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Synthesis of multi-substituted indene derivatives from aryl, vinyl, and alkyl/aryl carbinols

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Abstract

A divergent approach to highly substituted functionalized indenes has been developed. The two-step reaction involving nucleophilic addition reaction of aryl vinyl ketone, an ideal intermediate with aryl or alkyl nucleophilic reagent, followed by electrocyclization (Nazarov cyclization) in the presence of Lewis acid catalyst afforded indene derivatives in good to excellent yield.

Keywords: Aryl vinyl ketones; Electrocyclization; Indene derivatives; Nazarov cyclization; Nazarov cyclization precursors

Introduction

Nowadays, much attention has been focused on the development of more straightforward methods to access bioactive compounds in the field of synthetic organic chemistry. Among them, the highly substituted indene derivatives gained much attention because of their diverse biological activities[1] such as antimicrobial, anti-inflammatory, aromatase inhibitory, cytotoxicity, estrogen receptor modulators, and some anti-proliferative activities. These were widely occurring in many natural products[2] and used as building blocks for the synthesis of functional materials[3] and metallocene complexes for olefin polymerization[4] (Figure 1). Thus, the importance of indenes has aroused significant interests in the community of organic and medicinal chemistry. Consequently, a lot of efforts made towards the construction of this motif by using catalysts based on transition metals[5], allylic alcohols[6a-6c], homoallylic alcohol[6d], propargylic alcohol[6e, 6f], divinyl alcohol[7], the ring expansion of suitably substituted cyclopropenes[8], Lewis or brønsted acid-catalyzed Friedel−Crafts cyclization[9], intramolecular Friedel–Crafts reaction of Baylis–Hillman adducts[10], tandem reaction catalyzed by cationic gold(I) complexes[11], transition metal-catalyzed C−H activation[12], ruthenium-catalyzed carbonylative cyclization[13], enyne metathesis[14], and cross-coupling reactions[15].

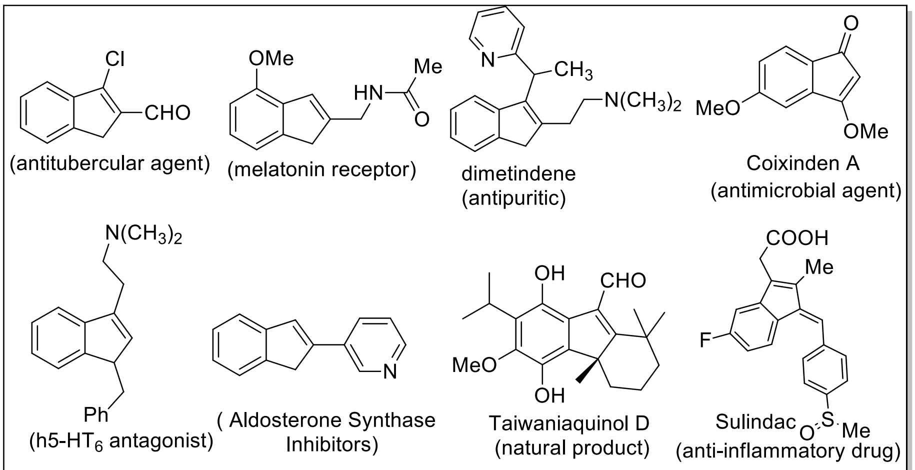


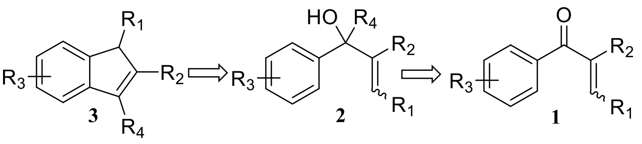
Figure 1: Selected examples of pharmaceuticals and natural product having indene skeletons

In spite of their quite effectiveness in synthesizing simple indenes, many of these strategies suffer from serious drawbacks such as the use of expensive and difficult-to-prepare catalysts/reagents, tedious reaction procedures or harsh reaction conditions with a low tolerance for functional groups. Most importantly, direct incorporation of multifunctional groups into the indene moiety is a difficult task. Therefore, still, there is a necessity to construct an effective and inexpensive divergent approach for the synthesis of highly substituted indene derivatives.

