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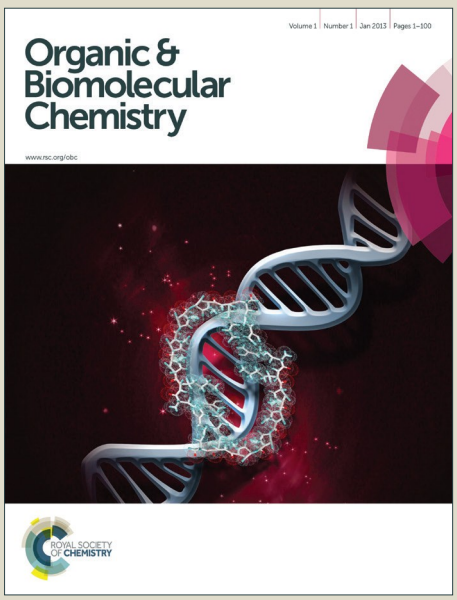



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# Acid-Promoted Cycloisomerizations of Phenylallenes Bearing Acetalic Functions at *ortho* Position: a Stereocontrolled Entry to Indeno-Fused Dioxepanes, Dioxocanes and Thioanalogues

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**The cycloisomerization reactions of allenes bearing cyclic acetal, thioacetal and dithioacetal subunits, when triggered either by the catalytic action of $AgSbF_6$ or by one equiv of $CF_3COOH$, gave rise to four different classes of indeno-fused 1,4-dioxa, oxathia and dithia heterocycles, in most cases as a single diastereomer. Acyclic acetals and dithioacetals are also suitable starting materials in similar transformations yielding 1,2-disubstituted indenes and 1,3-disubstituted 2-alkylideneindanes.**

Lewis acid catalysed addition of carbon nucleophiles to the carbonyl carbon atom of acetals with the replacement of one alkoxy group is a reaction commonly applied in organic synthesis for the formation of carbon-carbon bonds. Since the discovery in 1974 of the so-called Mukaiyama reaction,[1] consisting in the treatment of acetals with enol ethers in the presence of titanium tetrachloride to yield β-alkoxy ketones, numerous variations in the carbon nucleophiles used in related substitution processes of acetals have been reported.[2] Furthermore, a number of carbo- and heterocyclization processes based on the Lewis acid catalysed cycloisomerization of acetalic species bearing alkene[3] and alkyne[4] functionalities as internal nucleophiles have been widely documented.

Less common related cycloisomerization processes are those of allenes bearing acetalic functions,[5-7] the three more relevant examples are summarized in Figure 1. De Lera et al. reported the Brönsted and Lewis acid-catalysed rearrangement of 2-[(1*Z*)-hexa-1,3,4-trienyl]dioxolanes converting into tetrahydrocyclopenta-1,4-dioxins involving an electrocyclic ring closure of hydroxypentadienyl carbocations as the key mechanistic step [Eq. (1)].[5] Bhunia and Liu have disclosed the cycloisomerization of 1-(dimethoxymethyl) benzenes substituted by 3-alkenyl-1,2-propadienyl groups at the *ortho* position, leading to benzo-fused bicyclooctanes by the action

