative stereochemistry of the products was unequivocally assigned from a single crystal X-ray structural analysis of **3a**.[19]

In conclusion, we have demonstrated an interesting diastereoselective organocascade reaction between arylallylideneindane-1,3-dione and β-keto esters for synthesizing densely functionalized angularly-fused tetracycles through a consecutive sequence. Two salient features of the protocol are worth noting: the reaction was initiated by an exclusive 1,6-addition over the facile 1,4-addition,[20] and the two consecutive aldol reactions were executed with optimal regio- and chemoselectivities which minimized the generation of several undesirable products. To the best of our knowledge, this is the first example of a quadruple cascade sequence that efficiently afford functionalized spiro-fused carbocycles. In addition, an enantioselective organocascade approach was adopted to yield tetracycles with seven chiral centres including a quaternary centre through remote asymmetric 1,6-addition.

Experimental Section

General Procedure

To a solution of *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea catalyst **III** (10 mg, 0.02 mmol, 20 mol%), DABCO (2.2 mg, 0.02 mmol, 20 mol%) and (*E*)-2-(3-arylallylidene)indene-1,3-dione **1** (26.2 mg, 0.1 mmol, 1 equiv.) in $CHCl_3$ (0.2 mL, 0.5 M) was added ethyl acetoacetate **2** (28 μL, 0.22 mmol, 2.2 equiv.) under stirring at 25 °C. The reaction mixture was monitored by TLC until the consumption of **1** and then the reaction mixture was quenched by adding H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and crude reaction mixture was purified by silica gel flash column chromatography (ethyl acetate/hexane = 1:3) to afford corresponding fused spirocyclic product **3**.

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[19] CCDC 1511276 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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