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In Situ Formed Acetal-Facilitated Synthesis of Substituted Indene Derivatives from *o*-Alkenylbenzaldehydes

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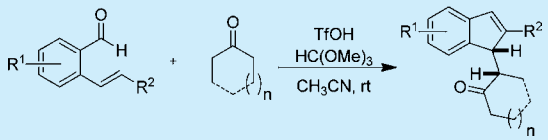
Supporting Information

ABSTRACT: A new protocol has been developed for the synthesis of indene derivatives in a diastereoselective manner from *o*-alkenylbenzaldehydes and enolizable ketones in the presence of trimethyl orthoformate and catalytic triflic acid. This method involves tandem *in situ* formed acetal-assisted Claisen–Schmidt condensation followed by 5-*exo*-*trig* cyclization/Michael addition in one-pot. It has also been shown that the chalcones derived from *o*-alkenylbenzaldehydes and ketones can effectively be transformed into indene derivatives in the presence of TfOH catalyst alone.



The indene skeleton is often encountered in many natural products[1] and functional materials.[2] Indene derivatives exhibit a wide range of biological properties.[3] In addition, they act as ligands to form different metallocene complexes, which have been extensively utilized as catalysts in the olefin polymerization process.[4] Because of the importance of the indene moiety, different methods have been established to construct the indene core. The existing methods mainly involve metal-catalyzed annulation reactions,[5] ring-expansion of substituted cyclopropenes,[6] Lewis acid or Brønsted acid-catalyzed Friedel–Crafts cyclization,[7] and transition metal-catalyzed C–H activation.[8] Lee and co-workers reported a triflic acid-catalyzed cyclization of diaryl- and alkyl aryl-1,3-dienes to synthesize substituted indene derivatives.[9] Yamamoto and co-workers disclosed an unprecedented rearrangement of arylalkynes bearing *ortho*-acetals to furnish indenol ethers in moderate to high yields under Pd-catalysis.[10] Recently, Qin et al. reported an intramolecular conjugate addition of alkene to α,β-unsaturated carbonyls to form naphthalene and indene derivatives.[11]

In our efforts to develop organic transformations using *in situ* formed acetal,[12] we have studied the reactions of *in situ* generated acetals of *o*-alkynylarylaldehydes using trimethyl orthoformate (TMOF) and triflic acid (TfOH) catalyst.[12c,f] We were curious to study the chemistry of *in situ* generated acetals of corresponding alkenyl derivatives i.e. *o*-alkenylbenzaldehyde **1** in the presence of TMOF and TfOH catalyst. We were delighted to notice that the reaction of *o*-alkenylbenzaldehydes **1** with ketones **2** in the presence of TMOF and catalyst TfOH gave substituted indene derivatives. It has to be mentioned that similar reaction with *o*-alkynylarylaldehydes resulted in naphthalene derivatives.[12f] The following sections present the details of our investigation on this reaction.

To optimize the reaction conditions, **1a** was treated with 1.2 equiv of cyclohexanone **2a** in the presence of 2.0 equiv of TMOF and 20 mol % TfOH in dichloromethane solvent at room temperature. The reaction completed in 30 min and resulted in the indene derivative **3a** in 75% isolated yield (Table 1, entry 1). Slightly improved yield of the product was noticed when the reaction was conducted in acetonitrile solvent (Table 1, entry 2). However, in nitromethane and dioxane it resulted in decomposed product mixture and 21% of **3a**, respectively (Table 1, entries 3 and 4). For further optimization study, acetonitrile was chosen as the solvent. Unfortunately, there was no reaction in the presence of catalysts such as trifluoroacetic acid and $HSbF_6{\cdot}6H_2O$ (Table 1, entries 5 and 6). The Claisen–Schmidt condensation product **4** was obtained in 18% yield with *p*-toluenesulfonic acid (Table 1, entry 7). Indene formation did not occur when Lewis acids were used (Table 1, entries 8–15).

We concentrated on using TfOH for further optimization experiments. The yield of the product was found to be decreased when the amount of catalyst loading was reduced to 10 mol % (Table 1, entry 16). Interestingly, this reaction worked without TMOF as well and gave moderate yield (51%) of the product **3a** after 24 h (Table 1, entry 17). Hence, the presence of TMOF increases both the rate and efficiency of the present transformation by forming more reactive acetal. Finally, a maximum yield of indene derivative **3a** (87%) was achieved when the reaction was performed in the presence of 2.5 equiv of TMOF and 25 mol % TfOH catalyst in acetonitrile solvent at rt (Table 1, entry 19).

