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Domino Hydroarylation–Cyclization Reaction: One-Pot Synthesis of Indane-Fused 3,4-Dihydrocoumarins

Jin Hyuck Joo[a] and So Won Youn[a,*]

[a] Department of Chemistry and Research Institute for Natural Sciences, Hanyang University, Seoul 133-791, Korea
Fax: (+82)-2-2299-0762; e-mail: sowony73@hanyang.ac.kr

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Abstract: A tin(II) triflate-catalyzed domino hydroarylation–cyclization reaction has been developed to access a wide-variety of methyleneindane-fused 3,4-hydrocoumarins. A judiciously selected bi-functional Lewis acidic catalyst has been successfully applied to promote two ring-closing events as a single-pot operation.

Keywords: cyclization; domino reactions; fused-ring systems; hydroarylation; tin

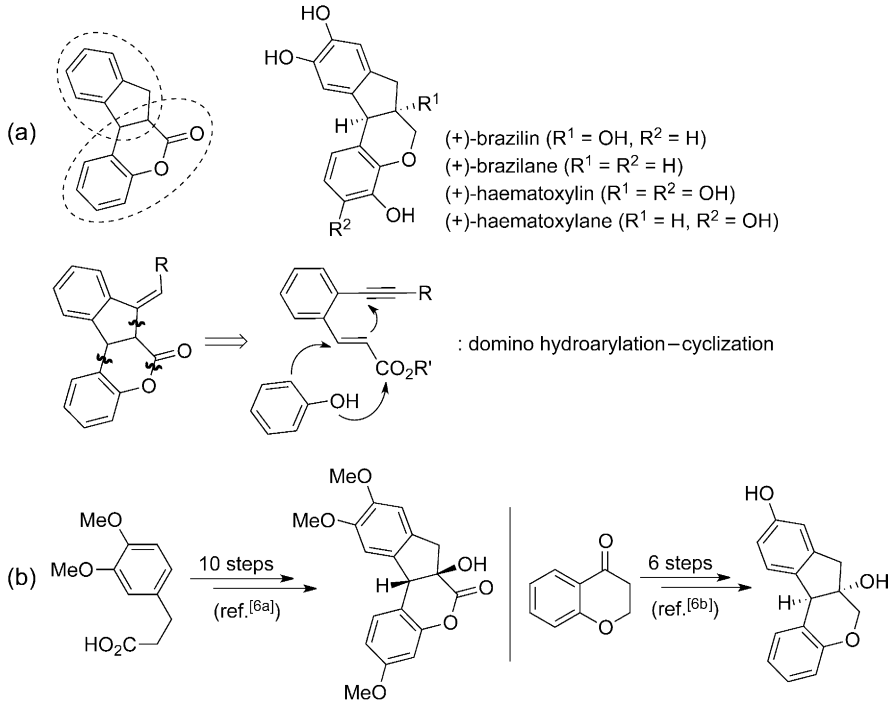
Introduction

Domino reactions are powerful synthetic transformations that render a high degree of molecular complexity from structurally simplified and easily accessible progenitor(s) in a highly efficient manner.[1] In particular, substrates bearing judiciously positioned carbon-carbon multiple bonds could be programmed to undergo sequential C–C and/or C–X (X = heteroatom) bond constructions, thereby furnishing a diverse array of (poly)cyclic compounds. As part of our ongoing interest in the domino synthesis of functionalized heterocycles,[2] herein we report a novel and highly efficient preparation of indane-fused 3,4-hydrocoumarin that originates from unification between a phenol and an *o*-alkynyl cinnamate *via* a formal hydroarylation–cyclization process. Indane-fused 3,4-hydrocoumarins are found in a wide collection of natural and designed substances, best known by the brazilin family of natural dyes (Scheme 1a).[3] Furthermore, functionalized 3,4-dihydrocoumarins[4] and indanes[5] are also valuable chemical entities in their own right. A cursory survey of the reported syntheses of "brazilin-like" indane-fused 3,4-hydrocoumarins revealed that the current methods largely required multi-step chemical operations from commercial starting materials (Scheme 1b).[6] In view of the molecular diversity and the largely untapped physical and biological potentials of these valuable structural motifs, an expedient synthetic protocol would be highly desirable.