As a part of our ongoing efforts directed towards the construction of indenes based on Nazarov cyclizations, we have accessed a variety of precursors towards the development of pharmaceutically important scaffolds[16]. With the aim of a generation of alternate Nazarov cyclization precursors[17], our research group recently developed dienyl oxiranes[16a], aziridines [16b], and donor-acceptor cyclopropanes [16c] as novel Nazarov cyclizations precursors for constructing indene derivatives in the presence of Lewis acid catalyst. Herein, we report an efficient two-step methodology for synthesizing highly functionalized indene derivatives using new aryl vinyl ketone**1** as key intermediates.

Results and Discussion

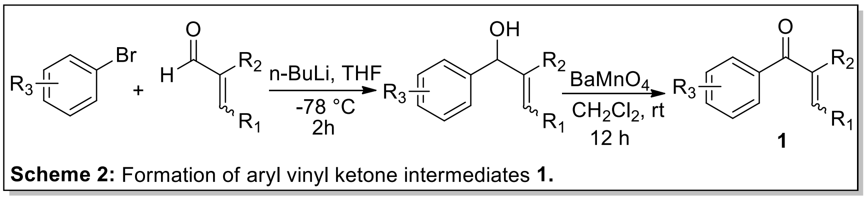
We now report the use of aryl vinyl ketone **1** as ideal intermediates in the development of novel and highly substituted indenes **3**. In our synthetic strategy, the construction of multiply substituted indene carbocycles is based on the nucleophilic addition of aryl or alkyl nucleophilic reagent into **1** to generate aryl vinyl tertiary carbinols **2** followed by electrocyclization reaction (Nazarov cyclization) in the presence of $BF_3.Et_2O$ as Lewis acidic catalyst to afford multi-substituted indenes **3**. The retrosynthetic scheme of this approach is represented in **Scheme1**.



Scheme 1: Retrosynthetic scheme for **3**

While the electrocyclization of secondary aryl vinyl carbinols is reported in the literature [6a-6c], [10], attempts of cyclization of differently substituted tertiary aryl vinyl carbinols **2** have not been explored. Such type of precursor can provide multi substituted indenes possessing a wide range of functionalities (R_4) in the five-membered ring of indenes.

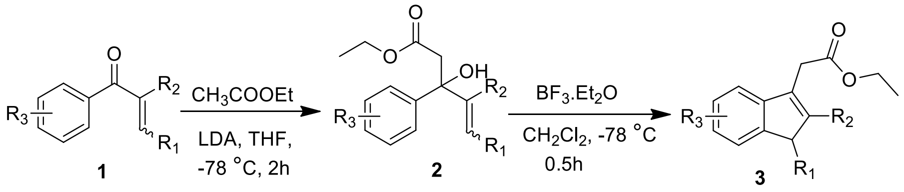
With this aim, initially, we have prepared some aryl vinyl ketones **1** which are already known in literature [16a, 16d] (except 1d and 1j as shown in Table 1 & 2) with a variety of substituent pattern on the aryl and vinyl system following literature procedure from commercially available differently substituted bromobenzene and α, ß-unsaturated aldehydes in the presence of n-BuLi followed by $BaMnO_4$ oxidation of the resulting secondary alcohol (**Scheme 2**).

