Generation of structural complexity enabled by gold catalysis: construction of highly strained tetracyclic bridgehead olefins

Xin Meng, Ziping Cao, Jinmao You

Key Laboratory of Life-Organic Analysis, Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu, 273165, China

Correspondence: Ziping Cao or Jinmao You
E-mail: caozp_qfnu@163.com or jmyou6304@163.com
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A class of highly strained tetracyclic bridgehead olefins has been achieved by gold-catalyzed reaction of ortho-alkynylbenzaldehydes with conjugated dienes. The process involves a chemo- and stereo-selective tandem intermolecular [3+2] cycloaddition/Prins-type ring closing reaction that allows the generation of structural complexity in a straightforward manner. The present report highlights these facts containing the selection of multi-site reactive substrates, the origin of structural stereoselectivity and the distinct reactive form of gold carbene. Undoubtedly, this will inspire researchers to design and discover new organic transformations for synthesis of cyclic compounds as well as useful applications.

Keywords: Structural complexity; gold; diene; bridgehead olefin; polycyclic compound


Complex polycyclic structures can be found in a large number of natural products and bioactive molecules. Therefore, the rapid and efficient construction of various cyclic skeletons has attracted extensively attentions and became one of the hot research topics in the synthetic community. The readily accessible starting materials, mild experimental conditions and simplistic operation with high efficiency are highly desired. Tandem/domino/cascade reactions that allow the formation of multiple chemical bonds in one pot have provided efficient methods for the synthesis of complex compounds [1].

In 2002, Yamamoto and co-workers developed a tandem gold-catalyzed benzannulation reaction of ortho-alkynylbenzaldehydes (1) with alkynes, which led to the formation of naphthyl ketone framework [2]. Following this seminal work, a variety of reaction partners possessing an unsaturated motif were employed to access cyclic skeletons [3-5]. It is well known that, all of alkenes, alkynes, aldehydes, allenies and conjugated dienes are valuable building blocks in synthetic organic chemistry. Moreover, these motifs could be modified with a functional group or designed in an intramolecular manner. By reactions of ortho-alkynylbenzaldehydes with these unsaturated motifs, many complex cyclic structures could be achieved in one step with the suitable selection of a metal catalyst as well as the appropriate control of reaction conditions. Especially, the utility of conjugated dienes, as a multi-site reactive organic intermediate with respect to other unsaturated compounds such as alkenes, have allowed the generation of complex
polycyclic compounds with more opportunities [6] (Figure 1).

Recently, a class of structural novel tetracyclic bridgehead olefins has been developed by Cao and co-workers [7]. This type of interesting structures, also so-called anti-Bredt compound [8], is generally difficult to be prepared by traditional methods. The gold catalyzed organic transformation could provide the potential possibilities to realize the construction of these types of highly strained skeletons [9-11]. Our design was based on the ortho-alkynylbenzaldehyde substrate which can be represented under two reactive forms 2 and 3 in the presence of a metal catalyst (Figure 1). Generally, benzopyrylium intermediate 2 is the preferred one, affording various cyclic products. The intermediate 3, containing a dipole and a concomitant carbene unit, should be able to produce complex polycyclic system with the selection of an appropriate partner. Through reaction of ortho-alkynylbenzaldehydes with conjugated dienes by gold catalysis, synthesis of a variety of highly strained tetracyclic bridgehead olefins (4) has been accomplished with high yield and diastereoselectivity (Figure 2). The formation of no [4+2] cycloaddition product that resulted from intermediate 2 was observed. The present strategy represents a mild, efficient, operational simplistic and unprecedented method to produce the tetracyclic bridgehead olefin skeleton.

The key part of mechanism for the formation of polycyclic product is excerpted in Figure 3 [7]. Intermediate 3 can be produced as previously proposed [3-5]. The endo-type [3+2] cycloaddition of dipole 3 with 2,3-dimethylbutadiene (as an example) led to the formation of an aurated intermediate which can be represented under two reactive forms 5 and 6.
The pronounced carbocationic nature of this intermediate can favor a Prins-type cyclization to lead to the formation of intermediate 7. The final formation of the bridgehead alkene (4) was proposed to proceed following three possible mechanistic pathways: 1) a 1,2-H shift / [Au] elimination sequence via intermediate 8 (Path 1), 2) a H⁺ elimination / S_e’-type protodeauration sequence via intermediate 9 (Path 2), or 3) a concerted hydrogen migration and [Au] elimination (Path 3).

Notably, the formation of the crucial three bonds involving the endo-type [3+2] cycloaddition and Prins-type ring-closing reaction constructs this polycyclic skeleton, as well as the privileged catalytic potentiality of gold complexes enables the generation of strained bridgehead alkene structures [12]. In other words, this transformation realized the bond formation of different sites of conjugated diene structure which allows the generation of molecular complexity in a straightforward manner. More interestingly, the gold carbene intermediate 5 can behave as a “carbocation” [13-15], which favor a Prins-type reaction to achieve the ring closure. This carbocationic nature of the carbene intermediate can stimulate us to design reasonably other reactions to access diversely structural products.

It should be also highlighted the present transformation proceeded in a high stereo- and chemo-selective manner. The origin of stereoselectivity can be rationalized in the endo-type [3+2] cycloaddition step. Following this step, the first stereocenters are created, and the generation of other stereocenters can depend on this initial step. Apparently, the unique bond order of cyclic frameworks has made the installment of molecules in a stereoselective way due to the energy barrier of bond formations. No experimental evidence to account for the observed chemoselectivity and structural limitations of diene compounds were described, whereas the implication of relevant DFT calculations could bring some insight into these facts in the next work.

In summary, we have developed an efficient approach to the synthesis of highly strained tetracyclic bridgehead olefins. This class of complex and strained polycyclic bridgehead olefin skeleton can be rapidly installed from readily accessible ortho-alkynylbenzaldehydes with conjugated
dienes by gold-catalyzed tandem reactions. The present cyclized strategy will inspire researchers to design and evaluate the synthesis of other complex cyclic products, especially, natural product-like and highly strained compounds as well as useful applications.

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