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Lewis Acid-mediated Formation of 1,3-Disubstituted Spiro[cyclopropane-1,2'-indanes]: The Activating Effect of the Cyclopropane Walsh Orbital

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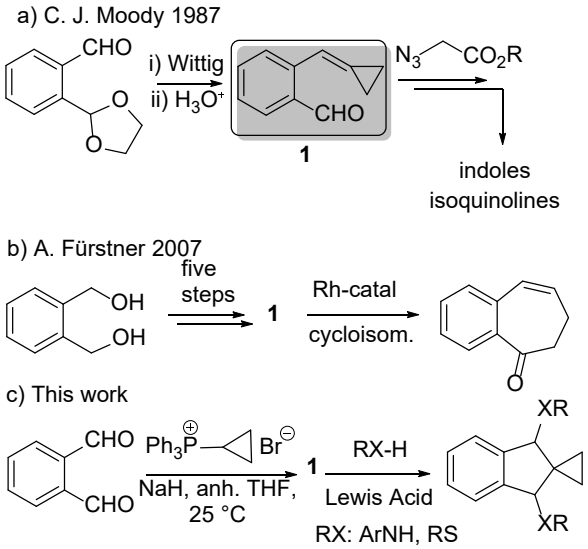
ABSTRACT

By virtue of its alkylidenecyclopropane moiety 2-(cyclopropylidenemethyl)benzaldehyde reacts with a range of amines or thiols under Lewis acid catalysis yielding the respective 1,3-bis(arylamino) or -bis(arylthio and alkylthio)indanes spirolinked to the cyclopropane ring at carbon 2. The reaction mechanism and the peculiar contribution of the cyclopropane ring have been scrutinized by DFT calculations.

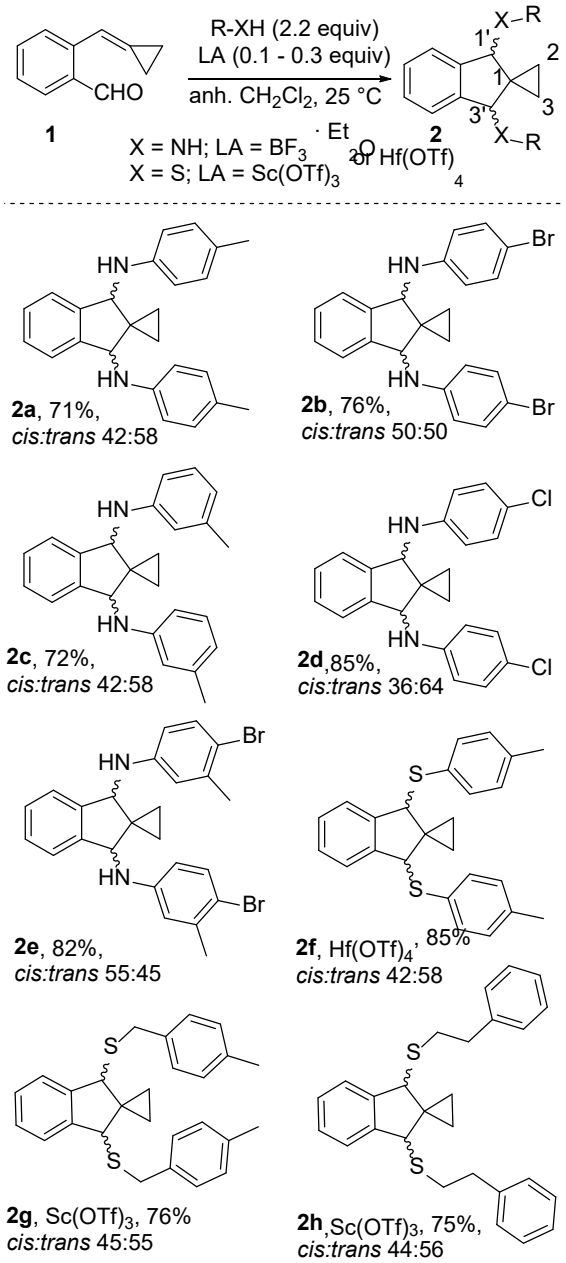
Alkylidenecyclopropanes are highly strained molecules although stable enough to allow its use in a variety of synthetic applications.[1–6] Indeed a plethora of applications of these reactive species have been disclosed in the last few years.[7–17] Benzylidenecyclopropanes functionalized at *ortho* position provide the opportunity for exploring intramolecular cyclizations involving both the 4-carbon

methylidenecyclopropane fragment and the nearby functional group at the benzene ring. Between this class of compounds, those bearing an *ortho*-amino/amido groups or other *N*-linked functionalities are perhaps the most widely explored mainly as result of the investigations due to the group of Shi.[18–36] In marked contrast only five, a very scarce number, of *ortho*-formyl substituted benzylidenecyclopropanes are known and their synthetic usefulness has been rarely studied. [37–39] Moody was the first to prepare *o*-formylbenzylidenecyclopropane **1** in 1987 starting from the monoethyleneacetal derived from *o*-phthalaldehyde by Wittig reaction with cyclopropyltriphenylphosphonium bromide followed by acetal hydrolysis and utilized it in his α–azidocinnamate synthetic methodology for preparing indoles and isoquinolines[38] (Scheme 1a). Twenty years later Fürstner also synthesized **1** starting from 1,2-bis(hydroxymethyl)benzene in five steps, including a Wittig olefination with 3-bromopropyltriphenylphosphonium bromide, ongoing to benzocycloheptenones by Rh-catalysed cycloisomerization of the key aldehyde via C-H activation at the formyl group (Scheme 1b).[39] Herein we disclose a more direct preparation of **1** in a single step and a novel application of this aldehyde in the synthesis of a new class of functionalized spiro compounds bearing cyclopropane and indane subunits (Scheme 1c).



Scheme 1. Previous reports on reactions of *o*-formylbenzylidenecyclopropane **1** (a and b) and present work (c).

