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Rhodium Carbenoid Mediated Cyclizations. Intramolecular Cyclopropanation and C-H Insertion Reactions Derived from Type II o-Alkynyl Substituted α-Diazoacetophenones

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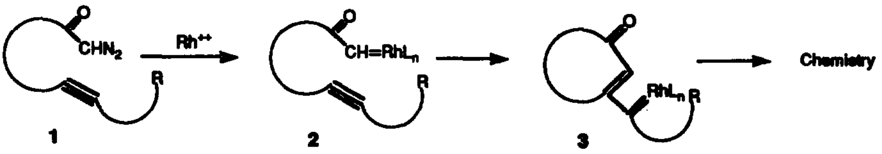
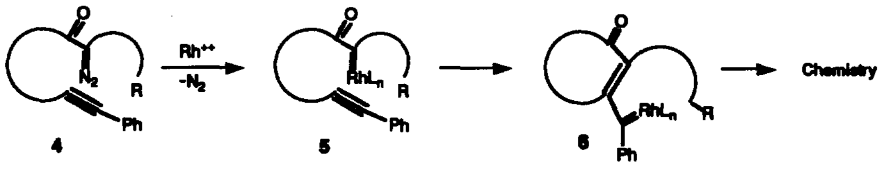
Abstract: The Rh(II) catalyzed reaction of alkynyl substituted diazo ketones gives rise to products derived from migration of the metal to the remote acetylenic carbon atom.

The metal-catalyzed reactions of α-diazocarbonyl compounds with alkenes and alkynes have been extensively employed in organic synthesis.[1-6] Recent work by our group has shown that the rhodium(II) catalyzed reaction of α-diazo ketones bearing tethered alkyne units represents a powerful method for the construction of a variety of polycyclic skeletons.[7,8] Exposure of the starting α-diazo ketone to a rhodium(II) catalyst results in cyclization of the α-keto carbenoid to an intermediate in which carbene-like reactivity has been transferred to one of the original alkyne carbon atoms. A neighboring functional group present on the backbone then traps the cyclized intermediate **3** *via* known carbene chemistry to give various products. Two basic structural variations can be achieved by altering the point of attachment of the functional group "*R*". We refer to these two modes as *type I* and *type II* internal cyclization routes. In our previous studies with *type I* molecules, we observed that the Rh(II) catalyzed reaction can result in cyclopropanation and C-H insertion.[7] Since chemical reactivity in the intramolecular cyclization process can be modified by choice of substituent and geometry,[4-6] we have undertaken an investigation of the chemistry of *type II* α-diazo ketones. The results reported below summarize various aspects of this effort.

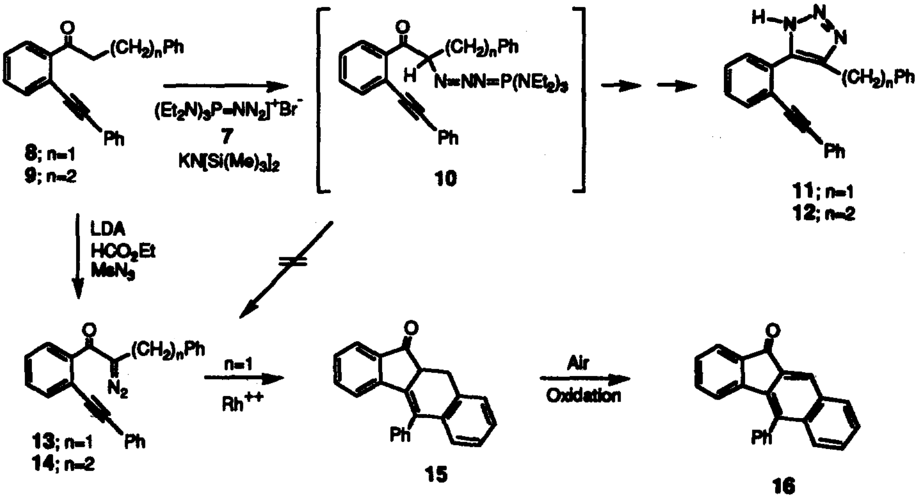
Type I

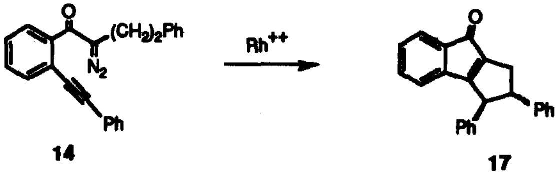


Type II



The base-catalyzed transfer of a diazo moiety to a methylene group adjacent to one or more electron withdrawing groups represents a well established protocol for α-diazo ketone synthesis.[9-12] The most commonly used reagents for diazo transfer have been tosyl[9] or mesyl azide,[10] though in recent years a number of other azido compounds and methods have been proposed.[11-13] Recently, McGuiness and Shechter reported on the use of azidotris(diethylamino)phosphonium bromide (7) as an efficient diazo transfer reagent.[13] This reagent only requires a catalytic amount of base and the product diazo compounds have been reported to be easily separated from the coproduct hexaethylphosphorimidic triamide hydrobromide. In our hands, however, the reaction of ketone 8 or 9 with

