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$AlCl_3$-Promoted Formal [2 + 3]-Cycloaddition of 1,1-Cyclopropane Diesters with *N*-Benzylic Sulfonamides To Construct Highly Stereoselective Indane Derivatives

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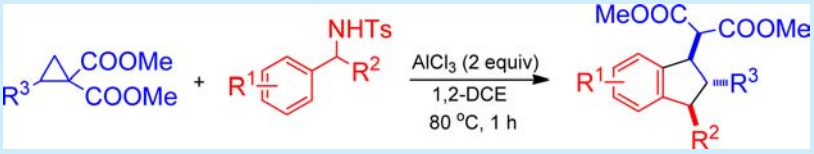
Supporting Information



ABSTRACT: An unprecedented $AlCl_3$-promoted formal [2 + 3]-cycloaddition of 1,1-cyclopropanes with readily available *N*-benzylic sulfonamides has been developed. Experimental evidence supports an unusual mechanism wherein the donor−acceptor cyclopropane serves as a source of 2-styrylmalonate rather than the "classical" 1,3-dipole. A broad range of 1,1-cyclopropanediesters undergo a carbocation-initiated cyclization reaction with *N*-benzylic sulfonamides to afford highly functionalized Indane derivatives in a fast and high-yielding procedure.

The Indane-based skeleton is found in a variety of natural products and pharmaceuticals.[1] Examples include dimeric resveratrol-derived natural products (Figure 1), which have the

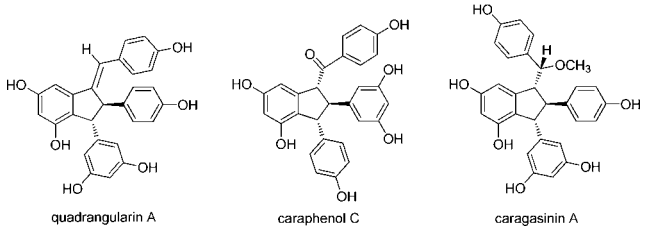


Figure 1. Structures of selected resveratrol-derived natural products.

virtue of potent antioxidant properties. Consequently, inspired by these important scaffolds, a variety of synthetic methods for their preparation have been developed.[2] In this context, we envisioned exploring the catalytic one-step construction of 1,2,3-trisubstituted indanes from cyclopropane derivatives and *N*-benzylic sulfonamides.

Donor−acceptor cyclopropanes are now popular in organic synthesis owing to their ready accessibility and good reactivity.[3] In most cases, a donor−acceptor cyclopropane can undergo Lewis acid promoted ring opening *via* cleavage of the σ-1,2-bond. The *in situ* generation of a 1,3-dipolar intermediate can enter formal [3 + 2]- or [3 + 3]-cycloaddition with multiple bonds to build five- or six-membered rings. It was recently shown that the generated 1,3-dipole could also undergo isomerization into the corresponding propenes *via* a prototropic shift.[4a] Donor−acceptor cyclopropanes are more easily available than the isomeric propenes. The cyclopropane-to-propene isomerization opens a synthetically valuable strategy that allows the one-stage assembly of polysubstituted rings from the formal dipoles. However, as far as we know, donor−acceptor cyclopropanes as the source of styrylmalonates was only involved in the dimerization of cyclopropanes.[4] This transformation applied to reactions with other compounds has never been reported.

Our group has been interested in the synthetic applications of carbon−nitrogen bond cleavage.[5] Readily accessible *N*-benzylic sulfonamides have emerged as unique alkylating agents to couple with a range of nucleophiles for the formation of a carbon−carbon bond through the acid-catalyzed cleavage of carbon−nitrogen bonds.[6,7] Herein, we demonstrate the use of cyclopropane diesters as the source of 2-styrylmalonates to react with electrophiles rather than nucleophiles in the presence of a Lewis acid to generate indanes, *via* formal [2 + 3]-cycloadditions. Formal [3 + 3]-cycloadditions with benzylic cations where cyclopropanes act as 1,3-dipoles to afford the six-membered rings was not found in this work (Scheme 1). The structure of compound **3c** was unambiguously demonstrated by X-ray diffraction analysis (Figure 2; also see the Supporting Information). A new understanding of the mechanism of this reaction will also be presented.

Our study started from the model reaction of cyclopropane **1a** with *N*-benzylic sulfonamide **2a** to optimize the reaction conditions (Table 1). Typical Lewis acids such as $FeCl_3$, $TiCl_4$, $BF_3{\cdot}OEt_2$, and $ZnBr_2$/TMSCl did not catalyze the reaction (Table 1, entries 11−14). Catalytic amounts of these Lewis acids were revealed to make **1a** decompose quickly. And the side reactions increased with a higher dosage of Lewis acids.

