Synergistic Catalysis

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Synergistic Catalysis: Metal/Proton-Catalyzed Cyclization of Alkynones Toward Bicyclo[3.*n*.1]alkanones**

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Abstract: *A highly efficient and practical synergistically metal/proton-catalyzed Conia–ene reaction for the synthesis of bicyclo[3.n.1]alkanones has been developed. This synergistic catalysis was successfully utilized in modifying natural compounds such as methyl dihydrojasmonate, α,β-thujone, and 5α-cholestan-3-one. Furthermore, the bridged carbonyl group of bicyclo[3.2.1]alkanones could be easily attacked by nucleophiles to give the ring-opened cycloheptenone products or bicyclo[4.2.1]amide in excellent yields. These reactions provide rapid access to a diverse range of cyclic structures from simple starting materials or naturally occurring compounds.*

Synergistic catalysis is a powerful synthetic strategy both in nature and in the laboratory.[1] It is a specialized approach to catalysis whereby at least two different catalysts act on two different reactive sites simultaneously to facilitate chemical reactions (Figure 1).[1c]

The highly strained bicyclo[3.*n*.1] system is the core structure of many important naturally occurring and biologically active substances[2] such as enaimeone A,[3] garcinol,[4] β-caryolanol,[5] taxol,[6] and hypoestoxide[7] (Scheme 1). Among them, taxol is the most notable molecule, which contains the bicyclo[5.3.1] system and shows potent antitumor activity. It is a commercial drug used to treat many types of cancer including ovarian cancer, breast cancer, lung cancer, and pancreatic cancer.[6]

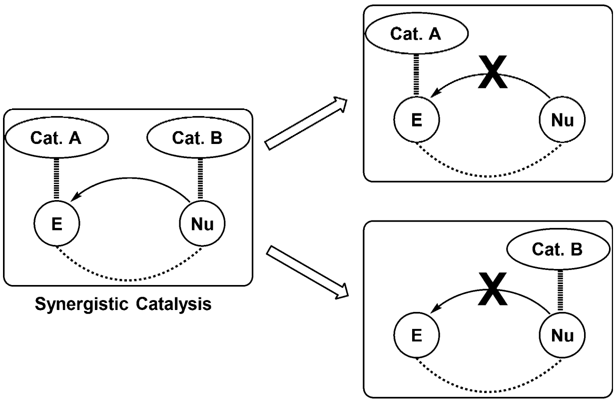
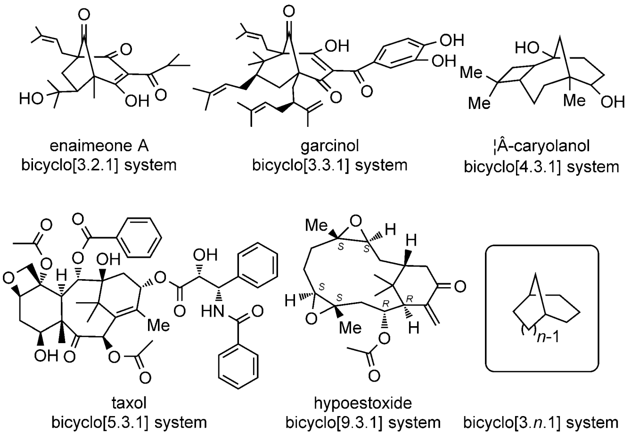


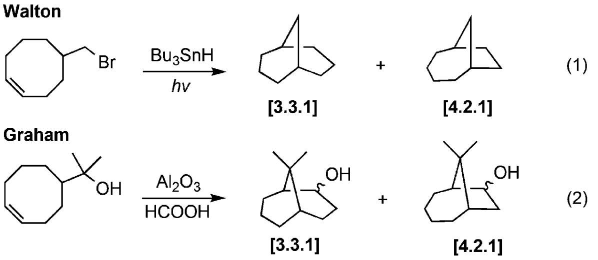
Figure 1. Synergistic catalysis.



Scheme 1. Bioactive or natural compounds bearing bicyclo[3.*n*.1] systems.

Owing to the promising biological properties and challenging structures of these bicyclic molecules, considerable research efforts have been devoted to develop efficient methods to construct these carbon-bridged medium-sized rings.[2,8] Traditionally, the bicyclo[3.*n*.1] systems were constructed through radical cyclization [Scheme 2, Eq. (1)][9] or cationic cyclization [Eq. (2)].[10] These methods generally suffered from low selectivities or inaccessibility of substrates.[9,10] Therefore, methods for the selective synthesis of bicyclo[3.*n*.1] systems would be of great importance.

