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Functionalization of Csp^3–H bond—$Sc(OTf)_3$-catalyzed domino 1,5-hydride shift/cyclization/Friedel–Crafts acylation reaction of benzylidene Meldrum's acids

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ABSTRACT

Under $Sc(OTf)_3$ catalysis, benzylidene Meldrum's acids bearing a tethered *p*-methoxyphenethyl group were observed to undergo a [1,5]-hydride shift/cyclization at room temperature, representing a mild Csp^3–H bond functionalization. The resulting spiro Meldrum's acid intermediates then underwent intramolecular Friedel–Crafts acylation, completing the one-pot, domino reaction. The reported protocol generates the 6-6-5-6 tetracyclic core of tetrahydrobenzo[*b*]fluoren-11-ones.

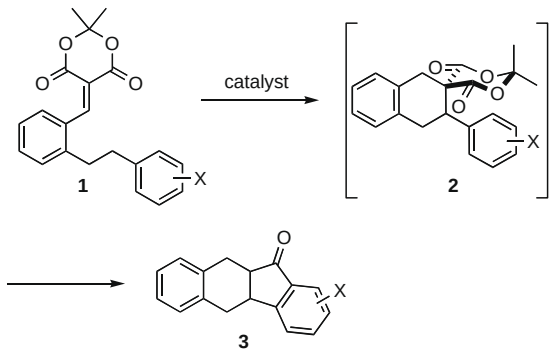
A renewed interest in the *tert*-amino effect and related [1,5]-hydride shift/cyclization reactions has been apparent in the recent literature as an efficient method of functionalizing Csp^3–H bonds.[1,2] This methodology has advanced from harsh thermal conditions and excess Lewis or Brønsted acids[3] to mild,[4] catalytic protocols.[5,6] In addition, progress has been made toward catalytic enantioselective variants[7] as well as finding applications in key disconnections of total syntheses.[8]

Examples of the *tert*-amino effect performing a [1,5]-hydride shift/cyclization onto Meldrum's acid derivatives have been reported in the literature under thermal conditions albeit in moderate yields.[9] Our group has had success employing alkylidene Meldrum's acids as conjugate addition acceptors[10] and has also exploited Meldrum's acid derivatives as powerful acylating agents,[11] both under catalytic Lewis acidic conditions.

As depicted in Scheme 1, we envisaged that a catalytic protocol analogous to the α,β-unsaturated acceptors reported (aldehydes, ketones and malonates) could be developed to promote a benzylic [1,5]-hydride shift/cyclization onto highly electrophilic[12] benzylidene Meldrum's acids **1** to afford spirocycles **2**, which would undergo intramolecular Friedel–Crafts acylation and generate complex tetracycles **3**.

We began our investigation by subjecting benzylidene Meldrum's acid **1a**[13] to a range of Brønsted and Lewis acids, having reasoned that the activating *p*-OMe group should be suitable for providing both stabilization for the developing carbocation during the hydride shift while being sufficiently π-nucleophilic for the subsequent FC acylation. Gratifyingly, several catalysts were found to successfully effect the desired reaction sequence as shown in Table 1. The best result came from conducting the reaction with $Sc(OTf)_3$ (10 mol %), which provided tetracycle **3a** in 48% yield. The use of toluene as solvent proved to be superior to nitromethane (entry 8), which had been optimal for previous Friedel–Crafts acylations with Meldrum's acids.[11]

As the yield for the domino process was still low, the focus then turned to studying the initial 1,5-hydride shift/cyclization step in more detail. It was postulated that the high temperature was decomposing benzylidene **1a** before complete conversion to **2a** could occur. Indeed, we were pleased to find that by performing the reaction at room temperature spirocyclic intermediate **2a** could be isolated in 90% yield (Table 2, entry 1).[14,15] The scope of the [1,5]-hydride shift/cyclization reaction was then investigated under these optimized conditions (Table 2). The *p*-NMe_2 group was also found to promote the reaction under catalytic conditions at 70 °C (Table 2, entry 2). Further exploration of substrates bearing



Scheme 1. General strategy.

