

Ag-Carbenoid-Initiated Catalytic Hydration Cascades: Rapid Construction of Functionalized Bicyclo[3.3.1]nonanes

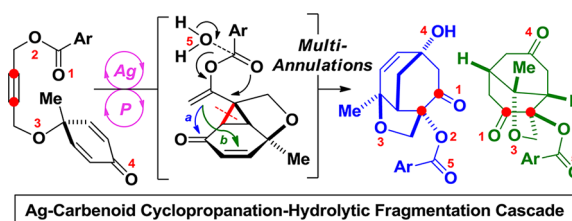
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ABSTRACT



Remarkable Ag-carbenoid-initiated enone cyclopropanation–hydrolytic fragmentation–competitive 1,2-vs-1,4 addition reaction cascades were uncovered on a range of propargylic esters tethered to cyclohexanones, leading to the highly efficient and stereospecific construction of densely functionalized bicyclo[3.3.1]nonanes under mild conditions.

Bicyclo[3.3.1]nonane represents a common structural motif present in many biologically meaningful natural products¹ as well as synthetic substances² and intermediates.³ The significant utilities of this class of

compounds thus have stimulated considerable synthetic efforts aimed at exploring efficient and stereoselective methodologies toward their preparations,⁴ particularly in the context of the rapid and controllable construction of architectural and stereochemical complexities centering around such frameworks bearing desirable functionalities. For this purpose it is exciting to witness that some recently accomplished total syntheses of bioactive natural products featuring bicyclo[3.3.1]nonane core structures, including such notable targets as members of *Lycopodium* alkaloids and *Vibisane*-type diterpenes,⁵ served as platforms for examinations of the state-of-the-art of those technologies.

Motivated by an ongoing research program focusing on the design and discovery of metallo-carbenoid species-enabled tandem catalysis processes⁶ for rapid construction of polycyclic complexities in a step- and atom-economical manner from much simpler “linear” substrates,⁷ we took a

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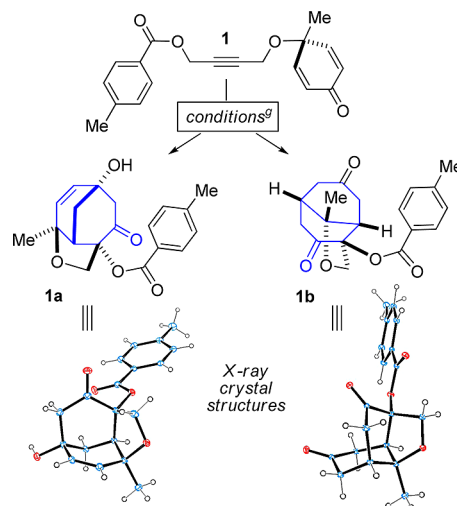
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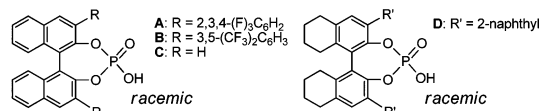
special interest in taking advantage of such reliable reactivities as electrophilic activations of carbon–carbon triple bonds by soft metals⁸ (Ag, Au, Pt, etc.) for the purpose of robust generation of desirable metallo-carbenoid intermediates. We report herein that, through synergistic interactions between orchestrated efforts and serendipity, an Ag-catalyzed cascade was uncovered on a range of propargylic esters tethered to cyclohexadienones, leading to the atom-economic formation of highly functionalized bicyclo[3.3.1]nonanes under very mild conditions and with complete stereochemical controls. The cascade appears to proceed mechanistically through an unusual sequence that involves Ag-carbenoid-initiated enone cyclopropanation, vinyl ester hydrolytic fragmentation, and competitive carbonyl addition-versus-conjugative addition as strategic events.⁹

The initial catalyst screenings conducted on a readily accessible model substrate **1** suggested cationic Ag to be a promising starting point, and the corresponding results were compiled in Table 1. When **1** was treated with 5% mol of AgSbF₆ in 1,2-dichloroethane (DCE) for two days, two products **1a** and **1b**, both featuring a highly functionalized bicyclo[3.3.1]nonane skeleton, were isolated (in 25% yield and 11/14 ratio) and structurally characterized by NMR spectroscopy and X-ray crystallography (entry 1). The transformation was essentially a hydration process¹⁰ in which a water molecule was incorporated into **1** to form the products. In this process, moist air acted as a viable and convenient source of water. Evidently, the above-uncovered reactivity and selectivity at this point were both low, but the rapid evolution of molecular complexity during this process through a potentially intriguing mechanistic course (*vide infra*) and the observed diastereospecificities demanded our immediate attention. Furthermore, although

