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Functionalization of Acetalic C(sp^3)-H Bonds by Scandium(III) Triflate-Catalyzed Intramolecular Redox Reactions: Tandem 1,4-Hydride Transfer/1,5-Cyclization Processes Leading to Protected 1-Indanones

Mateo Alajarin,[a,*] Marta Marin-Luna,[a] and Angel Vidal[a,*]

[a] Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, 30100 Murcia, Spain
Fax: (+34)-868-884149; phone: (+34)-868-887497; e-mail: alajarin@um.es or vidal@um.es

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Abstract: A new C–C bond forming reaction leading to adjacent quaternary carbons is reported. It is a one-pot hydride shift/cyclization process facilitated by the hydricity of the acetalic C–H bonds, with benzylidenemalonate fragments as electrophilic hydride acceptors, and the catalysis of scandium(III) triflate. The reaction products are 1,2-dihydroindane derivatives. Alkoxy and alkanethiolate groups can be also intramolecularly transferred from the acetalic carbon to the electrophilic benzylidenemalonate C=C bond.

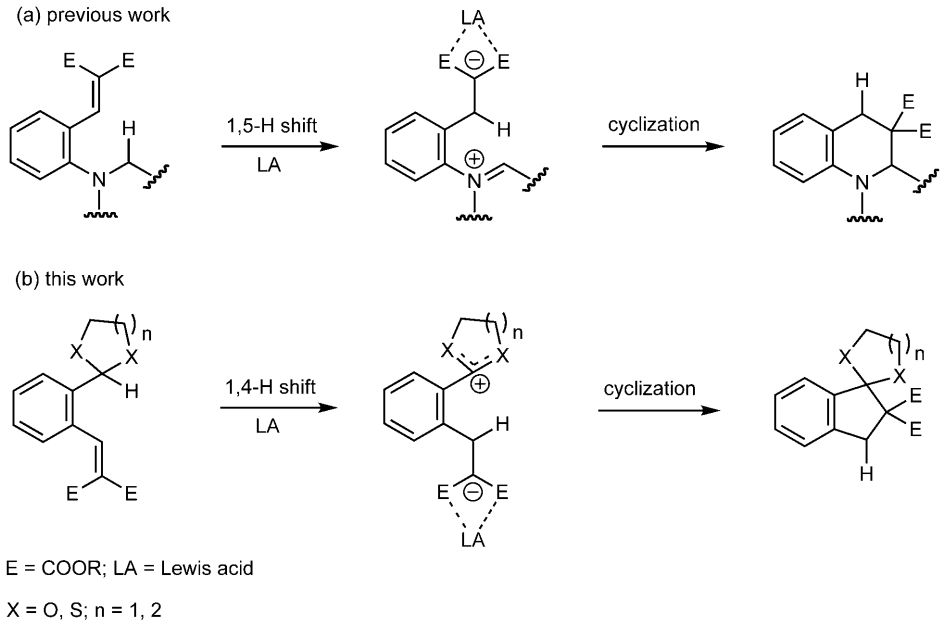
Keywords: acetals; cyclization; [1,4]-H shift; intramolecular hydride transfer; scandium triflate

C–H activation has long been considered a research theme of major interest.[1] The growing number of methods to functionalize C–H bonds is unlocking new perspectives in the synthesis of complex organic molecules and profoundly affecting the process of molecular design. In this context, the C–H bond functionalization is a rapidly growing playing field of new synthetic strategies and the C–H bonds are starting to be viewed as ubiquitous functional groups.[2]

Whereas biological C–H activation is widespread in nature, in conventional organic chemistry such activation has been long dominated by the metal-catalyzed insertion reactions and cyclometalations.[3] In the last decade a new class of one-pot transformations for C–H bond functionalization, known as intramolecular redox reactions, has been disclosed, processes which are initiated by an intramolecular hydride transfer and continued by a final cyclization step of the presumed dipolar intermediates.[4] Most of these tandem H-shift/cyclization processes are related to the long studied *tert*-amino effect,[5] whereas the rest of the examples are based on the special activation of C–H bonds adjacent to oxygen atoms[6] and arene groups[7] (Scheme 1, a).