Results and Discussion

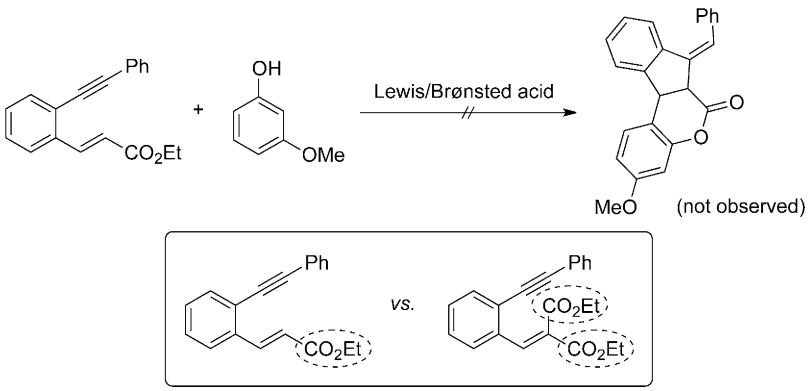
On close examination of the proposed domino reaction (Scheme 1a), the rationale for our synthetic design rests its foundation on two well-documented constituting chemical processes. First, Lewis/Brønsted acid-catalyzed hydroarylation of cinnamic acid derivatives with phenols is a reported method for the preparation of 3,4-dihydrocoumarins.[7] On the other hand, sequential conjugate addition–cyclization reactions of 2-alkynylbenzylidene ketones or malonates triggered by an external nucleophile has been demonstrated for the synthesis of highly substituted indanes.[8,9] As we shall see, our endeavor in merging these two processes in a domino-fashion began with the identification of an effective Lewis/Brønsted acid promoter.

In view of the series of bond-forming events as depicted in Scheme 1a, both the cinnamate and the alkyne are anticipated to undergo nucleophilic attack, presumably facilitated through Lewis/Brønsted acid activation of the respective functionalities. While it is possible to envisage a co-catalyst system with each of its constituents catering for the activation of the cinnamate and the alkyne, respectively, a single Lewis/Brønsted acid capable of activating both functionalities would be more appealing synthetically. Furthermore, for *o*-alkynyl cinnamate substrates bearing a non-activated alkyne, the Lewis/Brønsted acid of choice should function both as an oxophilic acid and as a π-acid.[10] With these mechanistic considerations in mind, our initial studies began with ethyl (2-phenylethynyl)cinnamate and 3-methoxyphenol as the test substrates in search of a suitable bi-functional cat-



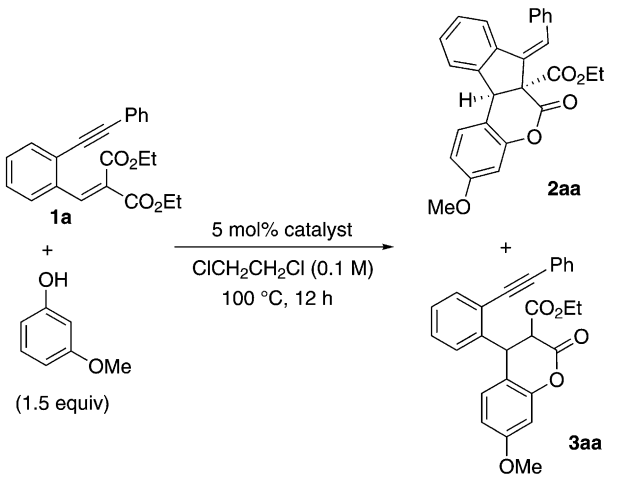
Scheme 1. Brazilin family natural products and synthetic plan for their analogues.

alyst. However, despite extensive experimentations, only starting materials could be detected or isolated after examining a wide variety of Lewis/Brønsted acid promoters and reaction conditions (Scheme 2). At this juncture, we reasoned the lack of reactivity could be remedied by introducing an additional carboxylate group to enhance the electrophilicity of the cinnamate olefin, and concomitantly provide a bi-dentate binding site to the Lewis/Brønsted acid promoter.[7d,11] Gratifyingly, the revised substrate (**1a**) underwent smooth coupling and ring formations with 3-methoxyphenol in the presence of 5 mol% of $Sn(OTf)_2$ to afford compound **2aa** in 74% yield (Table 1, entry 1).[12] $In(OTf)_3$ also proved effective for this transformation (Table 1, entry 2), while ytterbium, scandium, copper(II), and platinum(II) triflate salts and TfOH only afforded monocyclized product **3aa** in low to moderate yields. It is noteworthy that isolated **3aa** could be further converted to **2aa** in the presence of 5 mol% of $Sn(OTf)_2$ at 100 °C for 10 h in 99% yield. We further hypothesized the nucleophilicitiy of 3-methoxyphenol could be enhanced with the introduction of a base, however, addition of Na_2CO_3 had no noticeable effect and no reaction was observed in the absence of $Sn(OTf)_2$ (Table 1, entries 15–17). Interestingly, the combination of $SnCl_2$ and $Sc(OTf)_3$ also afforded the product **2aa** (Table 1, entries 8 *vs.* 20), whereas $SnCl_2$ alone was not an effective catalyst (Table 1, entry 18). These findings are path-pointing for the necessity of a "cationic-Sn(II) like" character



Scheme 2.

