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Superacid-Mediated Intramolecular Cyclization/Condensation: Facile One-Pot Synthesis of Spirotetracyclic Indanones and Indenes

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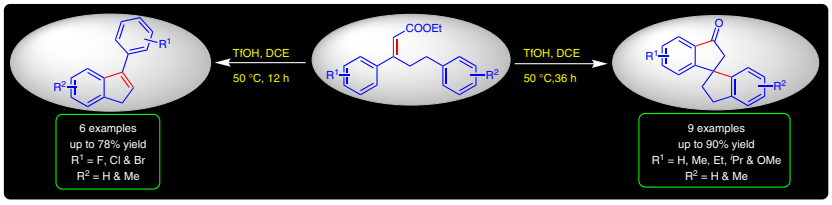

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Abstract A facile, superacid-promoted, domino, one-pot synthesis of novel spirotetracyclic indanones through intramolecular Friedel–Crafts acylation/alkylation of α,β-unsaturated cinnamic acid esters is presented. Interestingly, when the β-aryl group contained electron-withdrawing substituents such as fluoro, chloro, or bromo, the reaction took a different mechanistic path and afforded arylindenes as the end products.

Key words superacids, Friedel–Craft reaction, spiro compounds, indanones, indenes, domino reactions

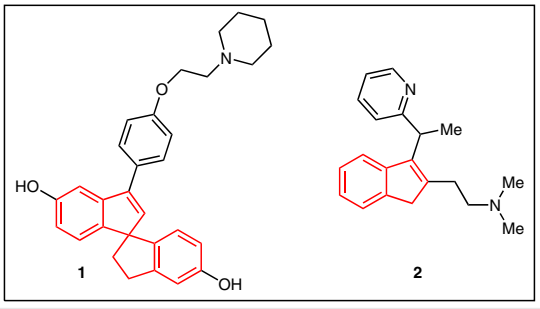


Figure 1 A biologically important indene and spirocyclic indene

Both indenes and spirotetracyclic indanones are privileged motifs in pharmaceutically active compounds, and these motifs are also present in naturally occurring compounds. Spirocyclic compounds have an sp^3 carbon atom common to two rings and are considered important scaffolds for ready access to a variety of cyclic products.[1] The development of new synthetic approaches for the construction of spirocyclic compounds is an interesting and challenging task in organic synthesis. For example, a spirotetracyclic indene constitutes the major cyclic core of the biologically active tertiary amine **1**,[2] a new framework for estrogen receptor ligands, in which it is assumed that a series of related compounds might have unprecedented biological properties due to their novel structural characteristics. In addition, the simple indene compound **2** [dimetindene (Fenistil)] is a well-known antihistamine drug (Figure 1).[3]

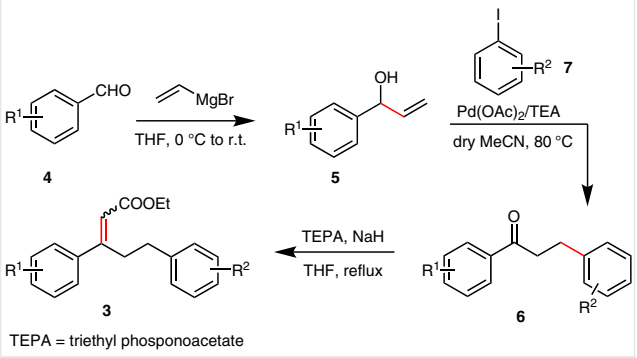
The Friedel–Crafts reaction remains a predominant method for C–C bond formation by aromatic electrophilic substitution.[4] Over the last few decades, developments have continued to be made in this Brønsted/Lewis acid catalyzed procedure.[5–7] However, few methods have been developed for the synthesis of spirotetracyclic indanones or of indenes. In this context, Brewster and Prudence[8] reported the synthesis of optically active 1,1′-spirobiindane and related compounds.

