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Poly(phosphoric acid) (PPA)-Promoted 5-*exo*-Cyclization of Iminium Ions Generated In Situ: A Facile Access to Functionalized Indene Derivatives

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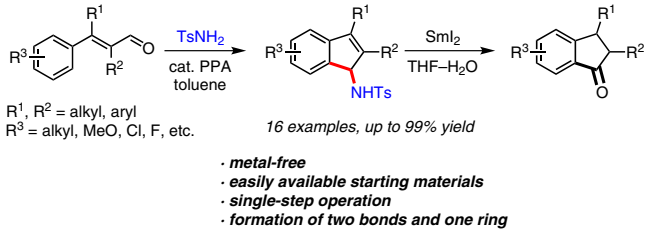

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Abstract A metal-free Brønsted acid promoted two-component reaction between cinnamaldehydes and sulfonamides is described. This cascade process provides a simple and atom-economical alternative synthesis of a range of functionalized indenes from easily available starting materials. The resulting *N*-indenylsulfonamides were readily converted into the corresponding indenylenamines or indanones.

Key words indenes, iminium ions, indanones, exocyclization, polyphosphoric acid, cascade reaction

The iminium ion based cyclization reaction is among the most important methods for the construction of cyclic systems, as it permits multiple transformations to take place in one step, and makes synthetic routes shorter and more efficient with substantial reductions in waste and time. Consequently, many protocols based on this reaction have been developed for the synthesis of complex structures. However, most of these are focused on the formation of nitrogen-containing heterocycles by an *endo* mode of cyclization (Figure 1).[1] One well-known transformation of this type is the Pictet–Spengler reaction, which has played a major role in organic synthesis for over a hundred years.[2] In contrast, the *exo* mode of cyclization has received limited attention, although it provides a unique opportunity to develop novel transformations for the efficient construction of carbocyclic skeletons.[3]

Functionalized indenes are an attractive family of carbocyclic compounds, and functionalized indene moieties are present in many biologically active molecules, functional materials, and transition-metal complexes[4] that attract continuing interest from synthetic chemists. A variety of methods, including inter- and intramolecular reactions, as well as ring-expansion and ring-contraction processes, have been developed to access various functionalized indenes.[5] In 2005, Takai and co-workers reported a rhenium-catalyzed [3+2] reaction of imines with alkynes to give indenylamine derivatives (Scheme 1),[6] which are promising building blocks in biological materials and medicines.[7] Following this pioneering work, several other advances were reported.[8] In 2009, Wang, Lu, and their co-workers developed another strategy for preparing substituted indenylamines by a cascade reaction of aziridines and propargyl alcohols, in which iminium ion cyclization plays a major role (Scheme 1).[9] Recently, our group reported an $FeCl_3$-catalyzed two-component reaction for the synthesis of indenylamine derivatives through cyclization of iminium ions generated in situ.[10] This method features a high efficiency in the generation of two new bonds and one five-membered ring in a single operation from readily accessible substrates. However, the reaction is limited to electron-rich substituted cinnamaldehydes. As a part of our ongoing program on C–O/C=O bond-functionalization reactions,[11] we report a metal-free poly(phosphoric acid) (PPA)-promoted procedure for

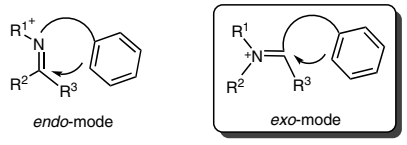
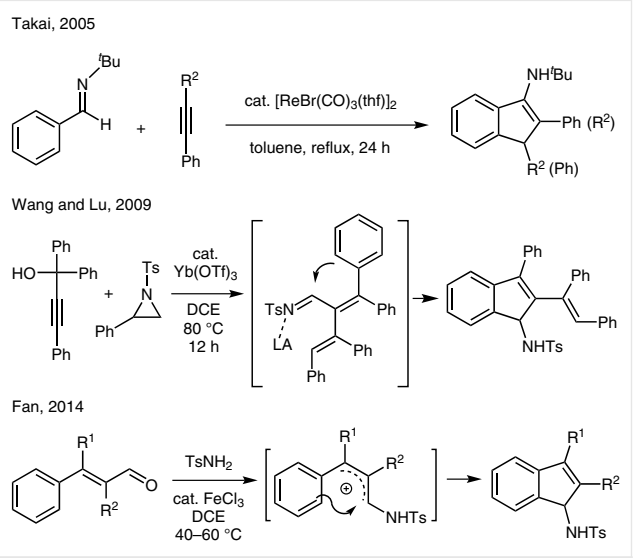