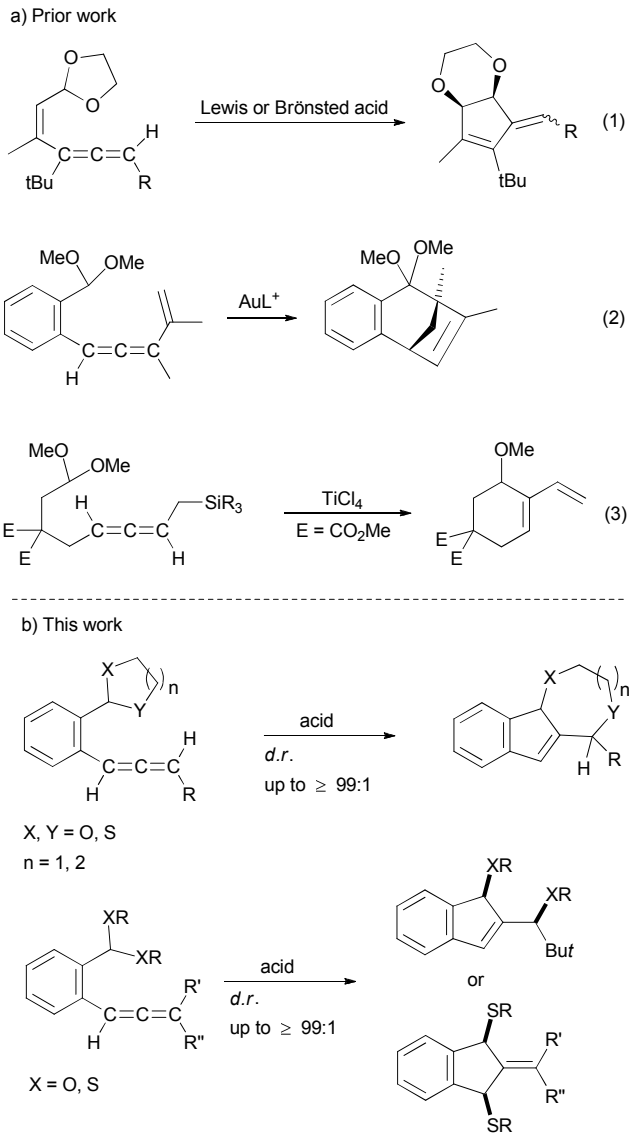


**Figure 1** Cycloisomerizations of allenes bearing acetalic functions

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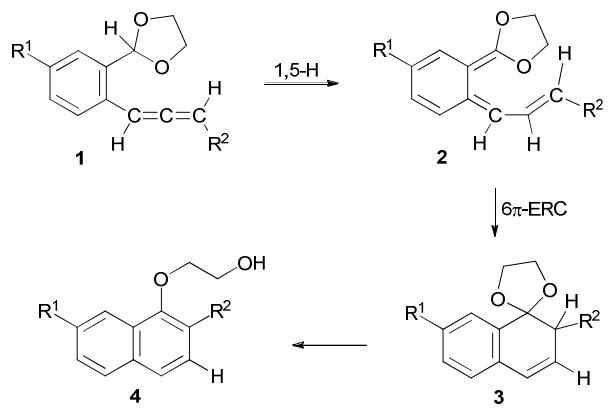
of $Au^+$ catalysts [Eq. (2)].[6] The relevance of these latter transformations relies on the unusual 1,3-addition of a $sp^3$-hybridized C–H bond to a vinylcarbenoid moiety. Takahashi, Ogasawara et al. showed that $TiCl_4$ and other Lewis acids promote the intramolecular electrophilic substitution/cyclization of substrates possessing acetal and (allenylmethyl)silane fragments tethered by a propylene chain, giving rise to conjugated vinylcyclohexenes [Eq. (3)].[7]

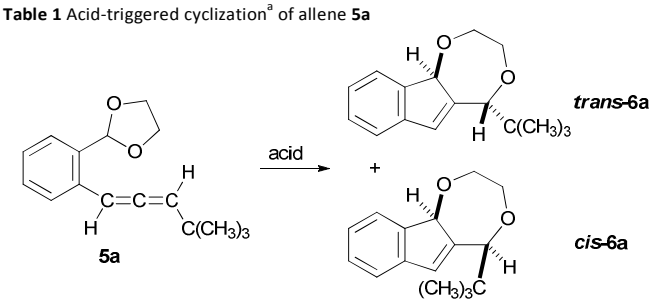
In this communication we disclose the Lewis and Brönsted acid-catalysed cycloisomerizations of acetals, thioacetals and dithioacetals derived from benzaldehydes bearing 1,2-propadienyl fragments at *ortho* position. We herein show that depending on the cyclic (e.g., 1,3-dioxolane, 1,3-dioxane, 1,3-oxathiane and 1,3-dithiolane) or acyclic nature of the acetalic function, the type of acid catalyst and the substituents at the terminal allenic carbon, these reactions can lead, chemo and diastereoselectively, to a variety of chemical entities containing indene-based scaffoldings.