We recently became engaged in the study of thermally-activated [1,5]-H shift/cyclization tandem reactions in which the hydrogen atom migrating in the first step is initially placed at the acetalic carbon atom of 1,3-dioxolane, -dithiolane, and -oxathiolane fragments, whereas the migration terminus is the central C(*sp*) carbon atom of heterocumulenic functions such as ketenimines and carbodiimides.[8] The initial [1,5]-H shift of these reactions was characterized as an intramolecular hydride transfer by means of computational DFT studies. In fact, those calculations showed the weakening and polarization of the acetalic C–H bond by hyperconjugative interaction of its σ* C–H orbital with the lone-pair electrons of the vicinal O and S heteroatoms of the (thio)acetalic functions, thus facilitating the hydride transfer to the electrophilic central heterocumulenic carbon. These results demonstrated for the first time the hydride donor ability (hydricity) of such acetalic functions.

We reasoned that related tandem processes are conceivable by changing the hydride-acceptor unit from heterocumulenes to other electrophilic functional groups, while keeping the acetalic functions as the hydride-releasing fragment. In this line, here we disclose a novel C(sp^3)–H functionalization reaction based on the formal tandem hydride shift/cyclization strategy by utilizing benzylidenemalonate fragments and related functions as hydride-acceptors, and 1,3-dioxolanes, 1,3-dithiolanes and 1,3-dithianes as hydride-donors, both complementary functional groups built

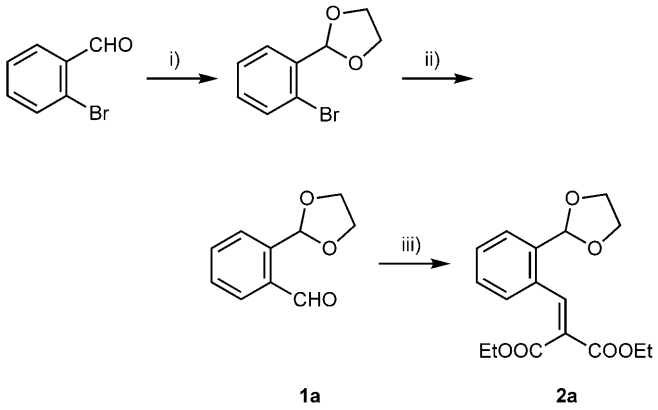


Scheme 1. Hydrogen shifts followed by cyclizations.

up on an *ortho*-substituted benzene scaffold. Interestingly, the putative hydride migration is a rare [1,4]-H shift, more scarcely reported than its [1,5]-H partner, and the subsequent cyclization step leads finally to the formation of a new sigma C–C bond linking adjacent quaternary carbon atoms (Scheme 1, b).