The Conia–ene reaction is an intramolecular, thermal or Lewis-acid-catalyzed reaction of unsaturated carbonyl com-



Scheme 2. Synthesis of bicyclo[3.*n*.1] systems.

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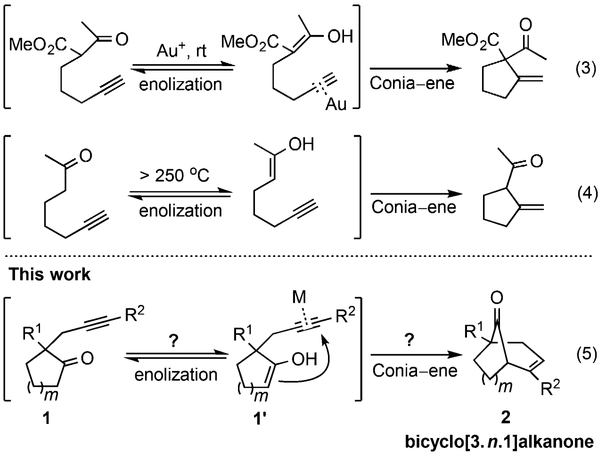
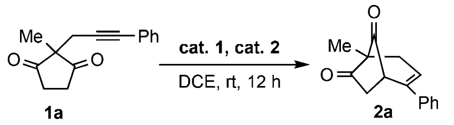
pounds to yield cyclized products.[11] In the Conia–ene reaction, the enolization of the ketone is the prerequisite for cyclization. The strong enolic character of the unsaturated β-ketoesters and β-diketones enables reactions to proceed at low temperature [Scheme 3, Eq. (3)].[11b–f] However, monoketone substrates required much harsher conditions with reaction temperatures higher than 250°C [Eq. (4)].[11a] We envisaged that if cyclic alkynone **1** was applied as the substrate, a Conia–ene cyclization process might be expected under certain catalytic conditions. Such strategy would provide rapid access to the highly strained bicyclo[3.*n*.1]alkanone **2** [Eq. (5)].



Scheme 3. Conia–ene reactions.

With this in mind, alkyne dione (**1a**) was chosen as the model substrate for this investigation. As shown in Table 1, the reaction was conducted in DCE at room temperature with 5 mol% metal salt as the catalyst. Gold(I) was initially applied as the catalyst because it has been shown to be a good promoter for the Conia–ene reaction.[11b] However, the desired bicyclo[3.2.1]alkanone product **2a** was not detected (entry 1). Other metal salts, like Ag^+, Cu^{2+}, In^{3+}, Fe^{3+}, were also inefficient for this transformation (entries 2–7). As pointed out above, the enolization of the ketone is the prerequisite for the Conia–ene cyclization. We reasoned that metal salts alone were not capable of enolizing the ketone, thus the consequent cyclization did not occur. Proton (H^+) is the simplest, and arguably the most versatile, catalyst for organic reactions, mediating an extraordinary range of biological and synthetic transformations, including the enolization of aldehydes or ketones.[1a,12] Inspired by these facts, we turned our attention to metal/proton synergistic catalysis, in which the metal (cat. 1) activates the carbon–carbon triple bond and the proton (cat. 2) promotes the enolization of the ketone. With $AgNTf_2$ being cat. 1, a series of different Brønsted acids (cat. 2) were then investigated (entries 8–13). When TsOH and CF_3COOH were added into the reaction system, a trace amount of the desired bicyclo[3.2.1]alkanone product **2a** could be observed (entries 8–9). Encouraged by this observation, a stronger Brønsted acid, TfOH, was then employed as the co-catalyst. Gratifyingly, the product **2a** could be obtained in almost quantitative yield (entry 10). Other acids, such as HCOOH, HCl, and $B(OH)_3$ were inefficient (entries 11–13). In addition to $AgNTf_2$/TfOH, other metal/TfOH combinations could also catalyze this transformation, with the yields ranging from 28% to 93% (entries 14–19). Among these metal salts, both silver and copper salts functioned equally well, giving yields of around 90% (entries 15–17). Inferior results were obtained for the combinations of IMes-Au^+/TfOH and $Fe(OTf)_3$/TfOH, with the yields dropping to 64% and 63%, respectively (entries 14 and 19). However, the yield was only 28% when $In(OTf)_3$/TfOH was utilized as the catalyst system (entry 18). The control reactions indicate that it is a synergistic catalysis process, as the Brønsted acid (cat. 2) alone could not catalyze the reaction (entries 20–25). The structure of bicyclo[3.2.1]alkanone **2a** was confirmed by X-ray diffraction analysis (see the Supporting Information).[13]

