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Lewis and Brønsted Acid Induced (3 + 2)-Annulation of Donor−Acceptor Cyclopropanes to Alkynes: Indene Assembly

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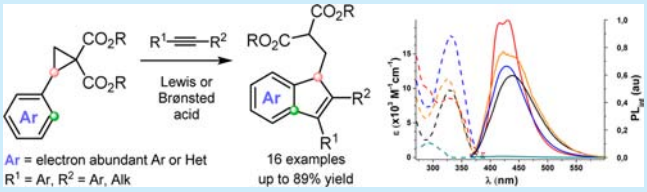
Supporting Information

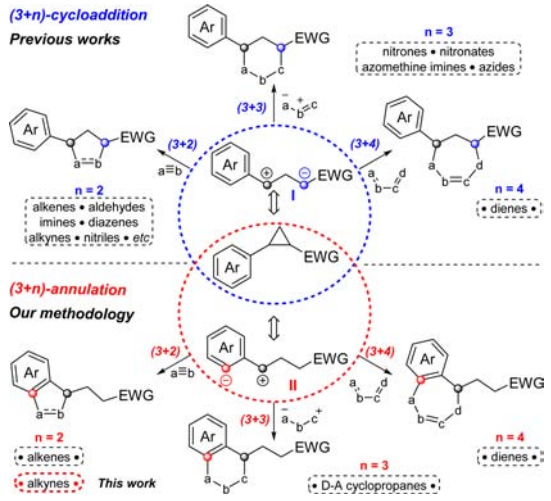
ABSTRACT: (3 + 2)-Annulation of donor−acceptor cyclopropanes to alkynes induced by both Lewis and Brønsted acids has been developed. The reaction provides a rapid approach to functionalized indenes displaying intense visible emission (λ_{max} = 430 nm, Φ = 0.28−0.34).



Activated strained-ring systems play a significant role in modern organic chemistry as polyfunctional building blocks with a wide variability in the nature and number of the atoms involved. Among these reagents, donor−acceptor (D−A) cyclopropanes, in which the highly strained three-membered ring is additionally activated with vicinal anion- and cation-stabilizing groups, occupy dominant positions.[1] In recent years, an array of straightforward synthetic accesses to principal carbo- and heterocycles was developed based on the various transformations of such cyclopropanes. These accesses compete with classical methods of ring assembly due to a variety of advantages inherent in D−A cyclopropanes, such as synthetic availability in racemic as well as in optically active form, a broad variability of donor and acceptor substituents because of modular synthetic approaches to these compounds, the presence of several reactive sites in their molecules, easy activation under mild reaction conditions, and high chemo-, regio-, and frequent stereoselectivity of their reactions. Moreover, the atom- and step-economic fashion as well as convergent character of synthetic strategies based on the D−A cyclopropane reactions make these compounds relevant reagents in the construction of complex molecular architectures, including natural products and medicines.[1,2]

The generally recognized ability of D−A cyclopropanes to react as synthetic equivalents of the evident 1,3-carbodipole **I** allows them to undergo (3 + *n*)-cycloadditions to various unsaturated compounds yielding mostly five-, six-, and seven-membered carbo- and heterocycles (Scheme 1).[3−5] Recently, we have found a new trend in reactivity of these cyclopropanes bearing electron-rich aryl or heteroaryl substituents as donor groups.[6] In this case, D−A cyclopropanes undergo (3 + *n*)-annulations as synthetic equivalents of 1,3-carbodipole **II** in which the nucleophilic site is localized in the *ortho*-position of the (hetero)aromatic substituent.