Various researchers have developed a rhodium(I)-catalyzed spirocyclization reaction that includes a 1,4-rhodium migration and provides a route to spirocyclic 1-indanones.[9] In 2001, Hashimoto and co-workers[10] described a catalytic asymmetric synthesis of 1,1′-spirobi[indene]-3,3′(2*H*,2′*H*)-dione through a double intramolecular C–H insertion process, whereas Boblak and Klumpp[11] reported superacid-promoted cyclodehydrations leading to functionalized indenes. Some notable acid-catalyzed reactions for the synthesis of spirocyclic compounds have also been reported from the research groups of Wang,[12a] Chan,[12b] Stark,[13] Padwa,[14a] Daisley,[14b] Reddy,[15] and Liang.[16]

In a continuation of our research into domino one-pot processes, we have developed a superacid-promoted synthesis of indanones, tetracyclic indoles, and indenones, starting from simple cinnamic acid esters,[17] and an efficient method for the synthesis of spirotetracyclic dihydrocoumarins in the presence of Lewis acids.[18] A mild and practical

method for the synthesis of (1,1-dimethyl-3-phenylbut-3-enyl)benzenes and indanes has also been established.[19] Herein, we report a superacid-mediated, efficient, domino one-pot synthesis of novel spirotetracyclic indanones from pendent β-aryl α,β-unsaturated ester derivatives. Unexpectedly, when the β-aryl group contained an electron-withdrawing group such as fluoro, chloro, or bromo, the reaction took a different mechanistic path and gave arylindenes[20] as the final products. The key bond formations in this strategy, particularly for the synthesis of spirotetracyclic indanones, are identical to those reported by Matsuda et al.[9e]

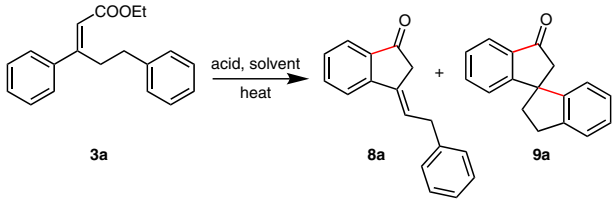
We began our study with the preparation of the pendent β-aryl α,β-unsaturated esters **3** from benzaldehydes **4**. Thus, addition of vinylmagnesium bromide to the benzaldehydes **4** gave the corresponding allylic alcohols **5** in excellent yields. Jeffery–Heck coupling[21] of the allylic alcohols **5** with iodoarenes **7** furnished the corresponding 1,3-diarylpropan-1-ones **6** in good to very good yields. Finally, the pendent β-aryl α,β-unsaturated esters **3** were synthesized in excellent yields from the corresponding ketones **6** by using standard Horner–Wadsworth–Emmons conditions (Scheme 1). Note that in most cases the cinnamic acid esters **3** were obtained as inseparable mixtures of *E*- and *Z*-isomers (see Supporting Information).



Scheme 1 Synthesis of ethyl cinnamates **3**

With the pendent β-aryl α,β-unsaturated esters **3** in hand, we explored their cyclization reaction with various acids to identify the optimal conditions. The *E*-isomer of ester **3a** (obtained by careful separation through column chromatography) was chosen as the model compounds for this study. Initial attempts using PTSA or $TiCl_4$ were unsuccessful, leading to the recovery of the starting material (Table 1, entries 1–4). Interestingly, the reaction with the Brønsted superacid TfOH at room temperature gave the expected spirotetracyclic ketone **9a** along with indenone **8a** (entries 5 and 6). Note that, in the case of the indene **8a**, the double bond isomerized to the *exo*-position. This might be because the *exo*-cyclic indenone **8a** is thermodynamically more stable than the *endo*-substituted indenone[17c] because the cyclopentadienone subunit of the *endo*-substituted indenone has antiaromatic character. The yield of spirotetracyclic 1-indanone **9a** increased on increasing the amount of acid (entry 7) and on increasing the temperature (entry 8). With less acidic methanesulfonic acid the reaction did not proceed and the starting material **3a** was recovered (entry 9). The reaction of **3a** with the Lewis acid $AlCl_3$ gave neither the desired product **9a** the recovered starting material (entry 10). The use of $CHCl_3$ as a medium gave the product in moderate yield (entry 11).

