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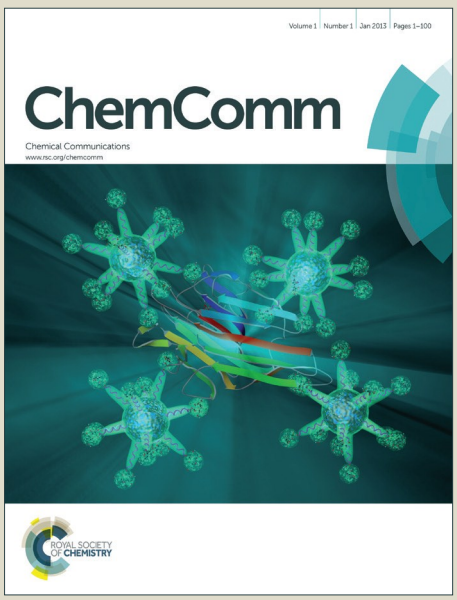

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Synthesis of highly strained bicyclic[3.*n*.1]alkenes by metal-catalyzed Conia-ene reaction

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A high yielding metal-catalysed Conia-ene reaction of 2-acetylenic ketones for the synthesis of bicyclo[3.*n*.1]alkenes has been developed. This simple and efficient 6-*endo*-*dig*-cyclization protocol enables the synthesis of a wide variety of bicyclic systems, present in many natural products.

The construction of a highly strained bicyclic[3.*n*.1] systems is still an important target to the synthetic organic community till to date, due to its presence in many biologically active natural products[1] such as enaimeone A,[2] hyperforing,[3] platensimycin[4] (Fig. 1). Although many approaches have been reported for the synthesis of such cyclic systems,[1] synthesis of bicyclo[3.*n*.1]alkanes from cycloalkane-1,3-diones are extremely rare.

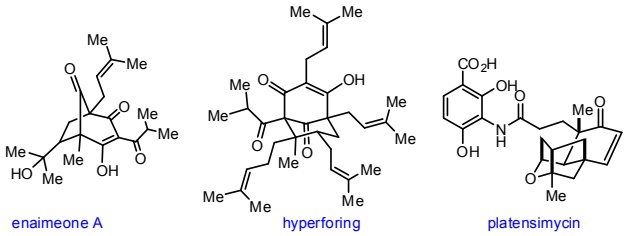
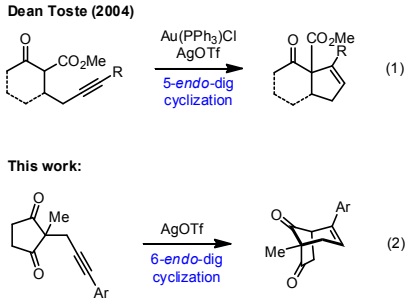


Fig. 1 Bicyclo[3.*n*.1] system containing bioactive natural products.

The first synthesis of bicyclo[3.2.1] skeleton was achieved by Kompa and Hirn in 1903 using an intramolecular Piria reaction.[5] In 1974, Hajos *et al*. reported the synthesis of bicyclo[3.2.1]octanedione derivatives starting from methyl-2-cyclopentane-1,3-dione and acrolein or methyl vinyl ketone using well known Michael reaction.[6] Dixon and co-workers recently exploited acid-catalyzed synthesis of bicyclo[3.*n*.1]alkenediones.[7] In recent elegant reports, synthesis of enantioselective bicyclo[3.*n*.1]octane derivatives also demonstrated.[8] More recently, Lam and co-workers disclosed an enantioselective synthesis of bicyclo[3.*n*.1]alkanes by chiral phosphoric acid-catalysed Michael cyclization of 2,2-disubstituted cyclic 1,3-diketones.[9]



Scheme 1 Metal catalyzed Conia-ene reaction.