Scheme 1. (3 + *n*)-Cycloaddition vs (3 + *n*)-Annulation of Donor−Acceptor Cyclopropanes and the Strategy of This Work



These reactions provide a rapid approach to (het)arene-annulated systems with various ring sizes. Currently, we have succeeded in the employment of this methodology for the assembly of five-, six- and seven-membered rings in the cores of indanes, tetralins, and dihydroanthracenes as well as more complex molecular skeletons via (3 + *n*)-cyclodimerizations of D−A cyclopropanes[6a,b,d] and their (3 + 2)- and (3 + 4)-annulation to alkenes[6b,c] and conjugated dienes.[5b,6e] Meanwhile, other unsaturated compounds that can furnish different ring

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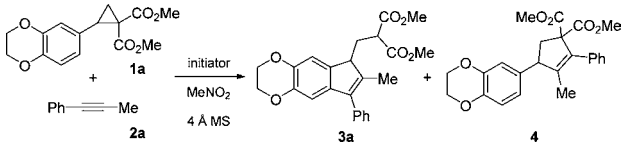
systems are still unexplored as counterparts of D−A cyclopropanes in (3 + *n*)-annulations.

This research focuses on the (3 + 2)-annulation of D−A cyclopropanes to alkynes, opening a new convenient route to polyfunctional indenes and cyclopentene-annulated heterocycles (Scheme 1). It is noteworthy that only rare examples of (3 + 2)-cycloaddition of D−A cyclopropanes to alkynes yielding cyclopentene derivatives have been reported up until now,[7] while formation of indenes and related compounds via (3 + 2)-annulation of these cyclopropanes remains an unknown process. The resulting indenes are new representatives of this important class of compounds, the members of which exhibit a broad variety of bioactivities[8] and fluorescence properties[8c,9] and serve as ligands in catalysts of stereoselective alkene polymerization, hydroamination, and other processes,[10] as well as precursors for preparation of functional materials,[11] etc.

We started this work with a search for optimal conditions using the reaction of 3,4-dialkoxyphenyl-substituted cyclopropane **1a** with phenylpropyne **2a** as a model (see the reaction scheme in Table 1). The choice of **1a** was based on its recently found ability to easily undergo (3 + 2)-annulation to alkenes[6c] and various (3 + *n*)-cyclodimerizations.[6b,d] A series of reactions was carried out with varying initiators, solvent polarity, reaction temperature, as well as ratio and concentration of reagents. Selected representative results are summarized in Table 1.

Table 1. Optimization of Reaction Conditions for the Model (3 + 2) Annulation between Cyclopropane 1a and Alkyne 2a[a,b]



entry	initiator (mol %)	temp (°C)	time (h)	yield of **3a**[b] (%)	yield of **4**[b] (%)
1	$SnCl_4$ (120)	25	4	57	19
2[c]	$SnCl_4$ (120)	−40	6	48	27
3	$TiCl_4$ (120)	20	20	59	4
4	**BF_3·Et_2O (120)**	**25**	**4.5**	**65**	
5	$Sc(OTf)_3$ (20)	25	20	41	
6	$ZnCl_2$ (20)	25	48	33	
7	$FeCl_3/SiO_2$ (20)	25	3	52	
8	MgI_2 (20)	25	72	*d*	*d*
9	$AlCl_3$ (120)	25	2	*d*	*d*
10	**TfOH (10)**	**25**	**24**	**71**	

[a]Conditions: 0.03 M solution of **1a** (1 equiv), **2a** (4 equiv). [b]Isolated yield. [c]$EtNO_2$ was used as a solvent. [d]Only products of polymerization were formed.

We have found that triggering the reaction with Lewis acids possessing different activating abilities does lead to the formation of the desired indene **3a**, though with variations in efficiency and selectivity (entries 1−7, Table 1). For example, when the reaction is carried out in $MeNO_2$ in the presence of $SnCl_4$ that has been previously found to be optimal for (3 + 2)-annulation of D−A cyclopropanes to alkenes, indene **3a** is formed together with (3 + 2)-cycloadduct **4** (entry 1). A considerable decrease in temperature only leads to a minor change in the **3a** to **4** ratio (entry 2). In the case of strongly activating Lewis acids, the best result was achieved by using BF_3·Et_2O which provides the highest chemoselectivity and yield of **3a** (entry 4). The reaction efficiency decreases with the decrease of activating ability of the employed Lewis acid (entries 5−7) due to intensification of polymerization. The replacement of $MeNO_2$ with the less polar CH_2Cl_2 leads to significant deceleration of the reaction and promotes side processes.