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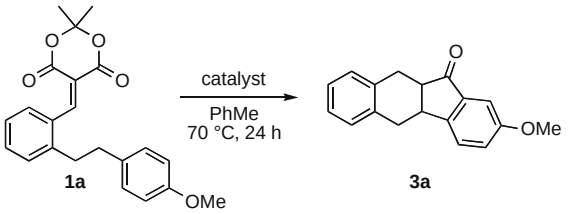
Table 1
Initial exploration of the domino sequence



1a **3a**

Entry	Catalyst	Loading (mol %)	Yield (%)
1	—	—	NR
2	$AlCl_3$	20	NR
3	$PdCl_2$	20	NR
4	$TiCl_4$	20	NR[a]
5	$Al(OTf)_3$	20	NR
6	$Sc(OTf)_3$	20	37
7	$Sc(OTf)_3$	10	48
8	$Sc(OTf)_3$	10	22[b]
9	TMSOTf	20	NR
10	$Mg(NTf_2)_2$	20	NR
11	$Sc(NTf_2)_2$	10	17
12	$BF_3{\cdot}OEt_2$	30	45
13	$BF_3{\cdot}OEt_2$	100	39
14	TFA	20	NR
15	TfOH	20	19

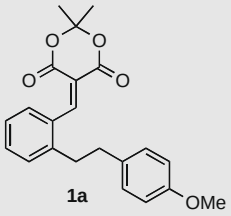
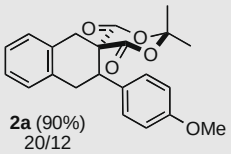
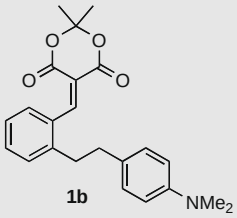
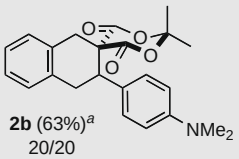
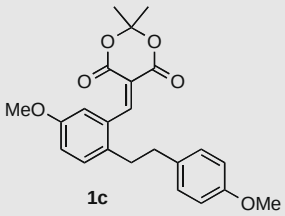
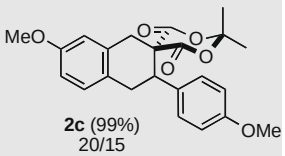
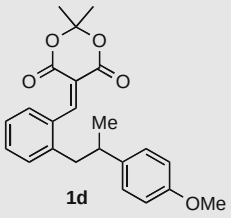
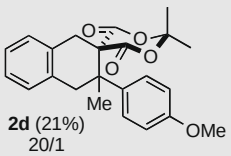
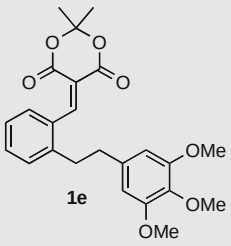
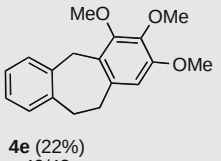
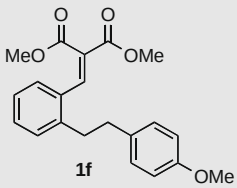
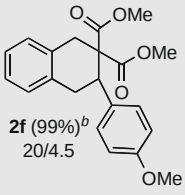
[a] Reaction performed at 50 °C.
[b] Nitromethane used as solvent.

a *p*-OMe revealed that substitution on the bridging aromatic moiety was tolerated in forming **2c** (entry 3) and an anticipated rate acceleration was observed in forming the all-carbon quaternary centre of **2d** (entry 4), which would proceed through a more stabilized tertiary carbocation. The 3,4,5-trimethoxy analogue **1e** was found to preferentially undergo a competing Friedel–Crafts alkylation, in addition to a reductive cleavage of Meldrum's acid moiety enroute to forming tricycle **4e** (entry 5) as the major product.[16] Furthermore, benzylidene malonate **1f** (Table 2, entry 6) also proved successful but needed an elevated reaction temperature (100 °C) as compared to the other entries owing to the superior electrophilicity of benzylidene Meldrum's acids.

Dialkoxy models **1g** and **1h** were found to undergo both pathways without an apparent bias (Scheme 2). Under optimized condition, the reaction of **1g** was sluggish, providing a 1.0:0.34:0.29 ratio of **1g**:**2g**:**4g** after 45 h as determined by the analysis of the ^{1}H NMR of the crude reaction mixture. Compounds **2g** and **4g** were isolated in modest yields. Similar results were obtained with **1h**, which led to a mixture of **1h**:**2h**:**4h** in a 1:0.56:0.67 ratio.

