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We report a new biomimetic (hetero)aryl-derived cyclopropanes cyclodimerization producing polyoxygenated indanes with exceptional stereoselectivity. Because in nature such indanes are formed *via* styrenes cyclodimerization, we draw a parallel between not only "*in vivo*" and "*in vitro*" processes, but also between alkenes and cyclopropanes reactivity.

As featured in:

See Ekaterina M. Budynina *et al.*, *Chem. Commun.*, 2013, **49**, 11482.

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View Journal | View Issue

Cite this: *Chem. Commun.*, 2013, **49**, 11482

Received 14th June 2013,
Accepted 3rd July 2013

DOI: 10.1039/c3cc44475a

www.rsc.org/chemcomm

A bioinspired route to indanes and cyclopentannulated hetarenes *via* (3+2)-cyclodimerization of donor–acceptor cyclopropanes†

Olga A. Ivanova,[a] Ekaterina M. Budynina,*[ab] Dmitriy A. Skvortsov,[a] Michelle Limoge,[c] Andrei V. Bakin,[c] Alexey O. Chagarovskiy,[ab] Igor V. Trushkov[ab] and Mikhail Ya. Melnikov[a]

A novel Lewis acid-catalyzed domino (3+2)-cyclodimerization of 2-arylcyclopropane-1,1-diesters and related stepwise cross-reaction of two different cyclopropanes were developed. These processes provide efficient and highly stereoselective access to polyoxygenated indanes and cyclopentannulated heteroarene derivatives, which display significant cytotoxicity against several lines of cancer cells (IC_{50} of 10^{-6}–10^{-5} M) while being non-toxic for normal cells.

The design of synthetic routes to complex compounds is often inspired by reactions which occur in nature and generally display outstanding efficiency, exceptional selectivity and atom economy. Among the numerous biomimetic reactions, one important process is the acid-catalyzed cyclodimerization of (hetero)arylalkenes, which provides a convenient approach to indanes and related cyclopentannulated heteroarenes.[1] In nature, cyclodimerization of oxygenated styrenes is the key step in biosynthesis of indane-based structures, *e.g.* diisoeugenol, pallidol, griffipavixanthone, laetevirenol A, quadrangularin A, parthenocissin A, parvifolol (Fig. 1) exhibiting cytotoxic,[2] antioxidant,[2a,3] and other[4] activities. This cyclodimerization proceeds *via* generation of a benzyl cation which attacks the C–C double bond of another styrene molecule followed by Friedel–Crafts cyclization (Scheme 1).

Our interests primarily focus on donor–acceptor (DA) cyclopropanes for which multiple chemical transformations are currently being intensively and successfully developed.[5] Multifaceted reactivity inherent to these compounds provides a significant advance in the synthesis of acyclic compounds (mostly *via* nucleophilic ring opening[6]) as well as a variety of ring systems *via* (3+*n*)-cycloadditions,[7] annulations,[8] cyclodimerizations,[9] and ring enlargement.[10]

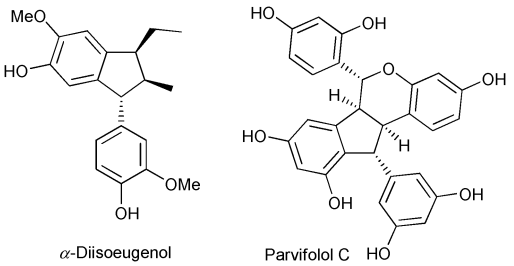
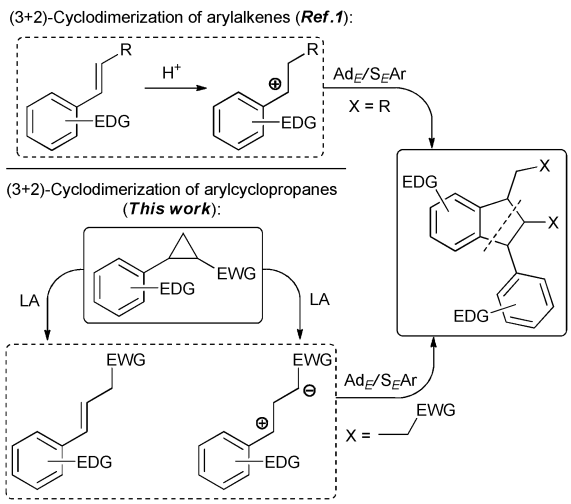


Fig. 1 Representatives of natural bioactive arylalkene dimers and their oxidized derivatives.



Scheme 1 Strategy for DA cyclopropanes-to-indanes cyclodimerization.