Typically, transformations of D−A cyclopropanes are induced by Lewis acids, whereas the use of Brønsted acids is a less widespread,[3e,12] despite such initiators being promising as environmentally friendly reagents and, thus, more preferable for industrial applications. In this work, we have carried out a brief screening of typical Brønsted acids, and TfOH was found to provide the best yield of **3a** though the reaction takes longer in this case (entry 10).

Consequently, we have studied reactivities of 2-(hetero)-arylcyclopropane-1,1-diesters toward a series of acetylenes. We have found that terminal alkynes as well as dialkylacetylenes, e.g., octyne-4, fail to produce indenes **3** under the studied conditions. Alkylarylacetylenes, such as 1-phenylpropyne (**2a**) and -butyne (**2b**) or tolans **2c,d** (Scheme 2) were found to be the best partners for (3 + 2)-annulation. Thus, the model cyclopropane **1a** chemoselectively reacts with tolan (**2c**) and its 4,4′-dimethoxy derivative **2d** exclusively via (3 + 2)-annulation leading to indenes **3b,c**. Analogous 3,4-dialkoxyphenyl derivatives **1b,c** readily give indenes **3d−j** in reactions with **2a−d**. It is noteworthy that in these cases indenes were formed as individual regioisomers with alkoxy substituents in the C(5) and C(6) positions of the indene core.

Among tested alkynes, tolan was found to have the lowest reactivity toward **1** that allowed for side reactions, such as dimerization and oligomerization of **1**, to occur. As a result, the corresponding indenes **3b,f,j** were formed in moderate yields. In the case of asymmetrically substituted alkynes **2a,b**, (3 + 2)-annulation proceeds with high regioselectivity and leads to the exclusive formation of 1-aryl-2-alkylindenes **3a,d,e,h,i**.

We have found that even the presence of a single activating alkoxy group in the *para*-position of aryl substituent, as it is in **1d**, is enough to promote (3 + 2)-annulation to **2b** while replacement of methoxy group by the less donating methyl prevents this process. Moreover, unforeseen mechanistic peculiarity was revealed for the (3 + 2)-annulation: Obtained indene **3k** was appeared to be regioisomeric to the expected structure. Analogously, reaction of 3-indolyl derivatives **1f,g** with **2a** leads to cyclopenta[*b*]indoles **3n,o**, which are formally arisen from annulations after cyclopropyl 1,2-shift.

(3 + 2)-Annulation of 3,4,5-trimethoxyphenyl derivative **1h** to **2a−c** affords pairs of regioisomeric indenes **3p−u**, wherein the products of "normal" (3 + 2)-annulation **3p,r,t** prevail over products of "cyclopropyl 1,2-shift" **3q,s,u**. Only 4,4′-dimethoxytolan **2d** provides exceptional selectivity of annulation with **1h** yielding the expected indene **3v** exclusively. In the case of 3,4-dialkoxy derivatives **1a−c**, the presence of identical alkoxy groups makes the same the outcomes of two possible paths of this reaction. Meanwhile, **1e** bearing two different alkoxy groups gives normal product **3l** and its regioisomer **3m** in 1:3 ratio.

