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Synthesis of Fully Substituted Dispirocyclohexanes by Organocatalytic [2 + 2 + 2] Annulation Strategy between 2-Arylideneindane-1,3-diones and Aldehydes

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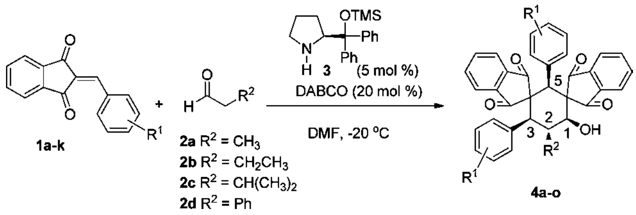
ABSTRACT



An interesting organocatalytic reaction between 2-arylideneindane-1,3-diones and aldehydes has been developed that gives fully substituted cyclohexanes that bear two all-carbon quaternary centers. The dispirocyclohexanes were obtained in reasonable-to-good chemical yields and with high stereoselectivities (>95:5 d.r. and up to 99% ee) using a catalytic amount of commercially available α,α-L-diphenylprolinol trimethylsilyl ether (5 mol %) and DABCO (20 mol %) in DMF at −20 °C. The reaction proceeds through a unique Michael/Michael/aldol reaction that requires 2 equiv of the 2-arylideneindane-1,3-dione.

Six-membered carbocycles are important structural motifs of many biologically active and pharmaceutical products.[1] The stereoselective formation of a six-membered ring system with multiple stereogenic centers from its acyclic precursors has attracted substantial attention for its usefulness in the total synthesis of natural products.[2] Among the developed methodologies, the cascade reaction is especially appealing owing to such decisive synthetic advantages as synthetic efficiency, atom economy, operational simplicity, and the minimal need for the isolation and purification process.[3] In the past few years, newly developed organocascade strategies have emerged as promising protocols for the synthesis of various structural complex molecules[4] with diverse structural substituents including cyclohexanes,[5] cyclohexenes,[6] and cyclohexanones.[7] Melchiorre,[8] Gong,[9] Wang,[10] and Chen[11] have discussed the use of 3-olefinic oxindoles to give a

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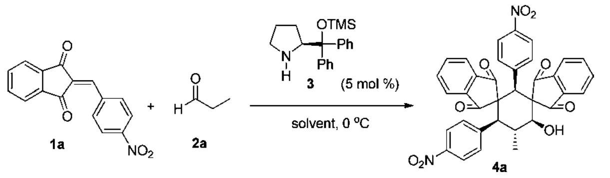
spiro[cyclohexanone-oxindole] scaffold. Organocascade reactions using oxindole derivatives have been demonstrated to be effective in constructing spirocyclic oxindoles.[12] Central to the organocascade process is the identification of suitable Michael acceptors. Several electron-deficient alkenes have been employed in organocascade reactions that involve enones, enals, and nitroalkenes.

The use of 1,3-indanedione and its derivatives in organocatalytic reactions for the synthesis of spirocyclic compounds has been documented in the literature.[13] However, to the best of our knowledge, the asymmetric synthesis of fully substituted dispirocyclohexanes by an organocascade-based method has not been reported. We present here an efficient synthesis of highly strained dispirocyclohexane derivatives from 2-arylideneindane-1,3-diones and aldehydes using a [2 + 2 + 2] annulation strategy.

α,α-L-Diphenylprolinol trimethylsilyl ether is now recognized as one of most useful catalysts in organocatalytic reactions.[14] Many organocascade reactions have been developed around this catalyst. Our research into the Michael/Michael/aldol reaction began using 2-arylideneindane-1,3-dione and propionaldehyde as model substrates in the presence of catalytic quantities of the α,α-L-diphenylprolinol organocatalyst at 0 °C with various solvents (Table 1). The reaction proceeded smoothly in MeOH to afford the desired product in 43% chemical yield but with only 11% enantioselectivity (Table 1, entry 1). The chemical yield and enantioselectivity were drastically improved when the reaction was carried out in DMF and CH_3CN (Table 1, entries 2 and 3). High chemical yield (72%) and diastereoselectivity ($>$95:5), but poor enantioselectivity (9% ee), were observed in CH_2Cl_2 (Table 1, entry 4). The reactivity was significantly lower when $CHCl_3$ was used (Table 1, entry 5). Although the stereoselectivity was retained, the reactivity fell markedly when the reaction was carried out in THF (Table 1, entry 6). Moderate chemical yields and unsatisfactory enantioselectivity were observed when the reaction was performed in ethyl acetate (Table 1, entry 7).

The desired product was obtained in an extremely low chemical yield in toluene (Table 1, entry 8), and no reaction proceeded in either hexanes or ether (Table 1, entries 9 and 10).

