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A Cascade Approach to Naphthalene Derivatives from *o*-Alkynylbenzaldehydes and Enolizable Ketones via in-situ-Formed Acetals

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Keywords: Fused-ring systems / Cyclization / Aldol reactions / Acetals

Using the in-situ-formed acetal strategy, a facile approach has been developed to synthesize naphthalene derivatives from *o*-alkynylbenzaldehydes and enolizable ketones. In situ acetal formation assists the condensation between *o*-alkynylbenzaldehydes and enolizable ketones to give chalcone derivatives under Brønsted acidic conditions. In situ acetal formation facilitates the reaction by increasing the electrophilicity of the carbonyl carbon of the *o*-alkynylaldehyde through oxonium ion formation, and also by enhancing the nucleophilicity of the α carbon of the ketone through the formation of an enol ether. The formed chalcones undergo *trans* to *cis* isomerization to effect alkyne–carbonyl metathesis to give naphthalene derivatives.

Introduction

o-Alkynylbenzaldehydes are versatile building blocks for the synthesis of different polyaromatic and heterocyclic derivatives.[1,2] Substituted naphthalenes are one such class of derivatives. They are useful compounds with applications in the fields of medicine[3] and materials.[4] Different approaches have been reported for the synthesis of substituted naphthalenes.[5] Yamamoto and coworkers reported an $AuCl_3$-catalysed formal [4+2] benzannulation between *o*-alkynylbenzaldehydes and alkynes for the synthesis of naphthyl ketones.[2a] Later, the same group developed an unprecedented [4+2] benzannulation between enynal units **1** and carbonyl compounds **2** for the construction of naphthalene derivatives using gold and copper salts as catalysts.[2c] In that report, a pyrylium ion **A** was proposed as the key intermediate, which undergoes an inverse-electron-demand-type hetero-Diels–Alder reaction with the enol form **B** of the ketone to give naphthyl ketone **3** as the major product (Scheme 1, equation i). It was anticipated that trace amounts of water might play an important role in the establishment of the keto–enol tautomerization of the ketone. Recently, Srinivasan and coworkers reported a method for the synthesis of naphthyl ketones by using $In(OTf)_3$ as the catalyst for the same [4+2] benzannulation under heating conditions.[2l] Both the catalysts [$AuBr_3$ and $In(OTf)_3$] required heating conditions to effect the naphthalene formation.

In our efforts to develop organic transformations using in-situ-formed acetals,[6] we found that alkyl ketones generate enol ethers via in-situ-formed acetals under Lewis/Brønsted acidic conditions in the presence of trimethyl orthoformate. It was demonstrated that the formed enol ether could be alkylated directly with various alcohols using either triflic acid (TfOH)[6d] or $AgSbF_6$.[6e] Recently, we reported an acetal-assisted intermolecular alkyne–carbonyl metathesis and intramolecular annulation between *o*-alkynylbenzaldehydes and alkynes in the presence of trimethyl orthoformate and catalytic Brønsted acid for the synthesis of substituted benzo[*a*]fluorene derivatives.[6c] The formation of the acetal intermediate in situ is crucial for the success of this reaction. Along these lines, we anticipated that the formation of an enol ether from a ketone, and formation of an acetal from *o*-alkynylbenzaldehyde, would facilitate the reaction between them. We have now discovered a method for the smooth formation of naphthyl ketones from *o*-alkynylbenzaldehydes and ketones at room temperature via in-situ-formed acetals (Scheme 1, equation ii).

In striking contrast to Yamamoto's report,[2c] this transformation is expected to take place through condensation between in-situ-formed acetal **D** and enol ether **E** derived from cyclohexanone to give chalcone **F**, followed by alkyne–carbonyl metathesis/annulation to give naphthyl ketone derivative **3** in one pot. This transformation does not take place without trimethyl orthoformate. Thus, in situ acetal formation assists the formation of the chalcone by increasing the electrophilicity of the carbonyl carbon of the *o*-alkynylaldehyde through oxonium ion formation. Also, the nucleophilicity of the α carbon of the ketone is enhanced through formation of an enol ether.