In 2004, Toste and co-workers reported the gold(I)-catalyzed 5-*endo-dig* carbocyclization of easily enolizable acetylenic dicarbonyl compounds.[10] Recently, Barriault also reported gold(I)-catalyzed carbocyclization of cyclic enol ethers.[11] During a program aimed at the desymmetrization of C_2-symmetric molecules,[12] we envisioned that cyclic 1,3-diketone can undergo an atom-economical Conia–ene reaction[13] to form bicyclo[3.2.1]alkene *via* 6-*endo-dig*-cyclization (Scheme 1).[14] The study is initiated with the cyclization of 2-acetylenic 1,3-diketone **1a** in presence of 10 mol% $Au(PPh_3)Cl/AgOTf$ in DCE at 90 °C for 4 h to get the desired bicyclo[3.2.1]octene **2a** in 85% yield (Scheme 2). The structure of **2a** was fully characterized by NMR spectroscopy, IR, and HRMS data. Single-crystal X-ray analysis of compound **2a** also unambiguously established its bicyclic[3.2.1] structure.[15]

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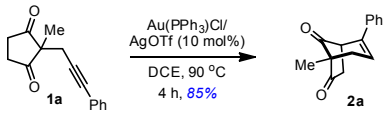
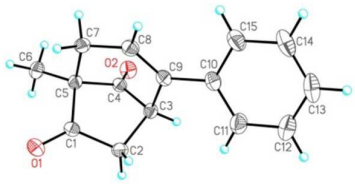
† Electronic supplementary information (ESI) available: General experimental procedures, NMR data, and single crystal X-ray data. CCDC 1412029. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x



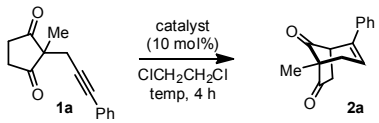


Compound 2a

Scheme 2 Initial attempt for reaction development and ORTEP diagram of compound **2a.**

With this initial result in hand, we decided to do an elaborated screening using various suitable catalysts and conditions shown in table 1. At the beginning, the desired bicyclic product **2a** was obtained in presence of AuCl/AgOTf catalytic system in almost similar amount of yield (table 1, entry 1). However, the reaction in presence of $Au(PPh_3)Cl/AgOTf$ at room temperature did not provide any product (table 1, entry 2). Meanwhile, we performed two simultaneous reactions with $Au(PPh_3)Cl$ and AgOTf as independent catalysts at 90 °C (table 1, entries 3-4). Interestingly, the desired product **2a** was not detected in case of gold catalyst whereas AgOTf catalyst gave

Table 1 Evaluation of Reaction Conditions for 6-*endo-dig*-Cyclization[a]



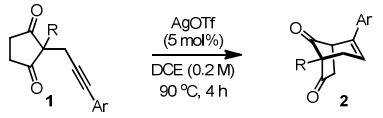
entry	catalyst (mol%)	temperature (°C)	yield (%) *b*
1	AuCl/AgOTf (10)	90	87
2	$Au(PPh_3)Cl/AgOTf$ (10)	rt	n.r.
3	$Au(PPh_3)Cl$(10)	90	n.r.
4	AgOTf (10)	90	98
5	$AgSbF_6$ (10)	90	94
6	$AgNTf_2$ (10)	90	90[c]
7	$AgClO_4$ (10)	90	91
8	$AgBF_4$ (10)	90	75
9	AgOAc (10)	90	n.r.
10	$AgNO_2$ (10)	90	n.r.
11	AgCN (10)	90	n.r.
12	Ag_2CO_3 (10)	90	n.r.
13	PhCOOAg (10)	90	n.r.
14	$Cu(OTf)_2$ (10)	90	n.r.
15	$Cu(OAc)_2$ (10)	90	88
16	**AgOTf (5)**	**90**	**96**
17	AgOTf (2)	90	64
18	AgOTf (5)	50	n.r.
19	AgOTf (5)	rt	n.r.

