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Published on Web 03/06/2003

# Catalytic Diastereoselective Synthesis of Diquinanes from Acyclic Precursors

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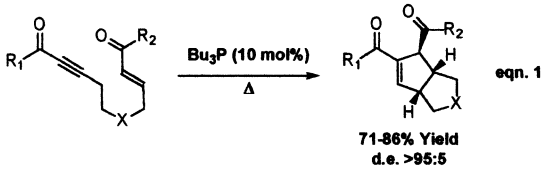
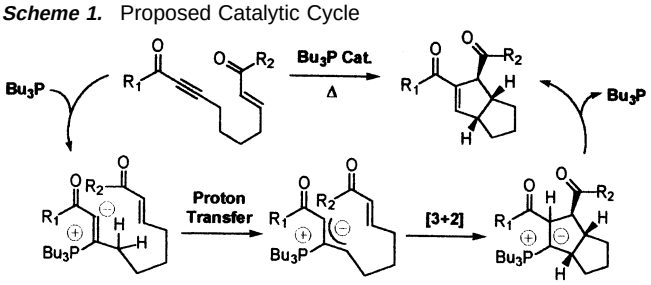
Cycloadditions represent an important class of chemical transformations that have found extensive use in the construction of complex molecular frameworks.[1] Intramolecular cycloadditions are of particular significance, as they enable expeditious entry to complex polycyclic ring systems from simple acyclic starting materials.[2] Recently, an organocatalytic method for [3 + 2] cycloaddition was reported by Lu, whereby 2-butynoates and 2,3-butadienoates serve as latent 1,3-dipoles, subject to catalytic activation via conjugate addition of tributylphosphine.[3a] Subsequently, a variety of electron-deficient $\pi$-unsaturated precursors have been demonstrated to function as dipolarophiles.[3b−e,4] Additionally, an enantioselective variant of this catalytic cycloaddition methodology has been reported by Zhang.[5] For such catalytic intermolecular cycloadditions, cycloadducts are generally obtained as mixtures of regio- and diastereoisomers. These issues of regio- and diastereoselectivity are potentially overcome through the development of related intramolecular processes, whereby concise access to diquinane substructures would be achieved from acyclic precursors. However, facile phosphine-catalyzed isomerization of 2-alkynoates to 2,4-dienoates renders the outcome of such intramolecular cycloadditions uncertain.[6] Here, we disclose that electron-deficient 1,7-enynes smoothly engage in intramolecular [3 + 2] cycloaddition upon exposure to substoichiometric quantities of tributylphosphine, without accompanying 2,4-dienoate formation. This methodology enables diastereoselective formation of substituted bicyclo[3:3:0] ring systems (eq 1).




As part of a catalysis program involving the use of enones as latent enolates,[7] the present author, along with Roush, recently disclosed a trialkylphosphine-catalyzed cycloisomerization of electron-deficient 1,5- and 1,6-dienes.[8] This discovery evoked interest in the design related organocatalytic transformations, which might be developed through variation of the nucleophilic and electrophilic partners. Inspired by the elegant work of Lu,[3,4] we considered the behavior of mono-enone mono-ynoates under conditions of nucleophilic catalysis, which, in turn, led to proposal of the catalytic cycle for intramolecular [3 + 2] cycloaddition depicted in Scheme 1.

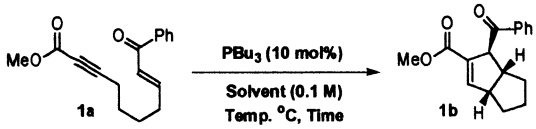
To assess the feasibility of the proposed transformation, tributylphosphine-catalyzed intramolecular cycloaddition of mono-enone mono-ynoate **1a** was attempted. Exposure of mono-enone mono-ynoate **1a** to standard conditions developed by Lu produced none of the desired bicyclic product **1b** (Table 1, entry 1). For reported butynoate-derived 1,3-dipoles, substitution of the ynoate in the $\gamma$-position is only described for doubly activated dipolarophiles, for example, maleates and fumerates. Additionally, known singly