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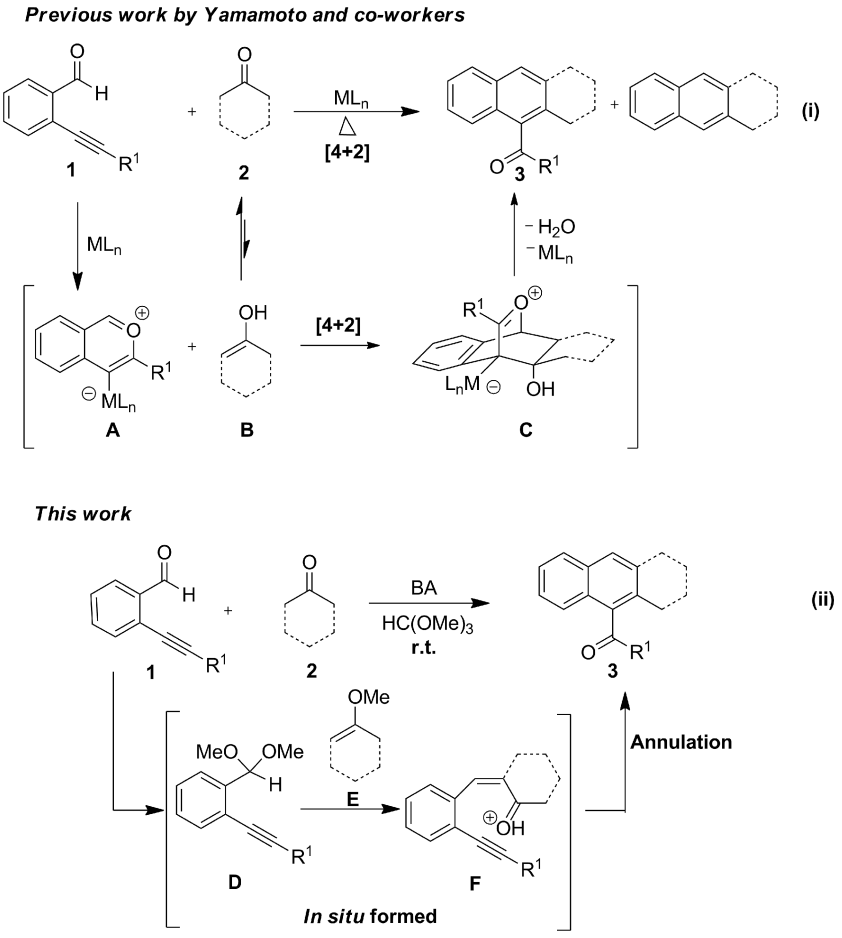


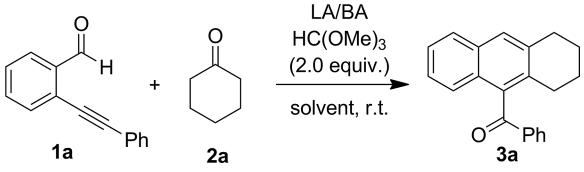
Scheme 1. Reaction of *o*-alkynylbenzaldehydes with enolizable ketones under Lewis/Brønsted acidic conditions (BA = Brønsted acid).

Results and Discussion

The reaction conditions for formation of naphthyl ketones were evaluated using *o*-alkynylbenzaldehyde **1a** and cyclohexanone (**2a**), and the results are summarized in Table 1.