One of our current research lines focus on highlighting the hydride-donor ability (*hydricity*)[8] of acetalic functions as an effective property for initiating thermally activated cyclizations of heterocumulenes, such as ketenimines and carbodiimides.[9] These cyclizations are in fact tandem intramolecular processes promoted by hydride-like 1,n-H shifts from acetalic carbon atoms to the central electrophilic carbon of the heterocumulenic fragment yielding reactive transient species that quickly cyclized into a diversity of more stable heteroaromatic systems. We have also shown that related tandem processes are feasible by changing the hydride-acceptor unit from heterocumulenes to other electrophilic functional groups such as benzylidenemalonate fragments.[10] Recently we achieved the conversion of 2-(1,3-dioxolan-2-yl)phenylallenes **1** into 1-(2-hydroxy)ethoxy-2-substituted naphthalenes **4** by a similar tandem strategy.[11] The central carbon atom of the allene function of **1** acted as the terminus of the initial 1,5-H shift from the acetalic C-2 of the 1,3-dioxolane ring (Scheme 1). The subsequent 6π-electrocyclic ring closure (ERC) of transient *ortho*-xylylene **2** and a final aromatization step of the resulting 1,2-dihydronaphthalene **3**, involving the ring opening of the 1,3-dioxolane unit, reasonably explain the formation of products **4**.




**Scheme 1** Thermal cyclization of phenylallenes bearing *ortho*-1,3-dioxolan-2-yl groups

**Table 1** Acid-triggered cyclization[a] of allene **5a**




| Entry | Acid | Equiv. | Yield (%) | *trans*:*cis*[b] |
|---|---|---|---|---|
| 1 | $AgSbF_6$ | 0.1 | 62 | 100:0 |
| 2 | AuCl | 0.2 | 90 | 50:50 |
| 3 | $LiClO_4$ | 0.1 | - | |
| 4 | $BF_3.Et_2O$ | 0.1 | 60 | 97:3 |
| 5 | $TiCl_4$ | 0.2 | 37 | 66:34 |
| 6 | $Sc(OTf)_3$ | 0.1 | 85 | 89:11 |
| 7 | $Yb(OTf)_3$ | 0.2 | 56 | 20:80 |
| 8 | $In(OTf)_3$/TfOH (9:1) | 0.1 | 58 | 97:3 |
| 9 | *p*-TsOH | 0.1 | - | |
| 10 | $CF_3COOH$ | 1.0 | 92 | 35:65 |
| 11 | $FeCl_3.SiO_2$ | 1.0 | 50 | 80:20 |

[a] ***Reaction conditions:*** 0.1 M solution in $CH_2Cl_2$ at 25 °C for 20 min.

[b] Determined by $^1H$ NMR spectroscopy in the crude products

With 2-(1,3-dioxolan-2-yl)phenylallenes **1** in our hands, we considered of interest to investigate their putative cycloisomerization reactions by acid-catalyzed variants. The first candidate in our preliminary experiments was the 1,3-disubstituted 1,2-propadiene **5a** (Table 1). We assayed a wide variety of reaction conditions by using different Lewis or Brönsted acids in amounts ranging from 0.1 to 1.0 equivalents, the most significant results are summarized in Table 1. *cis*/*trans* Indene-1,4-dioxepanes **6a** were the only products isolated from the reaction mixtures in those experiments, with the exception of the experiments in entries 3 and 9 which resulted unsuccessful. In these latter experiments, $LiClO_4$ did not alter **5a** whereas *p*-TsOH only gave rise to the hydrolysis of its acetalic function.

From the successful cases, we selected that catalysed by 0.1 equiv of $AgSbF_6$, showing the higher diastereoselectivity, as the optimal catalyst and reaction conditions for performing new experiments with a range of additional acetal-allenes. The results of these processes are gathered in Scheme 2. As shown, this cyclization methodology was applied to reactants bearing cyclic acetalic functions of diverse ring size such as 1,3-dioxolane (allenes **5a-c**) and 1,3-dioxane (allenes **5d,e**), others with mono or dithio substituted analogous functions, 1,3-oxathiolane or 1,3-dithiolane (allenes **5f,g**), as well as to acyclic acetals and dithioacetals (allenes **5h-m**). The 1,2-propadiene fragment was either 1,3-disubstituted (allenes **5a-i**) or 1,1,3-trisubstituted (allenes **5j-m**). In those cases where the reactants contain dithioacetalic functions (allenes **5g, i-m**) the silver catalyst was ineffective for promoting the cyclization, whereas a quick screening of other acid reagents showed that the better results were obtained by the use of 1.0 equiv of $CF_3COOH$. In all the assayed cases the cyclization resulted in the building of a new indene ring system formed by linking the acetalic carbon atom