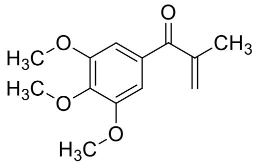
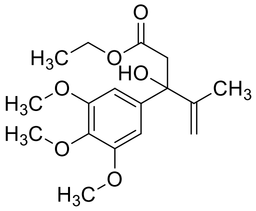
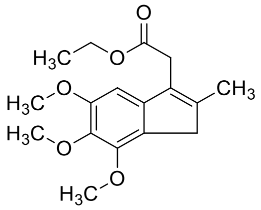
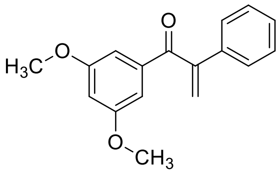
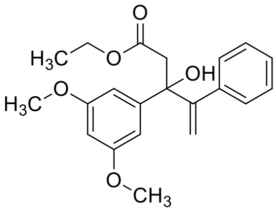
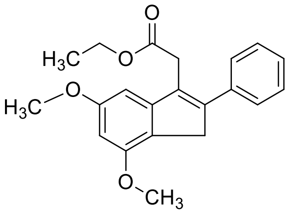
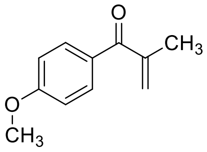
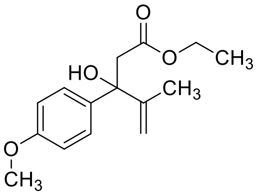
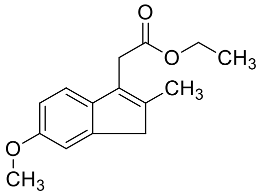
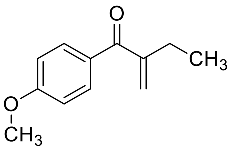
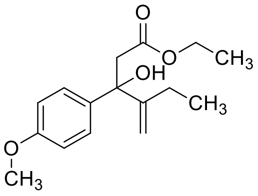
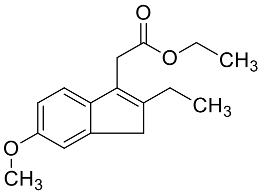
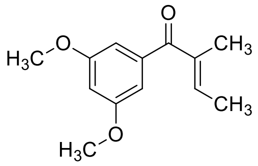
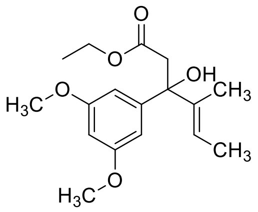
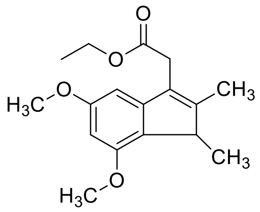


Scheme 2: Formation of aryl vinyl ketone intermediates **1.**

With the required intermediate keeping in hand, we tested for subsequent nucleophilic addition reaction with a nucleophilic reagent, ethyl acetate in the presence of LDA in THF at -78 °C. Successfully, we have achieved the expected aryl vinyl carbinols, tertiary alcohol in moderate to good yield (Table 1, entries 1-9). Then, we focused our attention to electrocyclization of these suitably substituted tertiary alcohols by treatment with the Lewis acid catalyst ($BF_3.Et_2O$) in CH_2Cl_2 at -78 °C. To our delight, this furnished a variety of indene substituted ethyl acetate as the only observed product (Table 1, entries 1-9) in good to excellent yield. Here we have screened a variety of aryl vinyl ketones having different substituents in the aryl ring as well as in the vinyl system, and the results are shown in Table 1. It showed that the presence of dimethoxy or trimethoxy group on the aryl vinyl ketone provided the corresponding indenes in good to excellent yields with almost similarity in respect of yield (Table 1, entries 1,2,5,6,7 &9). However, aryl vinyl ketones with monomethoxy group produced the corresponding indenes with significantly low yields (Table 1, entries 3 & 4). Gratifyingly, aryl vinyl ketone containing naphthalene moiety afforded the corresponding product in excellent yield (Table 1, entry 8), which further expanding the scope of this reaction strategy to explore into the other electron-rich polycyclic aryl vinyl ketones.

Table 1:Synthesis of ethyl 2-(substituted inden-3-yl)acetate **3** viatwo-step nucleophilic addition/Nazarov-type cyclization of aryl vinyl ketones **1**.



