Organic LETTERS

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Organocatalytic Synthesis of Substituted Spirocyclohexane Carbaldehydes via [4 + 2] Annulation Strategy between 2-Arylideneindane-1,3-diones and Glutaraldehyde

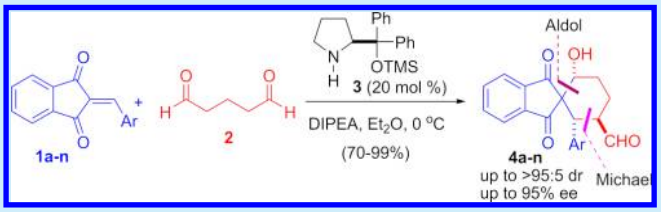
Shaik Anwar,[†,‡] Shao Ming Li,[†] and Kwunmin Chen*[,†]

[†]Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan 116, ROC

[‡]Division of Chemistry, Department of Sciences and Humanities, Vignan's Foundation for Science, Technology and Research-VFSTR (Vignan University), Vadlamudi 522 213 Guntur, Andhra Pradesh, India

Supporting Information

ABSTRACT: An organocatalytic domino reaction between 2-arylideneindane-1,3-diones and glutaraldehyde has been devised that gives functionalized spirocyclohexane carbaldehydes with an all-carbon quaternary center. The reaction proceeds through a Michael/Aldol sequence in good-to-high chemical yields and with high levels of stereoselectivity (up to >95:5 dr and 99% ee) in the presence of the α,α-L-diphenylprolinol trimethylsilyl ether 3 (20 mol %) and DIPEA (20 mol %) in ether at 0 °C.



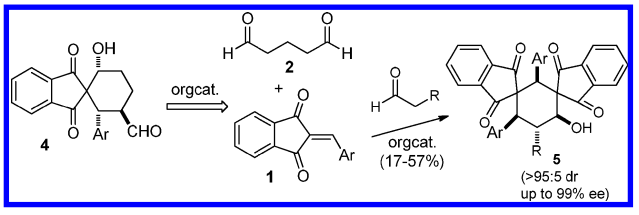
The 1,3-indanedione skeleton is an important component of many naturally occurring biologically active substances and has served as a substrate in numerous reactions.[1] In recent years, readily accessible 2-arylidene-1,3-indandiones have started gaining attention in the field of organocatalysis.[2] 2-Arylideneindane-1,3-diones are highly reactive 1,1-diactivated alkenes that have been used extensively as acceptors in the synthesis of symmetric and nonsymmetric spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones,[2a] spirocyclopropanation,[2b,c] asymmetric [3 + 2] annulations,[2d] and epoxidation.[2e] Moreover, 2-arylidene-1,3-indandiones have been used as dipolarophiles for the synthesis of spirocyclic[3] and dispiroheterocyclic[4] skeleta.

On the other hand, the use of aqueous pentane-1,5-dial[5] as a four-carbon unit has been efficiently utilized in the synthesis of substituted cyclohexanes,[6] tetrahydropyrans,[7] functionalized cyclopentenes,[8] pyrrolidines,[9] piperidines,[10] and 3-oxabicyclo-[3.3.1]nonan-2-ones.[11]

However, the efficient synthesis of substituted spirocyclic skeleta using 2-arylideneindane-1,3-diones and glutaraldehyde remains elusive. Very recently, we reported an interesting domino synthesis of dispirocyclohexane derivatives **5** between the reaction of 2-arylideneindane-1,3-diones and aldehydes (Scheme 1). The desired cyclohexanol derivatives were obtained in moderate chemical yields and excellent stereoselectivities (>95:5 dr and up to 99% ee).[12] As a further extension of this work, we envisioned that functionalized 1,3-indanedione-derived spirocyclohexane carbaldehyde **4** could be readily obtained by reaction of 2-arylideneindane-1,3-diones with dialdehyde **2** mediated by α,α-L-diphenylprolinol trimethylsilyl ether.[13] This Michael/Aldol sequence would eventually incorporate three stereocenters.