Table 1. Optimization studies for the reaction of **1a** with 3-methoxyphenol.



Entry	Catalyst	**1a** [%][a]	**2aa** [%][a]	**3aa** [%][a]
1	$Sn(OTf)_2$	–	80 (74)	–
2	$In(OTf)_3$	–	70	–
3	$Bi(OTf)_3$	100	–	–
4	$Mg(OTf)_2$	100	–	–
5	$Zn(OTf)_2$	100	–	–
6	$Fe(OTf)_3$	100	–	–
7	$Yb(OTf)_3$	65	–	35
8	$Sc(OTf)_3$	–	–	70
9	$Cu(OTf)_2$	90	–	10
10	AgOTf	100	–	–
11	Ph_3PAuCl/AgOTf (1:1)	100	–	–
12	$PtCl_2$/AgOTf (1:2)	90	–	10
13	TfOH	90	–	10
14	CF_3CO_2H	100	–	–
15[b]	$Sn(OTf)_2$	trace	92 (90)	trace
16[b,c]	$Sn(OTf)_2$	24	76	–
17[b,c]	–	100	–	–
18	$SnCl_2$	100	–	–
19[b]	$SnCl_2$/$In(OTf)_3$ (1:1)	7	80	–
20[b]	$SnCl_2$/$Sc(OTf)_3$ (1:1)	8	80	–
21[b,d]	$Sn(OTf)_2$	27	44	20
22[b,e]	$Sn(OTf)_2$	100	–	–
23[b,f]	$Sn(OTf)_2$	–	75	trace
24[b,g]	$Sn(OTf)_2$	27	44	11
25[b,h]	$Sn(OTf)_2$	trace	80	7

[a] Yields were determined by ^{1}H NMR using trichloroethylene as an internal standard. Values in parentheses indicate isolated yields.
[b] Using 1.2 equiv. 3-methoxyphenol for 24 h.
[c] With 1.2 equiv. Na_2CO_3 as an additive.
[d] In toluene.
[e] In THF.
[f] At 120 °C for 16 h.
[g] At 80 °C for 24 h.
[h] With 3 mol% $Sn(OTf)_2$.

for the reaction to take place. Ultimately, product **2aa** could be obtained in 90% yield (Table 1, entry 15) under our optimized reaction conditions (for details, see the Supporting Information).

While a variety of phenols could be employed for this reaction (Table 2), a clear electronic dependence was observed in which only naphthols and highly electron-rich phenols afforded the corresponding benzylidene indane-fused 3,4-hydrocoumarins in good to high yields. 3-Substituted phenols showed excellent regioselectivity, leading to products originating from nucleophilic addition at the less hindered C-4 position (Table 2, entries 1, 4, 5, and 9). Of all amine-containing phenols examined, $NHCO_2Et$ was the uniquely effective (Table 2, entry 9) while substrates bearing free NH_2, NMe_2, and NHBoc substituents were unreactive. It is noteworthy that, in all cases, only *E* isomers of the cyclized products were obtained stereoselectively. The structures of the cyclized products were inferred based on an X-ray crystallographic analysis of **2ac**[13] as well as by ^{1}H NMR analysis.

Next, *o*-alkynyl cinnamates with varying aryl and alkyne substitutions were examined (Table 3, entries 1–23). In general, the reactions proceeded uneventfully to generate the corresponding methyleneindane-fused 3,4-hydrocoumarins irrespective of the aryl substitution. Both terminal and internal alkynes were well tolerated for this reaction, where internal alkynes showed little electronic and/or steric dependence. Functional group compatibility for the developed protocol was also demonstrated for methoxy, hydroxy, halogen, cyclopropyl, ester, and nitro containing compounds, with the exception of desilylation for the TMS-substituted alkyne (**1o**). The *E* isomers of the cyclized products were obtained exclusively in most cases, apart from substrates **1c** and **1d** (Table 3, entries 2 and 3) and alkyl-substituted (Table 3, entries 16–22) alkynes. The structural validity of all products were supported by ^{1}H NMR, NOE experiments (compounds **2ca**, **2da**, **2qa**, and **2ra**), and X-ray crystallographic analysis (compounds **2ac** and **2qa**).[13]