Structural assignments for the synthesized indenes **3** were made by means of 2D NMR experiments, including $^1H-^{13}C$ HMBC and $^1H-^1H$ NOESY.[13]

We proposed the following mechanism for this (3 + 2)-annulation (**A** in Scheme 3). The reaction is initiated by Lewis or Brønsted acid triggered cyclopropane **1** ring opening to intermediate **I-1** followed by its electrophilic attack on **2** leading to the key intermediate **I-2**. Hypothetically, **I-2** has two obvious

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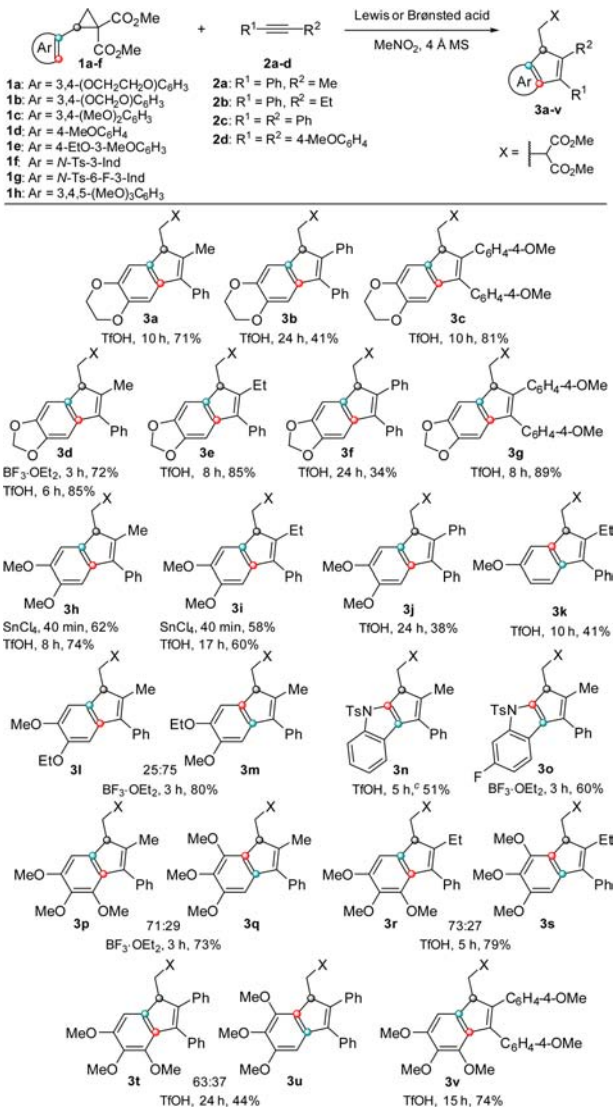
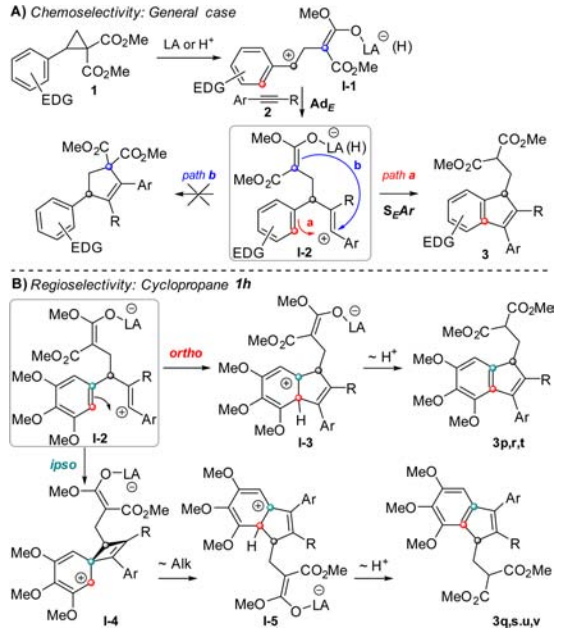
Scheme 2. Scope of (3 + 2)-Annulation of Cyclopropanes 1 to Alkynes 2[a,b]



[a]Reaction conditions: 0.03 M solution of **1** (1 equiv), **2** (4 equiv), TfOH (10 mol %), or LA (120 mol %). [b]Isolated yields. [c]Reaction was carried out at 50 °C.