Table 1. Ag-Catalysis Reactivity Screenings



entry ^a	AgSbF ₆ (mol %)	additive (10 mol %)	time (h)	solvent	yield (%) ^b		
					total	1a	1b
1	5	none	48	DCE	25	11	14
2	20	none	48	DCE	49	26	23
3	30	none	48	DCE	65	33	32
4	50	none	24	DCE	80	39	41
5	50	A	9	DCE	76	51	25
6	50	B	8	DCE	91	63	28
7	50	C	8	DCE	81	44	37
8	50	D	20	DCE	78	36	42
9	50	AuCl(PPh ₃)	2	DCE	19 ^c	12	7
10	50	B	8	DCM	70	46	24
11	50	B	8	Toluene	8	5	3
12 ^d	50	B	12	DCE	no reaction		
13^e	50	B	12	DCE	93	64	29
14 ^f	50	B	12	DCE	61	42	19



^a Conditions: **1** (0.30 mmol, 1.0 equiv) was mixed with AgSbF₆ catalyst and additive (0.03 mmol, 0.1 equiv) at rt and stirred for indicated time. ^b Yields refer to isolated materials. ^c Byproducts of known structures (ref 7e) were formed in 71% and 6% yield, respectively. ^d 80.0 mg of activated 4 Å MS were added. ^e 1.1 equiv of H₂O was added. ^f 2.2 equiv of H₂O were added. ^g The effects of other Ag catalysts and acids were also tested, see Supporting Information for details.

literature documentations collectively showed that migration of an acyloxy group toward a soft metal-activated triple bond in an electronically relatively unbiased propargylic ester system generally follows a 6-*endo-dig* trajectory,¹¹ the formation of **1a** and **1b** pointed to the predominance of an unusual 5-*exo-dig* reaction mode.¹²

When the loading of AgSbF₆ was gradually increased to 20%, 30%, and 50% (entries 2–4), the reactivities and product yields were improved to 49%, 65%, and 80% respectively, but the product ratios remained about 1/1. Remarkably, when a phosphoric acid¹³ **A** (10 mol %, racemic) was used as the additive (entry 5), a comparable

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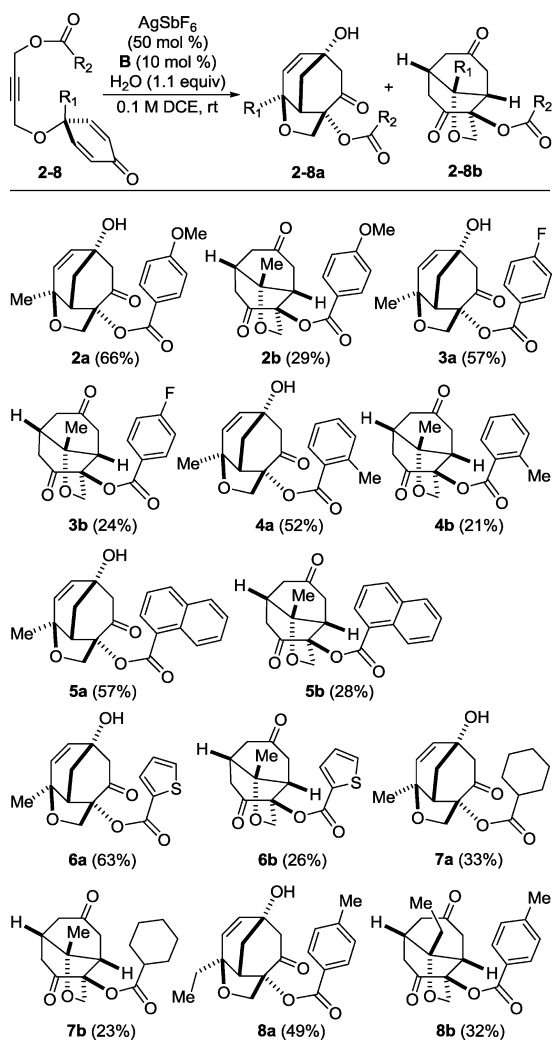
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Scheme 1. Survey of Reaction Scope