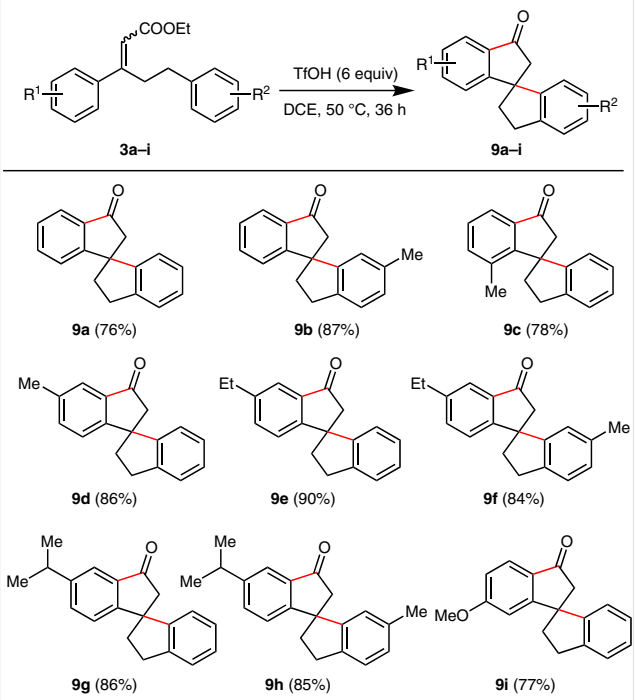
Table 1 Optimization of Conditions for the Synthesis of Spirocyclic 1-Indanone **9a**[a]



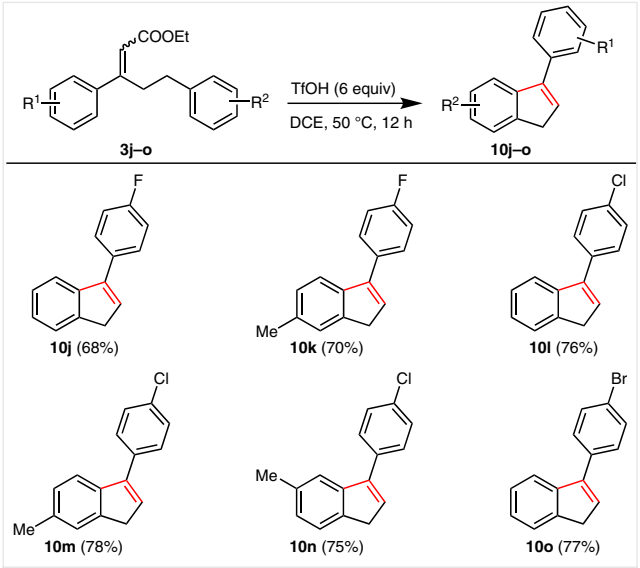
Entry	Acid (equiv)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	
					8a	**9a**
1	PTSA (2)	DCE	r.t.	12	0[c]	0[c]
2	$TiCl_4$ (2)	CH_2Cl_2	r.t.	24	0[c]	0[c]
3	H_2SO_4 (3)	CH_2Cl_2	r.t.	12	–[e]	–[e]
4	TfOH (3)	DCE	0 to r.t.	12	0[c]	0[c]
5	TfOH (3)	DCE	r.t.	12	60	20
6	TfOH (3)	DCE	50	24	20	40
7	TfOH (6)	DCE	50	24	0[d]	60
8	**TfOH (6)**	**DCE**	**50**	**30**	**0[d]**	**76**
9	MsOH (6)	DCE	50	30	0[c]	0[c]
10	$AlCl_3$ (3)	DCE	50	30	–[e]	–[e]
11	TfOH (6)	$CHCl_3$	50	30	0[d]	50

[a] All reactions were carried out on a 0.25 mmol scale of (*E*)-**3a** in the appropriate solvent (2 mL).
[b] Isolated yield of the chromatographically pure product.
[c] Only the starting material **3a** was recovered.
[d] No **8a** was formed.
[e] No products **8a**/**9a** were obtained and none of the starting material **3a** was recovered.

Among the screened conditions, the conditions show in Table 1, entry 8 were optimal. Therefore, these conditions were applied to the other substrates **3b–i** (as *E*-isomers or as mixtures of *E*- and *Z*-isomers) to examine the scope and limitations of the procedure. Gratifyingly, the method was amenable to various substrates possessing a range of functional groups on either aromatic ring, and it gave the corresponding spirotetracyclic indanones **9a–i** in very good to excellent yields (Scheme 2).



Scheme 2 Synthesis of spirotetracyclic indanones **9a–i** through acid-promoted acylation/alkylation of **3a–i**. All reactions were carried out on 0.25 mmol scale, and yields of the chromatographically pure products **9a–i** are reported.



Scheme 3 Synthesis of indenes **10j–o** through intramolecular acylation of the pendent β-unsaturated esters **3j–o**. All reactions were carried out on a 0.25 mmol scale of **3j–o**, and yields of chromatographically pure products **10j–o** are reported.