This process was effective for both diethyl and dimethyl malonate-derived substrates, however, di-*tert*-butyl malonate-derived substrate (**1w**) only afforded the monocyclized product (**4w**) where the reaction terminated after initial hydroarylation followed by decarboxylation (Table 3, entry 24). When one of the carboxylates was replaced with a ketone and irrespective of the olefinic geometry, our standard reaction conditions afforded the naphthalene derivatives **6** in close analogy to Zhang's report.[14] However, carrying out the reaction at ambient temperature generated benzopyran compounds **5** presumably *via* a Friedel–Craft/dehydrative cyclization process, and attempts to improve this reaction or induce further cyclization were unsuccessful [Eq. (1) and Eq. (2)].[15a–b] Lastly, cyano substrate **1z** also underwent the domino hydroarylation–cyclization to give product **2ea**, albeit in a modest 33% yield [Eq. (3)].[15c]

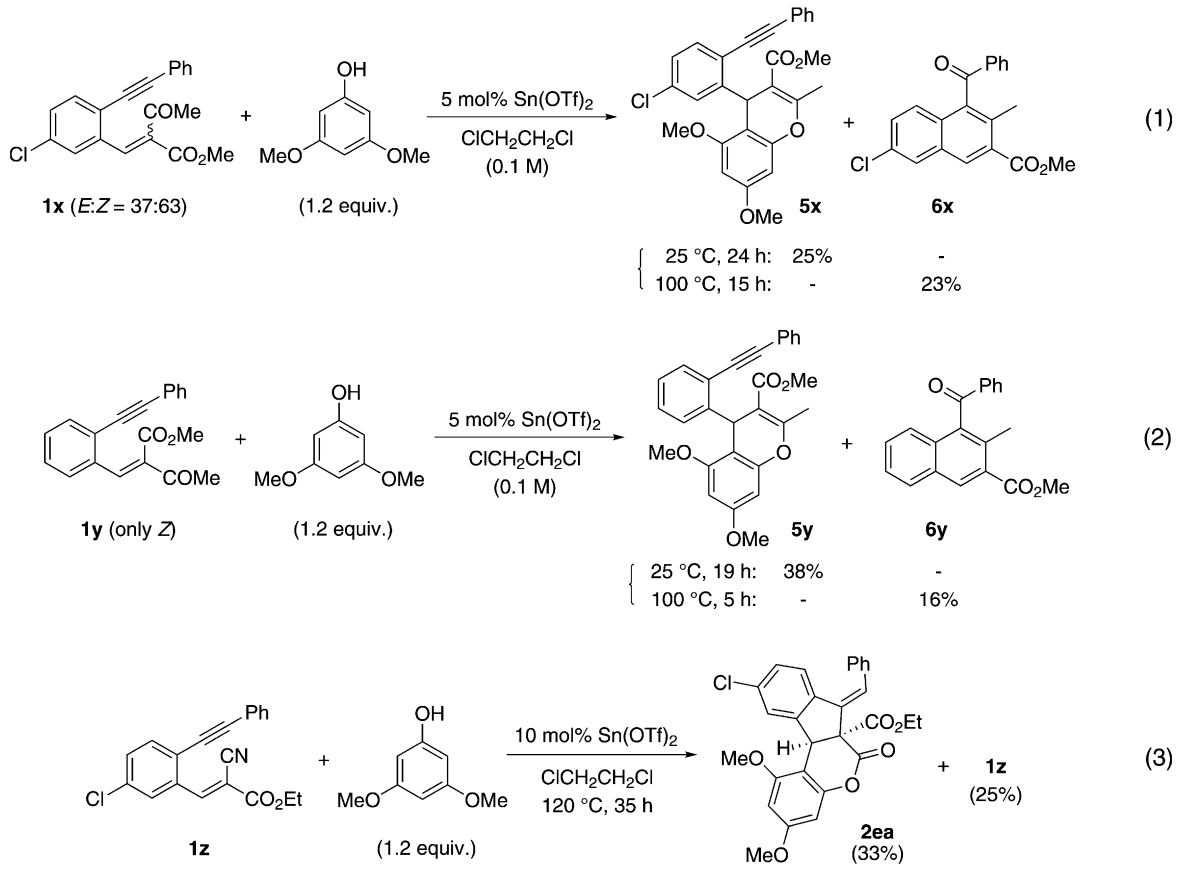
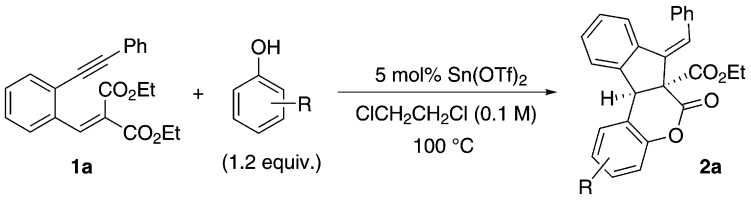