yield was obtained with a significantly reduced reaction time (76% over 9 h), and the **1a/1b** product distribution was doubled. With an analogous phosphoric acid additive **B** bearing four CF_3 groups, the yield reached 91% after just 8 h, and the product ratio was maintained (entry 6), suggesting the operation of sensitive stereoelectronic effects that such structurally highly comparable additives might have imposed on the reaction system. Two additional phosphoric acids **C** and **D** were also examined, and once again subtle structural variations of such additives were found to affect the reactivities considerably (entries 7–8). Not surprisingly, when 10% mol of $\text{AuCl}(\text{PPh}_3)$ was added, the substrate conversion was nearly quantitative, but the predominant pathways were evidently those of Au-catalysis (following the expected 6-*endo-dig* mode) rather than Ag-cascades (only 19% yield of **1a** and **1b** obtained), since the major products isolated were the dihydrofuran-fused cyclohexenone (71%) and its ring-opening structure (6%).^{7c} The solvent effects were briefly examined with DCM or toluene being employed in place of DCE, and both rendered the reactions less

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efficient. Finally, the effect of water was studied quantitatively. Careful scavenging of water using the activated 4 Å molecular sieves uneventfully led to complete inhibition of the reactivity (entry 12). Purposeful introduction of 1.1 equiv of water into the system gave the best result (93% yield, entry 13), and an excessive amount of water (2.2 equiv) was found to be detrimental (entry 14). These observations appeared to suggest intricate kinetic interplays between water incorporation and other steps within the catalytic cycle to be crucial for the success. These screening results therefore established the combination of $\text{AgSbF}_6/\text{B}/\text{H}_2\text{O}$ (1.1 equiv) to be the optimal catalyst system.¹⁴

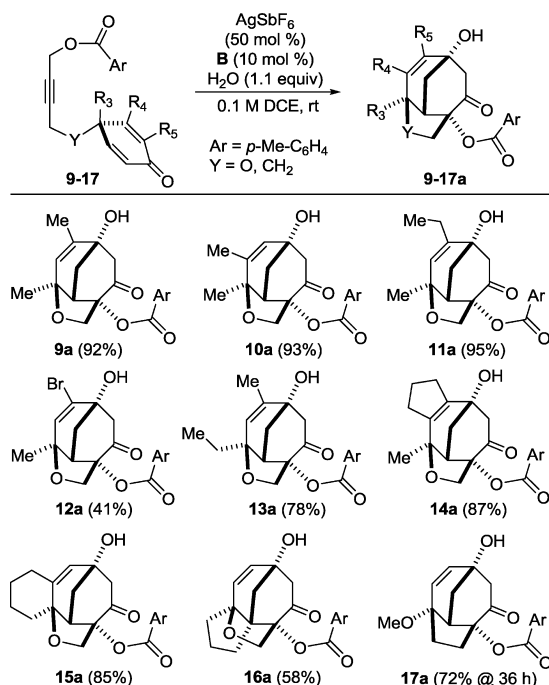
A series of propargylic esters tethered to symmetrical (i.e., prochiral) cyclohexadienones structured as **2-8** were next surveyed to determine the reaction scope. As summarized in Scheme 1, all substrates were transformed into their expected furan-fused bicyclo[3.3.1]nonane derivatives in good to excellent yields and in diastereomerically pure forms. While the ratios of products generally remained around 2/1, their combined yields responded somewhat sensitively to the stereoelectronic nature of R^1/R^2 substituents. With **1** taken as the reference, the substrate with its R^2 aryl ring bearing the electron-releasing OMe group (**2a/b**, 95% yield) was found to be more efficient than that substituted by the electron-withdrawing F atom (**3a/b**, 81%); sterically bulkier aryl esters (**4-5**) and a heteroaromatic ester (**6**) led to products of lower yields ranging from 73% to 89%; and notable losses in reactivities as well as selectivities were recorded with aliphatic ester **7** (56%, **7a/7b** = 1.4/1) as well as substrate **8** which has a larger ethyl group at the prochiral carbon center (81%, **8a/8b** = 1.5/1).