***Scheme 1.*** Proposed Catalytic Cycle




activated enone-based dipolarophiles are unsubstituted in the $\beta$-position. Thus, for **1a**, the kinetic advantage of intramolecular condensation is presumably offset by difficulties associated with the formation of a more highly substituted C−C bond between two secondary, rather than two primary, carbon centers. Gratifyingly, when the transformation was conducted at slightly elevated temperatures, a 17% isolated yield of the desired cycloadduct was isolated as a single isomeric product (Table 1, entry 2). Increased solvent polarity was found to facilitate the transformation. Substituting ethyl acetate for benzene, the isolated yield of cycloadduct **1b** was increased to 60% (Table 1, entry 3). Finally, using ethyl acetate as solvent at 110 °C in a sealed reaction vessel, the desired cycloadduct **1b** was obtained in 76% isolated yield as a single isomeric product (Table 1, entry 4).

***Table 1.*** Optimization of Intramolecular Phosphine-Catalyzed [3 + 2] Cycloaddition of Mono-enone Mono-ynoate **1a**[a]



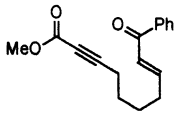
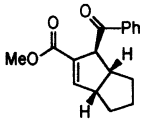
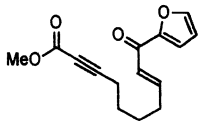
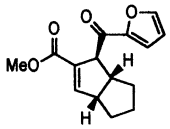
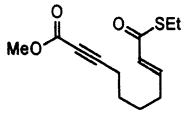
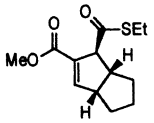
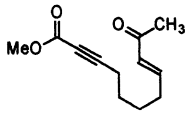
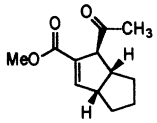
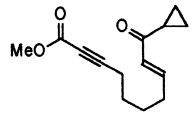
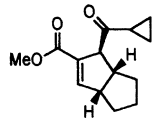
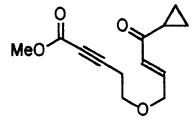
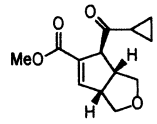
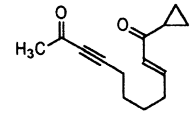
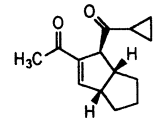
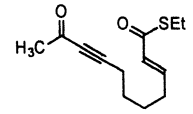
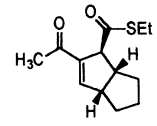

| entry | solvent | temperature (°C) | time (h) | yield[b] (recovered **1a**) |
|---|---|---|---|---|
| 1 | PhH | 25 | 48 | 0% (99%) |
| 2 | PhH | 60 | 28 | 17% (45%) |
| 3 | EtOAc | 60 | 28 | 60% (24%) |
| 4 | EtOAc | 110 | 40 | 76% (0%) |

[a] All reactions were performed in sealed tubes. [b] Isolated yields were calculated after purification by silica gel chromatography.

Under these optimized conditions, the scope of the phosphine-catalyzed [3 + 2] cycloaddition was explored. A survey of representative dipolarophiles demonstrates that the transformation is viable for aromatic, heteroaromatic, and aliphatic enone partners (Table 2, entries 1−4). Whereas cyclopropanes possessing adjacent $\pi$-unsaturation are generally incompatible with transition metal catalysts, cyclopropyl enoates **5a**−**7a** react smoothly under nucleophilic organocatalytic conditions to provide cyclopropane containing cycloadducts **5b**−**7b** in good yields (Table 2, entries 5−7). In addition to acetylenic esters, the cycloaddition of methyl ynones **7a** and **8a** demonstrates that acetylenic ketones also serve as latent 1,3-dipoles (Table 2, entries 7 and 8). Finally, heteroatoms