Based on our previous experience with the synthesis of benzo[*a*]fluorene derivatives,[6c] we investigated the reaction between 2-(phenylethynyl)benzaldehyde (**1a**) and cyclohexanone (**2a**) in the presence of trimethyl orthoformate (2.0 equiv.) and TfOH (20 mol-%) in dichloromethane at room temperature. The reaction was complete after 30 min, and the naphthalene product, phenyl(1,2,3,4-tetrahydroanthracen-9-yl)methanone (**3a**), was isolated in 72% yield (Table 1, entry 1). The yield of **3a** increased to 90% when the reaction was run in acetonitrile (Table 1, entry 2). Then, the reaction was tried with other Brønsted acid and Lewis acid catalysts using acetonitrile as the solvent. However, there was no reaction with TFA (trifluoroacetic acid), *p*TSA (*p*-toluenesulfonic acid), or $HSbF_6{\cdot}6H_2O$, even after 24 h at room temperature (Table 1, entries 3–5). With the Lewis acid catalysts $Cu(OTf)_2$ and $AuBr_3$, the reactions were not clean, and they resulted in complex mixtures of products (Table 1, entries 6 and 7). In the absence of trimethyl orthoformate, the starting material (i.e., **1a**) slowly started to degrade, and not even a small amount of the product was isolated (Table 1, entry 8). Then, we decreased the catalyst loading to 10 mol-%, and we found that the yield of **3a** decreased to 64% (Table 1, entry 9). Hence, the appropriate

Table 1. Optimization study for cyclic ketone.

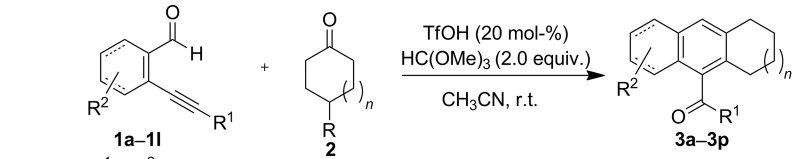


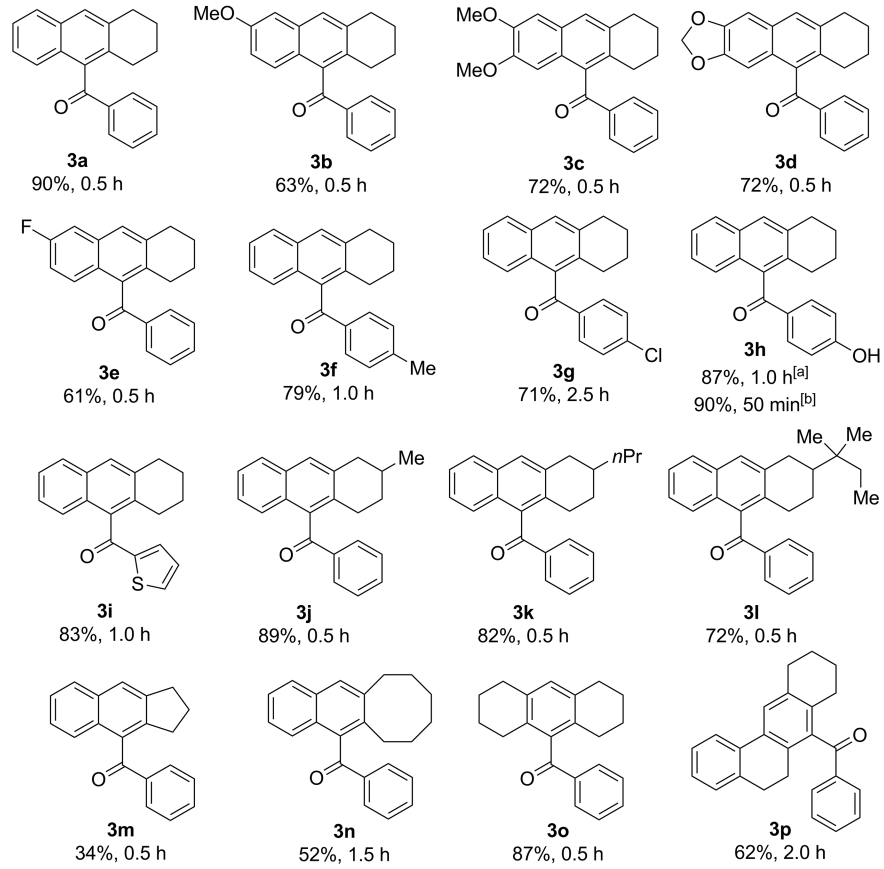
Entry	Solvent	Catalyst	Cat. [mol-%]	Time [h]	Yield [%][a]
1	CH_2Cl_2	TfOH	20	0.5	72
2	CH_3CN	TfOH	20	0.5	90
3	CH_3CN	$HSbF_6{\cdot}6H_2O$	20	24.0	n.r.
4	CH_3CN	*p*TSA	20	24.0	n.r.
5	CH_3CN	TFA	20	24.0	n.r.
6	CH_3CN	$Cu(OTf)_2$	5	6.0	–
7	CH_3CN	$AuBr_3$	5	5.5	–
8	CH_3CN[b]	TfOH	20	24.0	–
9	CH_3CN	TfOH	10	1.0	64
10	CH_3CN[c]	TfOH	20	24	51