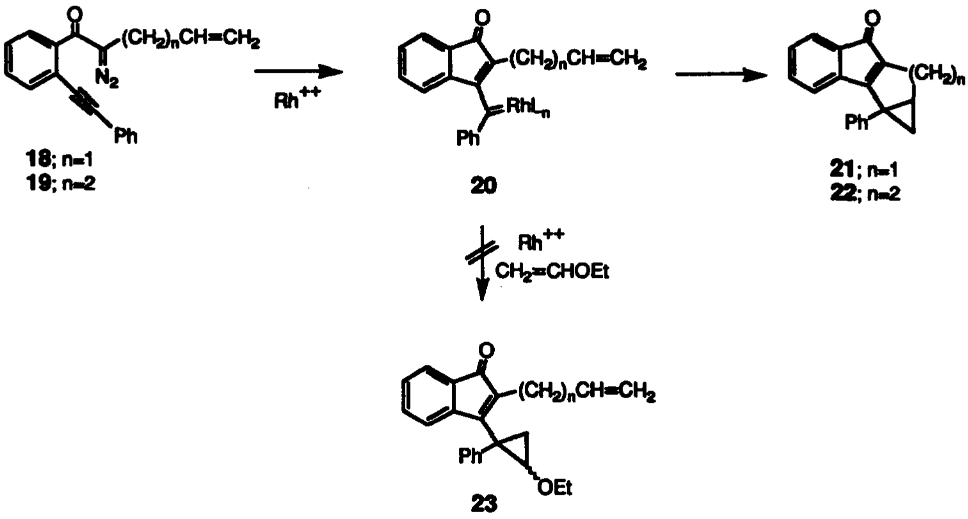




phosphonium bromide 7 afforded only triazole 11 or 12 in 76% and 62% yield, respectively. The formation of the triazole ring can be attributed to attack of the initially formed enolate onto the terminal nitrogen of 7 followed by an intramolecular Staudinger reaction[14] and a subsequent 1,3-hydrogen shift.

This difficulty was eventually overcome by treating the keto enolate with ethyl formate so as to produce a dicarbonyl compound which, on treatment with mesyl azide, afforded the desired diazo compound(s) in good yield.[15] When 13 was allowed to react with rhodium(II) acetate in benzene, initial cyclization produced a rhodium carbenoid (*i.e.*, 6) which underwent insertion into the neighboring aromatic ring to ultimately produce 16 in 75% yield. The structure of 16 was unequivocally established by an X-ray crystal structure analysis. When the reaction was carried out under an atmosphere of argon, it was possible to isolate **15** (40%) in addition to **16**. Compound **15** was readily oxidized to **16** when allowed to stand open to the air. The Rh(II) catalyzed reaction of α-diazo ketone **14** afforded **17** (70%) as the only isolable product. The formation of **17** involves insertion into the benzylic C-H bond and is consistent with other Rh(II) mediated insertions which generally exhibit a large preference for the generation of five-membered rings.[16]

As an extension of this methodology, the carbenoid cyclization reaction of α-diazo ketones **18** and **19** was next investigated. In both cases it was possible to isolate the bicycloalkanes derived from intramolecular cyclopropanation[17] (*i.e.*, **21** (67%) and **22** (81%)). We had previously found that o-alkynyl substituted α-diazoacetophenone derivatives produced vinyl carbenoids which could be trapped by electron rich π-bonds (*i.e.*, ethyl vinyl ether) to give indenyl cyclopropanes in 90% yield.[18] With this in mind, we attempted to trap the cyclized carbenoid intermediate **20** bimolecularly, by carrying out the reaction in the presence of a large excess of ethyl vinyl ether. In no case (**18**, **19**) were we able to detect any signs of the bimolecular adduct (*e.g.*, **23**). This observation indicates that bimolecular trapping of the cyclized rhodium carbenoid is significantly slower than either intramolecular cyclopropanation or insertion.



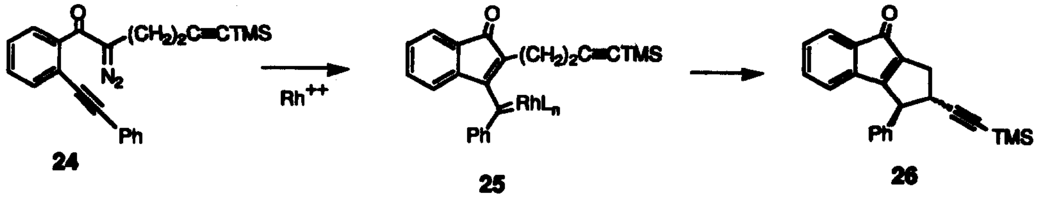
18; n=1
19; n=2

20

21; n=1
22; n=2

23

We also attempted to trap the cyclized rhodium carbenoid with an acetylenic π-bond. The insertion of alkynes into transition metal carbon bonds is a well documented reaction and has been observed in nearly all of the triads of transition metals.[19] Initial efforts focused on the rhodium(II) carbenoid catalyzed reaction of α-diazo ketone **24**. Treatment of **24** with Rh(II) acetate did not afford the product of internal attack on the acetylenic π-bond, instead only indenone **26** was obtained in 83% yield. Insertion of the rhodium carbenoid into the propargylic C-H bond is clearly preferred over attack at the acetylenic π-bond.



In conclusion, the Rh(II) catalyzed reaction of *type II* alkynyl substituted diazo ketones gives rise to products derived from migration of the metal to the remote acetylenic carbon atom. Further studies in this area are in progress and will be reported at a later date.

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