Entry	Aryl vinyl ketone	Tertiary alcohol(% yield)^a	Indenes(% yield)^b
1	 **1a**	 **2a**, 80%	 **3a**, 90%
2	 **1b**	 **2b**, 65%	 **3b**, 85%
3	 **1c**	 **2c**, 70%	 **3c**, 45%
4	 **1d**^{new}	 **2d**, 65%	 **3d**, 55%
5	 **1e**	 **2e**, 66%	 **3e**, 95%

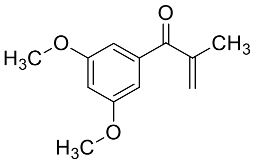
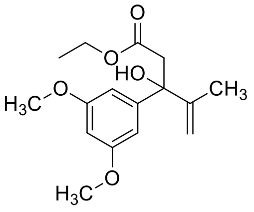
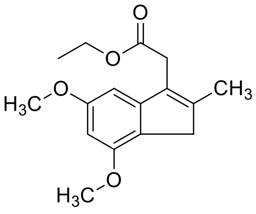
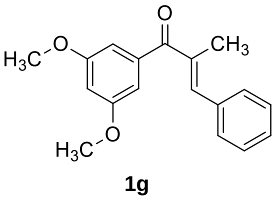
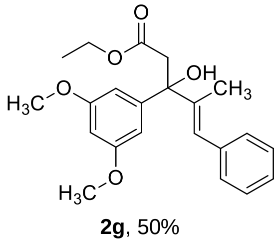
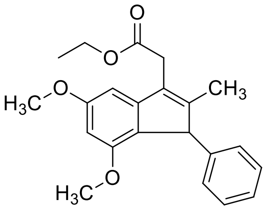
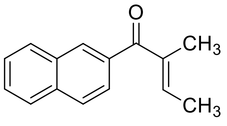
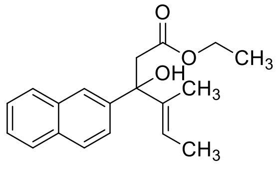
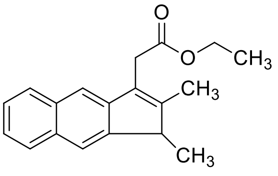
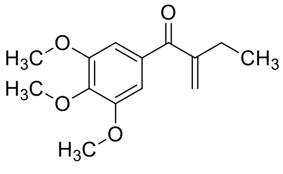
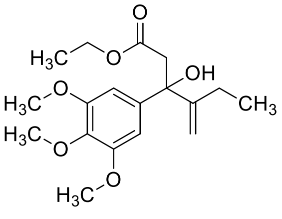
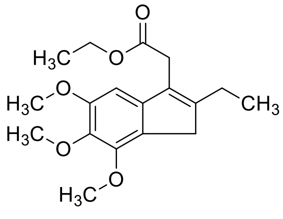
6	 **1f**	 **2f**, 95%	 **3f**, 88%

Table 1:Synthesis of ethyl 2-(substituted inden-3-yl)acetate**3**viatwo-step nucleophilic addition/Nazarov-type cyclization of aryl vinyl ketones**1**. (continued)

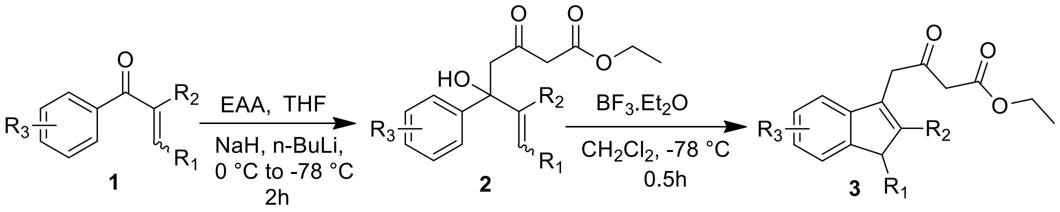
7	 **1g**	 **2g**, 50%	 **3g**, 97%
8	 **1h**	 **2h**, 85%	 **3h**, 95%
9	 **1i**	 **2i**, 75%	 **3i**, 88%

[a]Yield refers to pure products based on the recovery of starting material. [b]Yield refers to the pure isolated products characterized by NMR, IR and mass spectrometry.

