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Synthesis of Oxa-Bicyclic Ring Systems *via* a Tandem Rh(II) Catalyzed Cyclization-Cycloaddition Sequence

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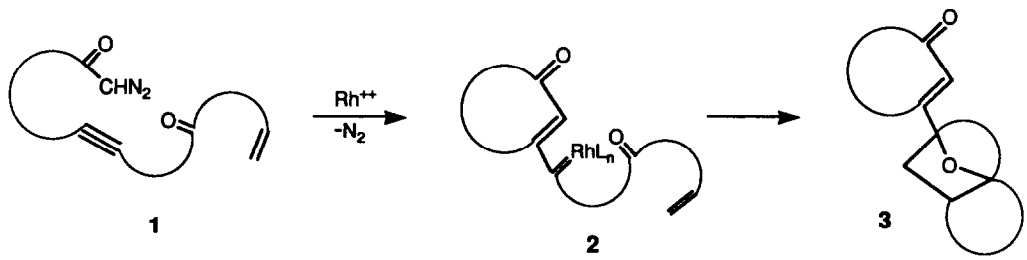
Abstract: A new annulation sequence leading to oxabicyclic ring systems is effected by treating o-alkynyl substituted α-diazoacetophenones containing tethered carbonyl groups with Rh(II) carboxylates in the presence of C-C π-bonds.

Tandem reactions are amongst the most useful synthetic methods available for generating several bonds or rings in a single step.[1-7] In recent years our research efforts have been concerned with the Rh(II) metal catalyzed reaction of α-diazo ketones and the application of the resulting carbenoid moiety to the selective formation of polycyclic systems. Two distinct methodologies have been formulated based upon this strategy; *alkyne-carbenoid metathesis*[8,9] and *tandem cyclization-cycloaddition*.[10] Both of these sequences have allowed the systematic formation of polycyclic systems from simple monocyclic or acyclic precursors. In an effort to further extend these studies, we envisaged a tandem strategy for the preparation of even more complex polycyclic ring systems which involves a merging of the above two methodologies. Addition of the rhodium stabilized carbenoid onto the adjacent acetylenic π-bond produces a cyclic vinyl carbenoid (**2**) which would reasonably be expected to undergo cyclization with the neighboring keto group to generate a carbonyl ylide intermediate. The 1,3-dipole could be trapped *in situ* to provide cycloadduct **3**. This overall process would

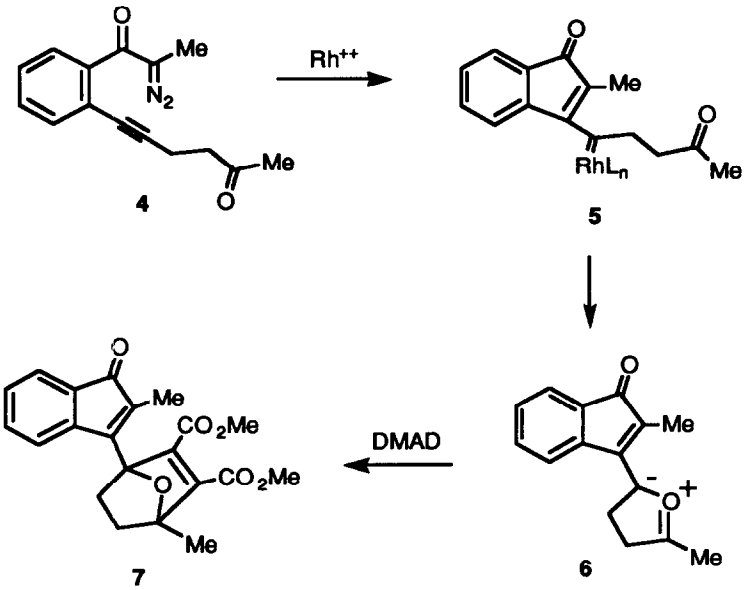


1 **2** **3**

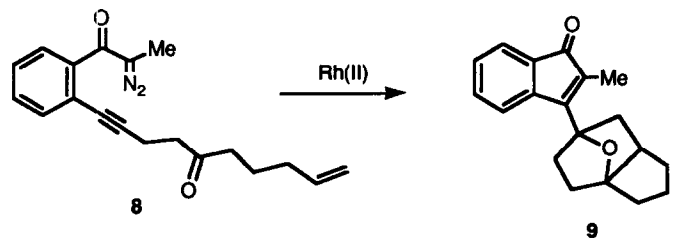
lead to a large increase in molecular complexity[11] in a single experimental operation in which three new C-C bonds have been formed. The novelty of the process lies in the method of carbonyl ylide generation, which, to our knowledge, is not precedented.[12]

For the initial evaluation of the strategy, α-diazo ketone **4** was prepared by treating methyl *o*-iodobenzoate with 5-hexyne-2-one ethylene ketal under typical Castro-Stephens arylation conditions.[13] Hydrolysis of the ketal and conversion of the resulting ketoester to diazo ketone **4** proceeded as required. Treatment of **4** with a catalytic amount of rhodium(II) octanoate at 25°C in methylene chloride with 1 equiv of dimethyl acetylenedicarboxylate afforded cycloadduct **7** in 97% yield.[14] This

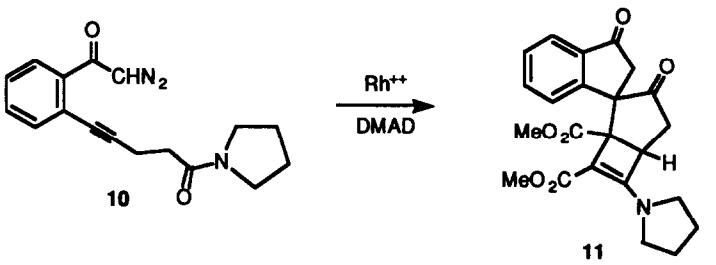
result can easily be accounted for in terms of the intermediacy of vinylcarbenoid **5** which cyclizes onto the oxygen atom of the neighboring carbonyl group to give the resonance stabilized dipole **6**. Dipolar cycloaddition of **6** across the activated π-bond of DMAD affords cycloadduct **7**.