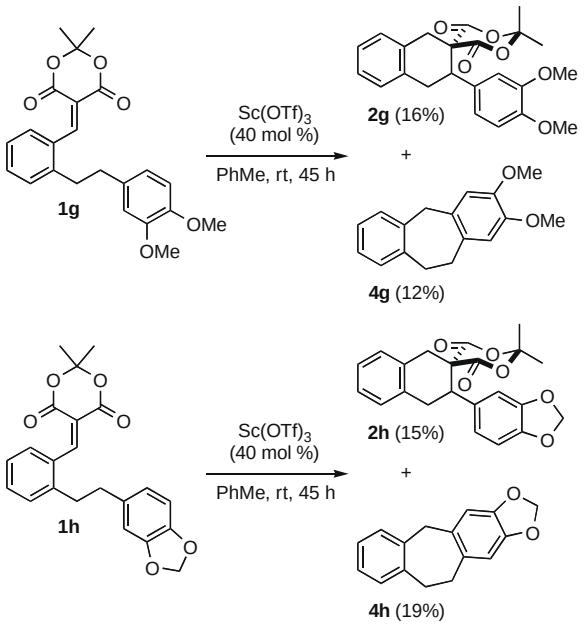
At this point the domino sequence was revisited having optimized the initial [1,5]-hydride shift/cyclization. It was found to be advantageous to sequentially stir the benzylidene Meldrum's acid at room temperature in the presence of $Sc(OTf)_3$, allowing for complete formation of the intermediate, before increasing the reaction temperature to 100 °C for the Friedel–Crafts acylation as depicted in Table 3. These tuned conditions furnished **3a** in 78% yield (entry 1) compared to the 48% yield in the preliminary investigation (Table 1, entry 7).[17,18] Despite the ability of **1c** to cleanly convert to the intermediate in high yield (Table 2, entry 3) only a moderate yield for the domino reaction was obtained (Table 3, entry 2); however, we were pleased to form tetracycle **3d** bearing the sterically congested all-carbon quaternary centre in good yield (entry 3) suggesting the poor yield in Table 2, entry 4 may have been attributed to product instability. Applying these conditions to the dialkoxy substrates **1g** and **1h** furnished the desired products **3g** and **3h**, respectively, in respectable yield in accord with their ability to convert to the *spiro*-intermediate, and considering the formation of three new bonds: a C–H and two C–C bonds.

Table 2
Scope of the $Sc(OTf)_3$-catalyzed [1,5]-hydride transfer/cyclization at room temperature

Entry	Substrate	Product (isolated yield) catalyst loading (mol %)/time (h)
1	 **1a**	 **2a** (90%) 20/12
2	 **1b**	 **2b** (63%)[a] 20/20
3	 **1c**	 **2c** (99%) 20/15
4	 **1d**	 **2d** (21%) 20/1
5	 **1e**	 **4e** (22%) 40/43
6	 **1f**	 **2f** (99%)[b] 20/4.5

[a] Reaction performed at 70 °C.
[b] Reaction performed at 100 °C.

In summary, a tandem one-pot formation of tetrahydrobenzo [*b*]fluoren-11-ones from benzylidene Meldrum's acids under Lewis acid catalysis, via [1,5]-hydride shift/cyclization/Friedel–Crafts acylation was described.



Scheme 2. Cyclization of substrates **1g** and **1h**.

Table 3
Scope of the domino reaction

Entry	Substrate	Catalyst loading (mol %)/time at rt (h)/time at 100 °C (h)	Product (yield)
1	**1a**	20/12/1.5	**3a** (78%)
2	**1c**	20/15/2	**3c** (55%)
3	**1d**	10/5/1	**3d** (61%)
4	**1g**	40/36/3	**3g** (52%)
5	**1h**	40/36/3.5	**3h** (41%)

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.007.