After the successful formation of desired indene derivatives, we were speculated to examine the generality, extending the further scope of this reaction. Thus, we envisioned this reaction strategy under the same reaction condition using ethyl acetoacetate as a versatile nucleophilic reagent which is synthetically equivalent to the direct alkylation of a ketone or an ester. Initially, we generated a secondary carbanion of the active methylene group of ethyl acetoacetate in the presence of sodium hydride, subsequently added aryl vinyl ketone. However, we did not observe the formation of any product, recovered the starting materials completely. This failure is apparent due to the less nucleophilicity as well as sterically hindered secondary carbanion, deterring the nucleophilic attack to the carbonyl.

Then, we decided to examine the nucleophilicity of primary carbanion generated from ethylacetoacetate by treatment with NaH followed by the addition of n-BuLi in THF at 0 °C. Delightfully, the addition of aryl vinyl ketone to the reaction mixture furnished the corresponding tertiary alcohol by the nucleophilic addition of primary carbanion formed from the methyl group of ethyl acetoacetate (Table 2, entries 1-7). These tertiary alcohols upon treatment with $BF_{3}.Et_{2}O$ under the same reaction condition afforded the desired indene derivatives containing ß-keto ester moiety (Table 2, entries 1-7). The simple aryl vinyl ketone having no methoxy group in the aromatic ring and naphthalene moiety containing aryl vinyl ketone (Table 2, entries 2 &7) also afforded the desired indenes with good yield implying the versatility of our strategy.

Table 2:Synthesis of ethyl 3-oxo-4-(substituted inden-3-yl)butanoate**3**viatwo-step nucleophilic addition/Nazarov-type cyclization of aryl vinyl ketones**1**.



