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Enantioselective Synthesis of Functionalized Polycarbocycles via a Three-Component Organocascade Quadruple Reaction

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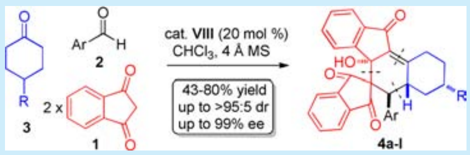
S Supporting Information

ABSTRACT: An efficient organocascade quadruple reaction was conducted to synthesize a functionalized spiropolycyclic scaffold in high chemical yields (43–80%) and excellent levels of stereoselectivity (up to >19:1 dr and 99% ee). The quadruple reaction proceeded smoothly between 1,3-indanedione and aromatic aldehydes with concomitant desymmetrization of prochiral 4-substituted cyclohexanones through the Knoevenagel/Michael/aldol/aldol reaction sequence catalyzed by a bifunctional thiourea catalyst. Two of the formed products were transformed into spirocyclic epoxides containing four contiguous quaternary centers.



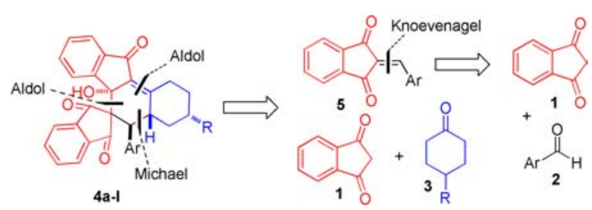
Since the resurgence of organocatalysis, the use of small organic molecules to catalyze various chemical transformations has emerged as a third discipline in contemporary asymmetric catalysis.[1] The use of organocatalytic reactions has grown rapidly, extending toward the total synthesis of natural products and synthesis of various structurally complex molecules through multicomponent cascade reactions.[2,3] Probing a multicomponent cascade reaction is challenging because of the difficulty involved in forming multiple bonds and controlling the chemo- and stereoselectivity in a one-pot process.[4,5] In 2006, Enders et al. reported a triple cascade reaction that delivered enantioenriched cyclohexenes with four consecutive stereogenic centers involving distinct modes of catalysis.[6,7] Subsequently, organocascade quadruple reactions providing structural complex products were reported. In addition to being environmentally friendly, this sophisticated advance in organocascade catalysis offers synthetic advantages for optimizing the efficiency of synthesis sequencing and minimizing chemical waste compared with classical methods that are time-consuming, involve lengthy sequences, and require purifying intermediates.[3,9c] In general, these reactions are initiated by a key transformation such as Michael,[8] oxa-Michael,[9] aza-Michael,[10] hydrogenation,[11] or Friedel–Crafts[12] reactions providing a complex scaffolds.

According to a thorough literature review, most prominent quadruple reactions involve using aldehydes and catalysis by chiral secondary amines via an enamine/iminium ion and/or hydrogen bond catalysis; the activation of unmodified ketones in an organocascade quadruple reaction remains elusive.[13] In addition, integrating desymmetrization of either prochiral or meso substrates into an organocascade quadruple reaction is rare and innovative. Organocatalytic desymmetrization of prochiral cyclohexanones has been reported previously.[14] In the present study, we attempted to realize an unprecedented three-component quadruple reaction accompanied by the desymmetrization of prochiral cyclohexanone, which is initiated by Knoevenagel condensation to afford enantioenriched and functionalized polycarbocycles.

In pharmacological and biologically active medicinal motifs, 1,3-indanedione derived spiro complex molecules prevail.[15] In performing multicomponent cascade reactions, 1,3-indanediones are useful candidates because the three contiguous electrophilic and nucleophilic reactive sites are akin to 1,3-dicarbonyl compounds.[16,17] The advantage is that such compounds can be readily transformed into more reactive dipolarophilic methylene compounds (2-arylidene-1,3-indanediones) through facile Knoevenagel condensation with benzaldehydes in the presence of a feebly basic amine.[17] Previously, we established two organocatalytic domino reactions between 2-arylidene-1,3-indanediones and aldehydes to afford the desired spirocyclohexanol derivatives in moderate to good chemical yields with excellent stereoselectivities.[18] Prompted by the aforementioned background and as a further development of the cascade reaction, we envisioned an organocatalytic quadruple cascade reaction involving a Knoevenagel/Michael/aldol/aldol sequence with the concomitant desymmetrization of prochiral cyclohexanones in a single process (Scheme 1).