Toward this, an initial investigation was carried out into the reaction of 2-arylideneindane-1,3-dione with aqueous glutaraldehyde (25%) in CH_2Cl_2 at 0 °C. The reaction proceeded smoothly in 87% chemical yield for the desired product **4a** (Table 1, entry 1). Low diastereomeric ratio (37:63) and high enantioselectivities were obtained (86 and 99% ee, respectively). The use of other chlorinated solvents failed to increase the stereoselectivty in the products (Table 1, entries 2 and 3).

Scheme 1. Domino Michael/Aldol Approach toward Spirocyclohexane Carbaldehyde



Although comparable reactivity was observed, the use of protic solvents resulted in poor diastereoselectivities (Table 1, entries 4−6).

The use of polar aprotic solvents such as CH_3CN and DMF lowered the diastereoselectivity and enantioselectivity for product **4a** (Table 1, entries 7 and 8). Next, etheral solvents were screened in the reaction (Table 1, entries 9−12). Among these, diethyl ether was found to be the solvent of choice under the present reaction conditions to give product **4a** with a high chemical yield of 91% and high enantioselectivity of 90% ee (Table 1, entry 12). A reversal of diastereoselectivity was observed when THF and Et_2O were used (Table 1, entries 10 and 12). The reactivity decreased slightly when nonpolar

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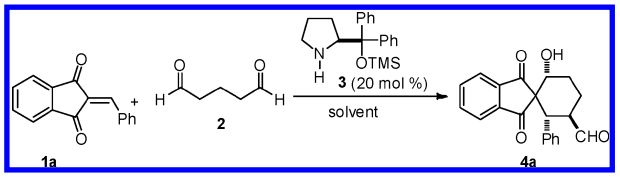
Table 1. Solvent Screening of Domino Michael/Aldol Reaction[a]



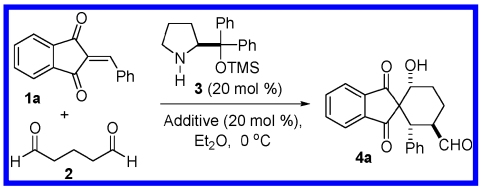
entry	solvent	time (h)	yield[b] (%)	dr[c]	% ee[d]
1	CH_2Cl_2	1	87	37:63	86/99
2	$CHCl_3$	1	78	48:52	85/99
3	DCE	1	98	29:71	78/99
4	MeOH	2	87	37:63	72/99
5	EtOH	1.5	94	41:59	66/93
6	IPA	1.5	94	44:56	73/95
7	CH_3CN	1.5	88	29:71	72/99
8	DMF	3	98	59:41	34/87
9	1,4-dioxane	9	83	45:55	74/96
10	THF	4.5	99	30:70	72/99
11	MTBE	2.5	86	81:19	85/97
12	Et_2O	1.5	91	82:18	90/95
13	toluene	1.5	81	84:16	89/99
14	EtOAc	4	78	62:38	75/98

[a]Unless otherwise specified, the reaction was carried out with 2-arylideneindane-1,3-dione **1a** (0.1 mmol), glutaraldehyde **2** (0.25 mmol), and α,α-L-diphenylprolinol trimethylsilyl ether **3** (20 mol %) in the solvent indicated (0.5 mL) at 0 °C. [b]Yield of the isolated products. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis.

solvents such as toluene were used (Table 1, entry 13). Finally, the use of ethyl acetate as solvent further decreased the reactivity and stereoselectivity of the reaction (Table 1, entry 14).

The domino sequence was further optimized (Table 2). Interestingly, the addition of 20 mol % of acidic additives decreased the stereoselectivity (Table 2, entries 1 and 2). However, the presence of basic additives significantly improved the outcome with only one major diastereoisomer being identified (Table 2, entries 3–6). The use of DABCO gave the product **4a** in 87% chemical yield and excellent dr of 97:3, with 91% ee (Table 2, entry 3). The chemical yield was further improved with along enantioselectivity (95% ee) when DIPEA was added as an additive (Table 2, entry 4). The reactivity dropped when an inorganic base was used, and the reaction required a relatively longer reaction time for conversion (Table 2, entry 5). Finally, the use of DMAP reduced the enantioselectivity of the reaction (Table 2, entry 6).