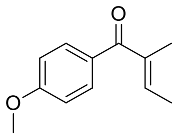
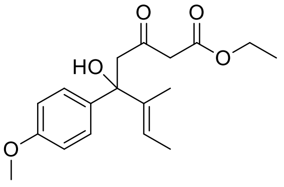
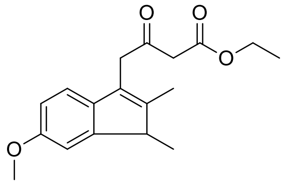
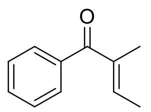
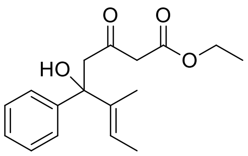
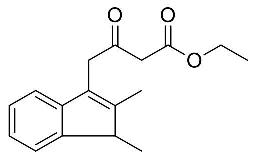
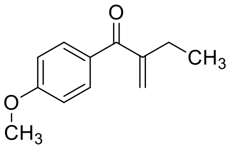
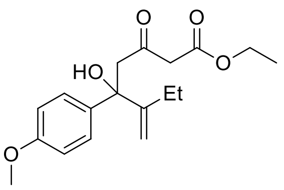
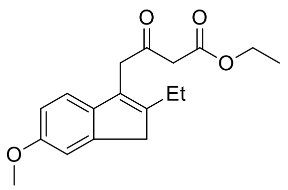
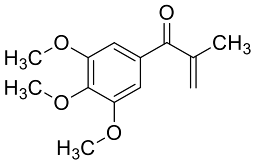
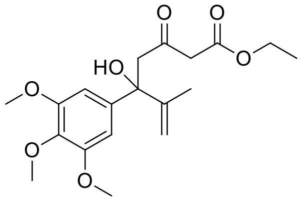
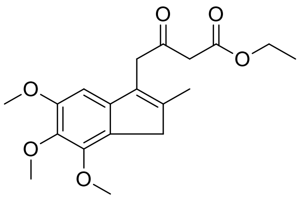
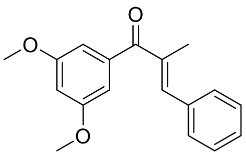
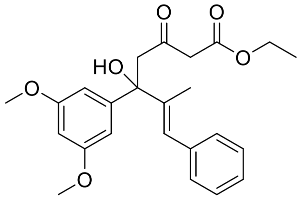
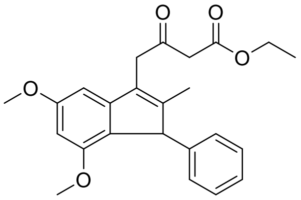
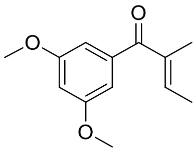
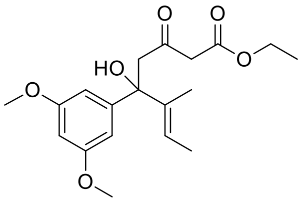
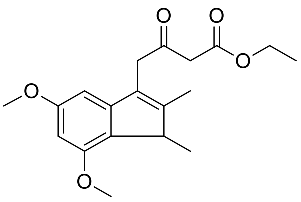
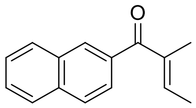
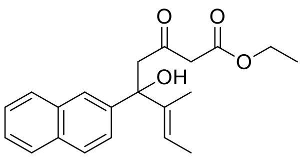
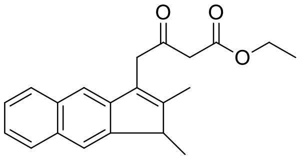
Entry	Aryl vinyl ketone	Tertiary alcohol (% yield)^{a}	Indenes (% yield)^{a,b}
1	 **1j**^{new}	 **2j**, 81%	 **3j**, 90%
2	 **1k**	 **2k**, 56%	 **3k**, 86%
3	 **1d**^{new}	 **2l**, 80%	 **3l**, 76%

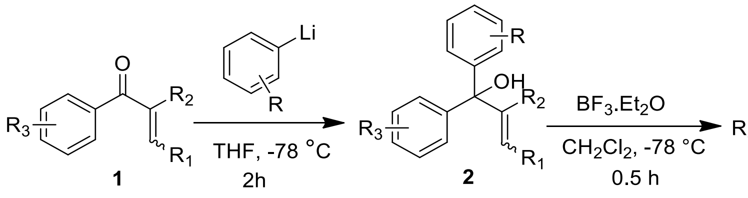
Table 2:Synthesis of ethyl 3-oxo-4-(substituted inden-3-yl)butanoate**3**viatwo-step nucleophilic addition/Nazarov-type cyclization of aryl vinyl ketones**1**. (continued)

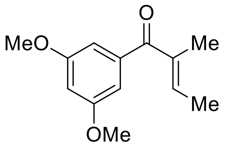
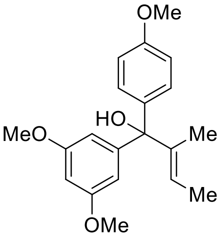
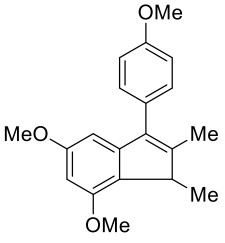
4	 **1a**	 **2m**, 78%	 **3m**, 82%
5	 **1g**	 **2n**, 85%	 **3n**, 86%
6	 **1e**	 **2o**, 75%	 **3o**, 89%
7	 **1h**	 **2p**, 75%	 **3p**, 82%