Initially, we investigated the organocascade process by using prominent chiral primary amine catalysts **I–III** and secondary amine catalyst **IV**; 1,3-indanedione, benzaldehyde, and prochiral 4-phenylcyclohexanone in $CHCl_3$ were employed at 25 °C. The

Scheme 1. Retrosynthetic Analysis for the One-Pot Synthesis of Spiropolycyclic Ring System



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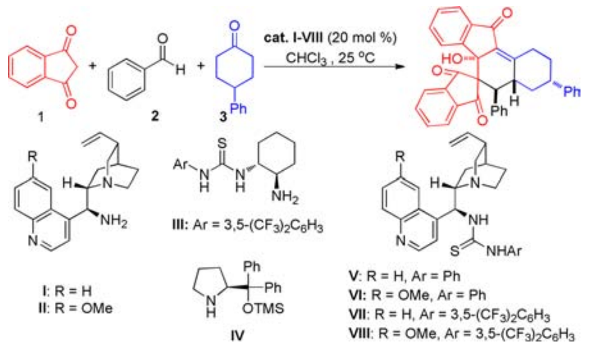
cascade process proceeded smoothly to furnish the desired polycarbocycles in moderate yields (up to 55%) with catalysts **I** and **II**, the product of which was only racemic (Table 1, entries 1 and 2). The Takemoto-type catalyst **III** afforded the product with poor enantioselectivity (Table 1, entry 3). The use of Jørgensen–Hayashi's catalyst **IV** failed to yield the desired product (Table 1, entry 4). We hypothesize that the synergetic hydrogen bonding that could arise between the bifunctional thiourea catalysts and the carbonyl groups of the 2-arylidene-1,3-indanedione and cyclohexanone promote superior enantioselectivity. To test our speculation, we examined various cinchonine- and quinine-derived bifunctional thiourea catalysts **V–VIII** in a one-pot organocascade reaction (Table 1, entries 5–8). The quinine-derived thiourea catalyst **VIII** appears promising; the desired product was obtained in 41% yield with 5:1 dr and 89% ee (Table 1, entry 8).

Table 1. Screening of Various Organocatalysts for the Optimization of the Reaction Conditions[a]

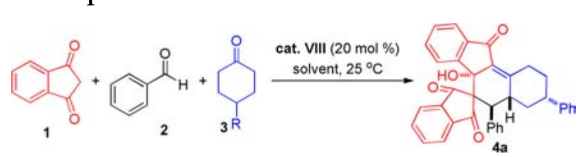


entry	cat.	time (d)	yield (%)[b]	dr[c]	% ee[d]
1	**I**	1.5	48	>19:1	0
2	**II**	1.5	55	>19:1	0
3	**III**	5	37	4:1	17
4	**IV**	7	n.d.		
5	**V**	7	45	4:1	55
6	**VI**	7	45	4:1	61
7	**VII**	5	37	4:1[d]	47
8	**VIII**	6	41	5:1	89

[a]The reactions were performed in the presence of 20 mol % of catalysts with 1,3-indanedione (0.2 mmol), benzaldehyde (0.1 mmol), and 4-phenylcyclohexanone (0.1 mmol) in the solvent indicated (0.5 mL) at ambient temperature. [b]Yield of isolated products. [c]Determined from ^{1}H NMR spectra of the crude reaction mixture. [d]Determined by chiral HPLC analysis for the major diastereomer (Chiralpak AD-H).

Subsequently, we optimized the reaction by using various nonpolar, polar protic, aprotic, and chlorinated solvents in the presence of thiourea catalyst **VIII** (Table 2). After scrutinizing various solvents, we realized that $CHCl_3$ could be an appropriate solvent because it afforded the desired product in 41% yield with 5:1 dr and 89% ee (Table 2, entries 1–8). Although the cascade product was isolated in 48% yield in 2-propanol, the product was racemic (Table 2, entry 5). This could be attributed to interruption of the hydrogen-bonding interaction between the thiourea catalyst **VIII** and the substrate in the protic solvent. Furthermore, we attempted to increase the reaction rate by sequestering the in situ formed water using molecular sieves (4 Å MS). We were able to reduce the reaction time from 6 to 4 days, and the desired spiro polycyclic product was obtained in moderate yields (up to 49%) with slightly improved enantioselectivity (up to 95% ee) (Table 2, entries 9–10). The reaction duration was reduced further, and the yield was improved by increasing the equivalents of prochiral 4-phenylcyclohexanone by 8 fold (Table 2, entries 11–13). Under the optimal conditions, the spiropolycyclic product was obtained in 77% yield with 4:1 dr and 95% ee in 2 days (Table 2, entry 11).