[a] Isolated yield; n.r.: no reaction; LA = Lewis acid. [b] Without trimethyl orthoformate. [c] 1.0 equiv. of trimethyl orthoformate was used.

conditions for naphthalene formation are: TfOH (20 mol-%), trimethyl orthoformate (2.0 equiv.), and acetonitrile as solvent at room temp. (Table 1, entry 2).

Using the optimized reaction conditions, the substrate scope was examined with cyclic ketones, and the results are presented in Figure 1. Saturated ring-fused naphthyl ketone derivatives with different substituents, including methyl, methoxy, acetal, fluoro, chloro, and hydroxy groups, were prepared from cyclic ketones in moderate to good yields. The TBDMS (*tert*-butyldimethylsilyl) group did not tolerate the reaction conditions, and deprotected naphthalene derivative **3h** was obtained in good yield. The same product was obtained in better yield from the corresponding hydroxy-substituted *o*-alkynylbenzaldehyde (i.e., **1h**). To our delight, thiophene tolerated the reaction conditions, and the corresponding naphthyl ketone (i.e., **3i**) was obtained in 83% yield. Various alkyl-substituted cyclohexanones (**2b**–**2d**) were examined, and the corresponding naphthyl ketone derivatives (**3j**–**3l**) were obtained in good yields. With cyclopentanone (**2e**) and cyclooctanone (**2f**), the corresponding naphthyl ketones (i.e., **3m** and **3n**) were obtained in 34 and 52% yields, respectively. The change from sp^2 to sp^3 hybridization in the reaction of the enol ether of cyclopentanone (five-membered ring) may be expected to be unfavourable due to an increase in I-strain. Thus, the reaction of **1a** with cyclopentanone under the present reaction conditions is expected to give a low yield of naphthalene derivative **3m**.[7] Gratifyingly, this transformation could be used on cyclohexene alkynylaldehyde **1k** to synthesize product **3o** in 87% yield. In addition, alkynylaldehyde **1l**, prepared from α-tetralone, could be used to synthesize polycyclic product **3p** in 62% yield. The applicability of the method was checked by





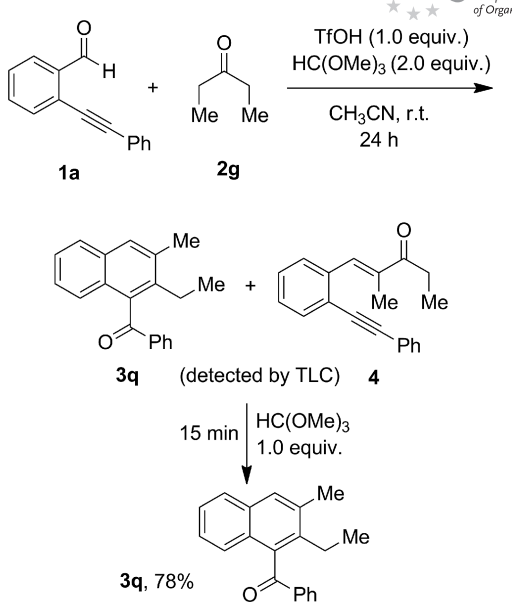
[a] Isolated yield from the corresponding TBDMS-protected *o*-alkynylbenzaldehyde derivative.
[b] Isolated yield from the corresponding hydroxy-substituted *o*-alkynylbenzaldehyde derivative.