Table 1. Solvent Effects of the Cascade Reaction in the Presence of Catalyst **3** at 0 °C[a]



entry	solvent	time/d	% yield[b]	dr[c]	% ee[d]
1	MeOH	5	43	>95:5	11
2	DMF	2	72	>95:5	44
3	CH_3CN	3	85	>95:5	49
4	CH_2Cl_2	5	72	>95:5	9
5	$CHCl_3$	7	28	>95:5	7
6	THF	5	32	>95:5	47
7	ethyl acetate	5	31	>95:5	21
8	toluene	7	14	>95:5	1
9	hexanes	7	–	–	–
10	ether	7	–	–	–

[a] Unless otherwise specified, the reaction was carried out with 2-arylideneindane-1,3-dione **1a** (0.1 mmol), propionaldehyde **2a** (0.2 mmol), and α,α-L-diphenylprolinol trimethylsilyl ether **3** (5 mol %) in the solvent indicated (0.2 mL) at 0 °C. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis.

The Michael/Michael/aldol reaction conditions were further optimized by screening various acidic and basic

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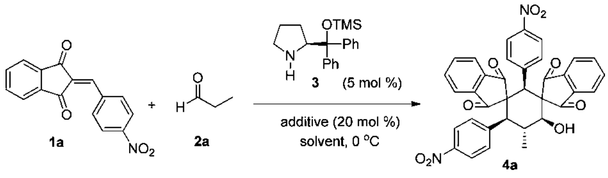
additives. The desired product was not obtained in the presence of strong acid additives such as TsOH and TFA (data not shown), perhaps, because protonation of the secondary amine hampered formation of the enamine. The reactivity increased with comparable stereoselectivity when the reaction was carried out in the presence of an acidic additive such as PhCOOH or acetic acid (Table 2, entries 1−2). Adding a basic additive to the reaction significantly improved the reactivity and chemical yields (96−99%) while maintaining stereoselectivities (Table 2, entries 3−5). In general, the stereoselectivity was improved when the reaction was carried out at −20 °C, regardless of whether an acidic or basic additive was used (Table 2, entries 6−9). The cooperative catalytic conditions were examined and failed to improve the stereochemical outcome in the cascade reaction (Table 2, entry 11). Finally, to our satisfaction, the stereoselectivity was further improved when the reaction was carried out in DMF in the presence of DABCO (Table 2, entry 12). The water content in this cascade reaction might be crucial to the observed reactivity and stereoselectivity.

Using the optimized reaction conditions, the scope and generality of this interesting cascade reaction was studied. The results are presented in Table 3. For all the substrates studied, various substituted 2-arylideneindane-1,3-diones that included electron-withdrawing and -donating substitutents were well tolerated under these conditions.

With an electron-withdrawing group in the 4-substituted 2-arylideneindane-1,3-diones, the reaction proceeded smoothly with propionaldehyde to give the desired fully substituted cyclohexanes with high stereocontrol (Table 3, entries 1−6). The enantioselectivity dropped slightly when a 3-nitro substituent analogue was used (Table 3, entry 7). On the other hand, it decreased when an electron-releasing substituent in the Michael acceptor was present (Table 3, entries 8−9). When a heterocyclic substituted Michael acceptor was used, the desired product was isolated with 52% chemical yield with good stereoselectivity (>95:5 dr and 80% ee) (Table 3, entry 11). Other nucleophilic partners were tolerated in the cascade reaction (Table 3, entries 12−15). The chemical structures of the dispirocyclohexanes were determined by IR, ^{1}H NMR, ^{13}C NMR, and HRMS analyses. Examination of the 500 MHz ^{1}H NMR spectrum of **4f** ($CDCl_3$) reveals that the four methine protons are located at the axial positions in the cyclohexane ring [H_1: 4.10 ppm (dd, 10.5, 7.0 Hz); H_2: 3.85 ppm (ddq, 12.5, 10.5, 6.5 Hz); H_3: 3.15 ppm (d, 12.5 Hz); and H_5: 3.94 ppm (s)]. The absolute stereochemistry was tentatively assigned by single crystal X-ray analyses of representative substituted products (**4k**).[15]

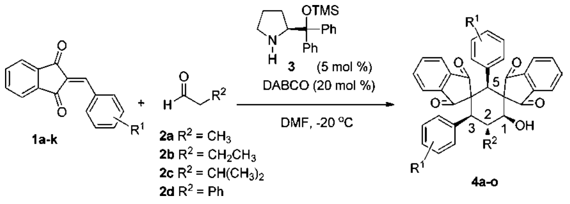
Table 2. Optimization of the Cascade Reaction[a]



entry	additive	solvent	time/d	% yield[b]	dr[c]	% ee[d]
1	PhCOOH	CH_3CN	2	46	>95:5	54
2	AcOH	CH_3CN	2	56	>95:5	58
3	DMAP	CH_3CN	0.5	96	>95:5	65
4	DABCO	CH_3CN	0.5	97	>95:5	67
5	Imidazole	CH_3CN	0.5	99	>95:5	67
6[e]	PhCOOH	CH_3CN	6	53	>95:5	82
7[e]	2-FBA	CH_3CN	4	51	>95:5	79
8[e]	AcOH	CH_3CN	7	37	>95:5	66
9[e]	DABCO	CH_3CN	3	53	>95:5	81
10[e]	DABCO	CH_3CN	3	64	>95:5	82
11[e]	PhCOOH DABCO	CH_3CN	3	57	>95:5	77
12[e]	**DABCO**	**DMF**	**2**	**55**	**>95:5**	**96**