Figure 1 Cyclization modes of iminium ions

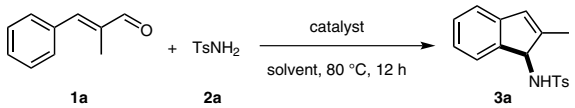


Scheme 1 Protocols for the formation of indenylamines

the synthesis of various indenylamine derivatives, which permits the use of either electron-rich or electron-deficient cinnamaldehydes as suitable substrates.

At the outset of this investigation, we focused our attention on the reaction of (2*E*)-2-methyl-3-phenylacrylaldehyde (**1a**, 1.0 equiv) with $TsNH_2$ (**2a**, 1.2 equiv) in the presence of 20 mol% of PPA as a catalyst in a range of solvents, to establish the optimal reaction conditions (Table 1). PPA was chosen as the catalyst because it is a cheap and environmentally benign Brønsted acid that has shown good catalytic ability in the Pictet–Spengler reaction.[1a] We found that the reaction medium critically affects the efficiency of this reaction. No reaction occurred in $MeNO_2$ or EtOH as the solvent (Table 1, entries 1 and 2), whereas in DCE or MeCN, the cyclization product **3a** was obtained in 9% and 15% isolated yield, respectively (entries 3 and 4). Gratifyingly, when the reaction was carried out in toluene (entry 5), a 91% yield of **3a** exclusively was obtained, with full conversion of **1a**. Increasing the reaction temperature or the catalyst loading had no obvious effects on the reaction (entry 6). However, lowering the amount of PPA from 20% to 15 mol% was clearly unfavorable for the reaction, as the yield of product **3a** decreased markedly to 34% (entry 7). On replacing PPA with H_3PO_4, only a trace of **3a** was obtained, along with unreacted **1a** and a small amount of the corresponding imine (entry 8). Other Brønsted acids such as HCl or H_2SO_4 were also found to be unsuitable for use as catalysts in this reaction (entries 9 and 10).

Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3a**

Entry	Catalyst (mol%)	Solvent	Yield[b] (%)
1	PPA (20)	$MeNO_2$	0
2	PPA (20)	EtOH	0
3	PPA (20)	DCE	9
4	PPA (20)	MeCN	15
5	PPA (20)	toluene	91
6	PPA (30)	toluene	92
7	PPA (15)	toluene	34
8	H_3PO_4 (20)	toluene	trace
9	HCl (20)	toluene	0
10	H_2SO_4 (20)	toluene	trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), solvent (3 mL), 80 °C, 12 h.
[b] Isolated yield.

Having established the optimal reaction conditions (Table 1, entry 5), we treated a range of aldehydes **1** with $TsNH_2$ to determine the scope and limitations of this PPA-promoted reaction (Table 2).[12]

The results show that a wide range of arylated acroleins are effective substrates in this system, furnishing the corresponding cyclization products in moderate to excellent yields (Table 2, entries 1–15). Generally, the reaction was facilitated by aldehydes that contain an electron-rich arene π-nucleophile. The introduction of an electron-withdrawing group, such as a chloro or fluoro group, on the phenyl ring resulted in moderate yields of the corresponding cyclization products (entries 14 and 15). Note that electron-deficient cinnamaldehydes such as **1n** failed to react with $TsNH_2$ in our previous work when $FeCl_3$ was used as the catalyst;[10] the present catalytic system is therefore more efficient with electron-deficient aldehydes. Additionally, methoxy-substituted aldehydes also gave better yields compared with those in our previous work (entries 5 and 6); the difference in the coordination abilities of PPA and $FeCl_3$ is probably responsible for this result. Interestingly, when 1- and 2-naphthyl-substituted acroleins **1g** and **1h** were used as substrates, the reaction occurred exclusively at the C-2 and C-1 positions through a 5-*exo* ring closure to give the benzene-fused indene-type products **3g** and **3h**, respectively, in high yields, without the formation of C-8 or C-3 ring-closure products (entries 7 and 8). The structure of the skeleton of *N*-indenylsulfonamide **3h** was determined by an X-ray single-crystal analysis (Figure 2).[13]