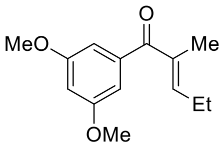
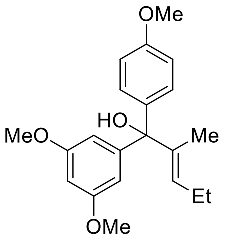
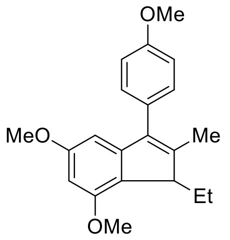
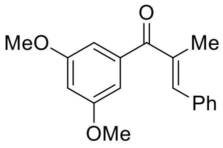
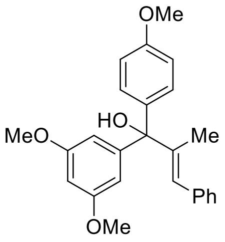
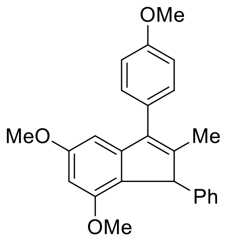
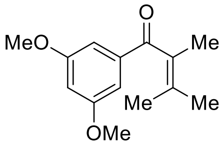
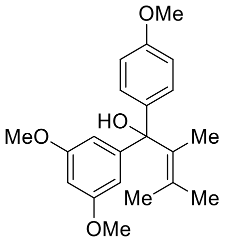
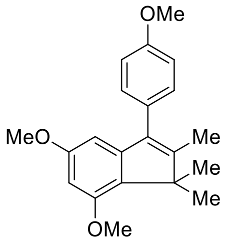
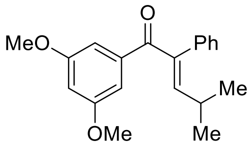
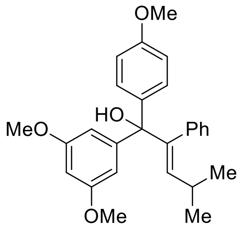
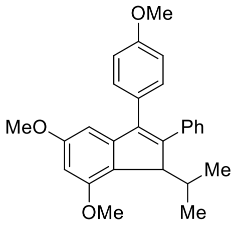
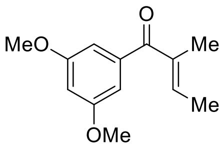
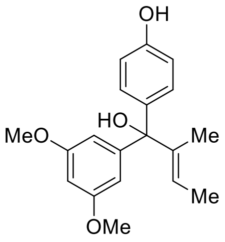
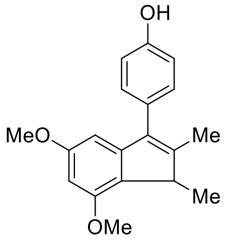
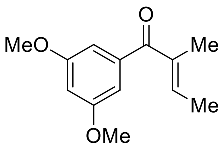
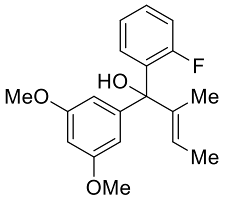
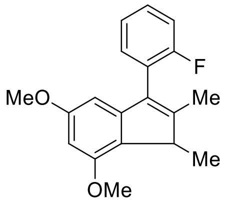
[a]Yield refers to pure products after column chromatography. [b]All products were characterized by NMR, IR and mass spectrometry.