Table 2. Optimization of the Reaction Conditions[a]



entry	solvent	time (d)	yield[b] (%)	dr[c]	% ee[d]
1	hexanes	7	n.d.		
2	toluene	4	28	6:1	31
3	ether	5	30	5:1	55
4	DMF	7	n.d.		
5	IPA	4	48	5:1	0
6	DCM	6	44	5:1	85
7	DCE	6	44	1:1[d]	65
8	$CHCl_3$	6	41	5:1	89
9[e]	DCM	4	49	5:1	95
10[e]	$CHCl_3$	4	46	6:1	93
11[e,f]	$CHCl_3$	2	77	4:1	95
12[e,f]	DCM	3	55	4:1	95
13[e,f,g]	$CHCl_3$	3	46	1:1[d]	85

[a]Unless otherwise noted, the reactions were performed in the presence of 20 mol % of catalyst **VIII** with 1,3-indanedione (0.2 mmol), benzaldehyde (0.1 mmol), and 4-phenylcyclohexanone (0.1 mmol) in the solvent indicated (0.5 mL) at room temperature. [b]Yield of isolated products. [c]Determined from ^{1}H NMR spectra of the crude reaction mixture. [d]Determined by chiral HPLC analysis for the major diastereomer (Chiralpak AD-H). [e]4 Å MS (100 mg) was added. [f]The reaction was carried out with 1,3-indanedione (0.2 mmol), benzaldehyde (0.1 mmol), and 4-phenylcyclohexanone (0.8 mmol). [g]The reaction was carried out at 0 °C.

The scope of the reaction was generalized by using various benzaldehydes containing electron-withdrawing and -releasing groups and prochiral cyclohexanones under the optimized conditions (Table 3). The benzaldehydes holding various electron-withdrawing (Table 3, entries 2–6), -donating (Table 3, entries 7–9), and heterocyclic substituents (Table 3, entry 10) provided the corresponding polycarbocyclic products **4b–j** in high yields, retaining their high diastereo- and enantioselectivity (up to 19:1 dr and 99% ee). However, the enantioselectivity of the product was only 19% ee when the aryl possessed the 4-nitro group substituent (28% yield and 19:1 dr) (data not shown). This reaction can be rationalized as hydrogen-bonding competition with the catalyst between the inherited 4-nitro group and the upcoming additional dicarbonyl of the 1,3-indanedione group. Moreover, the alkyl-substituted prochiral cyclohexanones were well desymmetrized, affording the corresponding spiro products **4k–l** with favorable enantioselectivity (Table 3, entries 11 and 12). The optimized conditions was applied in a scale up process (5-fold) in which the chemical and optical yields were sustained well (Table 3, entry 13). All spirocyclic products **4a–l** were characterized through IR, ^{1}H NMR, ^{13}C NMR, NOE (for **4a**), and HRMS analyses. The absolute configuration of the products were assigned on the basis of a single-crystal X-ray structural analysis of **4d** (Table 3).[19]

The organocascade quadruple reaction accompanying the desymmetrization of prochiral cyclohexanone can be assumed in

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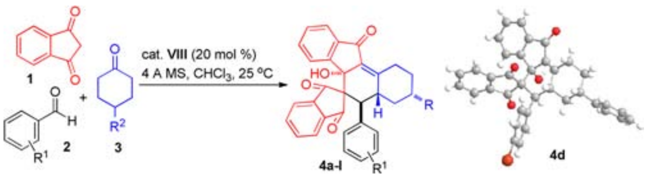
Table 3. Substrate Scope of the Cascade Reaction[a]