Table 1: Optimization of reaction conditions.[a]

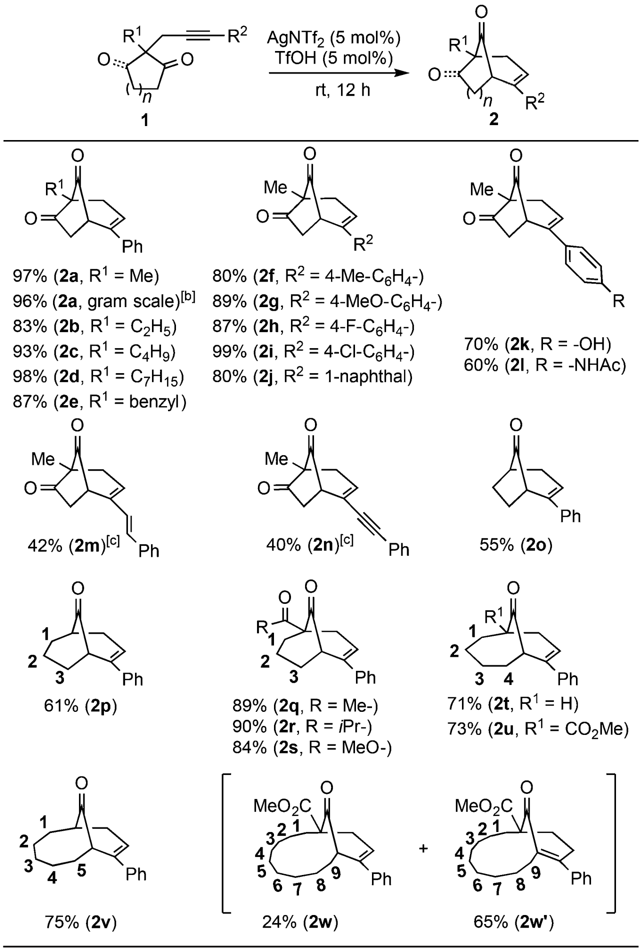


Entry	**Cat. 1** (5.0 mol%)	**Cat. 2** (5.0 mol%)	Yield[b]
1	IMesAuCl/$AgNTf_2$	–	n.r.
2	AgOTf	–	n.r.
3	$AgSbF_6$	–	n.r.
4	$AgNTf_2$	–	n.r.
5	$Cu(OTf)_2$	–	n.r.
6	$In(OTf)_3$	–	n.r.
7	$Fe(OTf)_3$	–	n.r.
8	$AgNTf_2$	TsOH	trace
9	$AgNTf_2$	CF_3COOH	trace
10	**$AgNTf_2$**	**TfOH**	**97%**
11	$AgNTf_2$	HCOOH	n.r.
12	$AgNTf_2$	HCl	n.r.
13	$AgNTf_2$	$B(OH)_3$	n.r.
14	IMesAuCl/$AgNTf_2$	TfOH	64%
15	AgOTf	TfOH	93%
16	$AgSbF_6$	TfOH	89%
17	$Cu(OTf)_2$	TfOH	90%
18	$In(OTf)_3$	TfOH	28%
19	$Fe(OTf)_3$	TfOH	63%
20	–	TfOH	n.r.
21	–	TsOH	n.r.
22	–	CF_3COOH	n.r.
23	–	HCOOH	n.r.
24	–	HCl	n.r.
25	–	$B(OH)_3$	n.r.

[a] Reaction conditions: **1a** (0.25 mmol), **cat. 1** (5.0 mol%), **cat. 2** (5.0 mol%), solvent (1.0 mL), rt; [b] Yield of the isolated product. IMes = 1,3-dimesitylimidazol-2-ylidene; n.r. = no reaction.

In light of the results in Table 1, the combination of $AgNTf_2$/TfOH in DCE at room temperature was then chosen as the optimal catalyst system to study the scope of this new transformation (Table 2). First, the reaction could be repeated in gram scale and gave the product **2a** in similar yield (96%). Second, the catalytic system could be successfully applied to a variety of alkynones **1**. For example, in addition to 2-methyl-

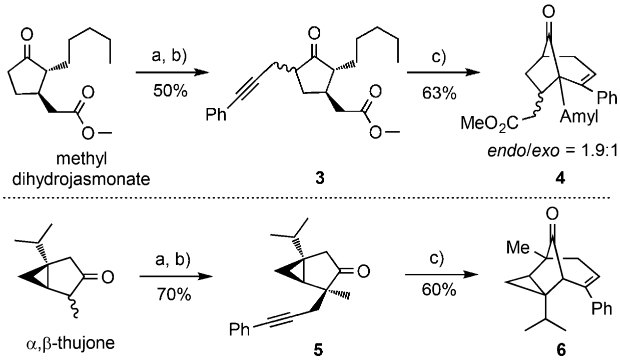
Table 2: Substrate scope.[a]



[a] **1** (0.25 mmol), AgNTf$_2$ (5.0 mol%), TfOH (5.0 mol%), DCE (1.0 mL), rt, 12 h; [b] **1a** (6.7 mmol, 1.5 g); [c] 50 °C, 12 h.