Following our recent interest in the chemistry of activated cyclopropanes[40–42] we became interested in expanding the synthetic applicability of aldehyde **1**. In our experience, this aldehyde could be advantageously prepared in only one experimental step, in 50% yield, by means of a Wittig reaction between *o*-phthalaldehyde and the P-ylide prepared *in situ* by treatment of commercially available cyclopropyltriphenylphosphonium bromide with sodium hydride in THF under strictly anhydrous conditions. With **1** in our hands we first addressed its reactions with primary arylamines with the aim of further elaborating the putative resulting imines via metal-catalyzed ring-opening of the cyclopropane ring. The planned condensation reactions between equivalent amounts of primary amines and **1** resulted to be trickier than initially expected. When equivalent amounts of the aldehyde and *p*-toluidine were reacted under a variety of habitual reaction conditions (in the presence of either dehydrating salts or acidic catalysts, in common solvents at different temperatures) the conversion of **1** was never complete (as detected by IR checking of the C=O band absorption at 1695 cm^{-1}), and complex mixtures resulted from which the expected imine could not be isolated. We also noted the apparent and unexpected high hydrolytic sensitivity of the putative imine when, in a series of successive IR spectra of aliquots of the reaction mixture, the intensity of the C=O band increased gradually as result of the repeated exposure of the reaction medium to the atmospheric humidity. When the reaction was carried out with boron trifluoride diethyl ethearate as catalyst (30%) and 2.2 equivalents of *p*-toluidine in anhydrous dichloromethane at room temperature, we were able to isolate a product in 71% yield with a ^{1}H-NMR and mass spectrum showing it was the result of combining one equiv of **1** plus two of amine minus one of water. Spectral data revealed that the obtained product was in fact the spiro[cyclopropane-1,2'-indane] **2a** bearing two *p*-tolylamino groups at 1' and 3' positions (Scheme 2). Four additional primary arylamines were next reacted with **1** under similar conditions for obtaining spiro compounds **2b-e** in comparable yields. Unfortunately, our attempts to extend the number of these processes by the utilization of alkylamines were unsuccessful, yielding only unresolved complex mixtures.



Scheme 2. Preparation of the spiro[cyclopropane-1,2'-indane] derivatives **2**.

Spirocyclic diamines **2** were obtained as mixtures of *cis* and *trans* isomers in ratios close to 1:1. The key feature for distinguishing between both isomers in each diastereoisomeric pair, as result of its different symmetry elements, is the equivalence between the two methylene groups of the cyclopropane fragment in the *trans* isomers of **2** and their inequivalence in the *cis* isomers (Scheme 2 and ESI). Notably, in the case of **2b** (Ar = 4-Br-C_6H_4) we were able to separate the *cis* isomer in pure form by fractional crystallisation from diethyl ether, thus obtaining monocrystals of ***cis*-2b** of enough quality

for X-ray crystal structure determination (Figure 1). In the solid state the cyclopentane ring of ***cis*-2b** adopts an envelope conformation with the spirocyclic carbon slightly deviated from the mean plane including the other four carbon atoms of the pentagonal ring. As presumed, this latter plane is practically perpendicular to that of the cyclopropane ring, forming an 89.9° angle. In the unit cell, aromatic interactions between two slightly shifted *p*-bromophenylamino rings of each contiguous two molecules of ***cis*-2b** are apparent.

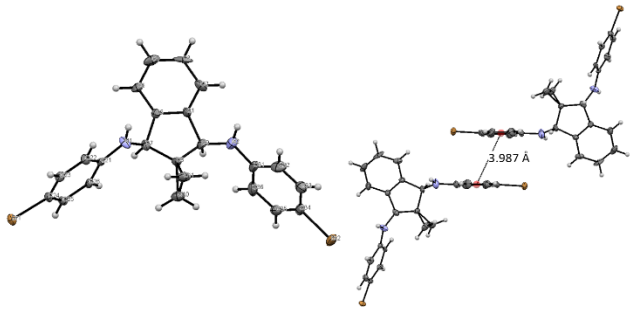
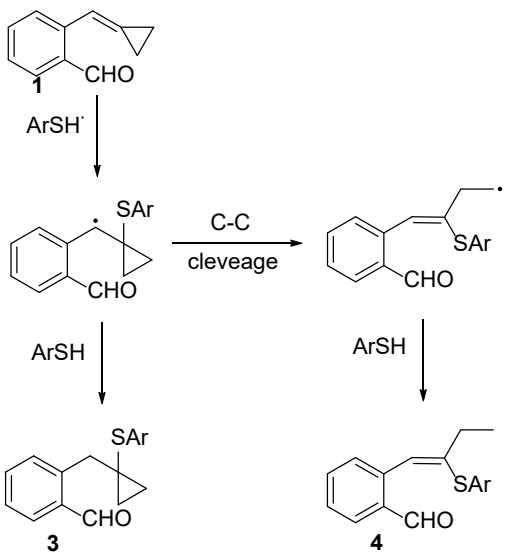


Figure 1. Different views of the solid-state molecular structure of **2b**. Thermal ellipsoids are drawn at the 50% probability level.

A second type of nucleophilic reagents, thiols, were also confronted with aldehyde **1** for exploring whether its reactions are similar or not to that of amines, particularly concerning the nature of the reaction products. By using *p*-toluenethiol as reagent we first essayed the same conditions used in the previous reactions with amines: 2.2 equivs of thiol, anhydrous CH_2Cl_2 as solvent and $BF_3 \cdot OEt_2$ (0.3 equivs) as catalyst at 25 °C under nitrogen. From this reaction we identified as the main reaction product a 1:1 diastereoisomeric mixture of *cis* and *trans* spiro[cyclopropane-1,2'-indane] **2f** in a global 22% yield. After extensive experimentation with several combinations of additional Lewis acids (0.1 to 0.3 equivs) and solvents the best reaction conditions resulted to be the use of $Hf(TfO)_4$ (0.1 equivs) as catalyst and CH_2Cl_2 as solvent, the yield of **2f** increasing up to 85% (42:58 *cis*:*trans* ratio). Fortunately,

***cis*-2f** and ***trans*-2f** could be partially separated by column chromatography. Similar reactions in which some other Lewis acids were used, in particular with In, Y or Sc triflates, yielded complex mixtures in which ***cis*+*trans*-2f** were detected (from trace to appreciable amounts, never higher than 50% yield) in all cases accompanied by the new benzaldehyde **3** (Scheme 3 and Supporting Information), in yields ranging from 11 to 51%, which was isolated in pure form by column chromatography. In the case of using $Pr(OTf)_3$ as catalyst, the reaction yielded ***cis*+*trans*-2f** (8%), benzaldehyde **3** (51%) and a second benzaldehyde **4** (18%) lacking the cyclopropane ring. The isolation of benzaldehydes **3** and **4** is interpreted as resulting from radical chain reactions originated by the unprevented *in situ* formation of arylthio radicals, most probably initiated by adventitious oxygen. These radicals add to the exocyclic C=C double bond, without or with cyclopropane fragmentation respectively, as previously described by Shi (Scheme 3).[43]

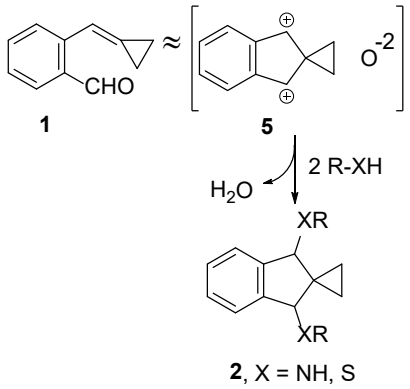


Scheme 3. Mechanistic proposal for the formation of benzaldehydes **3** and **4**.