Surprisingly, however, when the β-aryl group contained an electron-withdrawing group such as fluoro, chloro, or bromo, the reaction took a different mechanistic path and gave the corresponding arylindenes **10** as final products (Scheme 3). This might be due to the lower reactivity of the β-aryl moiety, such that it does not undergo acylation but instead eliminates ethyl acetate to give the aryl indenes **10j–o**.

A plausible reaction mechanism for the formation of spirocyclic indanones **9** and indenes **10** is shown in Scheme 4. Initially, the protic acid activates and isomerizes the carbonyl group of ester **3** to yield structure **A**. Double-bond isomerization of **A** results in the formation of structure **B** (path a). Intramolecular Friedel–Crafts acylation of **B** and rearomatization leads to the indenone **8**. Subsequent intramolecular Friedel–Crafts alkylation of indenone **8** with the second arene affords the spirocyclic indanone **9**. Alternatively, the pendent arene in **A** might react through intramolecular Friedel–Crafts alkylation to give indane ester **C** (path b). If the β-aryl group of **C** does not possess electron-withdrawing halo groups, it might undergo intramolecular acylation through path c to furnish the spirocyclic indanone **9**. However, if the β-aryl group does possess an electron-withdrawing halo group, it undergoes acid-mediated fragmentation through path d to give the carbocation intermediate **E** through liberation of ethyl acetate from the protonated species **D**. Finally, removal of a proton from **E** leads to the formation of indene **10**.

In conclusion, we have described a superacid-promoted intramolecular Friedel–Crafts acylation/alkylation of pendent β-aryl α,β-unsaturated cinnamic acid esters for the one-pot synthesis of novel spirotetracyclic indanones. When the β-aryl group contains electron-withdrawing groups such as fluoro, chloro, or bromo substituents, the reaction gives arylindenes.

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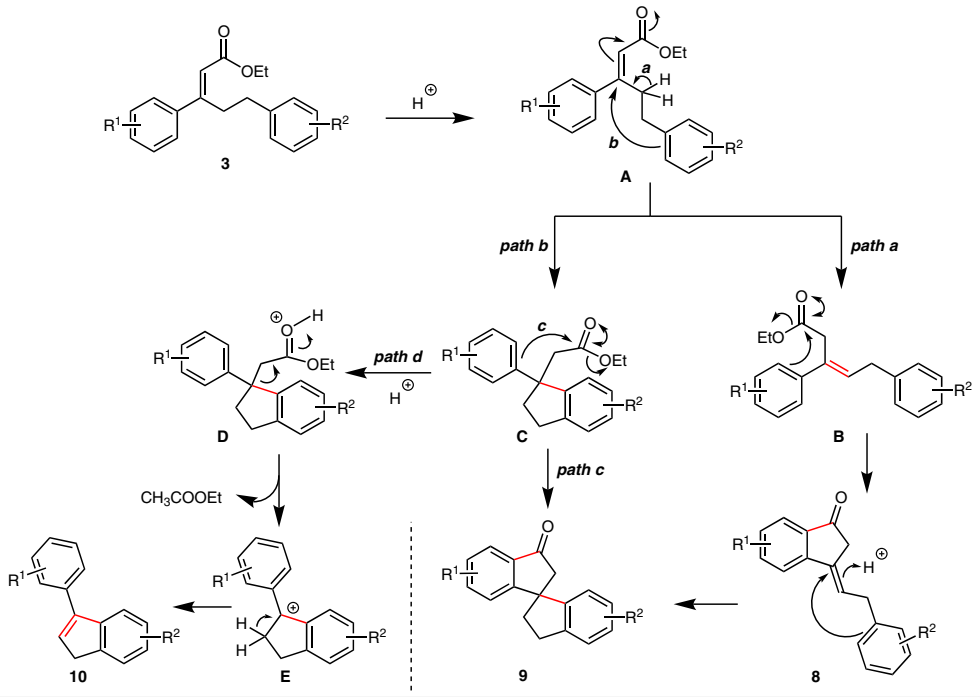
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590816.



Scheme 4 Plausible mechanism for the formation of the spirocyclic indanones **9** and indenes **10**

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(22) **Spirotetracyclic indanones 9; General Procedure**

An oven-dried Schlenk tube was charged with the appropriate β-aryl α,β-unsaturated ester **3a–i** (0.25 mmol) and DCE (2 mL) under N_2. TfOH (0.1 mL, 1.5 mmol) was then added and the mixture was stirred at 50 °C for 30–36 h until the reaction was complete (TLC). The reaction was quenched with aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with sat. brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, PE–EtOAc) to give the appropriate spirotetracyclic indanone **9a–i** (76–90%).