To our disappointment, cinnamic ketones such as (3*E*)-3-methyl-4-phenylbut-3-en-2-one failed to react, even under harsh conditions, presumably because of the lower electrophilicity of the carbonyl group of the ketone. Note that the presence of an α-substituent in the aldehyde substrate is crucial to this transformation; upon subjecting (*E*)-cinnamaldehyde or (*E*)-3-phenylbut-2-enal (**1p**) to this re-

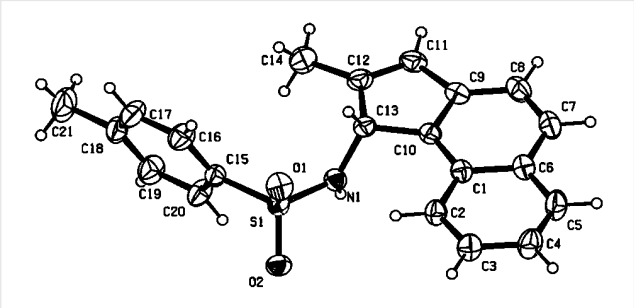


Figure 2 X-ray crystal structure of *N*-indenylsulfonamide **3h**

action, only the corresponding imines, along with the unreacted aldehydes, were obtained (Table 2, entry 16). 3,3-Diphenylacrylaldehyde (**1m**), which lacks an α-substituent, did, however, react (entry 13), presumably owing to its special structure in which the carbonyl group and one of the phenyl rings are oriented in a *cis*-fashion. These results are consistent with our previous work.[10]

Table 2 Reaction of Various Aldehydes with $TsNH_2$[a]

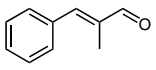
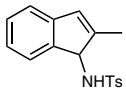
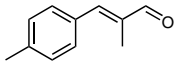
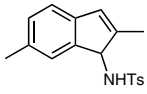
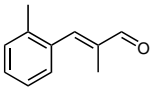
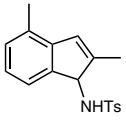
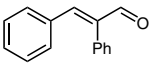
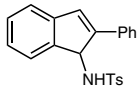
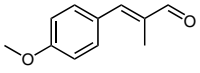
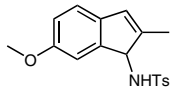
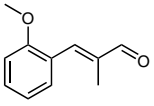
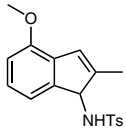
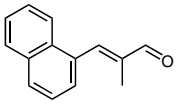
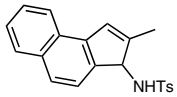
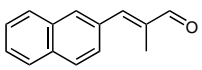
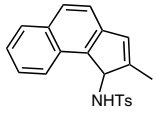
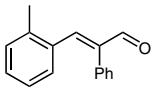
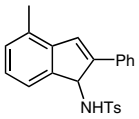
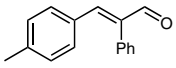
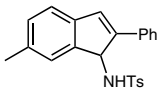
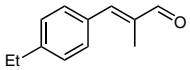
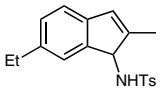
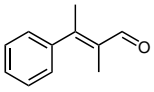
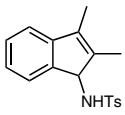
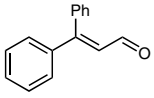
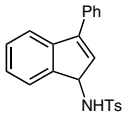
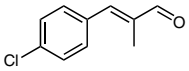
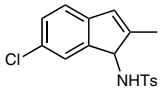
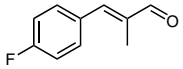
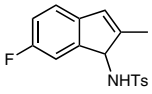
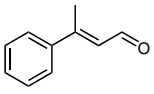
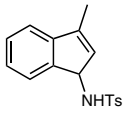
Entry	Substrate		Product		Temp (°C)	Time (h)	Yield (%)[b]
1	**1a**		**3a**		80	12	91
2	**1b**		**3b**		80	16	81
3	**1c**		**3c**		80	16	86
4	**1d**		**3d**		80	16	99
5	**1e**		**3e**		80	18	79
6	**1f**		**3f**		80	24	90
7	**1g**		**3g**		80	24	90
8	**1h**		**3h**		80	24	91