Additionally, we successfully extended this methodology to the $Sc(OTf)_3$-mediated reaction of **1** with the aliphatic 4-methylbenzylthiol and pehenethyl thiols, giving rise to ***cis*+*trans*-2g** (76% yield, 30:70

cis:*trans* ratio) and ***cis+trans*-2h** (75% yield, 44:56 *cis*:*trans* ratio), from which the nearly pure *trans* isomers were isolated by chromatographic purification (Scheme 2).

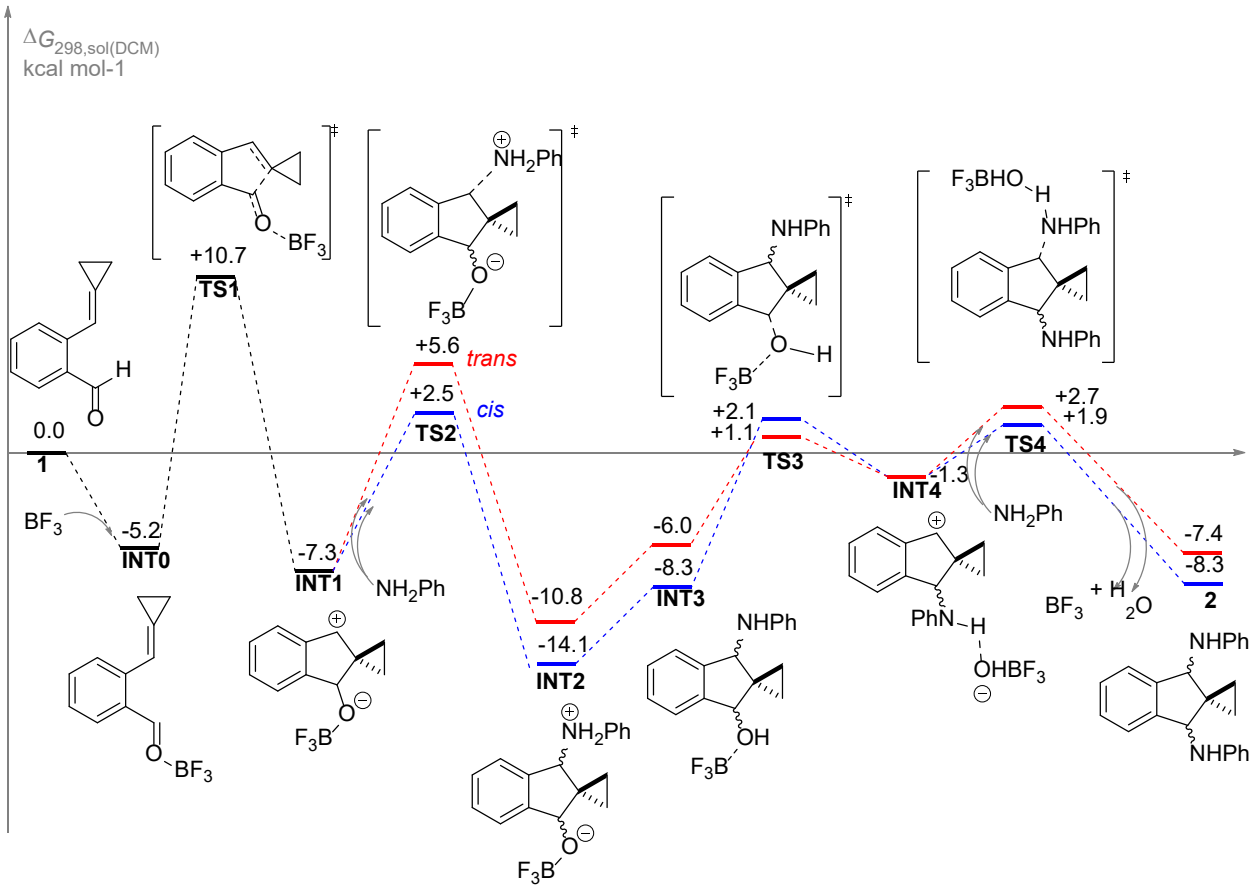
The conversions of *o*-formylbenzylidenecyclopropane **1** into 1',3'-$(XR)_2$ disubstituted spiro[cyclopropane-1,2'-indanes] **2** (X = NH, S) can be viewed as deoxygenative carbocyclizations of a 2,4-dien-1-al fragment enabling the one-pot preparation of the $(XR)_2$ disubstituted cyclopentenyl derivatives, which are spirocyclically linked to the preexisting cyclopropyl ring. In such view these processes are closely related to classic Lewis acid catalyzed Nazarov cyclizations of 1,4-dien-3-ones interrupted by the *in situ* capture of cationic cyclopentyl intermediates with nucleophiles.[1,44] Nevertheless, in the present reactions the 2,4-pentadien-1-al fragment shows as equivalent to a cyclopentyl dication **5**, probably with both carbonium centers being sequentially formed, thus facilitating a double nucleophilic addition at the 1 and 4 positions (Scheme 4). We have only found a closely related precedent of these processes in the conversions of dienal derivatives into fused cyclopentanes by the action of a gold catalyst in the presence of a few Nu-E reagents as reported by R. S. Liu et al. [45]



Scheme 4. Nucleophile capture of the equivalent dicarbocation of the alkylidenecyclopropane-benzaldehyde **1**.