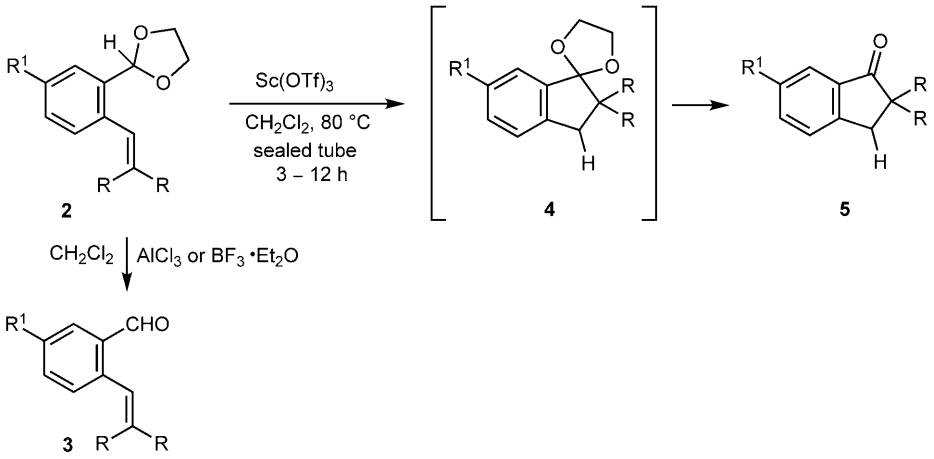
We first selected diethyl *ortho*-(1,3-dioxolan-2-yl)-benzylidenemalonate **2a** for our initial tests. Compound **1a** was readily prepared starting from *ortho*-bromobenzaldehyde in three simple steps: acetal formation with ethylenediol, halogen-lithium exchange with subsequent formylation to give the known *ortho*-phthalaldehyde monoacetal **1a**,[9] and further Knoevenagel condensation with diethyl malonate (Scheme 2).

The heating in solution of **2a** under different reaction conditions (acetonitrile 82 °C, benzene 80 °C, toluene 110 °C, toluene 180 °C sealed tube, nitrobenzene 211 °C, dimethylformamide 110 °C) proved to be inefficient for promoting the desired tandem process, in all cases the starting material was recovered unaltered along with small amounts of the acetal-hydrolyzed product **3a**. These discouraging results demonstrated that the styryl α-carbon atom of species **2a** is apparently less electrophilic than the central carbon of ketenimines or carbodiimides in the presumed hydride migration event. Activation of the hydride-acceptor properties of the benzylidenemalonate fragment was next pursued by the use of Lewis acids able to coordinate at the carbonyl oxygen atoms of the ethoxycarbonyl groups. Thus, we next attempted catalytic protocols with a few Lewis acids [$AlCl_3$, $BF_3{\cdot}Et_2O$, $Sc(OTf)_3$] in dichloromethane solution under a range of temperature conditions (Table 1 and Scheme 3).



Scheme 2. *Reagents and conditions*: i) $HO(CH_2)_2OH$, *p*-TsOH, benzene, reflux, 4 h; ii) *n*-BuLi, THF, −78 °C, 30 min, then *N*-formylpiperidine, THF, room temperature, 3 h; iii) diethylmalonate, piperidine, AcOH, benzene, reflux, 2 h.

Most of these attempts yielded mixtures of the starting material **2a** and the aldehyde **3a** resulting from the hydrolysis of the acetalic function (entries 1–5). Only the use of $Sc(OTf)_3$ as catalyst at 80 °C in a sealed tube (entries 6–8) provided some results indicating the viability of the planned synthetic strategy, these latter reactions giving rise to moderate yields of diethyl indan-1-one-2,2-dicarboxylate **5a**. Apparently, the oxophilicity of the catalyst promoted, as desired, the planned tandem process but also contributed to the hydrolysis of the acetalic function in the expected spirocyclic product **4a** (in fact detected in a small proportion by NMR monitoring in the first stages of the reactions) as well that of the starting dioxolane **2a**,



Scheme 3. Lewis acid-catalyzed [1,4]-H transfer/1,5-cyclization processes in *ortho*-(1,3-dioxolan-2-yl)benzylidenemalonates.

Table 1. Indan-1-one 2,2-dicarboxylates **5**.[a]