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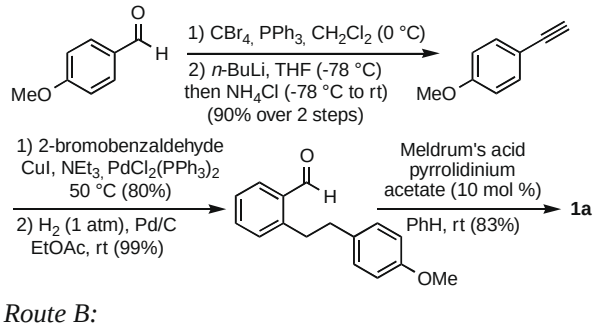
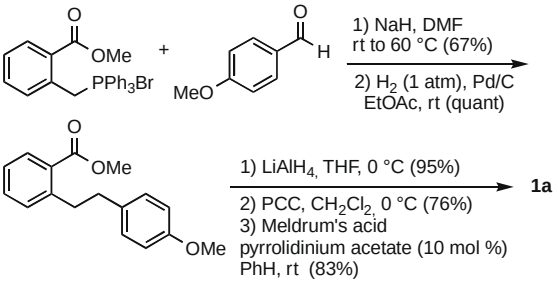
13. Benzylidene **1a** was prepared via two routes. See Supplementary data for details.

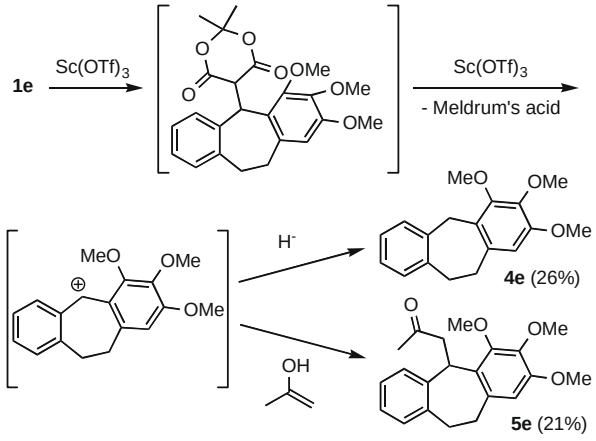
Route A:



Route B:



14. $Gd(OTf)_3$ was unable to promote the reaction under the optimized conditions or when performed in MeCN, in contrast to the rate enhancement over $Sc(OTf)_3$ exhibited in a related study, see Ref. 7.
15. *General procedure for [1,5]-hydride shift/cyclization:* In a glove box, benzylidene Meldrum's acid (generally 0.25 mmol), $Sc(OTf)_3$ (heated at 180 °C under high vacuum, 0.5 mm Hg for 2 h and stored in glove box) and toluene (distilled over CaH_2 then degassed, 0.1 M) were added to a glass vial equipped with a magnetic stir bar. The vial was then capped with a septum and stirred at the appropriate temperature; reaction progress was monitored by ^1H NMR. Products can be isolated either by diluting with CH_2Cl_2 and washing with H_2O (2×), brine (1×), drying over $MgSO_4$, filtering, and concentrating by rotary evaporation. The resulting crude mixture was purified by flash chromatography (silica gel and hexanes/EtOAc).
16. A 1.0:0.72:0.43 ratio of **1e**:**4e**:**5e** was obtained as determined by analysis of the ^1H NMR of the crude mixture. When **1e** was subjected to $Sc(OTf)_3$ (40 mol %) at 70 °C for 15.5 h, the reaction went to completion and tricyclic compounds **4e** and **5e** were isolated in 26% and 21% yields, respectively. The formation of **4e** and **5e** suggests that in the presence of $Sc(OTf)_3$, Meldrum's acid is eliminated following the intramolecular Friedel–Crafts alkylation to form a stabilized dibenzylic carbocation, which is subsequently reduced by a hydride to provide **4e**, or trapped by acetone to furnish **5e**. The source of hydride remains to be identified. Acetone is likely formed by the decomposition of Meldrum's acid. Such reduction process of benzylic Meldrum's acid is unprecedented.



17. *General procedure for domino reaction:* Reaction carried out as in *[1,5]-hydride shift/cyclization procedure* and once [1,5]-hydride shift/cyclization is completed as indicated by ^1H NMR (aliquots were withdrawn), the reaction vessel was immersed in a pre-heated 100 °C oil bath and stirred until full conversion had occurred as monitored by TLC. Caution: There is a slight pressure build-up since acetone and CO_2 are produced as byproducts. The reaction mixture was then diluted with CH_2Cl_2 and washed with H_2O (2×), brine (1×), dried with $MgSO_4$, filtered and concentrated by rotary evaporation. The resulting crude mixture was purified by flash chromatography (silica gel and hexanes/EtOAc)
18. Subjection of **2a** to $Sc(OTf)_3$ (20 mol %) at 100 °C for 1.5 h furnished **3a** in 60% yield.