Alternative competitive mechanistic pathways are conceivable for explaining the formation of the spiro-indane derivatives **2**. In order to shed light on this, all plausible mechanisms were theoretically

studied at DFT level using aniline as nucleophile, but we only show here the most energetically favourable one (Scheme 5 and Supporting Information). Initially, the coordination of Lewis acid BF_3 to the aldehyde **1** forms the complex **INT0** that easily cyclizes to the more stable intermediate **INT1**, which presents a bisected conformation with the cyclopropane ring orthogonal to the benzylic cation fragment, *via* the transition state **TS1** (+10.7 kcal · mol^{-1}). A molecule of aniline then approaches at the benzylic carbocation making a N-C bond following two alternative trajectories leading to the *cis* and *trans* diastereoisomers **INT2**. Our calculations reveal that the $\mathbf{TS2}_{\boldsymbol{cis}}$ is lower in energy respect to the $\mathbf{TS2}_{\boldsymbol{trans}}$ by 3 kcal · mol^{-1} probably due to the formation of a stabilising O···HN hydrogen bond between the OBF_3 and the NH_2 groups in the $\mathbf{TS2}_{\boldsymbol{cis}}$. After a prototropic shift towards **INT3**, carbocation **INT4** is further formed *via* a subsequent decoordination of the BF_3OH anion involving the transition state **TS3** ($\mathbf{TS3}_{\boldsymbol{cis}}$ = +1.1 and $\mathbf{TS3}_{\boldsymbol{trans}}$ = +2.1 kcal · mol^{-1}). Finally, a second *N*-attack onto the carbonium center of **INT4** followed by the departure of a molecule of water and the regeneration of the Lewis acid leads to the disubstituted spiro-indane derivatives **2**. These latest transition states *cis* and *trans* **TS4** are almost isonergetic ($\mathbf{TS4}_{\boldsymbol{cis}}$ = +1.9 kcal · mol^{-1}; $\mathbf{TS4}_{\boldsymbol{trans}}$ = +2.7 kcal · mol^{-1}).



Scheme 5. Computed mechanism for the transformation of **1** into **2** at the CPCM(DCM)/M06/ma-def2-TZVPP//PCM(DCM)/M06/6-31+G(d,p) theoretical level (1 atm, 298 K). Gibbs free energies are shown in kcal · · mol^{-1} relative to aldehyde **1**. The blue path refers to the relative *cis* disposition of substituents at 1' and 3' position along the reaction coordinate while the red one refers to that *trans*.

The rate-determining transition state **TS1** deserves some comments. This initial cyclization step is a kind of *iso*-Nazarov reaction although it could be otherwise described as a electrophile attack of the electron-deficient carbonyl carbon atom to the exocyclic C-C double bond.[46] An analysis of Wiberg bond indexes and Natural Bond Orbitals (NBO)[47,48] indicates that **TS1** is structurally closer to the precedent intermediate **INT0** than to **INT1** (see ESI)**.** Two disposition of the bulky substituent OBF_3 at the C3' were computed at **TS1**, that with OBF_3 located *out* of the forming ring being almost 11 kcal · mol^{-1} lower in energy (Figure 2). This might be associated to both the more planar disposition of that

substituent respect to the aromatic ring (*out*: -34.7° *vs in*: 79.5°) and to the longer distance of the C-C forming bond (*out*: 2.10 Å *vs in*: 2.01 Å) than when it is placed *in*, therefore, avoiding steric hindrance between both BF_3 and the cyclopropane moieties. Added to this, in both computed conformations of **TS1**, the incipient 5-membered cycle is slightly deviated from the planarity as reveal its inner dihedral angle (Figure 2).

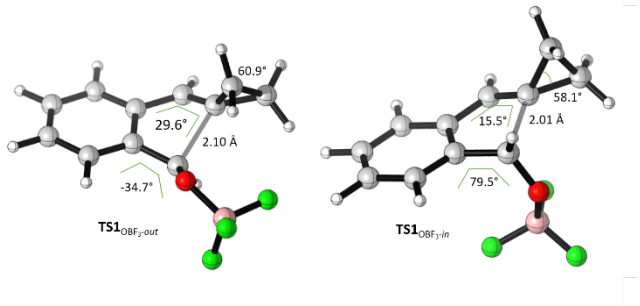


Figure 2. Computed transition structures **TS1** with OBF_3 *out* (left) and OBF_3 *in* (right). Relevant geometrical parameters are shown.

Furthermore, we suspected that the cyclopropane ring should play a fundamental role in the cyclization step, due to the strain release on increasing the *p* character associated to the rehybridization of the original cyclopropylidene carbon atom. Aiming to prove this allegation, we compared this step with related cyclization processes in which the cyclopropane ring is absent. Thus, we selected the BF_3 catalysed cyclization of 2,4-pentadienal (**TS1'**) and of *o*-vinylbenzaldehyde (**TS1''**).

Ellipticity of the electron density has been proved as a suitable descriptor to measure the electron density distortion due to the lateral overlapping of two *p* orbitals.[49,50] In this sense, we computed the ellipticity at the bond critical point of the C-C forming bond along the reaction coordinate of these three cyclization processes (Figure 3). In all cases, the higher values are located before reaching the transition state and they are lower than two points, showing a poor overlap between the *p*- orbitals of

both carbon atoms C1 and C3'. Remarkably, with the cyclopropane ring the ellipticity is lower than in the other two processes. This might be reasoned as due to the preferred frontal overlapping between the cited *p*-orbitals favoured by the stabilization of the incipient benzylic carbocation at C1' by the Walsh orbital of the cyclopropane.[51–53]

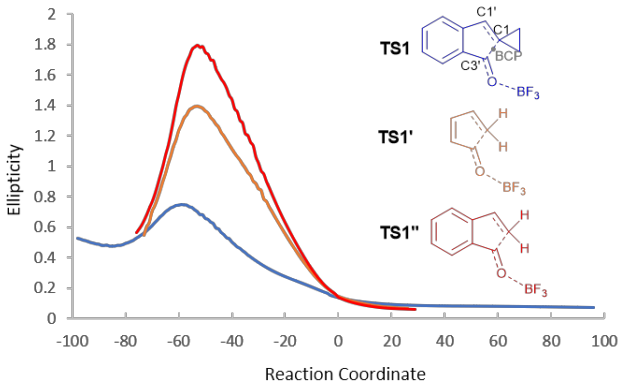


Figure 3. Ellipticity evolution at the $BCP_{C1\text{-}C3'}$ along the IRC.

This later stabilizing orbital alliance is neatly observed in the subsequent intermediate **INT1** in which the analysis of the NBO stabilizing orbital charge-transfer energies, *E*(2), predicts a contribution of +13.9 and +20.9 kcal · mol^{-1} from the two cyclopropane σ-bonding C-C orbitals towards both lobes of the empty *p*-orbital of the benzylic carbocation (Figure 4). Notwithstanding, whereas BF_3-catalyzed non-cyclopropane cyclizations (**TS1'**, **TS1''**) have been computed as endergonic transformations the cyclization of the benzaldehyde-BF_3 complex **INT0** is exergonic, the Walsh orbital stabilization at **INT1** might be the driving force in this latter case (see ESI).