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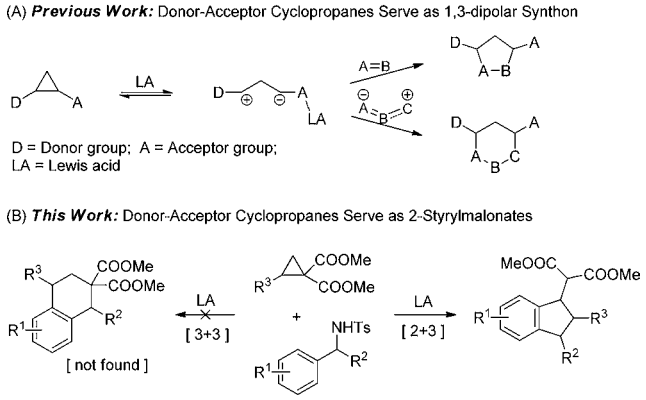
Scheme 1



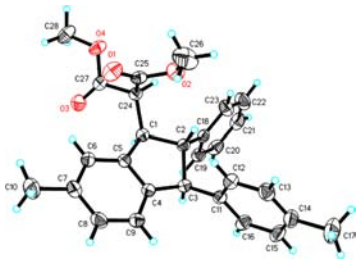
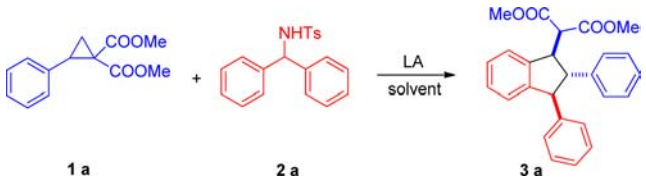


Figure 2. Molecular structure of compound **3c**.

Table 1. Optimization of Reaction Conditions between 1a and 2a[a]



entry	Lewis acid (mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	$AlCl_3$ (200)	1,2-DCE	80	1	73
2	$AlCl_3$ (200)	CH_3NO_2	80	1	45
3	$AlCl_3$ (200)	CH_3CN	80	24	NR[c]
4	$AlCl_3$ (200)	dioxane	80	24	27
5	$AlCl_3$ (200)	DCM	40	24	35
6	$AlCl_3$ (200)	1,2-DCE	40	24	40
7	$AlCl_3$ (200)	1,2-DCE	rt	24	trace[d]
8	$AlCl_3$ (150)	1,2-DCE	80	2	48
9	$AlCl_3$ (100)	1,2-DCE	80	2	15
10	$AlCl_3$ (20)	1,2-DCE	80	2	trace[d]
11	$FeCl_3$ (10)	1,2-DCE	80	2	dec[e]
12	$TiCl_4$ (100)	1,2-DCE	40	4	dec[e]
13	$ZnBr_2$/TMSCl (10)	1,2-DCE	80	2	dec[e]
14	$BF_3{\cdot}OEt_2$ (10)	1,2-DCE	80	2	dec[e]
15	$Sc(OTf)_3$ (10)	1,2-DCE	80	24	NR[c]
16	$Yb(OTf)_3$ (10)	1,2-DCE	80	24	NR[c]
17	$LnCl_3$ (100)	1,2-DCE	80	24	NR[c]

[a]The reaction was conducted with **1a** (0.25 mmol), **2a** (0.25 mmol), Lewis acid (*x* mol %), and solvent (1 mL). [b]Isolated yield. [c]No reaction. [d]Only a trace of **3a** was formed. [e]**1a** was decomposed.

Rare-earth metal salts like those of Sc, Yb, and Ln also failed to induce the reaction. No desired reaction occurred even if the catalyst loading increased and the reaction time extended. To our delight, the reaction worked very well in 1,2-DCE at 80 °C for 1 h under the catalysis of $AlCl_3$ (2 equiv) to give the desired product **3a** in 73% yield. Furthermore, the reaction was not efficient when the catalyst loading of $AlCl_3$ was changed to 1 or 1.5 equiv (Table 1, entries 8−9). Using catalytic amounts of $AlCl_3$ gave only a trace amount of **3a** (Table 1, entry 10). Efforts to enhance yield proved fruitless by replacing 1,2-DCE with CH_3NO_2, CH_3CN, dioxane, or DCM (Table 1, entries 2−5). Further variations of the reaction conditions (solvent, temperature, duration, Lewis acid loading) disclosed that this [2 + 3]-cycloaddition was the most efficient when it proceeded in 1,2-DCE for 1 h at 80 °C in the presence of $AlCl_3$ (2 equiv).