Entry	**2**	R	R^1	Catalyst (equiv.)	Temp. [°C]	**5** (yield [%])
1	**2a**	CO_2Et	H	$AlCl_3$ (0.1)	25	
2	**2a**	CO_2Et	H	$BF_3{\cdot}Et_2O$ (0.2)	80	
3	**2a**	CO_2Et	H	$Sc(OTf)_3$ (0.1)	25	
4	**2a**	CO_2Et	H	$Sc(OTf)_3$ (0.1)	50	
5	**2a**	CO_2Et	H	$Sc(OTf)_3$ (0.1)	60	
6	**2a**	CO_2Et	H	$Sc(OTf)_3$ (0.1)	80	**5a** (30)
7	**2a**	CO_2Et	H	$Sc(OTf)_3$ (0.2)	80	**5a** (58)
8	**2a**	CO_2Et	H	$Sc(OTf)_3$ (0.3)	80	**5a** (55)
9	**2b**	CO_2Me	H	$Sc(OTf)_3$ (0.2)	80	**5b** (54)
10	**2c**	CO_2Et	OMe	$Sc(OTf)_3$ (0.2)	80	**5c** (41)
11	**2d**	CO_2Me	OMe	$Sc(OTf)_3$ (0.2)	80	**5d** (35)

[a] Reactions were conducted on 0.6 mmol scale of benzylidenemalonate with a catalytic amount of $Sc(OTf)_3$ (0.12 mmol) in anhydrous dichlorometane (20 mL) at 80 °C in a sealed tube.

this latter event contributing to lowering the global yields in **5a**.

The use of 0.2 equivalents of $Sc(OTf)_3$ gave the best result (entry 7). Three additional reactions were run under such conditions (entries 9–11) giving access to the new indanones **5b–d** in medium yields. The presence of an MeO substituent in the *para* position to the alkenylic side-chain lowered the yield of the tandem hydride migration/cyclization/hydrolysis process (entries 10 and 11), a result probably related with the lowering of the electrophilic character of the benzylidene α-carbon atom, the hydride migration terminus, by the electron-donating *para*-MeO group. From a synthetic point of view, the conversion of compounds **2** into **5** mimics the intramolecular hydroacylation of 2-vinyl benzaldehyde systems,[10] in the present case by using an acetal-protected aldehyde. The original Rh-catalyzed reaction was reported to proceed in an extremely sluggish way with benzaldehydes bearing β-substituted 2-vinyl groups.[11]

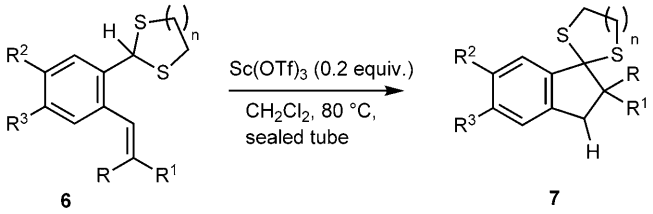
With the acetal-hydrolyzed *ortho*-formylbenzylidenemalonate **3a** in our hands as result of our initial attempts, we could prove that **3a** did not convert into the indanone **5a** under the habitual reaction conditions, thus ensuring that compounds **4** are intermediates in the processes leading from **2** to **5**.

In order to improve the efficiency of these or similar processes we made a substantial strategic variation. In our previous studies on tandem, thermally-activated [1,5]-H shift/cyclization reactions of acetalic ketenimines and carbodiimides we discovered that 2-monosubsituted 1,3-dithiolane and 1,3-dithiane fragments were also effective hydride-donor functions, although their hydricity was lower than that of their respective dioxygenated partners, 1,3-dioxolanes and 1,3-dioxanes. We reasoned that changing the dioxolane function of compounds **2** by a dithiolane or dithiane group could still give a chance for the occurrence of the desired tandem 1,4-hydride shift/cyclization sequence, although probably requiring slightly

Table 2. Spirocyclic 1,3-dithiolanes and 1,3-dithianes **7**.[a]