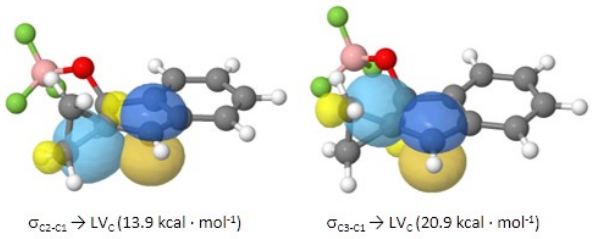
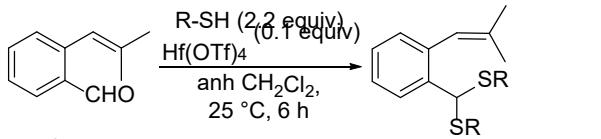


Figure 4. Orbital transfer stabilization energies at the intermediate **INT1**.[54,55]

In order to check experimentally our computational hypothesis we prepared the previously known[56] *ortho*-alkenyl benzaldehyde **6** lacking the cyclopropane ring. Not very surprisingly, when **6** was submitted to the addition of two different thiols under $Hf(OTf)_4$ catalysis at room temperature the reactions products were the simple dithioacetals **7a,b** in good to excellent yields (Scheme 6). These results support the essential role of the cyclopropane ring in this scarcely studied kind of interrupted cyclizations towards spiro-indane derivatives **2**.



6

7a, R = 4-$CH_3C_6H_5$, 75%
7b, R = 4-$CH_3C_6H_4CH_2$, 90%

Scheme 6. $Hf(OTf)_4$-mediated reaction of the *ortho*-alkenyl benzaldehyde **6** with thioles.

CONCLUSIONS

In conclusion, we herein show a peculiar Lewis-catalyzed strategy to synthesize 1,3-disubstituted spiro-1,2'-indanes by reacting 2-(cyclopropylidenemethyl)benzaldehyde with amines and thioles. DFT calculations predict a mechanism involving a first cyclization of the benzaldehyde-BF_3 complex followed by two nucleophile attacks of the amine/thiol over both benzylic positions of the spiro-indane

core. The usefulness of the cyclopropane ring in these cyclizations has been reasoned attending to the stabilization of the α-benzylic carbocation by its Walsh orbital.

EXPERIMENTAL SECTION

Computational Methods

Geometries of the molecules were optimized by using the M06 hybrid-functional[57] with the 6-31G+(d,p) basis sets.[58,59] Solvent effects were calculated with the PCM continuum solvation model for dichloromethane.[60] The nature of minimum and transition structures of all found stationary points on the potential energy surface was confirmed by frequency analysis at the same level of theory. The stability of the resulting wavefunctions were checked for all the optimized structures.[61] The computed thermochemical corrections at PCM-M06/6-31+G(d,p) level were combined with single point energies at the CPCM(DCM)/M06/ma-def2-TZVPP[62]//PCM(DCM)-M06/6-31+G(d,p) level to yield Gibbs free energies *G* at 298.15 K ($G_{298,sol}$). The SMD solvation model was activated in the single point calculations. The ellipticity values were calculated at every point of the reaction coordinate, in steps of 0.5 $amu^{1/2}$ Bohr along the path. The ultrafine grid implemented in Gaussian 09 E. 01 was used.[63] Single point calculations were performed by using the program ORCA 4.0.1.[64] NBO analysis were executed with NBO 7.0 at the PCM(DCM)-M06/6-31+G(d,p) level and NBO-orbitals were printed with the Jmol-NBO Visualization Helper.[47,48,54,55,65]

General experimental and analytical information

^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 300, 400 or 600 MHz. $^{13}C\{^{1}H\}$ NMR spectra were recorded in $CDCl_3$ at 100 or 150 MHz. The chemical shifts are reported in ppm (δ), relative to the resonance of $CDCl_3$ at δ = 7.26 ppm and of DMSO-d_6 at δ = 2.50 ppm for ^{1}H and for $^{13}C\{^{1}H\}$ relative to the resonance of $CDCl_3$ δ = 77.16 ppm and of DMSO-d_6 at δ = 39.5 ppm. Mass spectrometry was recorded on HPLC-MS TOF 6220 instrument.

Materials. Cyclopropyltriphenylphosphonium bromide, *o*-phthalaldehyde and different anilines, thiols and metal-triflates here used were commercially available.

The following substrates have been prepared according to the literature: 2-(2-methyl-1-propen-1-yl)benzaldehyde **6**.[56]

General synthetic procedures

2-Formylbenzylidenecyclopropane 1

A stirred solution of cyclopropyltriphenylphosphonium bromide (1.45 g, 3.8 mmol) and NaH (0.10 g, 3.8 mmol) in anhydrous THF (15 mL), was stirred at room temperature under nitrogen for 12 h. Then, a solution of *o*-phthalaldehyde (1.53 g, 11.4 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was heated at reflux temperature for 6 h. After cooling, water was added (20 mL) and extracted with diethyl ether (3 x 30 mL). The organic layers were combined and dried over magnesium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a residue that was purified by column chromatography (silica gel, ethyl acetate/hexanes 1:20 v/v) to furnish o-formylbenzylidenecyclopropane[39] (0.30 g, 1.9 mmol, 50%).

General Procedure for the Preparation of 1',3'-diarilamino-spiro[cyclopropane-1,2'-indenes] 2a-e

A mixture of 2-(cyclopropylidenmethyl)benzaldehyde **1** (0.24 g, 1.5 mmol) and the corresponding aniline (3.3 mmol), under nitrogen, was heated at 60 °C for 10 min. Then, anhydrous dichloromethane (5 mL) and boron trifluoride diethyl etherate (0.45 mmol) were added to the reaction mixture. Next, the resulting reaction mixture was stirred for 1 h at room temperature and then aqueous solution of sodium bicarbonate was added (20 mL). The organic layer was separated and the aqueous one extracted with dichloromethane (2 x 20 mL). The combined organic layer was washed with water (2 x 40 mL), dried over magnesium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a residue that was purified by column chromatography to furnish the corresponding N1',N3'-diaryl-1',3'-dihydrospiro[cyclopropane-1,2'-indene]-1',3'-diamine.