The above domino transformation can also be performed intramolecularly by attaching the trapping agent directly to the carbonyl group. Thus, diazoketone **8** was conveniently prepared from methyl 2-(5-hydroxy-1-pentynyl)benzoate, which in turn, was synthesized by the Castro-Stevens reaction of 4-pentyne-1-ol with methyl *o*-iodobenzoate. The domino cyclization sequence proceeded in excellent yield (*i.e.*, 97%) producing cycloadduct **9**.



In view of the observations described above, it was of interest to explore the effect of other carbonyl derivatives on the rhodium(II) catalyzed cyclization reaction. Incorporation of an amido carbonyl group on the side chain (*i.e.*, **10**) was found to dramatically alter the course of the reaction. Thus, treatment of α-diazo ketone **10** with Rh(II) octanoate in CH_2Cl_2 at 25°C in the presence of DMAD gave the rearranged cycloadduct **11** as a 1:1-mixture of diastereomers which could easily be separated and purified in yields varying between 45-70%. The cyclization-cycloaddition reaction to

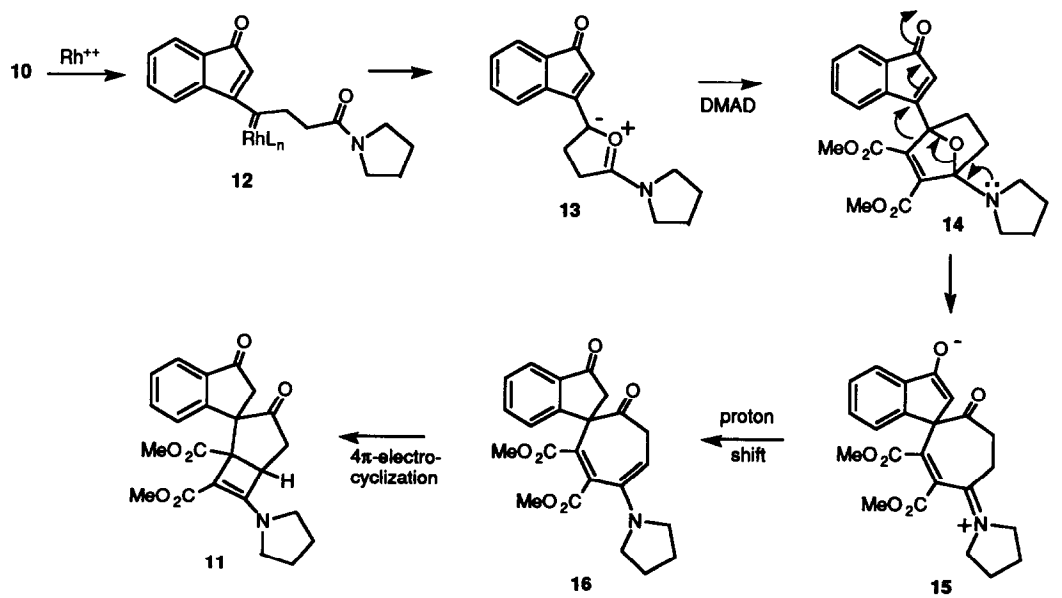


10 11

produce **11** is quite remarkable in its facility and mildness of reaction conditions. The structural assignment of **11** is based upon the following characteristic spectral data: the correct molecular weight was obtained from the HRCI mass spectrum; the ^{13}C-NMR spectrum indicates four carbonyl groups (162, 172, 204, and 210 ppm); the ^{1}H-NMR shows the α-methylene protons adjacent to the phenyl ketone at δ 2.45 and 2.65 (J_{AB}=17 Hz), the other set of methylene protons at δ 2.49 (*d*, 1H, J=17 Hz) and 2.78 (*dd*, 1H, J=17 and 10 Hz), a doublet for the methine proton at 3.72 (J=10 Hz), singlets at 3.05 (3H) and 3.53 (3H) and mutiplets centered at 1.95 (4H), 3.75 (2H), 3.95 (2H), and 7.2-7.8 (4H). Our assignment of **11** was further verified by a single crystal X-ray structure determination.

The mechanism of this unusual cycloaddition can only be speculated upon at this time and one possibility is outlined in Scheme I. Here it is proposed that the cyclization-cycloaddition sequence produces dipole **13** in the normal manner which cycloadds with DMAD to give **14**. Cycloadduct **14** can then proceed to **11** *via* a series of reactions. The first step involves oxabicyclic ring opening which is driven by the lone pair of electrons on nitrogen resulting in a Wagner-Meerwein rearrange-

Scheme I



ment to give **15**. This zwitterionic species then undergoes a proton shift to produce **16** which subsequently reacts *via* a 4π-electrocyclization[15] to generate the final product.

In conclusion, the Rh(II) catalyzed reaction of o-alkynyl substituted α-diazoacetophenone derivatives possessing tethered carbonyl groups results in an efficient annulation sequence with multiple bond formation. Further exploration of the rich chemistry of these diazo acetylenic ketones is being actively pursued in this laboratory and will be reported in due course.

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