Table 2. $Sn(OTf)_2$-catalyzed domino reaction of **1a** with various phenols.



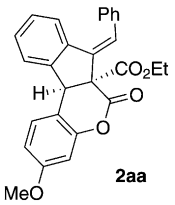
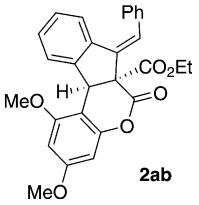
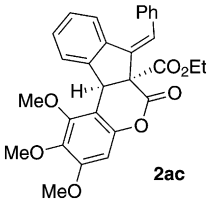
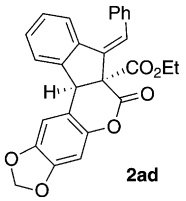
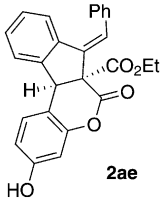
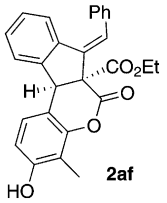
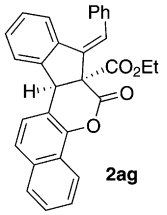
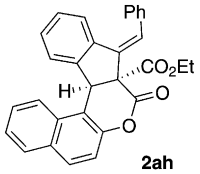
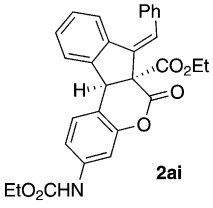
Entry	Phenol	Time [h]	Product	Yield [%][a]
1	3-methoxyphenol	24	 **2aa**	90
2	3,5-dimethoxyphenol	12	 **2ab**	93

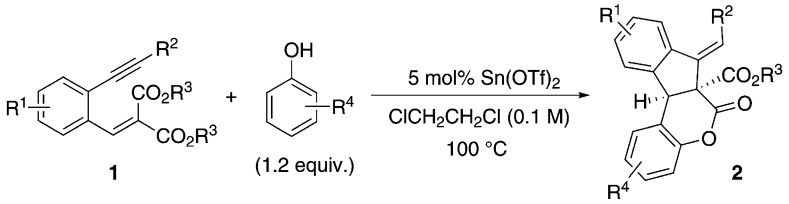
Table 2. (Continued)

Entry	Phenol	Time [h]	Product	Yield [%][a]
3	3,4,5-trimethoxyphenol	8	 **2ac**	96
4	sesamol	18	 **2ad**	98
5	resorcinol	18	 **2ae**	71
6	2-methylresorcinol	13	 **2af**	76
7	1-naphthol	24	 **2ag**	84
8[b]	2-naphthol	24	 **2ah**	76
9[b,c]	*N*-ethoxycarbonyl-3-aminophenol	28	 **2ai**	69

[a] Isolated yield.
[b] Performed at 120 °C.
[c] With 20 mol% $Sn(OTf)_2$.

Although the precise mechanism for this reaction is yet to be fully elucidated, we believe that the opening step of this domino process involved an initial hydroarylation of a $Sn(OTf)_2$-activated intermediate (**A**) with phenol to afford intermediate **B** (Scheme 3). Subsequent lactonization followed by an intramolecular nucleophilic addition of the so-obtained 1,3-dicarboxylate (presumably as its Sn enolate[12d,g]) onto the

Table 3. $Sn(OTf)_2$-catalyzed domino hydroarylation-cyclization reaction of **1** with phenols.