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with the central allenic *sp* carbon atom, with the simultaneous migration of one of the alkoxy or alkylthio groups from its original position toward either the external C-1 of the propadiene fragment (indenes **6a-c**, **7a,b**, **8**-**11**) or the internal C-3 of the same fragment (indanes **12**). In this way, these processes gave rise to a variety of indeno-fused heterocyclic systems, such as indeno-1,4-dioxepanes **6a-c**, indeno-1,4-dioxocanes **7a,b**, indeno-1,4-oxathiepane **8** and indeno-1,4-dithiepane **9**, as well to 2,3-disubstituted indenes such as the dialkoxy and bis(alkylthio) derivatives **10** and **11**, and the 1,3-bis(alkylthio)-2-alkylidene-1,2-dihydroindenes **12a-d**. All these species were obtained in yields ranging from medium to good. As far as the diastereoselection of these reactions is concerned, high diastereoselective ratios are obtained in most of the cases in Scheme 2. It is worth noting that under $Ag^+$ catalysis the sense of the diastereoselection favoured the formation of the *trans* diastereomers of the resulting indeno-fused heterocyclic systems, with the remarkable exception of the mixed acetal case (allene **5f**) in which the sense of the diastereoselection was reversed. In the same example it is worth remarking the totally chemoselective migration of the alkoxy fragment instead of the alternative alkylthio one. Bulky substituents at the external C-1 carbon of the allene fragment, such as *t*-butyl or phenyl, guaranteed excellent diastereoselectivities, whereas the less sterically demanding methyl group only reached 3:1 diastereoselective ratios (indenes **6b** and **7b**). In sharp contrast, the action of $CF_3COOH$ yielded mainly *cis* diastereoisomers of tricyclic (indene **9**) or bicyclic (indene **11** and indanes **12**) species. Under these reaction conditions, monosubstitution at C-1 of the allene moiety favoured the migration of the alkylthio group from the acetalic carbon atom toward that terminal allenic carbon atom (indenes **9** and **11**), whereas its disubstitution diverted the rearrangement toward the less substituted, internal C-3 carbon of the allene fragment (indanes **12**).

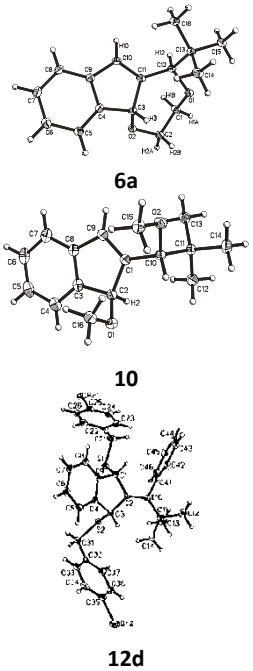
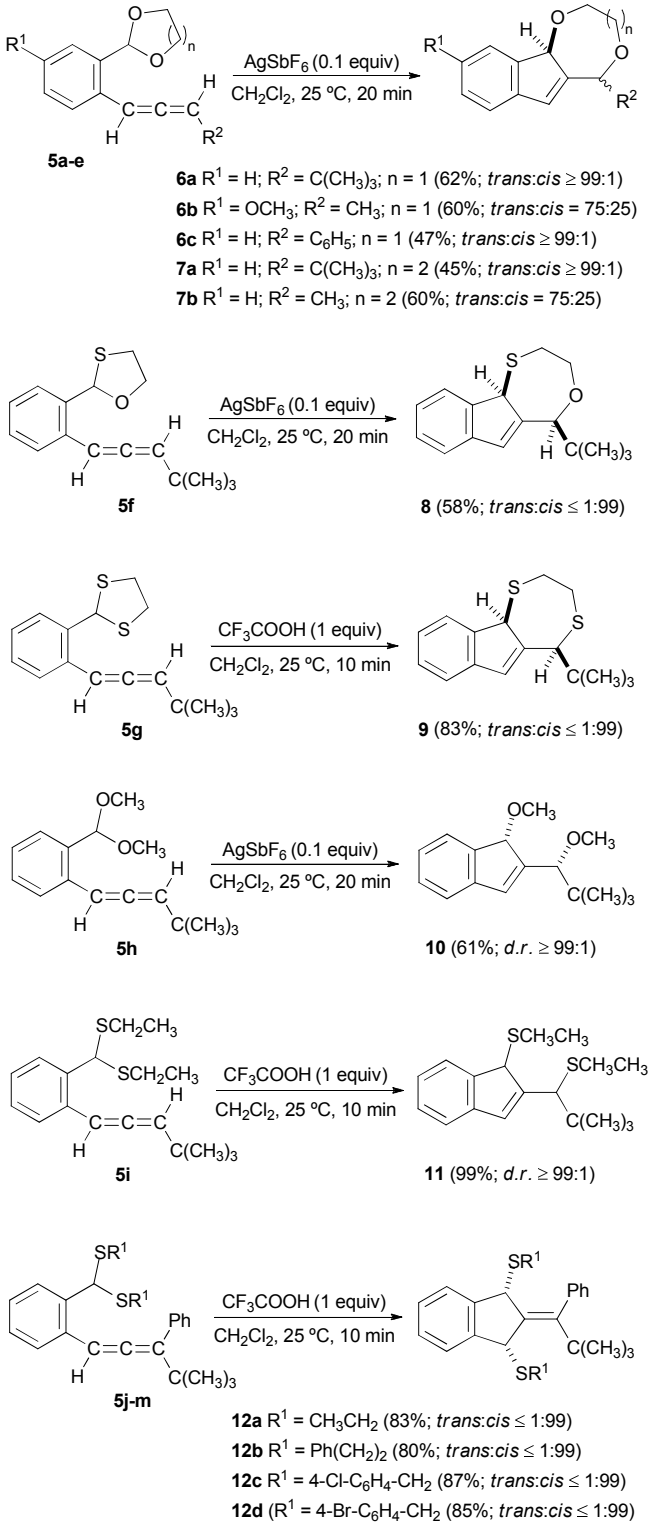