10.1021/ja030022w CCC: $25.00 

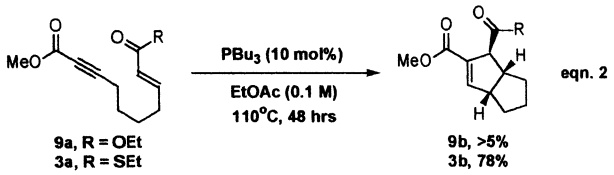
***Table 2.*** Intramolecular Phosphine-Catalyzed [3 + 2] Cycloaddition of Electron-Deficient 1,7-Enynes[a]

| Entry | Substrate | Product | Yield (%)[b] |
|---|---|---|---|
| 1 |  |  | 76 |
| | 1a | 1b | |
| 2 |  |  | 74 |
| | 2a | 2b | |
| 3 |  |  | 78 |
| | 3a | 3b | |
| 4 |  |  | 77 |
| | 4a | 4b | |
| 5 |  |  | 86 |
| | 5a | 5b | |
| 6 |  |  | 75[c] |
| | 6a | 6b | |
| 7 |  |  | 71 |
| | 7a | 7b | |
| 8 |  |  | 75 |
| | 8a | 8b | |

[a] Procedure: Tributylphosphine (10 mol %) was added to a 0.1 M solution of substrate in ethyl acetate, and the reaction was allowed to stir at 110 °C in a sealed tube until complete consumption of starting material, at which point the reaction mixture was evaporated onto silica and purified via silica gel chromatography. [b] Isolated yields were calculated after purification by silica gel chromatography. [c] For this single example, an epimeric product was produced in 10% isolated yield.

are tolerated in the tether connecting the reacting partners, as exemplified by the cycloaddition of ether containing mono-enone mono-ynoate **6a** (Table 2, entry 6).

In agreement with the suggested stepwise mechanism,[3c] the reaction was found to be highly sensitive to the electronic characteristics of the dipolarophile, with more electrophilic dipolarophiles providing increased yields of cycloadduct. For example, whereas enoate **9a** affords only trace quantities of the corresponding cycloadduct **9b**, the more electrophilic thioenoate **3a** produces the desired cycloadduct **3b** in 78% isolated yield under identical conditions (eq 2). These results are in accordance with those of Keck, who notes the enhanced performance of thioenoates in Morita−Baylis−Hillman-type cyclizations.[9]




eqn. 2

With the exception of ether containing mono-enone mono-ynone **6a**, all substrates provide cycloadducts in >95:5 de, as determined by $^1$H NMR. Phosphine-catalyzed isomerization to the corresponding 2,4-dienoates was not observed.[6] The relative stereochemistry of cycloadducts **1b**−**8b** was established by $^1$H NMR spectroscopic analysis. The stereochemical assignments of the cycloadducts **1b**−**8b** were corroborated by single-crystal X-ray diffraction analysis of furyl substituted cycloadduct **2b**. Attempted cycloaddition of the homologous 1,8-enynes resulted in dramatically reduced diastereoselectivities and yields.

In summary, the intramolecular phosphine-catalyzed [3 + 2] cycloaddition of electron-deficient 1,7-enynes represents a powerful method for the construction of bicylo[3.3.0] ring systems, enabling diastereoselective formation of three contiguous stereogenic centers in a single manipulation. Future studies will be devoted to the development of related phosphine-catalyzed transformations, including enantioselective variants of the methodology described herein.

**Acknowledgment.** Acknowledgment is made to the Robert A. Welch Foundation (F-1466), the NSF-CAREER program (CHE0090441), the Herman Frasch Foundation (535-HF02), the NIH (RO1 GM65149-01), donors of the Petroleum Research Fund administered by the ACS (34974-G1), the Research Corp. Cottrell Scholar Award (CS0927), the Alfred P. Sloan Foundation, and Eli Lilly for partial support of this research.

**Supporting Information Available:** Spectral data for all new compounds ($^1$H NMR, $^{13}$C NMR, IR, HRMS). X-ray crystallographic data for **2b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA030022W