2-phenylpropynyl cyclopentadione **1a**, various cyclopentadione-based alkyne dione derivatives with different R^1 and R^2 groups could be effectively converted to the desired bicyclo[3.2.1]alkanones (**2b–n**).[14] With different R^1 groups on the cyclopentadione ring, the yields were 83–98% (**2b–e**). The aryl substituents at R^2 have little effect on the yields (**2f–j**, 80–99%). Furthermore, the reactions smoothly occurred even for alkynones with free hydroxy or acetamido groups, albeit in lower yields (**2k–l**). Moreover, when the reaction temperature was enhanced to 50 °C, the reaction could be extended to the alkynones with one more alkenyl or alkynyl group, the yields were 42% (**2m**) and 40% (**2n**), respectively. In addition to the cyclopentadione-based alkyne dione derivatives, the cycloalkanones with only one carbonyl on the ring were also good substrates for this transformation (**2o–w**). For example, 2-phenylpropynyl-cyclopentanone gave **2o** in 55% yield. Having established the synergistic catalysis as a reliable and efficient process to construct bicyclo[3.2.1]alkanones, we then proceeded to explore the synthesis of other bicyclo[3.*n*.1]alkanones. A series of alkynones with different ring sizes of the alkynones **1** were then tested under the reaction conditions and found to work well. For example, cyclohexanone-, cycloheptanone-, and cyclooctanone-based alkynones provided the corresponding bicyclo[3.*n*.1]alkanones (*n* = 3, 4, 5) **2p–v** in 61–90% yields. Notably, the macrocyclic cyclododecanone-based alkynone could also be readily converted to the bicyclo[9.3.1]alkanone, leading to the products **2w** and **2w′** in 24% and 65% yield, respectively. A shift of the position of the carbon–carbon double bond is observed under acidic conditions. Actually, **2w** can be fully converted into **2w′** when prolonging the reaction time to 48 h.

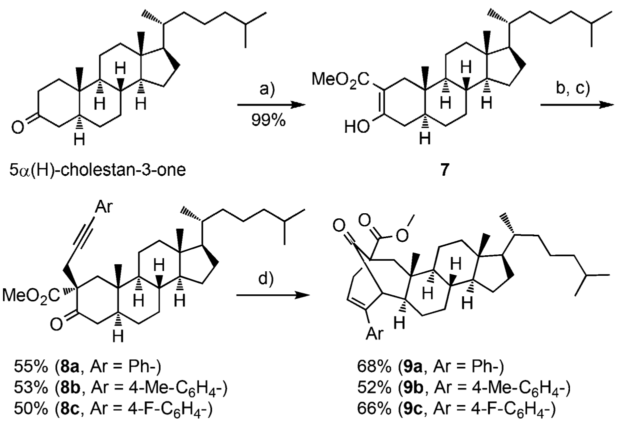
To demonstrate the applications of this methodology, the synergistically metal/proton-catalyzed Conia-ene reactions were then employed to modify the natural compounds methyl dihydrojasmonate and α,β-thujone, which contain a five-membered cyclic ketone moiety. Methyl dihydrojasmonate is a diffusive aroma compound, with the smell vaguely similar to jasmine.[15] Cyclopentanone-based alkynone **3** could be easily obtained from the commercial available methyl dihydrojasmonate through known procedures. Under the standard reaction conditions, the desired bicyclo[3.2.1]alkanone **4** was furnished in 63% yield (Scheme 4). Similarly, α,β-thujone can also be readily converted to alkynone **5**, which was then treated with AgNTf$_2$/TfOH leading to the desired bicyclo[3.2.1]alkanone **6** in 60% yield. It should be noted that only one isomer of **6** was observed (Scheme 4).