[a] Unless otherwise specified, the reaction was carried out with 2-arylideneindane-1,3-dione **1a** (0.1 mmol), propionaldehyde **2a** (0.2 mmol), α,α-L-diphenylprolinol trimethylsilyl ether **3** (5 mol %), and additives (20 mol %) in the solvent indicated (0.2 mL) at 0 °C. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] The reaction was carried out at −20 °C. 2-FBA: 2-Fluorobenzoic acid.

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



entry	**1** (R^1-)	**2** (R^2-)	product	time (d)	% yield[b]	dr[c]	% ee[d]
1	4-NO_2	CH_3	**4a**	2	55	>95:5	96
2	4-CO_2Me	CH_3	**4b**	4	46	>95:5	95
3	4-CF_3	CH_3	**4c**	4	42	>95:5	92
4	4-CN	CH_3	**4d**	2	57	>95:5	93
5	4-Cl	CH_3	**4e**	4	41	>95:5	91
6	4-Br	CH_3	**4f**	4	45	>95:5	90
7	3-NO_2	CH_3	**4g**	3	54	>95:5	85
8	4-OAc	CH_3	**4h**	4	40	>95:5	83
9	4-Me	CH_3	**4i**	4	40	>95:5	76
10	4-H	CH_3	**4j**	4	48	>95:5	75
11	thiophene	CH_3	**4k**	3	52	>95:5	80
12	4-NO_2	CH_2CH_3	**4l**	4	54	>95:5	90
13	4-CN	CH_2CH_3	**4m**	5	30	>95:5	82
14	4-NO_2	$CH(CH_3)_2$	**4n**	3.5	17	>95:5	83
15	4-NO_2	Ph	**4o**	6	45	>95:5	99

[a] Unless otherwise specified, the reaction was carried out with 2-arylideneindane-1,3-dione **1a**−**k** (0.1 mmol), aldehyde **2a**−**d** (0.2 mmol), α,α-L-diphenylprolinol trimethylsilyl ether **3** (5 mol %), and DABCO (20 mol %) in DMF (0.5 mL) at −20 °C. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis.

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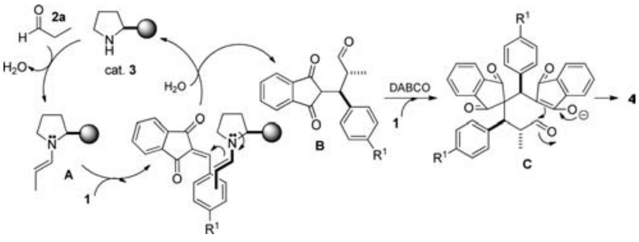
(15) In our early study of this work, we tried to crystallize the product for structure determination and moderate enantiomeric products were used. Interestingly, cocrystal structures of (+)/(−)-**4f** (recrystallized from 60% ee solution of hexanes/dichloromethane) were obtained. Many attempts of crystallization failed when high optical purity **4f** (90% ee) was used. Preliminary X-ray crystallographic data for compounds **4f** and **4k** can be found in the Supporting Information.

Scheme 1. Proposed Mechanism of the Cascade Reaction



The aforementioned organocascade reaction can be explained by the mechanism that is presented in Scheme 1. The α,α-L-diphenylprolinol catalyst reacts with the aldehydes to form the nucleophilic enamine (**A**) which undergoes Michael addition with the 2-arylideneindane-1,3-diones from the *si* face to give intermediate **B**. The presence of DABCO shifts the reaction toward the nucleophilic enol species, which then reacts with the second 2-arylidene-indane-1,3-dione to afford diindane 1,3-dione aldehyde **C**. Subsequently, the intramolecular aldol reaction affords the desired multisubstituted dispirocyclohexanes.

In summary, an efficient Michael/Michael/aldol reaction has been developed for synthesizing multisubstituted dispirocyclohexanes. The development of highly selective sequential transforming protocols is of significant importance in chiral nonracemic materials preparation. Various 2-arylideneindane-1,3-dione and aldehyde condensations were catalyzed by α,α-L-diphenylprolinol trimethylsilyl ether (5 mol %) and DABCO (20 mol %) in DMF at −20 °C to form functionalized dispirocyclohexanes with moderate chemical yields and high-to-excellent stereoselectivities (> 95:5 dr and up to 99% ee). The organocascade construction of three C−C bonds to generate a cyclohexane scaffold *via* a [2 + 2 + 2] annulation strategy, by one-pot sequential catalysis, is interesting. Other organocascade protocols are being studied in our laboratory.

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Supporting Information Available. Experimental procedures and copies of ^{1}H, ^{13}C NMR spectra and HPLC chromatographs for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.