We then examined the substrate scope of the present transformation using 2.5 equiv of TMOF and 25 mol % TfOH catalyst in acetonitrile solvent at rt, and the results are shown Table 2. Moderate to good yields of indene derivatives **3** with electron donating (such as OMe, Me) and electron accepting groups (such as F, Cl) could be obtained. Gratifyingly, the present transformation is suitable for the reaction of alkyl substituted *o*-alkenylbenzaldehyde **1f** ($R^2 = {}^t$Bu) (Table 2, entry 6). The reaction of **1a** with cyclopentanone **2c** resulted in a complex product mixture (Table 2, entry 8), perhaps due to the I-strain associated with cyclopentanone **2c** on going from sp^2 to sp^3 hybridization.[13] However, the reaction occurred smoothly

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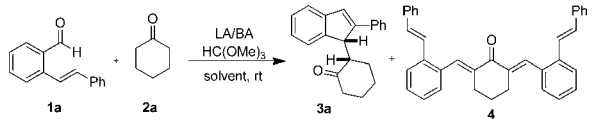
Table 1. Optimization Study



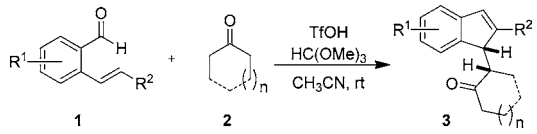
entry[a]	catalyst (mol %)	solvent	time (h)	yield (%)[b] 3a	4
1	TfOH (20)	CH_2Cl_2	0.5	75	
2	TfOH (20)	CH_3CN	0.5	77	
3	TfOH (20)	CH_3NO_2	1.0		
4	TfOH (20)	Dioxane	0.5	21	
5	TFA (20)	CH_3CN	24.0	NR	NR
6	$HSbF_6{\cdot}6H_2O$ (20)	CH_3CN	24.0	NR	NR
7	PTSA (20)	CH_3CN	24.0		18
8	$Cu(OTf)_2$ (5)	CH_3CN	24.0		35
9	$AuCl_3$ (5)	CH_3CN	24.0		
10	$Fe(OTf)_2$ (5)	CH_3CN	24.0	NR	NR
11	$La(OTf)_3$ (5)	CH_3CN	24.0	NR	NR
12	AgOTf (5)	CH_3CN	24.0	NR	NR
13	$AgSbF_6$ (5)	CH_3CN	24.0	NR	NR
14	$InCl_3$ (5)	CH3CN	24.0	NR	NR
15	$BF_3{\cdot}OEt_2$ (10)	CH_3CN	24.0	NR	NR
16	TfOH (10)	CH_3CN	0.5	61	
17	TfOH (20)	CH_3CN	24.0	51[c]	
18	TfOH (20)	CH_3CN	0.5	83[d]	
19	**TfOH (25)**	**CH_3CN**	**0.5**	**87[d]**	
20	TfOH (10)	CH_3CN	1.0	57[e]	

[a]All the reactions were carried out using 2.0 equiv of $HC(OMe)_3$ at rt. [b]Isolated yield. [c]Without $HC(OMe)_3$. [d]2.5 equiv of $HC(OMe)_3$ was used. [e]The reaction was conducted at reflux temperature. NR: no reaction.

with cyclooctanone **2d** to give the indene derivative **3h** in 70% yield (Table 2, entry 9). It is noteworthy to mention that all of the indene derivatives were obtained as single diastereomers except **3h**, which was obtained as an inseparable mixture of two diastereomers in 1:0.9 ratio. A plausible reason for the observed diastereoselection is provided in the mechanistic discussion. For the reactions involving acyclic ketones, a stoichiometric amount of TfOH was required to promote the reaction. The reactions of **1a** and **1c** occurred nicely with 3-pentanone in the presence of 1 equiv of TfOH and 2.5 equiv of TMOF to give the corresponding indene derivatives **3i** and **3j** in 72% and 63% yields, respectively (Table 2, entries 10 and 11).

It was observed that the construction of indene skeleton is dependent highly on the nature of the R^2 group of *o*-alkenylbenzaldehyde **1**. If R^2 is *p*-tolyl, corresponding *p*-tolyl substituted indene **3k** was furnished in 32% yield only along with 63% of naphthalene derivative **5** (Table 2, entry 12). Under reflux conditions, **3k** and **5** were obtained, respectively, in 31% and 52%. The structure of the compound **3k** was further confirmed by single crystal X-ray analysis.[14] Naphthalene derivative **5** was the exclusive product when R^2 is a better electron donating group such as *p*-anisyl and thiophene (Table 2, entries 13 and 14). The formation of naphthalene might have taken place via a [4 + 2] cycloaddition of pyran intermediate with the enol ether of cyclohexanone followed by elimination of aldehyde.[15] The electron donating R^2 group might facilitate the formation of pyran intermediate.[16] Similar pyran intermediates have been proposed in the Lewis acid/Brønsted acid catalyzed reaction of *o*-alkynylbenzaldehydes.[17] It should be noted that the substrates **1h** and **1i** decomposed and did not yield the