1',3'-Bis(4-methylphenyl)amine-spiro[cyclopropane-1,2'-indane] *cis*-2a and *trans*-2a

Eluent for column chromatography ethyl acetate/hexanes 1:5 v/v, yield: 71% (0.264 g, 1.07 mmol), colourless oil. ^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) = 7.25-7.18 (m), 6.88-6.86 (m), 6.70 (d, *J* = 9.0 Hz), 6.66 (d, *J* = 8.4 Hz), 5.64 (d, *J* = 9.6 Hz), 5.50 (d, *J* = 10.2 Hz), 5.05 (d, *J* = 10.2 Hz), 5.00 (d, *J* = 10.2 Hz), 2.15 (s), 2.14 (s), 0.89-0.86 (m), 0.64 (br s), 0.48-0.52 (m) . ^{13}C{^{1}H} NMR (DMSO-d_6, 150 MHz): δ (ppm) = 146.5 (s), 146.4 (s), 144.9 (s), 144.4 (s), 129.3, 129.2, 127.3, 127.1, 124.2 (s), 124.0, 123.5, 112.6, 112.5, 59.7, 58.4, 34.5 (s), 33.0 (s), 20.0, 8.8 (CH_2), 8.0 (CH_2), 3.6 (CH_2). HRMS (ESI) m/z: {[M + H]$^{+}$ ($C_{25}H_{27}N_2$) – [4-methylaniline] (C_7H_9N)} Calcd for $C_{18}H_{18}N$ 248.1434; Found 248.1469

1',3'-Bis(4-bromophenyl)amine-spiro[cyclopropane-1,2'-indane] *cis*-2b and *trans*-2b

Eluent for column chromatography ethyl acetate/hexanes 1:5 v/v, yield : 76% (0.356 g, 1.14 mmol), colourless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) = 7.26-7.21 (m), 7.17 (d, *J* = 8.8 Hz), 6.74-6.67 (m), 6.17 (d, *J* = 10.0 Hz), 6.01 (d, *J* = 10.4 Hz), 5.06 (d, *J* = 9.6 Hz), 5.04 (d, *J* = 10.0 Hz), 0.81-0.78 (m), 0.66-0.50 (m) . ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ (ppm) = 148.0 (s), 147.9 (s), 144.2 (s), 143.7 (s), 131.4, 127.6, 127.4, 124.1, 123.6, 114.4, 114.3, 106.2 (s), 59.5, 58.1, 34.2 (s), 32.8 (s), 8.8 (CH_2), 8.1 (CH_2), 3.8 (CH_2). HRMS (ESI) m/z: {[M + H]$^{+}$ ($C_{23}H_{21}Br_2N_2$) – [4-bromoaniline] (C_6H_6BrN)} Calcd for $C_{17}H_{15}BrN$ 312.0382; Found: 312.0378

1',3'-Bis(3-methylphenyl)amine-spiro[cyclopropane-1,2'-indane] *cis*-2c and *trans*-2c

Eluent for column chromatography ethyl acetate/hexanes 1:5 v/v, yield: 72% (0.268 g, 1.08 mmol), colourless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) = 7.27-7.20 (m), 6.96-6.92 (m), 6.66-6.54 (m), 6.34 (t, *J* = 7.0 Hz), 5.77 (d, *J* = 10.0 Hz), 5.61 (d, *J* = 10.4 Hz), 5.09 (d, *J* = 10.0 Hz), 5.05 (d, *J* = 10.4 Hz), 2.18 (s), 0.89-0.86 (m), 0.66-0.64 (m), 0.53-0.50 (m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ (ppm) = 148.9 (s), 148.8 (s), 144.9 (s), 144.3 (s), 137.9 (s), 137.8 (s), 128.8, 128.7, 127.3, 127.2, 124.0, 123.5, 116.8, 116.6, 113.0, 109.6, 109.5, 59.3, 57.9, 34.7 (s), 33.1 (s), 21.4, 8.7 (CH_2), 7.9 (CH_2), 3.4 (CH_2). HRMS (ESI) m/z: {[M + H]$^{+}$ ($C_{25}H_{27}N_2$) – [3-methylaniline] (C_7H_9N)} Calcd for $C_{18}H_{18}N$ 248.1434; Found: 248.1446

1',3'-Bis(4-chlorophenyl)amine-spiro[cyclopropane-1,2'-indane] *cis*-2d and *trans*-2d

Eluent for column chromatography ethyl acetate/hexanes 1:5 v/v, yield: 85% (0.342 g, 1.28 mmol), colourless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) = 7.28-7.21 (m), 7.07 (d, *J* = 8.8 Hz), 6.79-6.73 (m), 6.15 (d, *J* = 9.6 Hz), 5.99 (d, *J* = 9.6 Hz), 5.07 (d, *J* = 9.6 Hz), 5.05 (d, *J* = 9.6 Hz), 0.86-0.82 (m), 0.68-0.57 (m), 0.55-0.51 (m) . ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ (ppm) = 147.7 (s), 147.6 (s), 144.4 (s), 143.8 (s), 128.6, 127.6, 127.5, 124.1, 123.6, 118.9 (s), 118.8 (s), 113.8, 59.5, 58.1, 34.4 (s), 32.9 (s), 8.7 (CH_2), 8.1 (CH_2), 3.7 (CH_2) . HRMS (ESI) m/z: {[M + H]$^+$ ($C_{23}H_{21}Cl_2N_2$) – [4-chloroaniline] (C_6H_6ClN)} Calcd for $C_{17}H_{15}ClN$ 268.0888; Found 268.0891.

1',3'-Bis(4-bromo-3-methylphenyl)amine-spiro[cyclopropane-1,2'-indane] *cis*-2e and *trans*-2e

Eluent for column chromatography ethyl acetate/hexanes 1:5 v/v, yield: 82% (0.401 g, 1.23 mmol), colourless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) = 7.26-7.21 (m), 7.18 (d, *J* = 8.8 Hz), 6.78 (d, *J* = 2.8 Hz), 6.73 (d, *J* = 2.4 Hz), 6.56 (dd, *J* = 8.8, 2.8 Hz), 6.52 (dd, *J* = 8.8, 2.8 Hz), 6.02 (d, *J* = 9.6 Hz), 5.86 (d, *J* = 10.0 Hz), 5.06 (d, *J* = 10.4 Hz), 5.04 (d, *J* = 11.2 Hz), 2.21 (s), 0.87-0.83 (m), 0.68-0.58 (m), 0.55-0.51 (m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ (ppm) = 148.4 (s), 148.3 (s), 144.4 (s), 143.9 (s), 137.1 (s), 137.0 (s), 132.0, 127.5, 127.4, 124.0, 123.5, 114.7, 112.0, 111.9, 109.1 (s), 108.9 (s), 59.3, 57.9, 34.4 (s), 32.9 (s), 22.6, 8.7 (CH_2), 8.0 (CH_2), 3.5 (CH_2) . HRMS (ESI) m/z: {[M + H]$^+$ ($C_{25}H_{25}Br_2N_2$) – [4-bromo-3-metilanilina] (C_7H_8BrN)} Calcd for $C_{18}H_{17}BrN$ 326.0539; Found 326.0552.