Entry	6	R	R^1	R^2	R^3	n	Time [h]	**7** (yield [%])
1	**6a**	CO_2Et	CO_2Et	H	H	1	40	**7a** (73)
2	**6b**	CO_2Me	CO_2Me	H	H	1	40	**7b** (75)
3	**6c**	COMe	CO_2Me	H	H	1	40	**7c** (46)
4	**6d**	CO_2Et	CO_2Et	H	Me	1	30	**7d** (89)
5	**6e**	CO_2Me	CO_2Me	H	Me	1	30	**7e** (92)
6	**6f**	CO_2Et	CO_2Et	OMe	H	1	45	**7f** (57)
7	**6g**	CO_2Me	CO_2Me	OMe	H	1	45	**7g** (62)
8	**6h**	CO_2Et	CO_2Et	Cl	Cl	1	40	**7h** (81)
9	**6i**	CO_2Et	CO_2Et	H	H	2	80	**7i** (57)
10	**6j**	CO_2Me	CO_2Me	H	H	2	80	**7j** (63)

[a] Reactions were conducted on 0.6 mmol scale of benzylidene derivative with a catalytic amount of $Sc(OTf)_3$ (0.12 mmol) in anhydrous dichlorometane (20 mL) at 80 °C in a sealed tube.



Scheme 4. Lewis acid-catalyzed [1,4]-H transfer/1,5-cyclization processes in benzylidene derivatives **6**.

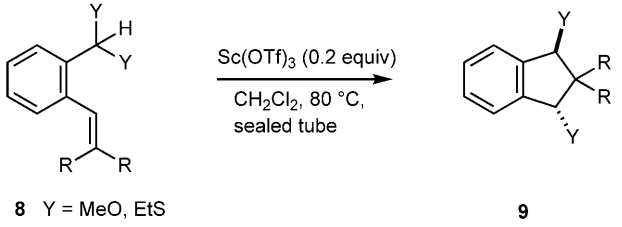
harsher reaction conditions, but this change would hopefully suppress the disturbing hydrolysis of the acetalic function aided by the oxophilic Lewis acid catalyst.

With this aim in mind, we next approached the preparation of a series of benzylidene derivatives **6** bearing 1,3-dithiolane and 1,3-dithiane functions at the *ortho* position. After some experiments, including the preparation of *ortho*-(1,3-dithiolan-2-yl)benzaldehyde[12] and its condensation with dialkyl malonates, we found as the better synthetic route to compounds **6** the trans-thioacetalization of the easily accessible dioxolane-malonates **2** with 1,2-ethanedithiol and 1,3-propanedithiol in the presence of bromodimethylsulfonium bromide.[13]

We were pleased to find out that heating CH_2Cl_2 solutions of compounds **6** at 80 °C in a sealed tube for 30–80 h and in the presence of $Sc(OTf)_3$ (0.2 equiv.) cleanly provided the spirocyclic products **7** in medium to good yields (Scheme 4 and Table 2).

The reaction was applied to a number of benzylidene malonates (entries 1,2 and 4–10) and to one benzylidene acetylacetate (entry 3) as electrophilic functions, generally using 1,3-dithiolanes as hydride-releasing units but also 1,3-dithianes (entries 9 and 10). In these latter cases the yields of **7** are lower than those obtained with 1,3-dithiolanes (compare entries 1 and 2 with 9 and 10, respectively) and the reactions required longer times for completion (see Table 2). These differences in reactivity are in accord with the results of our previous experiments with dithioacetalic heterocumulenes, where the 2-substituted 1,3-dithiane group was shown to be slightly less reactive than its dithiolane partner. These results confirmed the feasibility of the planned synthetic strategy. Although the yields of these reactions are not excellent, the spirocyclic products **7** are totally free of carbonyl-deprotected impurities **5** and the formation of a bond between two aliphatic quaternary carbon atoms is remarkable from a structural point of view.

When a similar methodology was applied to benzylidene malonates bearing non-cyclic acetalic functions, as the dimethyl acetals **8a** and **b**, the reaction products resulted to be the *trans*-1,3-dimethoxyindane 2,2-dicarboxylates **9a** and **b** (Scheme 5 and Table 3).



Scheme 5. Lewis acid–catalyzed [1,4]-Y transfer/1,5-cyclization processes in benzylidenemalonates bearing non-cyclic acetalic functions.