**Figure 2** Solid-state molecular structures of **6a**, **10** and **12d**. Thermal ellipsoids are drawn at 50% probability level

For the elucidation of the structure and configuration of all the reaction products depicted in Scheme 2, the X-ray structural determination of compounds **6a**, **10** and **12d** was especially helpful (Figure 2)[12], along with the employment of the habitual analytical and spectroscopic techniques (see Supplementary Information).




**Scheme 2** Acid-triggered cyclization of acetalic allenes

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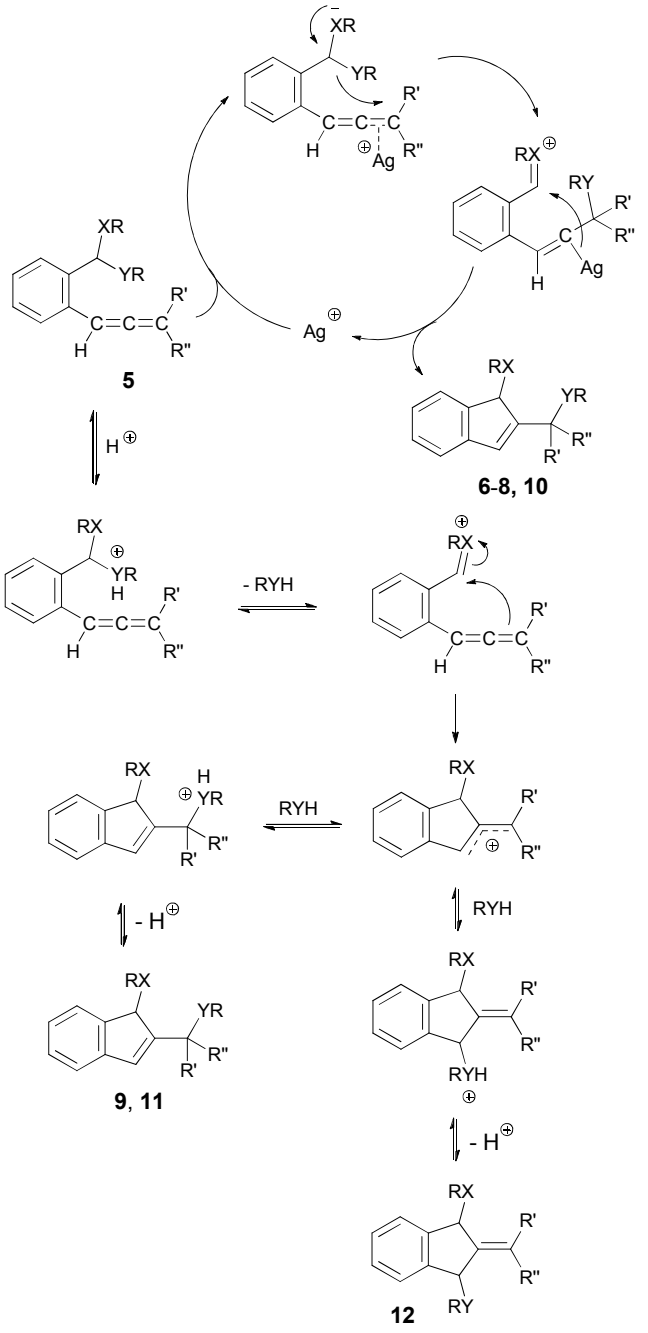
These cycloisomerization processes can be mechanistically interpreted as summarized in Scheme 3. In the Lewis acid catalysed path, the $Ag^+$ cation first activates the allene moiety by coordination with its C=C π bonds. This is followed by the anionotropic migration of the RY group assisted by the lone pairs at the heteroatom of the RX fragment remaining linked to the original acetalic carbon. In all cases the migrating group becomes linked to the terminal C-1 carbon atom of the allene, most probably for the sake of keeping the stabilizing conjugation of the styrene fragment in the resulting organosilver intermediate. The final C-C bond formation links the original acetalic and central allenic carbon atoms, simultaneously releasing the $Ag^+$ cation for reentering into the catalytic cycle. Alternatively, the protonation of the acetalic allenes by the action of $CF_3COOH$ would occur at one heteroatom of the acetalic function, causing its fragmentation into one equiv of thiol (RYH in Scheme 3) and the corresponding heteroatom-stabilized benzylic cation. This latter species is reasonably expected to be a short-lived intermediate, quickly cyclizing by interaction with the nearby allene fragment via C-C formation, most probably in an irreversible form as this cyclization leads to a more stable, new benzylic carbenium ion with additional allylic stabilization. The addition of the formerly liberated thiol could then take place in two regiochemical modes, by adding either at the exocyclic or the endocyclic positively-charged carbon atom of the new carbenium ion (the respective C-1 or C-3 carbons of the original allene moiety). As