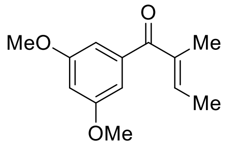
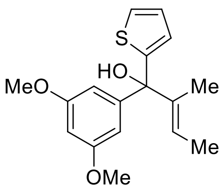
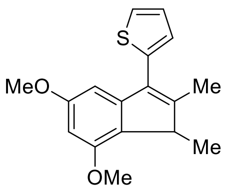
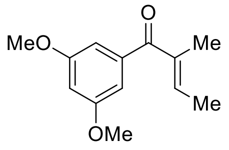
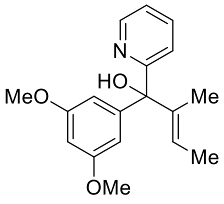
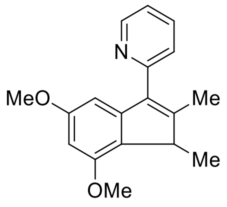
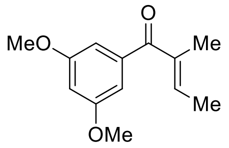
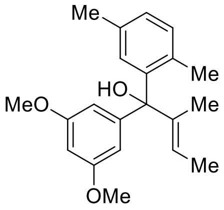
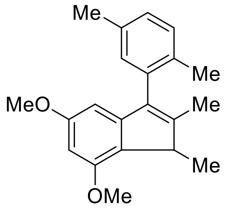
Finally, in order to access most versatile aryl substituted indene derivatives, we have examined the addition of a variety of aryl lithium reagents, generated in situ from commercially available aryl bromides in the presence of n-BuLi solution in THF into the aryl vinyl ketone intermediates. Successfully, we have achieved the expected aryl vinyl carbinols, tertiary alcohol (Table 3, entries 1-9) in good to excellent yield which upon electrocyclization under the same reaction condition furnished a variety of highly substituted aryl indenes as the only observed product (Table 3, entries 1-9) in good to excellent yield. In order to examine the effect of electronic nature and the position of different substituents on this reaction course, we employed a thorough investigation. Initially, we have carried out the nucleophilic addition of *p*-methoxy phenyl lithium generated in situ with different aryl vinyl ketones only varying in ß-position in respect of substituent such as methyl, ethyl, phenyl, isopropyl or dimethyl followed by subsequent electrocyclization reaction. However, we did not observe any significant effect of these on the formation of either tertiary carbinols or final cyclized indenes in terms of the yield (Table 3, entries 1-5). Then we switched to further extend with differently substituted phenyl lithium (Table 3, entries 6, 7&10) and heteroaromatic lithium compounds (Table 3, entries 8 & 9). We observed that presence of -OH, -F or less electron rich dimethyl phenyl resulted in indenes with relatively less yield (Table 3, entries 6, 7 & 10) and electron deficient pyridine ring afforded less yield compared to electron rich thiophene moiety (Table 3, entries 8 and 9). Various functional groups such as methoxy, fluoro, and electron-rich thiophene aromatic system or electron deficient pyridine ring were tolerated under this reaction condition.

Table 3:Synthesis of ethyl 3-aryl-substituted indene **3**viatwo-step nucleophilic addition/Nazarov-type cyclization of aryl vinyl ketones**1**.



Entry	Aryl vinyl ketone	Tertiary alcohol (% yield)[a]	Indenes (% yield)[a,b]
1	 **1e**	 **2q**, 81%	 **3q**, 91%

2	 **1l**	 **2r**, 83%	 **3r**, 91%
3	 **1g**	 **2s**, 84%	 **3s**, 88%
4	 **1m**	 **2t**, 87%[c]	 **3t**, 88%
5	 **1n**	 **2u**, 88%	 **3u**, 95%
6	 **1e**	 **2v**, 71%	 **3v**, 79%
7	 **1e**	 **2w**, 78%	 **3w**, 80%

8	 **1e**	 **2x**, 83%	 **3x**, 85%
9	 **1e**	 **2y**, 78%	 **3y**, 62%
10	 **1e**	 **2z**, 78%[c]	 **3z**, 79%

[a]Yield refers to pure products after column chromatography. [b]All products were characterized by NMR, IR and mass spectrometry. [c]Crude yield as both unreacted starting material and product appeared in the same R_f,

Conclusion

In summary, we have explored an efficient synthetic strategy to access various functionalized indenes derivatives in good to excellent yield having the advantage of operational simplicity and easily accessible starting materials. In addition, based on this strategy we may access a large variety of indene-based scaffolds useful for the development of bioactive compounds, some functional materials and ligand precursors for metallocene catalyst systems. Our current research efforts are directed towards the synthesis of a wide variety of functionalized indenes and their derivatization with the aim of evaluation of their biological activity which will be reported in due course.

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