Table 2. Optimization of the Domino Michael/Aldol Reaction[a]

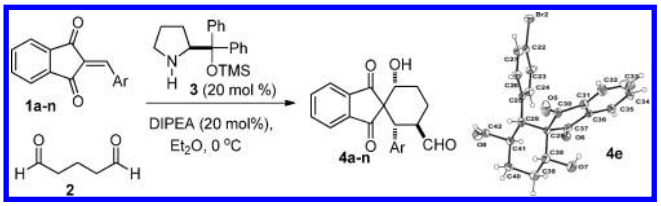


entry	additive	time (h)	yield[b] (%)	dr[c]	% ee[d]
1	PhCOOH	1	92	70:30	82
2	AcOH	1	99	60:40	87
3	DABCO	2.5	87	97:3	91
4	DIPEA	6.5	99	93:7	95
5	K_2CO_3	9	87	94:6	90
6	DMAP	4	98	95:5	79

[a]Unless otherwise specified, the reaction was carried out with 2-arylideneindane-1,3-dione **1a** (0.1 mmol), glutaraldehyde **2** (0.25 mmol), α,α-L-diphenylprolinol trimethylsilyl ether **3** (20 mol %), and an additive (20 mol %) in diethyl ether (0.5 mL) at 0 °C. [b]Yield of the isolated products. [c]Determined by ^{1}H NMR. [d]Major diastereomer. Determined by chiral HPLC analysis.

With the optimized reaction conditions identified, we next explored the substrate scope of this domino Michael/Aldol reaction. Various functional groups were screened in **1a–n** to better understand group tolerance (Table 3).

Table 3. Substrate Scope of the Domino Michael/Aldol Reaction[a]



entry	1	Ar-	4	time (h)	yield[b] (%)	dr[c]	% ee[d]
1	**1a**	C_6H_5	**4a**	6.5	99	93:7	95
2	**1b**	4-$OAcC_6H_4$	**4b**	5	73	95:5	90
3	**1c**	4-$MeOC_6H_4$	**4c**	24	95	95:5	95
4	**1d**	4-MeC_6H_4	**4d**	24	98	93:7	83
5	**1e**	4-BrC_6H_4	**4e**	3	78	92:8	91
6	**1f**	4-FC_6H_4	**4f**	4	77	91:9	93
7	**1g**	4-ClC_6H_4	**4g**	4	78	89:11	90
8	**1h**	4-$NO_2C_6H_4$	**4h**	5	82	89:11	82
9	**1i**	3-$NO_2C_6H_4$	**4i**	4	68	89:11	87
10	**1j**	4-$CF_3C_6H_4$	**4j**	4	89	77:23	80
11	**1k**	4-CNC_6H_4	**4k**	5	86	92:8	86
12	**1l**	4-$CO_2MeC_6H_4$	**4l**	12	70	>95:5	82
13	**1m**	2-thiophene	**4m**	12	95	>95:5	95
14	**1n**	3-thiophene	**4n**	12	96	>95:5	95

[a]Unless otherwise specified, the reaction was carried out with 2-arylideneindane-1,3-dione **1a–n** (0.1 mmol), glutaraldehyde **2** (0.25 mmol), α,α-L-diphenylprolinol trimethylsilyl ether **3** (20 mol %), and DIPEA (20 mol %) in diethyl ether (0.5 mL) at 0 °C. [b]Yield of the isolated products. [c]Determined by ^{1}H NMR. [d]Major diastereomer. Determined by chiral HPLC analysis.