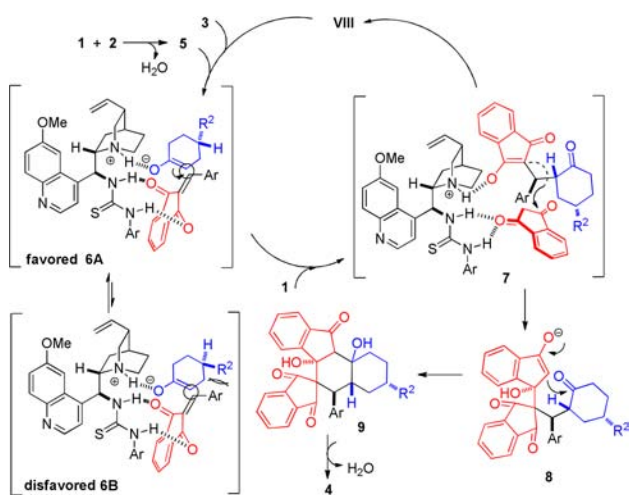


entry	R[1]	R[2]	4	time (h)	yield[b] (%)	dr[c]	% ee[d]
1	H	Ph	**4a**	48	77	4:1	95
2	4-CF_3	Ph	**4b**	24	43	7:1	86
3	4-Cl	Ph	**4c**	19	63	>19:1	93
4	4-Br	Ph	**4d**	27	70	>19:1	91
5	2-Br	Ph	**4e**	27	71	>19:1	97
6	4-CO_2Me	Ph	**4f**	27	80	>19:1	98
7	4-OMe	Ph	**4g**	30	61	12:1	87
8	3-OMe	Ph	**4h**	30	75	>19:1	99
9	4-Me	Ph	**4i**	30	69	5:1	85
10	3-thienyl	Ph	**4j**	27	70	10:1[e]	91
11	3-OMe	^{i}Pr	**4k**	30	55	2:1[e]	92
12	3-OMe	^{t}Bu	**4l**	30	69	>19:1	87
13[f]	4-Br	Ph	**4a**	48	67	>19:1	91

[a]Unless otherwise noted, the reactions were performed in the presence of 20 mol % of catalyst **VIII** and 4 Å MS (100 mg) with 1,3-indanedione (0.2 mmol), benzaldehyde (0.1 mmol), and 4-phenylcyclohexanone (0.8 mmol) in the solvent indicated (0.5 mL) at ambient temperature. [b]Yield of isolated products. [c]Determined from ^{1}H NMR spectra of the crude reaction mixture. [d]Determined by chiral HPLC analysis for the major diastereomer (Chiralpak AD-H or AS-H). [e]Determined from chiral HPLC analysis of the column purified product. [f]Reaction was carried out with 1,3-indanedione (1.0 mmol), benzaldehyde (0.5 mmol), and 4-phenylcyclohexanone (4.0 mmol).

acid/base catalysis when catalyzed by **VIII**. The plausible mechanism is depicted in Scheme 2. The cascade process

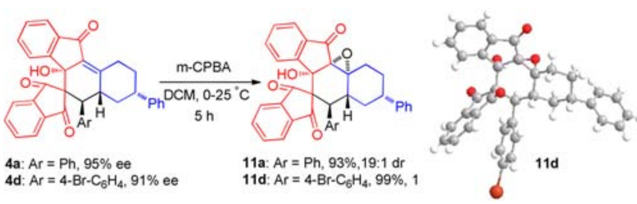
Scheme 2. Proposed Reaction Mechanism



initiated by a base-catalyzed process through Knoevenagel condensation of 1,3-indanedione **1** and benzaldehyde **2** led to the formation of 2-arylidene-1,3-indanediones **5**. The bifunctional organocatalyst **VIII** synergistically activated the nucleophile prochiral cyclohexanone **3** and electrophile 2-arylidene-1,3-indanediones **5** through hydrogen bonding. In addition, the tertiary amine moiety of the organocatalyst **VIII** acted as a base and deprotonated the cyclohexanone **3** that triggered the Michael addition to the 2-arylidiene-1,3-indanedione **5** with the concomitant desymmetrization of prochiral cyclohexanone **3** through the favored transition state **6A**. The tricarbonyl intermediate underwent an asymmetric intermolecular aldol reaction with an additional 1,3-indanedione **1** through the transition state **7**, affording tetracarbonyl **8**. Furthermore, a susceptible intramolecular aldol condensation of **8**, followed by dehydration led to the formation of the desired polycyclic cascade product **4**.

Chiral epoxides are excellent precursors for synthesizing chiral vicinal diols, diamines, amino alcohols and allylic alcohols.[20] Given this high synthetic utility, the olefinic functional group in the spiro product was further transformed into the corresponding epoxide. Under standard *m*-CPBA oxidation conditions, the products possess five contiguous stereogenic centers, including three quarternary centers in excellent yields with high diastereoselectivity (Scheme 3). The absolute configuration of the α-epoxy compounds was unambiguously assigned through a single-crystal X-ray analysis of **11d**.[19]

Scheme 3. Synthetic Applications of the Products 4a and 4d



In conclusion, we demonstrated a highly efficient, three-component organocascade quadruple reaction by employing 1,3-indanedione, aryl aldehydes, and prochiral 4-substituted cyclohexanones. The acid/base-catalyzed quadruple reaction proceeded smoothly via a Knoevenagel/Michael/aldol/aldol condensation sequence that accompanied the desymmetrization of prochiral cyclohexanones. The enantioenriched spiropolycyclic functionalized derivatives were obtained in high yields with excellent diastereo- and enantioselectivity. The formed products were transformed into a spirocyclic epoxy motif containing four contiguous quarternary centers. Further exploitation of the organocascade strategy is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and the characterization of all products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01040.

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Notes

The authors declare no competing financial interest.

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