Table 3. Indane 2,2-dicarboxylates **9**.[a]

Entry	8	R	Y	Time [h]	*trans*-**9** (yield [%])
1	**8a**	CO_2Et	OMe	4	**9a** (53)
2	**8b**	CO_2Me	OMe	6	**9b** (45)
3	**8c**	CO_2Et	SEt	15	**9c** (75)
4	**8d**	CO_2Me	SEt	15	**9d** (68)

[a] Reactions were conducted on 0.6 mmol scale of benzylidenemalonate with a catalytic amount of $Sc(OTf)_3$ (0.12 mmol) in anhydrous dichlorometane (20 mL) at 80 °C in a sealed tube.

In this case the reaction course is interpreted in terms of a tandem 1,4-methoxide shift/cyclization process in which the alkoxy substituent proved to be a better migrating group than the acetalic hydrogen atom. This order of migrating ability is not especially surprising when considering an anionotropic rearrangement,[14] and is reflected in the shorter reaction times required for taking the reactions to completion (4–6 h). The *trans* configuration of compounds **9a** and **b** is established following their solution ^{13}C NMR spectra, where only one carbonyl carbon is distinguishable. This is indicative of the C_2 symmetry axis of structures *trans*-**9**, whereas the isomeric *cis* species should show two signals for the otherwise non-equivalent carbonyl carbon atoms of the two CO_2Et or CO_2Me groups at C-2 (C_s symmetry).[15] The yields in which *trans*-**9a** and **b** were obtained are rather modest, most probably reflecting the contribution of the $Sc(OTf)_3$ catalyst to promote the partial hydrolysis of the acetalic function of **8a** and **b** in the course of the thermal treatment in CH_2Cl_2 solution, even when the habitual precautions are taken to ensure dry reaction conditions. As expected, better yields were reached with the dimethyl dithioacetals **8c** and **d**, easily available by transthioacetalization of the corresponding cyclic acetals **2** with EtSH in the presence of bromodimethylsulfonium bromide, although the lower reactivity of these dithioacetals when compared with their oxygenated partners is again apparent, these reactions requiring somewhat longer reaction times. The stereochemical outcome of these tandem 1,4-ethanethiolate shift/cyclization processes is also the exclusive formation of the *trans*-**9c** and **d** diastereoisomers.

In summary, in this communication we disclose a new approach to C–H bond functionalization based on the activation of an unsaturated moiety, a C=C bond doubly substituted by carboxylate functions in one terminus, by an electrophilic metal catalyst, $Sc(OTf)_3$. This process is coupled with the cleavage of an acetalic C–H bond in the context of an uncommon 1,4-hydride shift, and followed by a final 1,5-cyclization for yielding a single bond between two quaternary carbon atoms, the originally acetalic one and that of the C=C bond bearing the electron-withdrawing groups. This strategy is not strictly limited to the use of hydride donors of the cyclic acetalic type (1,3-dioxolane, 1,3-dithiolanes and 1,3-dithianes), as it may be diverged to the preferential migration of alkoxy or alkanethiolate groups when acyclic acetalic functions replace the cyclic ones. These latter results open a wide spectrum of potential new tandem processes of similar nature by the involvement of diverse anionotropic rearrangements in the first mechanistic step, some of which are currently under study in our laboratories.

Experimental Section

Typical Experimental Procedure for the Preparation of Compounds 5, 7 and 9

(Thio)acetal **2**, **6** or **8** (0.6 mmol), scandium(III) triflate (0.12 mmol) and anhydrous dichloromethane (20 mL) were loaded into a dry sealed tube and then heated in an oil bath set to 80 °C. When all the starting material was consumed, as indicated by the TLC of reaction aliquots (3–80 h), the reaction was quenched with saturated sodium bicarbonate (20 mL) and vigorously shaken. The aqueous layer was extracted with dichloromethane (2×20 mL) and the combined organic phases were dried over magnesium sulfate. Then, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography.

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