Table 2 (continued)

Entry	Substrate	Product	Temp (°C)	Time (h)	Yield (%)[b]
9	**1i** 	**3i** 	40	48	82
10	**1j** 	**3j** 	40	48	73
11	**1k** 	**3k** 	40	48	82
12	**1l** 	**3l** 	80	16	80
13	**1m** 	**3m** 	80	16	75
14	**1n** 	**3n** 	80	16	64
15	**1o** 	**3o** 	80	16	61
16	**1p** 	**3p** 	80	16	0

[a] Reaction conditions: aldehyde **1** (0.2 mmol), $TsNH_2$ (0.24 mmol), solvent (3 mL).
[b] Isolated yield.

Next, we examined the scope of the amine by using aldehyde **1a** as the substrate (Scheme 2). Benzenesulfonamide (**2b**) and 4-chlorobenzenesulfonamide (**2c**) reacted smoothly with aldehyde **1a** to give the desired *N*-indenylsulfonamides **3ab** and **3ac** in 87% and 83% yield, respectively. However, aniline (**2d**), 4-nitroaniline (**2e**), and piperidine (**2f**) failed to react. With methanesulfonamide (**2g**) or benzamide (**2h**), the corresponding cyclization products **3ag** and **3ah** were obtained along with the corresponding imines and inseparable mixtures.

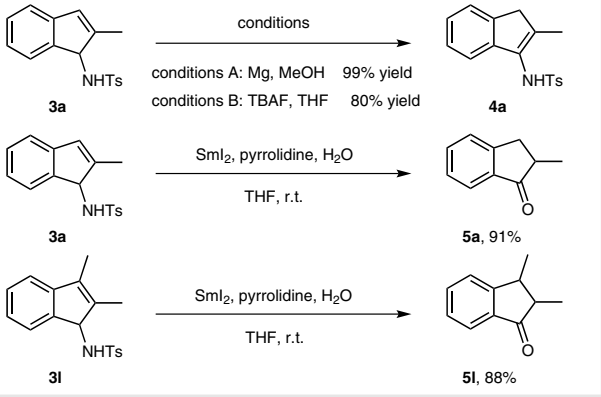
Subsequently, the derivation of the *N*-indenylsulfonamide **3a** was carefully investigated (Scheme 3). Initial attempts to remove the *N*-tosyl group under a variety of conditions[14] (sodium naphthalide, Mg/MeOH, SmI_2, LAH/THF,

1a **2b–h** **3ab–ah**

2b	$PhSO_2NH_2$	87% (80 °C, 12 h)
2c	4-Cl-$PhSO_2NH_2$	83% (80 °C, 12 h)
2d	$PhNH_2$	0% (100 °C, 12 h)
2e	4-$O_2NC_6H_4NH_2$	0% (100 °C, 12 h)
2f	piperidine	0% (100 °C, 12 h)
2g	$MeSO_2NH_2$	5% (100 °C, 24 h)
2h	$PhCONH_2$	15% (100 °C, 24 h)

Scheme 2 Reaction of aldehyde **1a** with various amines

or NaOH/MeOH) failed to afford the deprotected product. However, on treatment with Mg/MeOH, **3a** was transformed into the indenylenamine **4a** in almost quantitative yield. Interestingly, treatment of **3a** with SmI_2, pyrrolidine, and water[15] in THF gave indanone **5a** in 91% yield without the formation of the detosylation product (Scheme 3); other indenylamines such as **3l** also underwent this transformation smoothly under similar conditions.[16] The reason for this transformation is not clear at present,[17] and further experimental and mechanistic studies are underway in our group.