Figure 1. Scope of the reaction with cyclic ketones.

carrying out the reaction of **1a** with cyclohexanone on a 3.0 mmol scale. The corresponding naphthalene derivative (i.e., **3a**) was obtained in 84% yield under the optimized reaction conditions. Unfortunately, the transformation is not suitable when R^1 is an alkyl substituent.

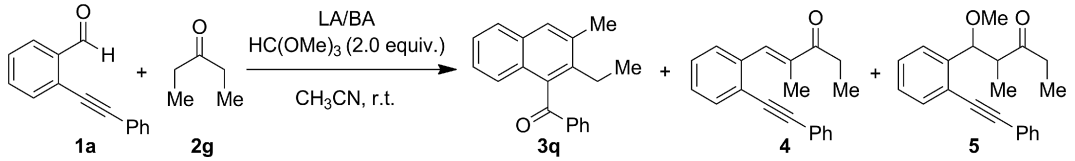
Next, the reaction was attempted using acyclic ketones. However, the optimized reaction conditions for cyclic ketones were not suitable for the acyclic ketone 3-pentanone (**2g**), and it gave a complex mixture of products (Table 2, entry 1). Therefore, our attention turned to finding suitable reaction conditions for naphthalene formation from acyclic ketones, and the results are shown in Table 2. The TfOH loading was increased to 1.0 equiv., which resulted in 52% of naphthalene product **3q**, along with condensation product **4** in 28% yield after 24 h (Table 2, entry 2). To our delight, the yield of **3q** dramatically increased to 82% when the reaction was carried out using 3.0 equiv. of trimethyl orthoformate and 1.0 equiv. of TfOH for 30 min (Table 2, entry 3). In a control reaction, the reaction of **1a** and **2g** was carried out with 1.0 equiv. of TfOH and 2.0 equiv. of trimethyl orthoformate in acetonitrile solvent at room temp. This reaction resulted in two spots in TLC; one corresponded to naphthalene product **3q**, and the other (more polar) spot corresponded to chalcone **4**. This reaction did not go to completion, even after 24 h. Upon addition of 1.0 equiv. of trimethyl orthoformate to the reaction mixture, we found that the polar spot corresponding to chalcone **4** completely disappeared within 15 min to give a single spot on TLC corresponding to naphthalene derivative **3q**. Compound **3q** was isolated in 78% yield by column chromatography (Scheme 2). Hence, in situ acetal formation not only helps the smooth Claisen–Schmidt condensation, but also here assists the *trans* to *cis* isomerization[8] of chalcone **4** to promote alkyne–carbonyl metathesis/annulation for the construction of naphthalene derivatives.

The use of Lewis acid catalysts such as $Cu(OTf)_2$ and $In(OTf)_3$ gave the product (i.e., **5**) in 98 and 80% yields, respectively (Table 2, entries 4 and 5). It has to be mentioned that such a direct aldol reaction of a ketone has not been reported before. Ketones in the form of silyl enol ethers have to be used in reactions with acetals.[9] The synthetic scope of our finding is under evaluation. Using gold-catalysed alkyne–carbonyl metathesis,[10] product **5** could be converted into naphthalene **3q** in excellent yield (Scheme 3). However, the same catalytic system was inefficient for the direct synthesis of naphthalene **3q** from **1a** and **2g**, as it resulted in a lower yield of **3q**. In this experiment, aldehyde **1a** and ketone **2g** underwent Claisen–Schmidt reaction first to give product **5**, which then gave naphthalene product **3q** by alkyne–carbonyl metathesis/annulation. We realized this from the TLC analysis while monitoring the progress of the reaction. These results suggest that the formation of the naphthalene skeleton might not take place by a [4+2] benzannulation pathway in the presence of trimethyl orthoformate. Thus, in-situ-formed acetals react by a different mechanism for the construction of naphthalenes from *o*-alkynylbenzaldehydes and enolizable ketones.



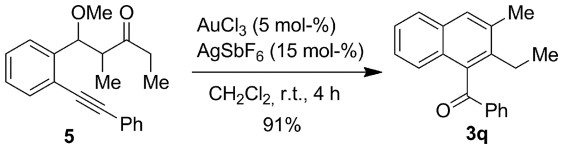
Scheme 2. Control experiment.