Table 2. Substrate Scope[a]



entry	1	2	3
1	**1a**, R^1 = H; R^2 = Ph	**2a**	**3a**, R^1 = H; R^2 = Ph (87%, 30 min)
2	**1b**, R^1 = 4,5-(OCH_2O); R^2 = Ph	**2a**	**3b**, R^1 = 4,5-(OCH_2O); R^2 = Ph (79%, 15 min)
3	**1c**, R^1 = H; R^2 = 4-Cl-C_6H_4	**2a**	**3c**, R^1 = H; R^2 = 4-Cl-C_6H_4 (74%, 2 h)
4	**1d**, R^1 = 4,5-$(OMe)_2$; R^2 = Ph	**2a**	**3d**, R^1 = 4,5-$(OMe)_2$; R^2 = Ph (69%, 15 min)
5	**1e**, R^1 = 5-F; R^2 = Ph	**2a**	**3e**, R^1 = 5-F; R^2 = Ph (77%, 45 min)
6	**1f**, R^1 = H; R^2 = ^{t}Bu	**2a**	**3f**, R^1 = H; R^2 = ^{t}Bu (61%, 30 min)
7	**1c**, R^1 = H; R^2 = 4-Cl-C_6H_4	**2b**	**3g**, R^1 = H; R^2 = 4-Cl-C_6H_4 (69%, 2 h)
8	**1a**, R^1 = H; R^2 = Ph	**2c** (n= 0)	Not clean (n = 0)
9	**1a**, R^1 = H; R^2 = Ph	**2d** (n = 3)	**3h**, R^1 = H; R^2 = Ph (70%, 1 h), n = 3; *dr* = 1:0.9
10[b]	**1a**, R^1 = H; R^2 = Ph	**2e**	**3i**, R^1 = H; R^2 = Ph (72%, 30 min)
11[b]	**1c**, R^1 = H; R^2 = 4-Cl-C_6H_4	**2e**	**3j**, R^1 = H; R^2 = 4-Cl-C_6H_4 (63%, 1 h)
12	**1g**, R^1 = H; R^2 = 4-Me-C_6H_4	**2a**	**3k** (32%, 30 min) **5** (63%, 30 min)
13	**1h**, R^1 = H; R^2 = 4-OMe-C_6H_4	**2a**	**5** (76%, 30 min)
14	**1i**, R^1 = H; R^2 = 2-thiophene	**2a**	**5** (74%, 30 min)
15	**1j**	**2a**	**5** (50%, 30 min) **6** (26%, 30 min)
16	**1k**	**2a**	Not clean
17	**1a**, R^1 = H; R^2 = Ph	**2f**	Not clean

[a]All the reactions were carried out using 1.0 equiv of *o*-alkenylbenzaldehyde **1**, 1.2 equiv of enolizable ketone **2**, 2.5 equiv of $HC(OMe)_3$, and 25 mol % of TfOH at rt. [b]1.0 equiv of TfOH was used.

naphthalene derivative in the absence of trimethyl orthoformate. Hence, the *in situ* formed acetal might have played a crucial role in the formation of naphthalene derivatives. Then the reaction was tried with the substrate **1j** having an additional methyl group on the alkene with cyclohexanone under the optimized reaction conditions. The reaction resulted in two naphthalene derivatives **5** and **6** in 50% and 26% yields, respectively (Table 2, entry 15). The formation naphthalene derivative **6** from **1j** by intramolecular cyclization is already known in the literature under

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gold catalysis,[18] whereas the naphthalene product **5** would have resulted from **1j** via [4 + 2] cycloaddition reaction. The present reaction conditions were not suitable for the reactions involving alkenylaldehyde **1k** and acetophenone since the reactions resulted in complex product mixtures (Table 2, entries 16 and 17).

We believe that the reaction proceeds via the initial formation of chalcone type intermediate from aldehyde and enolizable ketone by Claisen−Schmidt condensation[12c,f] followed by 5-*exo-trig* cyclization to afford indene derivatives.[11] In order to check the intermediacy of chalcones in the indene formation, chalcones **7** were prepared and subjected to the standard reaction conditions. The reaction of **7a** completed in 3.0 h and resulted in the indene derivative **3l** in 91% yield. This reaction proceeded even in the absence of trimethyl orthoformate with 5 mol % TfOH alone to result in the indene product **3l** in excellent yield after 3.5 h. Using this protocol we prepared Cl, Br, OMe, and thiophene substituted indene derivatives as shown in Figure 1.