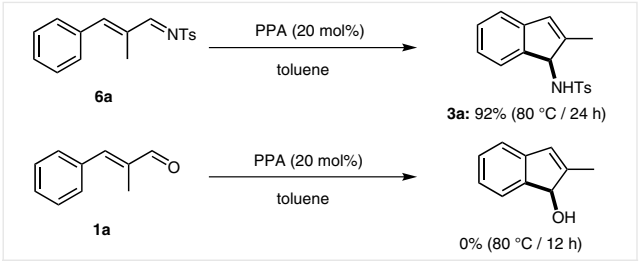


Scheme 3 Derivation experiments

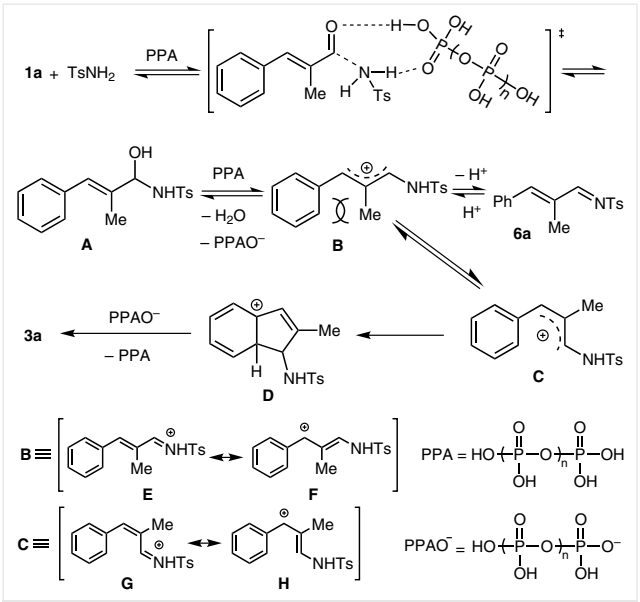
Next, we examined the transformation of sulfonamide **3a** into the corresponding indenone under the reported conditions using tetrabutylammonium fluoride (TBAF) or I_2/K_2CO_3.[8a,9] However, none of the desired product was obtained under these conditions. Treatment of sulfonamide **3a** with I_2/K_2CO_3 led to an intractable mixture, whereas on treatment with TBAF, **3a** was converted into the indenylenamine **4a** in 80% yield (Scheme 3).

With the aim of understanding the mechanism, two control experiments were conducted (Scheme 4). First, on treatment with 20 mol% of PPA in toluene at 80 °C, the previously prepared aldimine **6a** was smoothly converted into sulfonamide **3a** in 92% isolated yield. Note that at the beginning of this reaction a proportion of **6a** decomposed into aldehyde **1a** and $TsNH_2$, but these disappeared by the time the reaction was complete. Secondly, reaction of **1a** under the optimized conditions for 12 hours without addition of $TsNH_2$ resulted in no cyclization product being obtained. The reaction is therefore unlikely to involve a cyclization/substitution process.

On the basis of the above results and previous studies,[10,18] we propose the tentative reaction pathway shown in Scheme 5. Initially, nucleophilic addition of $TsNH_2$ to the carbonyl group of the aldehyde **1a** with the aid of PPA gives the amino alcohol intermediate **A**, which is dehydrated after protonation of the hydroxy group by PPA to afford a resonance-stabilized cationic intermediate **B** (a hybrid of the resonance structures of iminium ion **E** and allylic cation **F**). Intermediate **B** can be transformed into the corresponding imine **6a** or its isomer **C** (a hybrid of resonance structures of **G** and **H**) through loss of a proton or a bond-rotation procedure, respectively. Subsequently, intermediate **C** undergoes an intramolecular aza-Friedel–Crafts reaction (or 4π-electrocyclization) followed by loss of a proton to give product **3a**. In this ring-closure reaction, isomerization of the cationic intermediate **B** to its geometrical isomer **C** is necessary before cyclization can occur. This process is facilitated by the cinnamaldehyde having an α-substituent, because this induces an $A_{1,2}$ strain between the α-substituent and the aromatic group. Additionally, the generation of the key intermediates **B** and **C** also benefits from the presence of an electron-donating group at the α-position. Indeed, (2*Z*)-2-bromo-3-phenylacrylaldehyde is completely inert to this transformation, even under harsh reaction conditions.



Scheme 4 Control experiments



Scheme 5 Tentative reaction pathway

In summary, we have developed a novel cascade approach to the synthesis of functionalized indene derivatives by condensation of substituted cinnamaldehydes with sulfonamides. Electron-rich and electron-deficient cinnamaldehydes are both suitable as substrates. This Brønsted acid catalyzed two-component reaction has some indubitable advantages, such as the ready availability of the starting materials and catalyst, the simplicity of the metal-free procedure, and its high atom-economy. Additionally, we found that the resulting indenylamines can be transformed into the corresponding indanones by treatment with SmI_2, pyrrolidine, and water; this transformation has not been reported previously and is expected to find widespread use in related reactions. Further studies on these reactions are in progress in our group.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589009.