Table 2. Optimization study for acyclic ketone.



Entry	Solvent	Catalyst	Cat. [equiv.]	Time [h]	Yield [%][a] 3q	4	5
1	CH_3CN	TfOH	0.2	24.0	–	–	–
2	CH_3CN	TfOH	1.0	24.0	52	28	–
3	CH_3CN	TfOH[b]	1.0	0.5	82	–	–
4	CH_3CN	$Cu(OTf)_2$	0.05	3.0	–	–	98
5	CH_3CN	$In(OTf)_3$	0.05	5.0	–	–	80
6	CH_3CN	$AuCl_3/AgSbF_6$	0.05	24.0	61	–	–

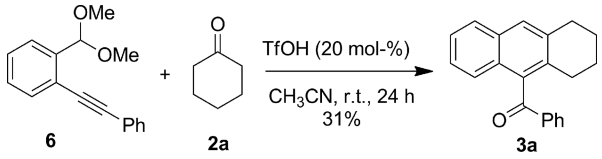
[a] Isolated yield. [b] 3.0 equiv. of trimethyl orthoformate was used.



Scheme 3. Gold-catalysed heteroalkyne metathesis.

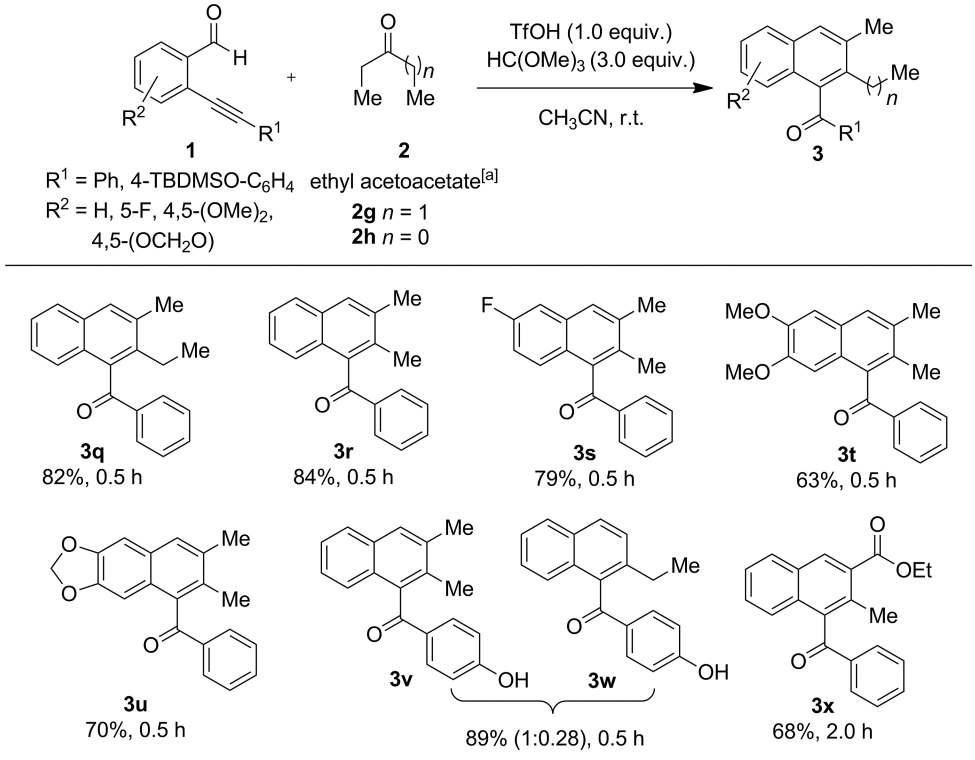
Using a stoichiometric amount of TfOH and 3 equiv. of trimethyl orthoformate, the substrate scope was studied with acyclic ketones (Figure 2). Using acyclic ketone 2-butanone (**2h**), only one of the possible naphthalene derivatives (**3r**–**3u**) was obtained with various *o*-alkynylbenzaldehydes. However, both of the possible naphthyl ketone derivatives (**3v** and **3w**) were obtained in a 1:0.28 ratio starting from a TBDMS-protected *o*-alkynylbenzaldehyde derivative. In this reaction, the TBDMS group was deprotected, and the corresponding hydroxy-substituted naphthyl ketones were obtained in 89% yield. Interestingly, naphthyl ketone derivative **3x** with an ester substituent could be prepared from ethyl acetoacetate and **1a** in 68% yield. It is noteworthy that 20 mol-% of TfOH was sufficient for the synthesis of naphthalene derivative **3x**.