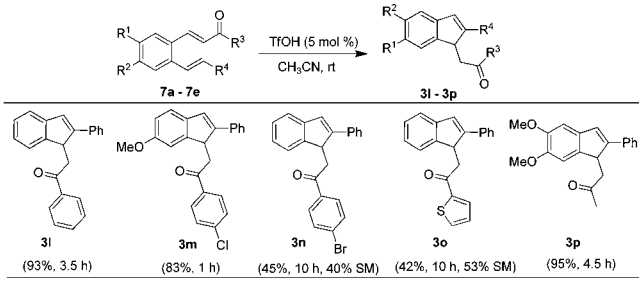
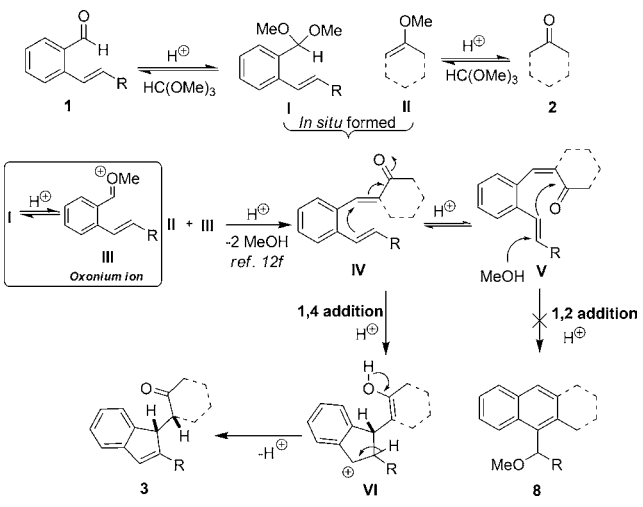


Figure 1. Cyclization of chalcone derivatives to substituted indenes.

The reactions were sluggish when R^3 of the chalcone is electron donating in nature such as *p*-Br-phenyl and thiophene and the corresponding indene derivatives (**3n** and **3o**) were isolated in 45% and 42% yields, respectively, along with their respective unreacted starting materials. This may be due to the fact that electrophilicity of carbonyl carbon of these substrates is reduced by electron donating nature of *p*-Br-phenyl and thiophene.

A plausible mechanistic pathway for the construction of indene framework from *o*-alkenylbenzaldehyde is depicted in Scheme 1. Having established the intermediacy of chalcones (Figure 1),[12c,f] Claisen−Schmidt condensation is expected to take place between the more reactive oxonium ion **III** generated from *in situ* formed acetal **I** from *o*-alkenylbenzaldehyde **1** and the enol ether **II** derived from ketone **2** to afford chalcone type intermediate **IV**. Since the chalcone derivative gives the indene derivative just in the presence of catalyst TfOH alone, the role of trimethyl orthoformate is to facilitate the formation of chalcone from **1** and **2**. There are two possible modes of reaction with the intermediate **IV**. It can undergo either 1,4-addition (conjugate alkenylation)[19] to result in indene derivative **3** or 1,2 addition to result in naphthalene derivative **8**. However, the formation of indene is preferred due to the proximity of the double bond carbon with *β*-carbon of the enone. Moreover, for the pathway involving 1,2-addition to happen, trans to cis isomerization has to happen first to form intermediate **V**. Protonation of the enol ether intermediate **VI** will occur from the convex face (*syn* to indene H) to give single diastereomer exclusively. It is speculated that the formation of **3h** as a diastereomeric mixture might be due to the conformational flexibility of the cyclooctene ring, which will allow the protonation to occur from either side in the intermediate **VI**.

Scheme 1. Plausible Mechanism for Indene Formation



In summary, we have developed a new protocol for the diastereoselective synthesis of indene derivatives from *o*-alkenylbenzaldehydes and enolizable ketones in the presence of trimethyl orthoformate and catalytic triflic acid via cascade Claisen−Schmidt and Michael reactions. We have also shown that the chalcones derived from *o*-alkenylbenzaldehydes and ketones can effectively be transformed into indene derivatives in the presence of TfOH catalyst alone. With electron-donating R^2 group in the *o*-alkenylbenzaldehyde, naphthalene product is formed perhaps via a different mechanism with the cleavage of R^2CH group. However, this observation needs a detailed study to understand the mechanism of this reaction. A possible extension to develop an enantioselective version using chiral Brønsted acid catalysis is under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, $^1H/^{13}C$ spectroscopic data of all new compounds, and X-ray data for compound **3k** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01695.

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Notes

The authors declare no competing financial interest.

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