Here, based on the ability of (hetero)aryl-derived DA cyclopropanes to serve as a source of benzyl cations[8a,b,9,11] and, at the same time, to undergo isomerization to styrene derivatives[9a,12] we hypothesize the existence of previously unknown DA cyclopropane-to-indane cyclodimerization (Scheme 1), which is similar to

[a] *M.V. Lomonosov Moscow State University, Department of Chemistry, Leninskie Gory, 1-3, 119991 Moscow, Russia. E-mail: ekatbud@kinet.chem.msu.ru; Fax: +7 495 9391814; Tel: +7 495 9391316*

[b] *Federal Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Chemical Synthesis, ul. Samory Mashela 1, Moscow 117997, Russia*

[c] *Department of Cancer Genetics, Roswell Park Cancer Institute, Elm and Carlton Sts., Buffalo, NY 14263, USA*

† Electronic supplementary information (ESI) available. CCDC 930605. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc44475a

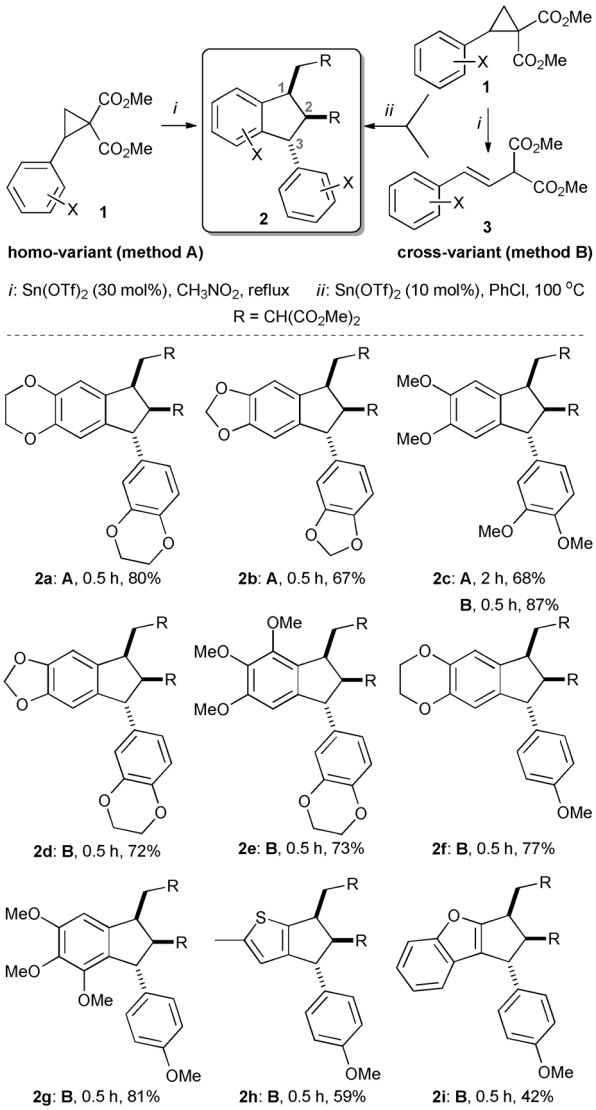
dimerization of oxygenated styrenes in nature. We succeeded in developing this bioinspired Lewis acid-catalyzed (3+2)-cyclodimerization for cyclopropane-1,1-diesters **1** containing electron-enriched aryl substituents.

Currently, several types of Lewis acid-triggered DA cyclopropane cyclodimerization exist.[9] Selectivity with regards to the desired cyclodimer can be efficiently tuned by some reaction parameters, such as nucleophilicity of the aryl group in DA cyclopropanes, activation ability of the catalyst, reaction temperature and solvent polarity. Search for substrates suitable for the DA cyclopropane-to-indane dimerization revealed that the aryl group in the initial compound should contain donor substituents which activate cyclopropane towards ring opening to form a benzyl cation as well as activate *ortho*-positions to final Friedel–Crafts reaction. Therefore, optimization of the reaction conditions was carried out for 3,4-dialkoxyphenyl-substituted cyclopropane **1a** as a model compound under variation of Lewis acids, solvent polarity and reaction temperature.† The best yield of dimeric product **2a** was achieved when 0.2 M solution of **1a** in nitromethane was treated with 30 mol% of $Sn(OTf)_2$ followed by reflux.

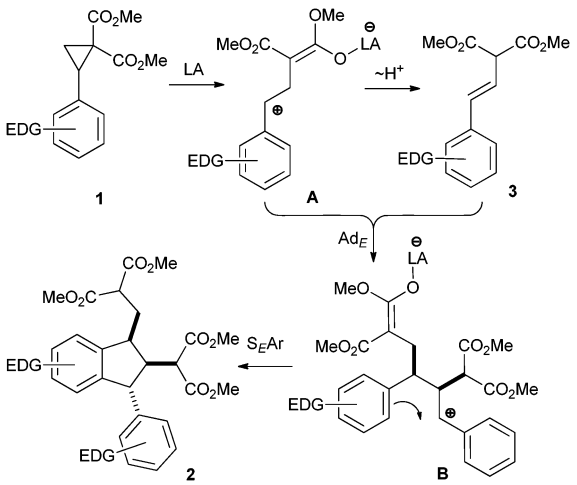
Next, under optimized conditions we carried out this reaction for other 3,4-dialkoxyphenyl-substituted DA cyclopropanes **1b,c** and obtained corresponding indanes **2b,c** in good yields (Scheme 2). According to NMR data, in each case dimerization produced **2** as a single isomer. The structure of **2c** was determined by X-ray analysis†[13] that revealed a *cis*-arrangement of alkyl substituents at the C1 and C2 atoms *versus* a *trans*-arrangement of aryl groups at the C3 atom.