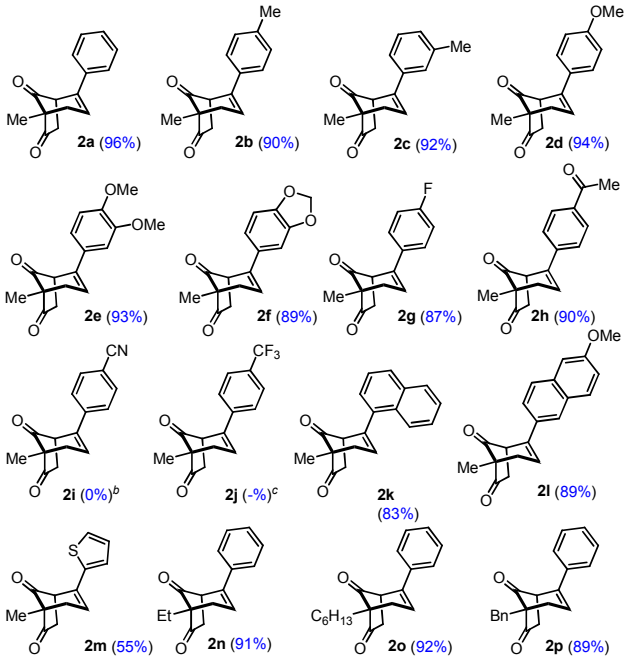
[a]The reaction was carried out with **1a** (0.1 mmol) in DCE (0.2 M) for 4 h. [b]Determined by ^1H NMR analysis with an internal standard, 1,1,2,2-tetrachloroethane. [c] Reaction carried out for 12 h.

bicyclo[3.2.1]alkene **2a** in 98% yield. According to the previous reports,[13] cationic metal catalyzed Conia–ene reaction proceeded *via* the formation of a metal-alkyne complex and subsequent enolization of the ketone. Even though $Au(PPh_3)Cl$ is an alkyne activator,[16] the reaction of **1a** did not produce the desired bicyclic adduct **2a**, presumably due to its inability to enolize the ketone. Next, various silver catalysts such as $AgSbF_6$, $AgNTf_2$, $AgClO_4$, $AgBF_4$, AgOAc, $AgNO_2$, AgCN, Ag_2CO_3, PhCOOAg were screened to further optimize the reaction conditions (table 1, entries 5-13). The reaction was successful in presence of $AgSbF_6$, $AgNTf_2$, $AgClO_4$, and $AgBF_4$ as catalysts where product was obtained in good to excellent yields, although $AgNTf_2$ took longer reaction time (12 h) for completion (table 1, entries 5-8). The formation of product **2a** was not observed using AgOAc $AgNO_2$, AgCN, Ag_2CO_3, PhCOOAg as catalysts where starting material **1a** was recovered as such (table 1, entries 9-13). In case of copper catalysts, $Cu(OTf)_2$ afforded the product **2a** in 88% yield, but the carbocyclization with $Cu(OAc)_2$ did not yield any desired product (table 1, entries 14-15). Overall, 10 mol% of AgOTf gave the best yield among all other catalysts screened. Similar result was also obtained with 5 mol% of AgOTf catalyst loading and did not show any significant variation on reaction yield, but 2 mol% of AgOTf gave only 64% of yield of **2a** in 4 hours (table 1, entries 16-17). However, the reaction did not proceed further at 50 °C as well as at room temperature (table 1, entries 18-19).

With the optimal reaction condition in hand, the substrate scope was explored in this AgOTf-catalyzed 6-*endo-dig* carbocyclization. The reaction was carried out with the starting material bearing electron-donating and electron-withdrawing groups on the aromatic ring in addition to electron rich naphthalenes as well as hetroaromatic ring systems. The reaction of the electron-rich aryl alkynones afforded the corresponding products **2a**-**f** in good to excellent yields (Table 2). Weakly deactivating flouro- and acetyl-substituted alkynone also furnished bicyclo[3.2.1]alkenes **2g** and **2h**, respectively in similar yields. In case of the strong electron-withdrawing substituents, formation of 4-CN substituted bicyclo[3.2.1]alkene **2i** was not observed and starting material was recovered without any significant loss. However, the carbocyclization of CF_3-substituted alkynone gave a complex mixture (Table 2, **2j**). With naphthalene substituents, the reactions proceeded smoothly providing the products in high yields (Table 2, **2k-l**). In addition, hetroaromatic substituent such as thiophine gave product **2m** in moderate yield. The carbocyclization of **1** with different substituents (ethyl, hexyl and benzyl) on the cyclopentadione ring furnished corresponding products (**2n**-**p**) in excellent yields.