Electron-donating, halo-substituted, electron-withdrawing, and heterocyclic substitutents were all well tolerated under the optimized conditions. Acetoxy substituent **1b** gave a reasonable chemical yield with a high stereoselectivity (Table 3, entry 2). The use of methoxy and methyl substituents in **1c** and **1d** almost took 1 day for complete consumption of starting materials (Table 3 entries 3 and 4). This decrease in reactivity may be due to unfavorable creation of electron density for a nucleophilic enamine attack at the carbon atom of 2-arylideneindane-1,3-dione. Halogen substituents **1e–g** showed a similar reactivity profile, with reaction completion in 3–4 h (Table 3, entries 5–7). The enantioselectivity dropped slightly when 3-nitro substituent **1i** was used (Table 3, entry 9). The stereoselectivity decreased further when strong electron-withdrawing group 4-trifluoromethyl substituent **1j** was used (77:23 dr and 80% ee, Table 3, entry 10). This may be due to the rapidly Aldol–retro-Aldol equilibrating reaction of the spiroindanone framework.[14] The heterocyclic substituted Michael acceptors **1m,n** gave the

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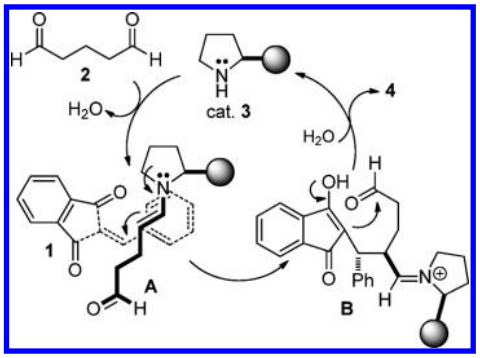
desired product with good stereoselectivity (>95:5 dr and 95% ee) (Table 3, entries 13 and 14).

The chemical structures of the spirocyclohexane carbaldehyde **4a**–**n** were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS analyses. The absolute configuration was unambiguously determined by single-crystal X-ray analyses of a representative bromo-substituted product (**4e**).[15]

The aforementioned domino reaction can be explained by the mechanism depicted in Scheme 2. The α,α-L-diphenylprolinol

Scheme 2. Proposed Mechanism for the Domino Michael/Aldol Reaction



catalyst reacts with the dialdehyde **2** to form the nucleophilic enamine (**A**). The nucleophilic conjugate attack occurs from the *si* face of the enamine to the *re* facial of the 2-arylideneindane-1,3-dione to give intermediate (**B**). Subsequent intramolecular aldol reaction followed by hydrolysis affords the desired multi-substituted spirocyclohexane carbaldehyde **4**. The stability of the product **4** can be further explained by the fact that the hydroxy, aryl, and the aldehyde functionalities all lie in the equatorial position. One of the carbonyl groups in the 1,3-indanedione may orient in the pseudoaxial position of the chair conformation, thereby avoiding 1,3-diaxial interactions.

In summary, an efficient organocatalytic domino reaction between 2-arylideneindane-1,3-diones and glutaraldehyde has been developed that gives functionalized spirocyclohexane carbaldehydes with an all-carbon quaternary center. Various substituted 2-arylideneindane-1,3-dione reacted smoothly with aqueous glutaraldehyde solution catalyzed by α,α-L-diphenylprolinol trimethylsilyl ether **3** (20 mol %) and DIPEA (20 mol %) as an additive. The reaction proceeds through a sequential Michael/Aldol process in high chemical yields and with stereoselectivities up to >95:5 dr and 95% ee when run in ether at 0 °C. This one-pot sequential catalysis for construction of substituted spirocyclohexane carbaldehydes with three stereocenters via a formal [4 + 2] annulation strategy is synthetically useful.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and copies of ^{1}H NMR, ^{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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kchen@ntnu.edu.tw.

Notes

The authors declare no competing financial interest.

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(15) Detailed X-ray crystallographic data are available from the CCDC,12 Union Road, Cambridge CB2, 1EZ, UK for product **4e** (CCDC 957552).

■ NOTE ADDED AFTER ASAP PUBLICATION

The TOC/abstract graphic contained errors and was replaced on June 6, 2014.

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