Interestingly, when propargylic esters tethered to asymmetrically substituted cyclohexadienones **9-17** ($\text{Y} = \text{O}$ or CH_2) were subjected to similar conditions, bicyclo[3.3.1]nonenes with bridgehead hydroxy groups (i.e., 1,2-addition products, *vide infra*) were exclusively formed and again with complete diastereochemical control (Scheme 2). The general trend was thus the preservation of a more substituted (thus presumably less reactive) double bond in the product. Various linear (**9-13**) and cyclic (**14-16**) substitutions and a methylene linkage (**17**) in the substrate structures were tolerated, and the corresponding products¹⁵ were produced smoothly with a respectable average yield of 78%. It merits attention due to, in the case of **16**, the structure of its product **16a** being clearly indicative of a reaction “pattern switch” (when compared to the **15**-to-**15a** transformation) as the R^3/R^4 cyclopentane ring originally fused with the cyclohexadienone unit of **16** formally flips to the bridgehead junction in **16a**. Such a contrast appears to suggest the intriguing activation effect of the more substituted cyclohexadienone double bond by the five- but not six-membered ring, as the smaller ring is notably less accommodative for geometrical strains incurred by a planar alkene and an adjacent tetrahedral carbon.

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(15) With **9** as the exemplifying substrate, an HRMS study confirmed ¹⁸O isotope incorporation when 1.1 equiv of H_2^{18}O was employed.

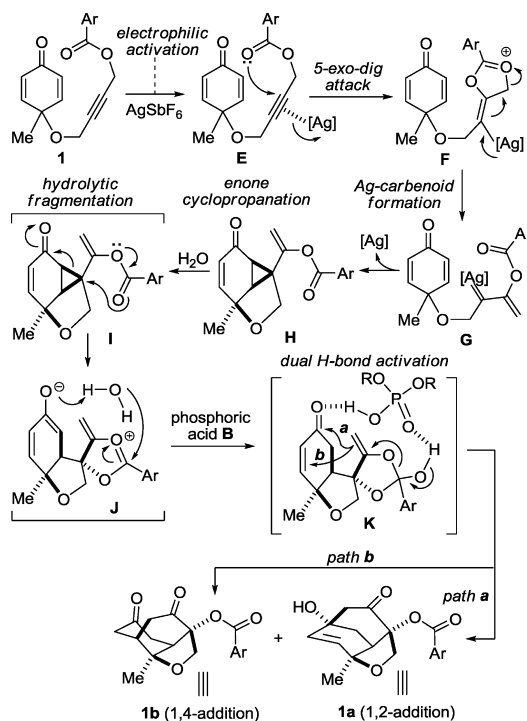
Scheme 2. Reactivities on Substituted Cyclohexadienones



Mechanistically, we believe that these uncovered reactivities could be collectively rationalized with the cascade sequence outlined below (Scheme 3). The electrophilic activation of **1** by means of Ag cation complexation with its triple bond would trigger an acyloxy migration in the shown *5-exo-dig* trajectory to generate the putative species **F**, which then rearranges to the key vinyl Ag-carbenoid intermediate **G**. Cyclopropanation on the (less-substituted) enone double bond then leads to the formation of tricyclic vinyl ester **H**. The incorporation of water into **H** would proceed through a skeletal rearrangement event involving the plausible intermediacies of **I** and **J**, thereby producing a labile vinyl orthoformate structure **K**. The superior promoting effects that phosphoric acid additives demonstrated over other monofunctional protic acids examined likely originate from their abilities in bringing about desirable “dual” activations on **K** via a pair of spatially complementary H-bonds. Subsequent vinyl orthoformate collapse would occur competitively through 1,2-carbonyl addition (path **a**) or 1,4-conjugative addition (path **b**) to the enone moiety, leading to the final products **1a** and **1b**, respectively.

In summary, we have disclosed herein that a simple combination of AgSbF₆/phosphoric acid formulated a remarkably efficient catalytic system that was capable of atom-economically converting a range of propargylic esters tethered to cyclohexadienones into highly functionalized

Scheme 3. Mechanistic Proposal



bicyclo[3.3.1]nonanes under very mild conditions, with complete stereochemical control, and in single-step manipulations. These reaction cascades appeared to mechanistically proceed through a unique sequence involving Ag-carbenoid species *in situ* generation via the *5-exo-dig* mode, subsequent initiation of enone cyclopropanation, cyclopropyl vinyl ester hydrolytic fragmentation, and competitive carbonyl addition-versus-conjugative addition events. We believe that this discovery could help shed new light on the expanding potentials of Ag catalysis by means of some highly robust yet elusive metallo-carbenoid intermediates. The results thus suggest promise for exploring new and rapid complexity-building multiannulations strategies.

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Supporting Information Available. Experimental procedures, X-ray crystallographic analysis, and ¹H and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.