Scheme 3. Proposed Mechanism



ways for 1,5-cyclization. The first one is an intramolecular Friedel–Crafts reaction (path **a**) affording indene **3** apparently via formation of a π-complex between the electron-rich aryl fragment and vinyl cation in **I-2**;[6e] this ensures close proximity for the reacting centers. The second direction, 1,5-cyclization to cyclopentene (path **b**), requires a change in conformation and does not occur under the optimized conditions.

Formation of isomeric indenes in the (3 + 2)-annulation can be explained in terms of *ortho*- and *ipso*-attacks of vinyl cation on the aromatic ring in **I-2** (in Scheme 3 (**B**) this transformations are demonstrated using an example of cyclopropane **1h**). The *ortho*-attack gives the expected indene via σ-complex **I-3**, while the alternative *ipso*-attack leads to spiro-fused σ-complex **I-4**[14] followed by alkyl 1,2-shift and regioisomeric indene formation. DFT calculations[13] confirm that cyclization of **I-2** proceeds under kinetic control due to extremely high reactivity of vinyl cation. Thus, despite unexceptional higher stability of **I-3** in comparison with ***I4***, *ipso*-attack is an exclusive process for 3-indolyl- and 4-methoxyphenyl derivatives **1d,f,g**. Introduction of an additional alkoxy group activating *ortho*-attack decreases regioselectivity of **I-2** cyclization although *ipso*-attack remains predominant (e.g., **1e**). *Ortho*-attack becomes a major route when the second alkoxy group occurs to activate this process (e.g., **1h**). Stabilization of a vinyl cation by 4-methoxy group (e.g., **2d**) makes *ortho*-attack preferable both kinetically and thermodynamically.

2,3-Diarylindenes **3b,c,f,g** were found to be visibly fluorescent with emission maxima at ca. 430 nm, displaying large Stokes shifts (ca. 7000 cm^{-1}) (Figure 1) and good quantum yields (Φ = 0.28–0.34).[13] The presence of a triarylethylene system has a crucial effect on the ability of **3** to fluoresce. For example, **3d**, substituted with a methyl instead of an aryl group at the C(2) position, was proven to be nonemissive in the visible range (green solid line in Figure 1).

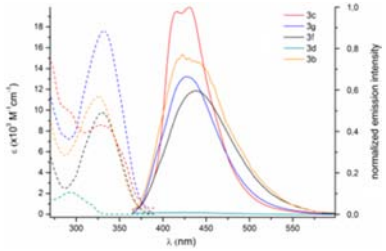


Figure 1. Absorption (dashed lines) and normalized fluorescence (solid lines) spectra of indenes **3b–d,f,g** in CH_2Cl_2.

According to our preliminary in vitro experiments toward HEK293, MCF7, and A549 cell lines, indenes **3** do not exhibit any cytotoxicity up to concentrations of 0.25 mM.[13]

The presence of a side chain functionalized with a malonyl motif allows indenes **3** to be purposefully modified or coupled with appropriate partners to achieve desired functional properties. For example, the ester moiety in **3** can be easily hydrolyzed, while high nucleophilicity of the aryl fragment promotes its further acylation (Scheme 4).

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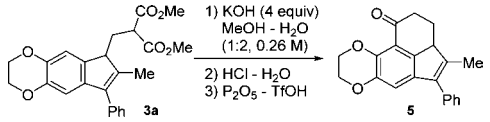
Scheme 4. Example of Malonyl Motif Use in Indenes 3 Modification



In conclusion, we have developed (3 + 2)-annulation of D−A cyclopropanes containing electron-abundant (hetero)aryl substituents as donor groups to alkynes. This new (3 + 2)-annulation provides a shortcut approach to functionalized indenes in up to 89% yields. The proposed mechanism and the results of DFT calculations supported formation of regioisomeric indenes via kinetically controlled *ortho*- and *ipso*-attack within highly reactive vinyl cation as the key intermediate. The intense emission of synthesized indenes, the possibilities for synthetic modification of their functionalized side chain, along with the absence of any noticeable cytotoxicity, make these compounds promising precursors for the design and development of biophysical probes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as NMR, IR, and MS spectra and elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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