6′-Methyl-2′,3′-dihydro-1,1′-spirobi[inden]-3(2*H*)-one (9b)

Brown viscous liquid; yield: 54 mg (87%); TLC: R_f (**3b**) = 0.50, (**9b**) = 0.60 (PE–EtOAc, 96:4, UV detection). IR (MIR-ATR): 2922, 2851, 1710, 1601, 1461, 1287, 1236, 816, 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.8 Hz, 1 H, ArH), 7.57 (ddd, *J* = 7.3, 7.3, and 1.0 Hz, 1 H, ArH), 7.41 (ddd, *J* = 7.3, 7.3, and 1.0 Hz, 1 H, ArH), 7.27 (d, *J* = 7.8 Hz, 1 H, ArH), 7.21 (d, *J* = 7.8 Hz, 1 H, ArH), 7.08 (d, *J* = 7.8 Hz, 1 H, ArH), 6.57 (s, 1 H, ArH), 3.19–3.00 (m, 2 H, CH_2), 2.94 (d, *J* = 18.6 Hz, 1 H, CH_aH_b), 2.87 (d, *J* = 18.6 Hz, 1 H, CH_aH_b), 2.55–2.44 (m, 1 H, CH_2), 2.40–2.30 (m, 1 H, CH_2), 2.22 (s, 3 H, $ArCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9 (s, C=O), 161.6 (s, ArC), 149.0 (s, ArC), 140.2 (s, ArC), 136.9 (d, ArC), 136.0 (s, ArC), 135.4 (d, ArCH), 128.1 (d, ArCH), 127.8 (d, ArCH), 125.1 (d, ArCH), 124.3 (d, ArCH), 123.3 (d, ArCH), 123.0 (d, ArCH), 54.4 [s, $C(CH_2)_2$], 52.4 (t, CH_2), 42.9 (t, CH_2), 30.8 (t, CH_2), 21.2 (q, $ArCH_3$). HRMS (APCI+): *m/z* $[M + H]^+$ calcd for $C_{18}H_{17}O^+$: 249.1274; found: 249.1279.

(23) **Indenes 10; General Procedure**

An oven-dried Schlenk tube was charged with the appropriate β-aryl α,β-unsaturated ester **3j–o** (0.25 mmol) and DCE (2 mL) under N_2. TfOH (0.1 mL, 1.5 mmol) was then added and the mixture was stirred at 50 °C for 12 h until the reaction was complete (TLC). The reaction was quenched with aq. $NaHCO_3$ and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with sat. brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, PE–EtOAc) to give the appropriate indene **10j–o** (68–78%).

3-(4-Chlorophenyl)-5-methyl-1*H*-indene (10n)

Brown viscous liquid; yield: 47 mg (78%). TLC: R_f (**3n**) = 0.45, (**10n**) = 0.60 (PE–EtOAc, 97:3, UV detection). IR (MIR-ATR): 2920, 1726, 1613, 1487, 1393, 1288, 1093, 1014, 885, 803, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 8.3 and 2.0 Hz, 2 H, ArH), 7.47 (dd, *J* = 8.3 and 2.0 Hz, 3 H, ArH), 7.38 (s, 1 H, ArH), 7.14 (d, *J* = 8.3 Hz, 1 H, ArH), 6.58 (t, *J* = 2.0 Hz, 1 H, CH=C), 3.49 (d, *J* = 2.0 Hz, 2 H, CH_2), 2.45 (s, 3 H, $ArCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0 (s, ArC), 143.7 (s, ArC), 141.7 (s, ArC), 135.8 (d, ArC), 134.6 (s, ArC), 133.3 (s, ArC), 131.7 (d, ArCH), 129.0 (d, 2 C, ArCH), 128.7 (d, 2 C, ArCH), 125.9 (d, ArCH), 123.9 (d, ArCH), 120.7 (d, CH=C), 37.8 (t, CH_2), 21.6 (q, $ArCH_3$). HRMS (APCI+): *m/z* $[M + H]^+$ calcd for $C_{16}H_{14}Cl^+$: 241.0779; found: 241.0787.