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

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A high yielding metal-catalysed Conia-ene reaction of 2-acetylenic ketones for the synthesis of bicyclic[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 products1 such as enaimeone A,2 hyperforing,3 platensimycin4 (Fig. 1). Although many approaches have been reported for the synthesis of such cyclic systems,1 synthesis of bicyclic[3.n.1]alkanes from cycloalkane-1,3-diones are extremely rare.

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

The first synthesis of bicyclic[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]octane 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

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 C2-symmetric molecules,12 we envisioned that cyclic 1,3-diketone can undergo an atom-economical Conia–ene reaction13 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(PPh3)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

Scheme 1 Metal catalyzed Conia-ene reaction.
With the 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(PPh₃)Cl/AgOTf at room temperature did not provide any product (Table 1, entry 2). Meanwhile, we performed two simultaneous reactions with Au(PPh₃)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 2b. However, the reaction in presence of Au(PPh₃)Cl/AgOTf at room temperature did not provide any product (Table 1, entry 1). The formation of compound 2a was not observed using AgOAc, AgNO₃, AgCN, and Ag₂CO₃ as catalysts where product was obtained in good to excellent yields, although AgNTf₂ took longer reaction time (12 h) for completion (Table 1, entries 5-8). The formation of product 2a was not observed using AgOAc, AgNO₃, AgCN, and Ag₂CO₃ 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-end-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 heteroaromatic ring systems. The reaction of the electron-rich aryl alkynes afforded the corresponding products 2a-f in good to excellent yields (Table 2). Weakly deactivating fluoro- and acetyl-substituted alkyn has 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 CF₃-substituted alkynec 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, heteroaromatic substituent such as thiophene 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.
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-membered alkynones 3 were easily underwent carbocyclization to afford bicyclo[3.3.1]alkenes 4c and 4d in good yields. Similarly, 7-membered alkynones 3e could also be readily converted to the desired bicyclo[3.4.1]decenes 4e in 72% yields (table 3).

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

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
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<tr>
<td>1a</td>
<td>96%</td>
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<tr>
<td>1b</td>
<td>90%</td>
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<tr>
<td>1c</td>
<td>92%</td>
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<tr>
<td>1d</td>
<td>94%</td>
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<tr>
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<td>93%</td>
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<tr>
<td>1n</td>
<td>92%</td>
</tr>
<tr>
<td>1o</td>
<td>92%</td>
</tr>
<tr>
<td>1p</td>
<td>89%</td>
</tr>
</tbody>
</table>

* 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. 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-Cyclization of acyclic diketone
Conclusions

In summary, the synthesis of highly strained bicyclic[3.2.1]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[3.2.1] 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.

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Notes and references

14 During the preparation of this manuscript, a report of 6-endo-dig-cyclization appeared; for reference, see: S. Zhu, Q. Zhang, K. Chen and H. Jiang, Angew. Chem., Int. Ed., 2015, DOI: 10.1002/anie.201504964.
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.