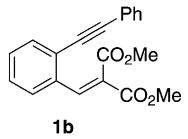
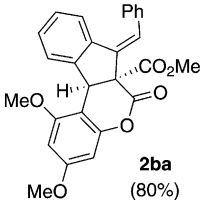
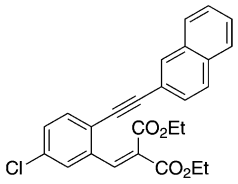
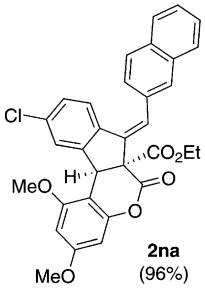
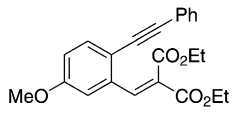
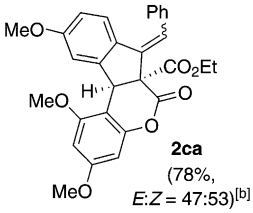
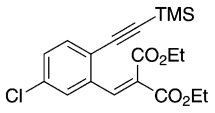
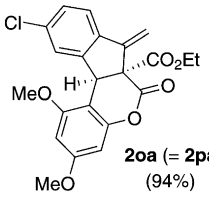
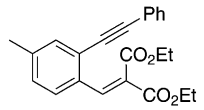
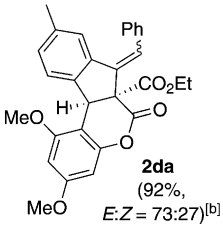
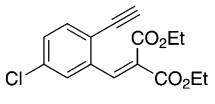
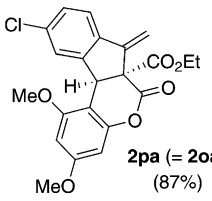
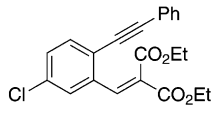
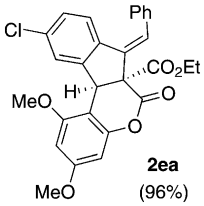
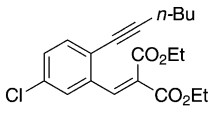
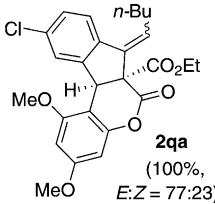
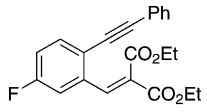
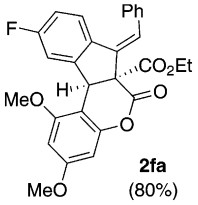
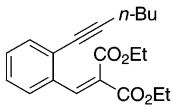
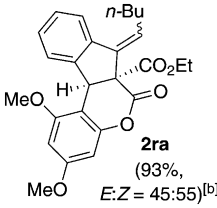
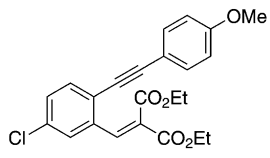
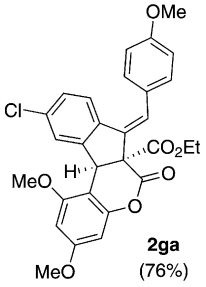
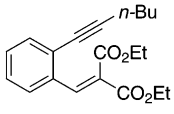
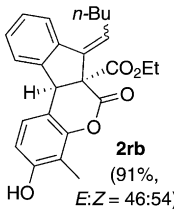
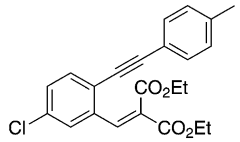
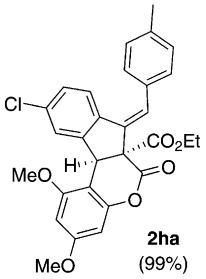
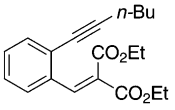
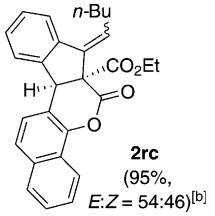
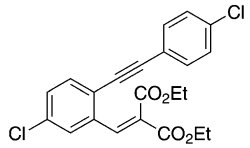
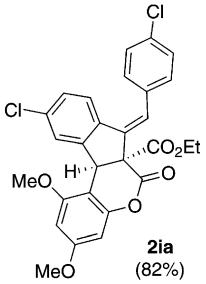
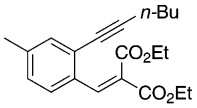