Preparation of 1',3'-Bis(arylthio)-spiro[cyclopropane-1,2'-indanes] by reaction of 2-(cyclopropylidenmethyl)benzaldehyde 1 and thiols under Lewis acid catalysis

To a solution of 2-(cyclopropylidenmethyl)benzaldehyde **1** (0.16 g, 1 mmol) in anhydrous dichloromethane (20 mL) under nitrogen, the corresponding thiol (2.2 mmol) and hafnium triflate (0.07 g, 0.1 mmol) (Procedure A) or scandium triflate (0.24 g, 0.5 mmol) (Procedure B) were added. The reaction mixture was stirred for 6 h at room temperature. Then, water was added (50 mL) to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with

dichloromethane (3 x 20 mL). The combined organic layer was washed with an aqueous saturated solution of $NaHCO_3$ (25 mL), dried over magnesium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a residue that was purified by column chromatography.

1',3'-Bis(4-methylphenylthio)-spiro[cyclopropane-1,2'-indanes] *cis*-2f y *trans*-2f

Yield: Procedure A 85% (0.33 g, 0.85 mmol); Procedure B 76% (0.29 g, 0.76 mmol)

1',3'-Bis(4-methylbenzylthio)-spiro[cyclopropane-1,2'-indanes] *cis*-2g y *trans*-2g

Yield: Procedure A 42% (0.18 g, 0.42 mmol); Procedure B 76% (0.35 g, 0.76 mmol)

1',3'-Bis(phenethylthio)-spiro[cyclopropane-1,2'-indane] *cis*-2h y *trans*-2h

Yield: Procedure B 75% (0.31 g, 0.75 mmol)

1',3'-Bis(4-methylphenylthio)-spiro[cyclopropane-1,2'-indane] *trans*-2f

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: 0.19 g, 0. 49 mmol, 49% (Procedure A), 0.15 g, 0.39 mmol, 39% (Procedure B), colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.24-7.18 (m, 4 H), 7.15-7.13 (m, 4 H), 7.05-7.03 (m, 4 H), 4.21 (s, 2 H), 2.34 (s, 6 H), 1.30-1.34 (m, 2 H), 0.71-0.75 (m, 2 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) = 143.6 (s), 137.2 (s), 132.7, 131.0 (s), 129.4, 127.6, 124.6, 58.3, 32.0 (s), 21.1, 11.4 (CH_2). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{25}S_2$ 389.1392; Found 389.1409.

1',3'-Bis(4-methylphenylthio)-spiro[cyclopropane-1,2'-indane] *cis*-2f

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: 0.14 g, 0.36 mmol, 36% (Procedure A), 0.143 g, 0.37 mmol, 37% (Procedure B), colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.36-7.34 (m, 4 H), 7.18-7.16 (m, 2 H), 7.15-7.12 (m, 4 H), 7.01-6.99 (m, 2 H), 4.25 (s, 2 H), 2.37 (s, 6 H), 1.28-1.24(m, 2 H), 0.95-0.91 (m, 2 H) . ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) = 143.8 (s), 137.3 (s), 133.2, 132.3 (s), 129.6, 127.5, 124.7, 60.9, 33.0 (s), 19.8 (CH_2), 21.1, 10.4 (CH_2). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{25}S_2$ 389.1392; Found 389.1391.

1',3'-Bis(4-methylbenzylthio)-spiro[cyclopropane-1,2'-indane] *trans*-2g

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: 0.079 g, 0.19 mmol, 19% (Procedure A), 0.13 g, 0.31 mmol, 31% (Procedure B), colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.32-7.29 (m, 2 H), 7.21-7.19 (m, 2 H), 7.01-6.96 (m, 8 H), 4.04 (s, 2 H), 3.39 (d, 2 H, *J* = 12.4 Hz), 3.30 (d, 2 H, *J* = 12.4 Hz), 2.21 (s, 6 H), 1.22-1.18 (m, 2 H), 0.59-0.55 (m, 2 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) = 143.1 (s), 136.5 (s), 134.7 (s), 129.1, 128.8, 127.8, 125.0, 55.6, 34.2 (CH_2), 30.0 (s), 21.1, 13.2 (CH_2). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}S_2$ 417.1705; Found 417.1723.

1',3'-Bis(4-methylbenzylthio)-spiro[cyclopropane-1,2'-indane] *cis*-2g

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: 0.034 g, 0.08 mmol, 8% (Procedure A), 0.10 g, 0.35 mmol, 25% (Procedure B), colourless oil.^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.22-7.19 (m, 2 H), 7.17-7.15 (m, 2 H), 7.08 (d, 4 H, *J* = 7.6 Hz), 6.98 (d, 4 H, *J* = 7.6 Hz), 3.81 (s, 2 H), 3.60 (d, 2 H, *J* = 12.4 Hz), 3.46 (d, 2 H, *J* = 12.4 Hz), 2.21 (s, 6 H), 1.16-1.12 (m, 2 H), 0.71-0.67 (m, 2 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) = 143.5 (s), 136.5 (s), 134.9 (s), 129.1, 128.8, 127.8, 124.9, 55.8, 35.5 (CH_2), 31.7 (s), 21.1, 18.6 (CH_2), 12.0 (CH_2). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}S_2$ 417.1705; Found 417.1726.