stated above, monosubstitution at C-1 allows the preferent addition of the thiol molecule to this carbon atom, thus keeping the styrene-like stabilization, whereas disubstitution directed the nucleophilic thiol toward the C-3 carbon atom, most probably by steric reasons. Within this mechanistic frame, the exclusive formation of the *cis* diastereomers of 1,3-disubstituted 2-alkylidene indanes **12** is also rationalized under steric terms, as their *trans* partners should be more sterically congested.[13] The final deprotonation during the basic work-up (washing with saturated aq $NaHCO_3$ solution) then yielded the respective carbocyles.




**Scheme 3** Mechanistic proposal

## Conclusions

In summary, we have disclosed herein the results of the cyclization of phenylallenes bearing acetalic functions at *ortho* position by the action of Lewis and Brönsted acids. This synthetic methodology has been shown to constitute an easy entry to a range a new indeno-fused heterocycles of the type 1,4-dioxepane, 1,5-dioxocane, 1,4-dithiepane and 1,4-oxathiepane, when the acetalic function at the starting allene is built inside a cyclic 1,3-dioxygenated ring or its mono and dithio analogous. It is also applicable to acyclic acetals and dithioacetals yielding respectively 2,3-disubstituted indenes and 1,3-disubstituted 2-alkylideneindanes depending on the degree of substitution at the external carbon atom of the allene moiety.

**Acknowledgements**

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12 CCDC-1052427 (**6a**), CCDC-1052428 (**10**) and CCDC-1052072 (**12d**) contain the supplementary crystallographic data for this communication.

13 The *cis* diastereomer of **12** easily relieve part of its intrinsic steric strain by slightly bending the optimal geometry around the exocyclic C=C double bond in order to move away the two substituents at the exocyclic carbon atom from the two alkylthio substituents at the 1 and 3 carbons of the indane ring. The *trans* isomers cannot alleviate enough their steric congestion in a similar way as for competing in stability with their *cis* partners. This assumption has been corroborated by simple DFT calculations (See Supplementary Information).

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