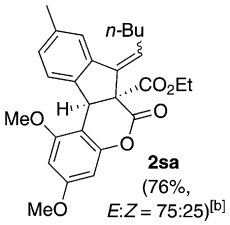
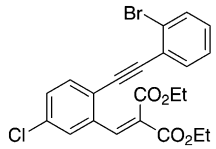
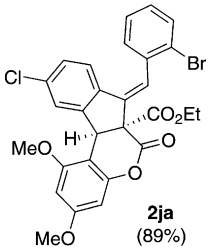
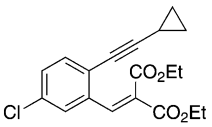
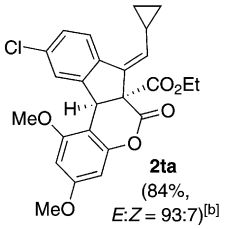
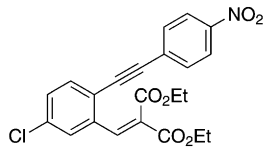
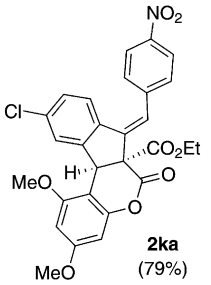
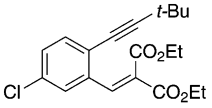
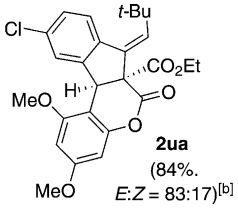
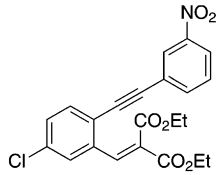
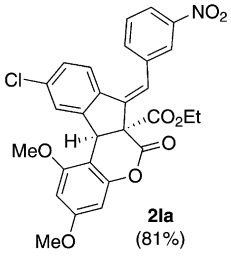
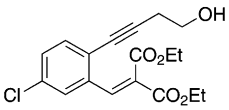
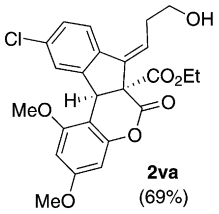
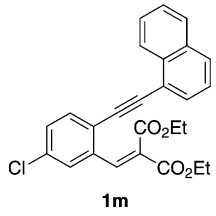
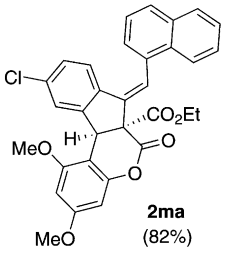
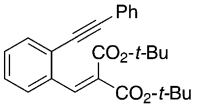
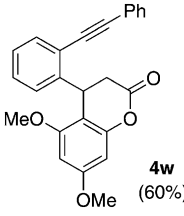
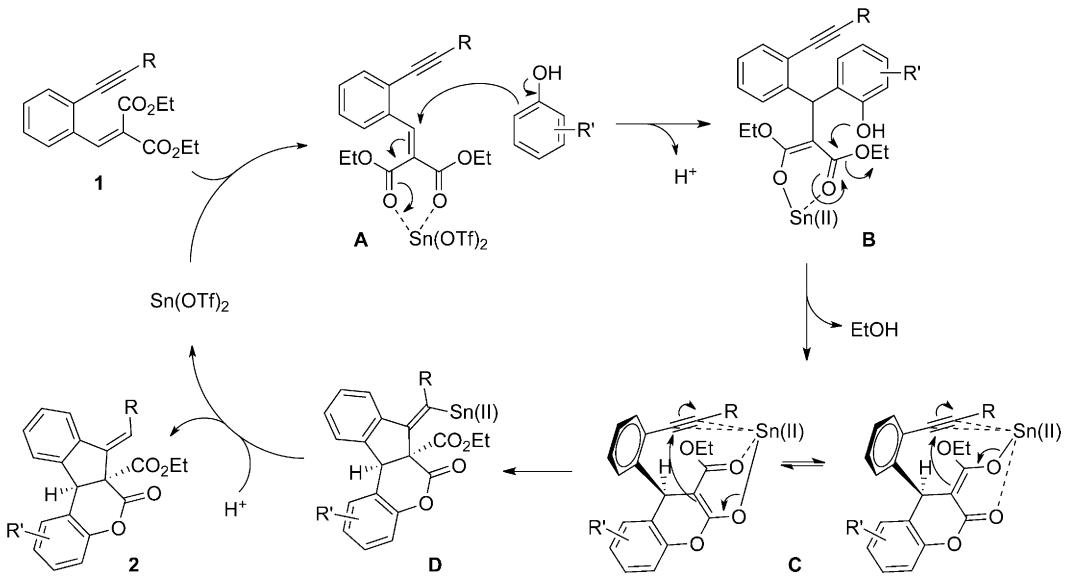
Entry	Substrate	Time [h]	Product (Yield)[a]	Entry	Substrate	Time [h]	Product (Yield)[a]
1	 **1b**	1	 **2ba** (80%)	13	 **1n**	5	 **2na** (96%)
2	 **1c**	9	 **2ca** (78%, *E*:*Z* = 47:53)[b]	14	 **1o**	2	 **2oa** (= **2pa**) (94%)
3	 **1d**	13	 **2da** (92%, *E*:*Z* = 73:27)[b]	15	 **1p**	4	 **2pa** (= **2oa**) (87%)
4	 **1e**	11	 **2ea** (96%)	16	 **1q**	15	 **2qa** (100%, *E*:*Z* = 77:23)[b]
5	 **1f**	21	 **2fa** (80%)	17	 **1r**	13	 **2ra** (93%, *E*:*Z* = 45:55)[b]
6	 **1g**	17	 **2ga** (76%)	18	 **1r**	9	 **2rb** (91%, *E*:*Z* = 46:54)[b]