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(12) ***N*-(1*H*-Inden-1-yl)benzenesulfonamides 3a–p; General Procedure**
$TsNH_2$ (0.24 mmol) and PPA (20 mol%) were added to a stirred solution of aldehyde **1** (0.20 mmol) in toluene (2 mL), and the resulting mixture was stirred at 40–80 °C until the aldehyde was completely consumed (TLC). The reaction was then quenched by addition of sat. aq $NaHCO_3$ (3 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The organic layers were

combined, washed with brine, dried (Mg_2SO_4), and filtered. The solvent was removed in vacuo, and the residue was purified by column chromatography [silica gel, PE–EtOAc (10:1)].

4-Methyl-*N*-(2-methyl-1*H*-inden-1-yl)benzenesulfonamide (3a)

White solid; yield: 55 mg (91%); mp 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.2 Hz, 2 H), 7.37–7.33 (m, 2 H), 7.18–7.16 (m, 2 H), 7.07 (m, 1 H), 6.97 (m, 1 H), 6.32 (s, 1 H), 4.70 (d, *J* = 9.5 Hz, 1 H), 4.54 (d, *J* = 9.5 Hz, 1 H), 2.47 (s, 3 H), 1.89 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 143.5, 143.3, 143.1, 138.4, 129.7, 128.3, 127.7, 127.1, 124.8, 123.2, 120.2, 62.3, 21.5, 13.7. HRMS (ESI): *m/z* [M + NH_4]$^+$ calcd for $C_{17}H_{21}N_2O_2S$: 317.1318; found: 317.1315.

***N*-(2,3-Dimethyl-1*H*-inden-1-yl)-4-methylbenzenesulfonamide (3l)**

White solid; yield: 50 mg (80%); mp 175–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.2 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.26–7.20 (m, 1 H), 7.08 (d, *J* = 7.4 Hz, 1 H), 7.00 (t, *J* = 7.4 Hz, 1 H), 6.77 (d, *J* = 7.3 Hz, 1 H), 4.69 (d, *J* = 9.2 Hz, 1 H), 4.44 (d, *J* = 9.2 Hz, 1 H), 2.48 (s, 3 H), 1.94 (s, 3 H), 1.81 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.2, 143.5, 142.8, 138.7, 137.9, 134.0, 129.8, 128.3, 127.3, 125.0, 123.0, 118.3, 62.4, 21.6, 11.1, 10.3. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{19}NNaO_2S$: 336.1029; found: 336.1035.

(13) CCDC 965333 contains the supplementary crystallographic data for **3h**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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(16) **2-Methylindan-1-one (5a); Typical Procedure**

To a solution of SmI_2 (0.13 M in THF; 16 mL, 2.1 mmol) was added **3a** (0.52 mmol, 155.6 mg) followed by H_2O (15.6 mmol, 0.28 mL) and pyrrolidine (10.4 mmol, 0.86 mL) under an argon atmosphere. The mixture immediately turned white upon addition of pyrrolidine. The mixture was then stirred for 0.5 h at r.t., then diluted with EtOAc (6 mL) and treated with 0.5 M aq HCl (4 mL). The aqueous phase was extracted with EtOAc (2 ×), and the organic phases were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography [silica gel, PE–EtOAc (20:1)] to give a yellow oil; yield: 69 mg (91%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.7 Hz, 1 H), 7.61–7.56 (m, 1 H), 7.45 (d, *J* = 7.7 Hz, 1 H), 7.37 (t, *J* = 7.4 Hz, 1 H), 3.44–3.36 (m, 1 H), 2.79–2.66 (m, 2 H), 1.32 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 209.4, 153.4, 136.4, 134.6, 127.3, 126.5, 124.0, 42.0, 35.0, 16.3. HRMS (EI): *m/z* [M$^+$] calcd for $C_{10}H_{10}O$: 146.0726; found: 146.0725.

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