With the optimized conditions in hand, the applicability of the reaction was examined on a series of cyclopropanes **1** and *N*-benzylic sulfonamides **2** (Table 2). Both sulfonamides with weak electron-donating groups (**2b**, **2c**) and electron-withdrawing groups **2d** on the phenyl rings worked well to give the corresponding products in good yields (entries 2−4). However, a somewhat diminished yield was obtained with the more electron-withdrawing fluoro group on both phenyl rings (entry 5). Sulfonamide **2f** possessing a strong electron-donating methoxyl group on the phenyl ring afforded the desired product only in trace amounts (entry 6). It is noteworthy that the regioselectivity of intramolecular alkylation was highly dependent on the electron nature of the two phenyl groups in *N*-bisbenzylic sulfonamide. The cyclization occurred exclusively on the phenyl ring rather than the electron-deficient 4-chlorophenyl ring in unsymmetric aromatic rings (entry 4). A substrate bearing the methyl group on the phenyl ring of *N*-benzhydryl sulfonamides could afford two products (**3b**:**3b**′ = 7:3) which failed to be separated from each other.[8] Next, a range of cyclopropanes were allowed to react with *N*-benzylic sulfonamides (**2a**) (entries 8−18). In general, good results were obtained when a weak electron-donating group (Me) and a weak electron-withdrawing group (such as halogens) were present on the benzene ring of the cyclopropanes (entries 10−14). The best case was with the 4-chlorophenyl ring which afforded **3j** in a good yield of 96%. Cyclopropanes with substituents at the *para*-position of the benzene ring gave the corresponding products in higher yields than cyclopropanes which possessed substituents at the *ortho*- or *meta*-position of the benzene ring (entries 12−14). Significantly, halogens and ester groups which were successfully introduced into the products may be used as a handle for further synthetic transformations. The reason that cyclopropanes bearing a MeO, CF_3, or NO_2 group at the *para*-position of the benzene ring gave poor yields of the products (entry 9 and entries 15−16) may be due to their extreme reactivity.[9] The reaction also cannot proceed well with cyclopropanes (**1k** and **1l**) (entries 17−18), which were decomposed quickly in this system. The stereochemistry of compounds **3a**, **3c**, **3m** were confirmed by NOESY spectroscopy, and the stereochemistry of the rest of products were demonstrated by analogy with the X-ray diffraction and NOESY analysis.

The results obtained with Indane products give some clues into the mechanism involved in this transformation, in which cyclopropanes directly participate as propenes. In an effort to gain insights into the mechanism, we conducted the cyclopropane-to-propene isomerization experiment and obtained styrylmalonate successfully.[4a] The reaction can also proceed smoothly to furnish the desired product **3h** in comparable yields when the corresponding styrene was employed to replace cyclopropane (Scheme 2). On the basis of our results and

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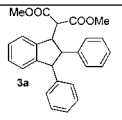
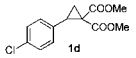
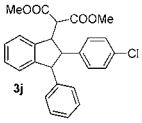
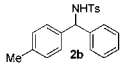
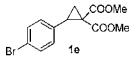
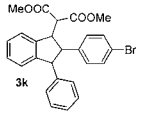
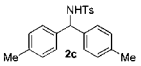
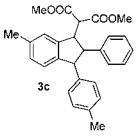
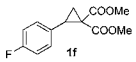
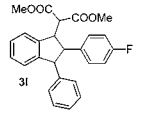
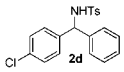
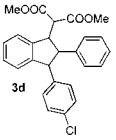
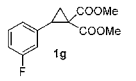
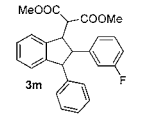
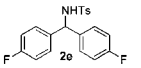
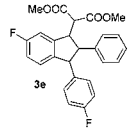
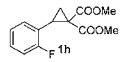
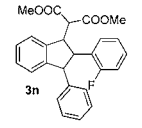
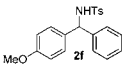
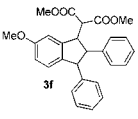
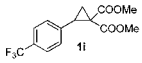
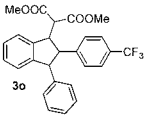
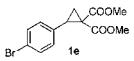
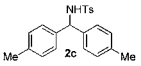
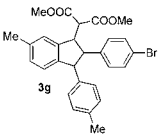
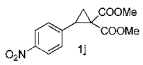
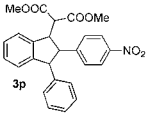
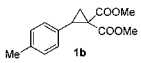
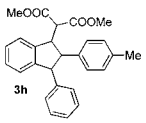
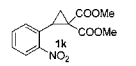
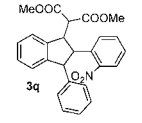
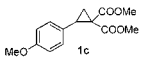
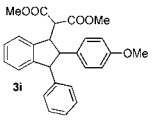
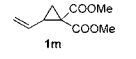
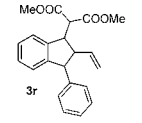
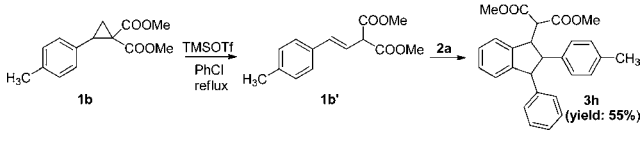
Table 2. $AlCl_3$-Catalyzed Cycloaddition of Cyclopropanes with Sulfonamides[a]