Table 3. (Continued)

Entry	Substrate	Time [h]	Product (Yield)[a]	Entry	Substrate	Time [h]	Product (Yield)[a]
7	 **1h**	10	 **2ha** (99%)	19[c]	 **1r**	24	 **2rc** (95%, *E*:*Z* = 54:46)[b]
8	 **1i**	4	 **2ia** (82%)	20	 **1s**	3	 **2sa** (76%, *E*:*Z* = 75:25)[b]
9	 **1j**	8	 **2ja** (89%)	21	 **1t**	3	 **2ta** (84%, *E*:*Z* = 93:7)[b]
10	 **1k**	15	 **2ka** (79%)	22	 **1u**	23	 **2ua** (84%. *E*:*Z* = 83:17)[b]
11	 **1l**	23	 **2la** (81%)	23	 **1v**	4	 **2va** (69%)
12	 **1m**	8	 **2ma** (82%)	24	 **1w**	3	 **4w** (60%)

[a] Isolated yield.
[b] The ratio of two inseparable isomers was determined by ^{1}H NMR.
[c] Performed at 120 °C.



Scheme 3. Possible mechanism for the $Sn(OTf)_2$-catalyzed domino hydroarylation–cyclization reaction.

activated alkyne (**C**) led to the indane ring-closure, and proto-destannylation to give the methyleneindane-fused 3,4-hydrocoumarin **2**. A coordinated transition state as depicted by intermediate **C** could be invoked in close analogy to those previously reported by Yamazaki and co-workers.[10b–d] The preferential formation of the *E* isomer could be accounted for through a conformation where steric interactions are minimized.

Conclusion

In summary, we have developed a $Sn(OTf)_2$-catalyzed domino hydroarylation–cyclization reaction to access a wide variety of methyleneindane-fused 3,4-hydrocoumarins. The success of this reaction featured the application of a judiciously selected bi-functional Lewis acidic catalyst to promote two ring-closing events as a single-pot operation. In view of the relatively unexplored physical and biological potential of indane-fused 3,4-hydrocoumarins, and their traditional syntheses that generally required lengthy chemical manipulations, the technology described herein should enable a rapid entry to a diverse collection of polycyclic "brazilin-like" analogues for further investigations.

Experimental Section

General Procedure for $Sn(OTf)_2$-Catalyzed Domino Reaction of 1 with Phenols

To a solution of **1** and phenol (1.2 equiv.) in $ClCH_2CH_2Cl$ (0.1 M) in sealed vial was added $Sn(OTf)_2$ (5 mol%). The resulting mixture was stirred at 100 °C for the reported time. After the reaction was completed, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, successively washed with 1 N NaOH solution and distilled water, and extracted with CH_2Cl_2 (three times). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford the corresponding product **2**.

(*E*)-Ethyl 7-benzylidene-3-methoxy-6-oxo-6,6a,7,11b-tetrahydroindeno[2,1-*c*]chromene-6a-carboxylate (2aa): Brown oil (EtOAc:*n*-hexane = 1:5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (t, *J* = 7.2 Hz, 3H), 3.81 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 5.05 (s, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.91 (s, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.30–7.38 (m, 4H), 7.48 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 48.8, 55.5, 62.7, 66.3, 102.4, 111.3, 112.0, 123.9, 124.7, 127.6, 127.8, 128.4, 128.5, 128.8, 129.0, 129.8, 136.3, 136.5, 138.1, 143.8, 151.0, 160.2, 164.9, 168.6; HR-EI-MS: *m/z* = 426.1470 $(M)^+$, calcd for $C_{27}H_{22}O_5$: 426.1467.

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