To further confirm the involvement of the acetal in this reaction, a control reaction was carried out using acetal **6** prepared from **1a**. Upon reaction of **6** with cyclohexanone in the presence of TfOH (20 mol-%) in CH_3CN, 31% of naphthyl ketone derivative **3a** was isolated (Scheme 4). TLC analysis of the progress of the reaction revealed that aldehyde **1a** was formed along with the product. The aldehyde was formed through deprotection of the acetal in the presence of the acid catalyst, and it slowly decomposed over time. In addition, the reaction of substrate **1a** with 1-methoxycyclohex-1-ene (**II** in Scheme 5) in the presence of TfOH (20 mol-%) was checked. But this reaction resulted in a complex mixture of products as vinyl ether **II** was deprotected to give cyclohexanone soon after the addition of acid. This is consistent with observations made during the optimization (Table 1, entry 8). Hence we believe that the presence of trimethyl orthoformate maintains the concentration of acetals required for the reaction to take place.



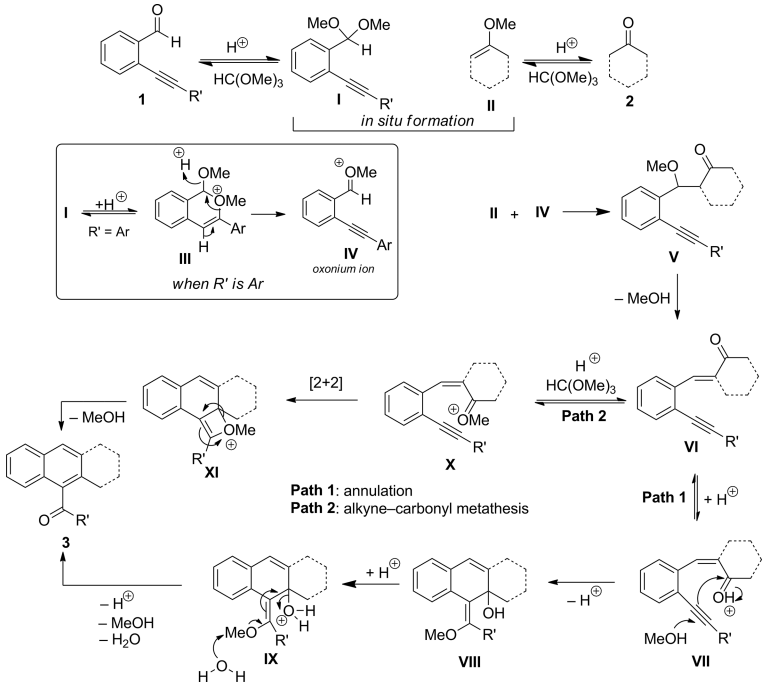
Scheme 4. Reaction of acetal **6** with cyclohexanone.

Based on our results, a mechanism for the formation of naphthyl ketone **3** can be proposed, as shown in Scheme 5. Initially, condensation might take place between enol ether **II**, derived from the ketone, and oxonium ion **IV**, which could form from *o*-alkynylbenzaldehyde **1**. Intermediates **II** and **IV** are both expected to form in the presence of trimethyl orthoformate and TfOH. This condensation will result in the formation of chalcone-type intermediate **VI** via intermediate **V**. The fact that products **4** and **5** are formed supports this pathway. Intermediate **VI** can, in principle, be



[a] 20 mol-% TfOH and 2.0 equiv. of TMOF were used.