Table 2 Evaluation of cyclopentane-1,3-dione substrate scope[a]

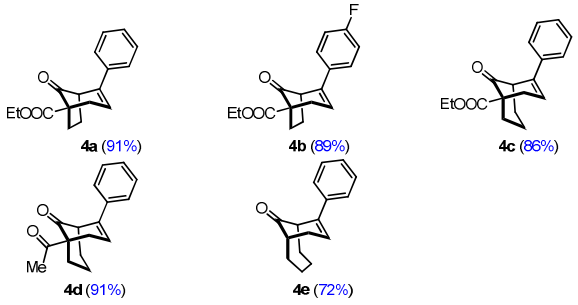




[a] Reaction conditions: AgOTf (5 mol %), DCE (0.2 M), 90 °C, 4 h; Yields of products isolated after column chromatography. [b] Starting material was recovered. [c] Complex reaction mixture.

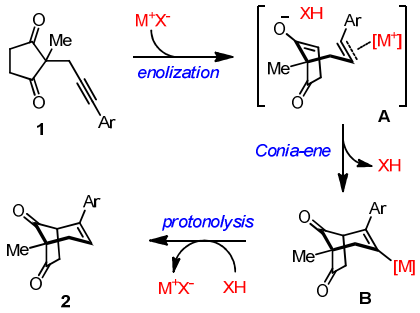
The 6-*endo-dig*-carbocyclization was also successful using five- to seven-membered substituted cycloalkanones in which one carbonyl group was part of the ring (table 3). Intramolecular cyclization of five-membered cyclic *β*-keto esters to give bicyclo[3.2.1]alkenes **4a** and **4b** in 91% and 89% yields, respectively. Six-memebered alkynones **3** were easily underwent carbocyclization to afford bicyclo[3.3.1]alkenes **4c** and **4d** in good yields. Similarly, 7-membered akynones **3e** could also be readily converted to the desired bicyclo[3.4.1]decenes **4e** in 72% yields (table 3).

Table 3 Evaluation of substrate ring size scope[a]



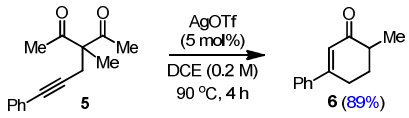
[a] Reaction conditions: AgOTf (5 mol %), DCE (0.2 M), 90 °C, 4 h; Yields of products isolated after column chromatography.

We envisioned that the mechanism would involve in the activation of alkyne group followed by nucleophilic attack on metal-alkyne complex **A** by the enol form of the 1,3-diketone to give vinyl-metal intermediate **B** which on subsequent protonolysis forms the product **2**.[13b] Here, counteranion (X^-) facilitate the formation of enol to drive in the Conia-ene reaction (Scheme 3).



Scheme 3 Plausible 6-*endo-dig* carbocyclization mechanism

Next, we investigated the cyclization of acyclic diketone **5** (Scheme 4). Surprisingly, the cyclohex-2-enone **6** was formed through a 6-*endo-dig* cyclization followed by olefin migration and subsequent removal of acetyl group *via* C-C bond cleavage in 89% yield.



Scheme 4 6-*endo-dig*-Cyclyzation of acyclic diketone

Conclusions

In summary, the synthesis of highly strained bicyclic[3.*n*.1]alkenes has been achieved by a metal-catalyzed Conia-ene reaction of 2-acetylenic ketones. The utility of this 6-*endo*-*dig*-cyclization reaction allows the synthesis of a variety of bicyclic [3.*n*.1] systems that are present in many natural products. Application of this method, including an asymmetric version, are currently underway in our laboratory and will be reported in due course.

The Department of Science and Technology (DST), New Delhi, India, is acknowledged for the award of a Start-up Research Grant (young scientists) to RC. SK thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, and KKG thanks DST, New Delhi, for a research fellowship. The authors thank Dr. S. Chandrasekhar for valuable discussions.

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15 CCDC-1412029 (**2a**) contains the supplementary crystallographic data for this paper†. This data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk.

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