Scheme 4. Modification of methyl dihydrojasmonate and α,β-thujone: a) ketone (1.0 equiv), propargyl bromide (1.0 equiv), LDA (1.0 equiv), THF, −78 °C–rt, 12 h; b) ArI (1.5 equiv), PdCl$_2$(PPh$_3$)$_2$ (10 mol%), CuI (20 mol%), NEt$_3$ (1.5 equiv), THF, 40 °C 12 h; c) AgNTf$_2$ (5 mol%), TfOH (5 mol%), DCE, rt, 12 h. DCE = dichloroethane; LDA = lithium-diisopropylamide; Tf = trifluoromethanesulfonate.

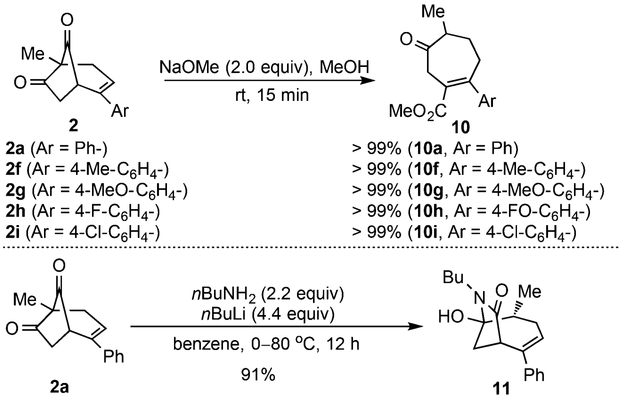
To further demonstrate the synthetic utility of this synergistic catalytic method, the structure modification was also applied to the steroid 5α-cholestan-3-one. As shown in Scheme 5, 5α-cholestan-3-one was initially converted to the steroid-based alkynones **8** in good yields, which were then subjected to the standard catalytic conditions affording the desired bicyclo[3.3.1]alkanones **9** in 52–68% yield (Scheme 5).

With the bicyclo[3.*n*.1]alkanones **2** in hand, it is speculated that the bridged C=O group would exhibit higher electrophilicity than nonbridged C=O group toward nucleophiles.[16] Thus, a ring-opening reaction would occur accordingly to give the cycloheptane derivatives. For example, when bicyclo[3.2.1]alkanones **2a**, **2f**, **2g**, **2h**, and **2i** were treated with MeONa, the desired cycloheptenones **10a**, **10f**, **10g**, **10h**, and



Scheme 5. Modification of 5α-cholestan-3-one: a) dimethyl carbonate (3.1 equiv), NaH (2.5 equiv), KH (0.28 equiv), THF, 60 °C, 0.5 h; b) ketone (1.0 equiv), propargyl bromide (2.0 equiv), Cs_2CO_3 (1.5 equiv), acetone, 50 °C, 12 h; c) ArI (1.5 equiv), $PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), NEt_3 (1.5 equiv), THF, rt, 12 h; d) $AgNTf_2$ (5 mol%), TfOH (5 mol%), DCE, rt (**9a** and **9c**) or 50 °C (**9b**), 24 h.

10i were generated in quantitative yields. When $BnNH_2$ was used as the nucleophile, the bicyclo[4.2.1]amide **11** was obtained in 91% yield (Scheme 6).



Scheme 6. Further transformations of bicyclo[3.2.1]alkanones **2**.

In summary, a highly efficient and practical synergistically metal/proton-catalyzed Conia–ene reaction for the synthesis of bicyclo[3.*n*.1]alkanones ($n = 2$–9) was developed. Importantly, this synergistic catalysis was successfully utilized for modifying natural compounds bearing the cyclic ketone units, such as methyl dihydrojasmonate, α,β-thujone, and 5α-cholestan-3-one. Furthermore, the bridged carbonyl group of bicyclo[3.2.1]alkanones **2** could be easily attacked by nucleophiles to give the ring-opened cycloheptenone products **10** or bicyclo[4.2.1]amide **11** in excellent yields. These reactions provide rapid access to a diverse range of cyclic structures from simple starting materials or naturally occurring compounds. Owing to the excellent substrate scope and mild reaction conditions, this synergistic catalyst system holds considerable potential for the construction of complex molecules. Investigations on the asymmetric version, a detailed reaction mechanism, and additional applications of this reaction are underway in our laboratory.

Experimental Section

General procedure for the synthesis of bicyclo[3.*n*.1]alkanones **2**: To a stirred solution of DCE (1.0 mL) at room temperature was added **1** (0.25 mmol), $AgNTf_2$ (0.0125 mmol, 5 mol%) and HOTf (0.0125 mmol, 5 mol%). The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, mixture of hexane/ethyl acetate).

Keywords: bicyclo[3.*n*.1]alkanones · Conia–ene reaction · cycloheptanone · enolization · synergistic catalysis

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