1',3'-Bis(phenethylthio)-spiro[cyclopropane-1,2'-indanes] *cis*-2h and *trans*-2h

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: 0.31 g, 0.75 mmol, 75% (Procedure B), colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.30-7.26 (m), 7.19-7.04 (m), 70.1-6.98 (m), 4.09 (s), 3.90 (s), 2.75-2.57 (m), 2.51-2.34 (m), 1.17-1.08 (m), 0.81-0.76 (m), 0.66-0.62 (m). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) = 143.4 (s), 143.1 (s), 140.5 (s), 140.4 (s), 128.4, 128.3, 127.8, 126.3, 125.0, 124.9, 56.5, 55.6, 36.1 (CH_2), 36.0 (CH_2), 32.5 (CH_2), 31.4 (s), 31.1 (CH_2), 30.0 (s), 18.4 (CH_2), 13.2 (CH_2), 12.1 (CH_2). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}S_2$ 417.1705; Found 417.1711.

1',3'-Bis(phenethylthio)-spiro[ciclopropane-1,2'-indane] *trans*-2h

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: 0.17g, 0.4 mmol, 40% (Procedure B), colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.42-7.40 (m, 2 H), 7.32-7.28 (m, 6 H), 7.22 (tt, 2 H, *J* = 0.8, 4.8 Hz), 7.12 (d, 4 H, *J* = 7.6 Hz), 4.21 (s, 2 H), 2.79-2.79 (m, 4 H), 2.62-2.57 (m, 2 H), 2.53-2.48 (m, 2 H), 1.28-1.26 (m, 2 H), 0.79-0.74 (m, 2 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) = 143.1 (s), 140.5 (s), 128.4, 128.3, 127.7, 126.3, 125.0, 55.7, 36.1 (CH_2), 31.2 (CH_2), 30.0 (s), 13.2 (CH_2). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}S_2$ 417.1705; Found 417.1720.

Benzaldehydes 3 and 4

Benzaldehyde 3

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: 51%, with $Pr(OTf)_3$ and 48% with $Y(OTf)_3$, colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 10.06 (s, 1 H), 7.84 (dd, 1 H, *J* = 1.6, 7.6 Hz), 7.52 (td, 1 H, *J* = 1.6, 7.6 Hz), 7.41-7.36 (m, 2 H), 7.33-7.30 (m, 2 H), 7.13 (d, 2 H, *J* = 8.0 Hz), 3.42 (s, 2 H), 2.34 (s, 3 H), 1.07-1.05 (m, 2 H), 0.95-0.94 (m, 2 H),. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) = 192.1, 141.1 (s), 135.9 (s), 134.6 (s), 133.2, 132.3 (s), 131.2, 130.6, 129.7, 129.0, 127.0, 37.3 (CH_2), 26.4 (s), 20.9, 14.7 (CH_2). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{19}OS$ 283.1151; Found 283.1149.

Benzaldehyde 4

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: 18%, with $Pr(OTf)_3$, colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 10.26 (s, 1 H), 7.87 (dd, 1 H, *J* = 1.6, 7.6 Hz), 7.55 (td, 1 H, *J* = 1.2, 7.2 Hz), 7.45 (d, 1 H, *J* = 7.6 Hz), 7.37-7.41 (m, 1 H), 7.21-7.19 (m, 2 H), 7.07-7.05 (m, 3 H), 2.37-2.31 (m, 2 H), 2.31 (s, 3 H), 1.17 (t, 3 H, *J* = 7.2 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ (ppm) = 13.6, 21.0, 30.4 (CH_2), 125.1, 127.4, 129.2, 129.4 (s), 129.6, 130.8, 132.3, 133.3, 133.5 (s), 137.4 (s), 140.3 (s), 143.3 (s), 192.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{19}OS$ 283.1151; Found 283.1124.

Reaction of 2-(2-methyl-1-propen-1-yl)benzaldehyde with thiols under Lewis acid catalysis

To a solution of 2-(2-methyl-1-propen-1-yl)benzaldehyde **6** (0.19 g, 1.2 mmol) in anhydrous dichloromethane (20 mL) under nitrogen atmosphere, the corresponding thiol (2.6 mmol) and hafnium

triflate (0.09 g, 0.12 mmol) (Procedure A) or scandium triflate (0.29 g, 0.6 mmol) (Procedure B), were added. The reaction mixture was stirred at room temperature for 30 min. Then, water was added (50 mL) to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with a saturated solution of $NaHCO_3$ (25 mL), dried over magnesium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a residue that was purified by column chromatography.

Dithioacetal 7a

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: Procedure A 75% (0.35 g, 0.9 mmol); Procedure B 85% (0.40 g, 1.02 mmol), colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.71-7.68 (m, 1 H), 7.26-7.20 (m, 6 H), 7.06-7.04 (m, 5 H), 6.22 (s, 1 H), 5.68 (s, 1 H), 2.32 (s, 6 H), 1.90 (d, 3 H, *J* = 1.2 Hz), 1.58 (d, 3 H, *J* = 1.2 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) = 137.6 (s), 137.5 (s), 137.1 (s), 137.0 (s), 132.5, 131.3 (s), 129.8, 129.4, 127.8, 127.3, 126.8, 122.7, 57.4, 25.8, 21.1, 19.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{27}S_2$ 391.1549; Found 391.1547.

Dithioacetal 7b

Eluent for column chromatography ethyl acetate/hexanes 30:1 v/v, yield: Procedure A 90 % (0.45 g, 1.08 mmol), colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.89 (dd, 1 H, *J* = 1.6, 8.0 Hz), 7.28 (td, 1 H, *J* = 1.2, 7.6 Hz), 7.23 (td, 1 H, *J* = 1.2, 7.6 Hz), 7.06-7.04 (m, 5 H), 7.00-6.98 (m, 4 H), 5.59 (s, 1 H), 4.69 (s, 1 H), 3.74 (d, 2 H, *J* = 13.6 Hz), 3.47 (d, 2 H, *J* = 13.6 Hz), 2.38 (s, 6 H), 1.64 (d, 3 H, *J* = 1.2 Hz), 1.57 (d, 3 H, *J* = 1.2 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) = 136.2 (s), 137.1 (s), 136.9 (s), 136.4 (s), 135.1 (s), 129.9, 129.0, 128.9, 127.9, 127.2, 126.9, 122.4, 46.7, 36.1 (CH_2), 25.6, 21.0, 19.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{30}NaS_2$ 441.1681; Found 441.1687.

ASSOCIATED CONTENT

Supporting Information: Copies of NMR spectra, crystallographic information and experimental and computational data. The Supporting Information is available free of charge at https:// pubs.acs.org/doi/10.1021/xxx.

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ACKNOWLEDGEMENTS

This work was supported by the MINECO (Project CTQ 2017-87231-P) and the Fundación Seneca-CARM (Project 20811/PI/18).

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