1 2 3

entry	sub. 1	sub. 2	prod. 3	yield (%)[b]	entry	sub. 1	sub. 2	prod. 3	yield (%)[b]
1	**1a**	**2a**	 **3a**	73	10	 **1d**	**2a**	 **3j**	96
2	**1a**	 **2b**	**3b:3b'=7:3**[e]	74	11	 **1e**	**2a**	 **3k**	82
3	**1a**	 **2c**	 **3c**	78	12	 **1f**	**2a**	 **3l**	86
4	**1a**	 **2d**	 **3d**	68	13	 **1g**	**2a**	 **3m**	57
5	**1a**	 **2e**	 **3e**	50	14	 **1h**	**2a**	 **3n**	65
6	**1a**	 **2f**	 **3f**	trace[c]	15	 **1i**	**2a**	 **3o**	trace[c]
7	 **1e**	 **2c**	 **3g**	73	16	 **1j**	**2a**	 **3p**	13
8	 **1b**	**2a**	 **3h**	62	17	 **1k**	**2a**	 **3q**	nd[d]
9	 **1c**	**2a**	 **3i**	trace[c]	18	 **1m**	**2a**	 **3r**	nd[d]

[a]The reaction was conducted with **1** (0.25 mmol), **2** (0.25 mmol), Lewis acid (2 equiv), and solvent (1 mL). [b]Isolated yield. [c]Only a trace of **3f** was formed. [d]No product was detected. [e]See ref 8.

Scheme 2. Isomerization of Cyclopropane 1b into Styrylmalonate 1b′ for Mechanistic Study of the Formal [2 + 3]-Cycloaddition



previous related reports,[4e,f] a possible mechanism for the formation of polysubstituted indanes was proposed (Scheme 3). It is assumed that cyclopropane **1** is subjected to $AlCl_3$-promoted isomerization to styrylmalonate **5** *via* small ring-opened 1,3-zwitterion **4**. *N*-Benzylic sulfonamide **2** is subjected to $AlCl_3$-promoted sp^3 carbon−nitrogen bond cleavage to generate benzyl cation **6**. Further electrophilic attack of carbocation **6** onto the double C═C bond of styrylmalonate **5** produces a new zwitterion **7**. It should be realized that styrylmalonate **5** reacts as an Al-complex and the generated **7** is highly stabilized by the negative charge from the ester groups in coordination with the $AlCl_3$. Intermediate **7** would then undergo an intramolecular Friedel−Crafts cyclization to furnish the final product **3** with one molecule of NH_2Ts as the only byproduct.

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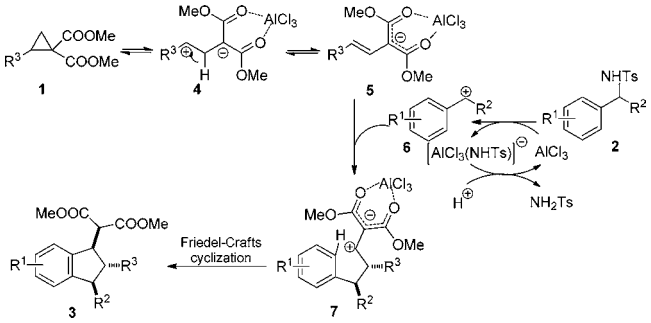
Scheme 3. A Mechanistic Proposal for the Formal [2 + 3]-Cycloaddition



In summary, we have developed an unprecedented and interesting formal [2 + 3]-cycloaddition strategy for the construction of polysubstituted indanes from cyclopropanes and *N*-benzylic sulfonamides. Cyclopropanes are employed as the source of 2-styrylmalonates reacting with benzylic cations to build five-membered rings. Thus, this finding certainly enlarges the application field of a one-stage synthesis of complex polysubstituted cyclic structures from simple and readily available donor−acceptor cyclopropanes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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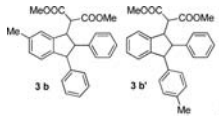
(8) The cyclization occurred highly dependent on the electronic property of the two aryl moieties, and substrates of the two products:



3b : 3b' = 7 : 3

(9) The efforts to enhance yields proved fruitless when the reactions were conducted at lower temperatures (50 °C, rt, 0 °C, −30 °C). Cyclopropanes bearing the MeO, CF_3, or NO_2 group were decomposed and produced some byproducts when using a prolonged reaction time at lower temperatures.

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