Figure 2. Scope of the reaction with acyclic ketones.



Scheme 5. Plausible mechanism.

transformed into product **3** by one of two ways. In path 1, intermediate **VI** establishes an equilibrium with its *cis* isomer **VII** through protonation. Annulation, followed by attack of the methanol generated during the formation of **II** and **IV**, would result in intermediate **VIII**. Upon protonation, this intermediate would lose a molecule of methanol and water to give naphthyl ketone derivative **3**. On the other hand, another mechanism given in path 2 is also possible. In the presence of trimethyl orthoformate and TfOH, the oxonium intermediate **X** derived from chalcone **VI** can form by *trans*-to-*cis* isomerization. This will undergo intramolecular [2+2] cycloaddition to give oxetene intermediate **XI**.[10] It is known that oxonium ions facilitate such [2+2] carbonyl–alkyne cycloadditions.[9,10b,10c,10f] Upon cycloreversion, intermediate **XI** will generate naphthyl ketone derivative **3**. However, path 1 is more realistic because of the strain associated with intermediate **XI** in path 2.

Conclusions

We have developed a domino reaction for the synthesis of naphthyl ketone derivatives from *o*-alkynylbenzaldehydes and ketones in the presence of trimethyl orthoformate and TfOH. Interestingly, this transformation occurs at room temperature. This cascade reaction involves a condensation between *o*-alkynylbenzaldehydes and enolizable ketones, followed by annulation/alkyne–carbonyl metathesis. In situ acetal formation assists the formation of chalcone by increasing the electrophilicity of carbonyl carbon of the *o*-alkynylbenzaldehyde through oxonium ion formation, and also by enhancing the nucleophilicity of the α carbon of the ketone through formation of an enol ether. This reaction is expected to proceed by a different mechanism from that reported for the construction of naphthalenes from *o*-alkynylbenzaldehydes and enolizable ketones under gold catalysis. In addition, the *trans*/*cis* isomerization that is necessary for heteroalkyne metathesis/annulation is also facilitated by the reactions conditions.

Experimental Section

General Information: Chemicals and solvents were obtained from commercial suppliers. Starting materials were prepared by following known literature procedures. Trimethyl orthoformate and acetonitrile were obtained from Merck. Triflic acid was purchased from Sigma–Aldrich. THF was dried with sodium, and freshly distilled before use. ^{1}H and ^{13}C NMR spectra were recorded with a 400 MHz spectrometer in solution in $CDCl_3$, with tetramethylsilane as internal standard. IR spectra were recorded with an FTIR-5300 spectrometer. High-resolution mass spectra (HRMS) were recorded using the ESI-Q-TOF technique. Melting points were determined with a visual melting range apparatus. TLC was carried out using silica gel plates 60 F254, and compounds were visualized with UV light and/or by treatment with Seebach solution [phosphomolybdic acid (2.5 g), $Ce(SO_4)_2$ (1 g), H_2SO_4 (conc.; 6 mL), H_2O (94 mL)], followed by heating. Column chromatography was carried out on silica gel (100–200 mesh) using mixtures of ethyl acetate and hexanes as eluent. All the *o*-alkynylbenzaldehydes were prepared by following the standard Sonogashira coupling reaction procedure, and data of the prepared *o*-alkynylbenzaldehydes matches reported literature data.[2]

General Procedure for the Synthesis of Naphthalene Derivatives 3: Triflic acid (20 mol-%) was added to a solution of compound **1** (1.0 equiv.), ketone **2** (1.2 equiv.), and trimethyl orthoformate (2.0 equiv.) in acetonitrile (5 mL/mmol) at room temperature. The resulting mixture was stirred at room temperature under a nitrogen atmosphere. The reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated under reduced pres-

sure. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc) to give pure compound **3**.

For acyclic ketones, 1.0 equiv. of TfOH and 3.0 equiv. of trimethyl orthoformate were used.

Acknowledgments

The authors thank the Department of Science and Technology (DST), New Delhi for financial support. S. M. is grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi for a fellowship.

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