We proposed that dimerization of **1** proceeds through the formation of styrylmalonates **3** as intermediates (Scheme 3). This hypothesis is based on our recent results[9a,12] concerning ability of DA cyclopropanes to undergo Lewis acid-induced isomerization to **3** *via* small ring-opened 1,3-zwitterion **A**. In the case of the studied dimerization, a balanced combination of appropriate concentration of **1**, moderate activating ability of a Lewis acid and high polarity of a solvent appears to provide compromise conditions for the co-existence of **A** and **3** in the reaction medium. Further electrophilic attack of **A** onto **3** produces a new zwitterion **B** which undergoes Friedel–Crafts cyclization to indane **2** chemoselectively, while the coupling of a benzyl cation with a malonate moiety does not occur at all.

Cyclodimerization of **1** to **2** exhibited exceptional chemo-, regio- and diastereoselectivity. High chemoselectivity of **B** cyclization can be explained by π-stacking between the electron-depleted benzyl cation and the electron-enriched second aromatic ring that provides proximity of these two reaction sites. The same preference of electrophilic attack onto the *ortho*-position of the aryl substituent over the malonyl moiety was recently found in the related reactions of DA cyclopropanes bearing electron-enriched (hetero)-aryl groups.[8a,b,9c,14] Among the two *ortho*-positions (C2 and C6) of the aryl group, only the less sterically hindered C6 position is found to be reactive towards the benzyl cation that gives rise to high regioselectivity of electrophilic substitution. The exclusive formation of 1,2-*cis*-2,3-*trans* isomers of **2a–c** is in good accordance with the results of related reactions,[1b,c] for which the authors explained such stereoselectivity also in terms of π-stacking. Meanwhile, stereoselectivity of the second stage of dimerization,



Scheme 2



Scheme 3 Proposed mechanism.

when relative configuration of C2 and C3 centers arises, correlates to the relative thermodynamic stability of 1,2-*cis*-2,3-*trans* and all-*cis* isomers. Our *ab initio* calculations for diastereomers of **2c** at the B3LYP/6-311G** level showed that the 1,2-*cis*-2,3-*trans*-isomer is 16.0 kJ mol^{-1} more stable than the *cis,cis*-isomer.

To confirm the proposed mechanism we carried out the dimerization of **1c** stepwise through its isomerization to styrylmalonate **3c** which was then involved in a reaction with **1c** under the above reaction conditions (Scheme 2). As a result, the desired product **2c** was obtained in a high yield.

Stepwise (3+2)-cyclodimerization of DA cyclopropanes **1** opens a simple synthetic route to "cross-dimers" containing two different (hetero)aryl moieties, which is especially important for the search of novel bioactive compounds. For the development of this strategy we prepared styrylmalonates **3a,b**, containing benzodioxan-6-yl and 4-methoxyphenyl groups, and carried out their reactions with aryl- and heteroaryl-derived DA cyclopropanes **1a,b,d–g**. Corresponding "cross-dimers" **2d–i** were obtained as individual diastereomers in up to 81% yield (Scheme 2).

Natural dimers of oxygenated styrenes are mostly known antitumor and antioxidative agents. Therefore, it was natural to expect such types of bioactivity for structurally similar indanes **2**. We studied cytotoxicity of synthesized indanes **2a–i** against several cell lines and revealed the selective effect of **2a–i** towards tumor *versus* normal cells. Thus, all compounds were found to be non-toxic for mammary gland epithelium cells MCF-10A, while exhibiting toxicity against tumor cell lines with an IC_{50} of 10^{-6}–10^{-5} M.†

In conclusion, we have developed a novel type of Lewis acid-catalyzed DA cyclopropane (3+2) cyclodimerization which represents a biomimetic domino-process and opens a straightforward route to polysubstituted oxygenated indanes. A mechanistic insight into this dimerization allowed us to develop a related stepwise cross-reaction of two different cyclopropanes which provides a convenient synthesis of "cross-dimers" including cyclopentannulated hetarene derivatives. Nontoxicity in relation to normal cells *versus* significant toxicity for tumor cell lines makes the synthesized compounds promising candidates for the research towards their anticancer activity.

We thank the Russian Foundation for Basic Research (projects 12-03-00717, 12-03-31418, 12-03-33182) and Ministry of Education and Science of Russian Federation (contract 8466) for support of this work. The NMR measurements were carried out in the Laboratory of Magnetic Tomography and Spectroscopy, Faculty of Fundamental Medicine of Moscow State University.

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