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Formation of Macrocycles by Catalytic Intramolecular Aromatic Cycloaddition of Metal Carbenes to Remote Arenes

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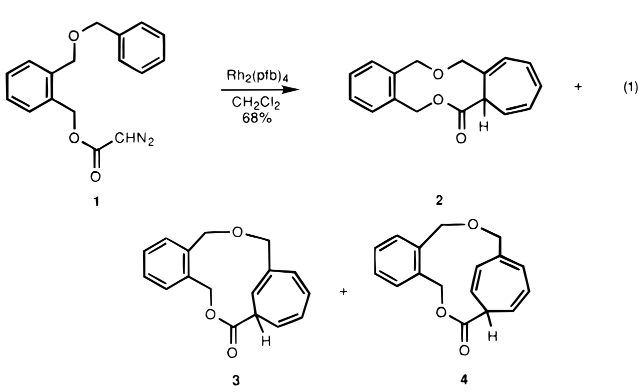
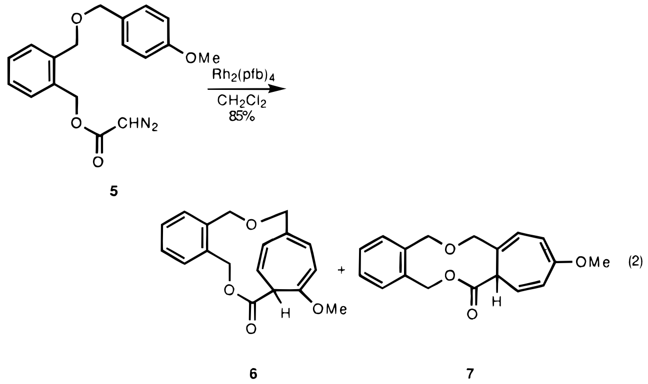
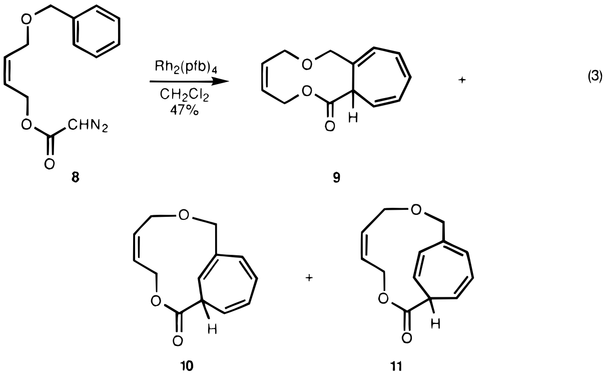
Aromatic cycloaddition of carbenes with aromatic compounds is now a common transformation for reactions of diazocarbonyl compounds catalyzed by dirhodium(II) carboxylates.[1−3] Intermolecular reactions of ethyl diazoacetate with monosubstituted benzenes produce two or more cycloheptatriene carboxylates with substituent-dependent regiocontrol.[4,5] Intramolecular aromatic cycloaddition reactions of diazocarbonyl compounds provide facile entry into bicyclo[5.*n*.0] systems,[6−9] but ring sizes have been limited to $n = 3$ or 4.[1−3] Recently, the feasibility of macrocyclization in metal carbene transformations has been demonstrated in intramolecular cyclopropanation reactions of selected diazoacetates having double bonds sufficiently remote from the carbene center to form cyclopropane-fused 11- to 13-membered rings.[10] We now report that macrocyclization by intramolecular cycloaddition of metal carbene intermediates on remote aromatic rings is not only feasible but is also a general transformation of diazoacetates and diazo ketones, even in competition with proximal cyclopropanation.

Diazoacetate **1** was prepared from 1,2-benzenedimethanol. Diazo decomposition of **1** using dirhodium(II) perfluorobutyrate, $Rh_2(pfb)_4$, in refluxing dichloromethane resulted in the formation of three aromatic cycloaddition products from reaction with the remote benzyl group at the 1,2-, 2,3-, and 3,4-positions (eq 1) in 68% isolated yield. Reactions were performed under standard conditions without the use of high-dilution methods. Regioselectivity in product formation was 75:12:13 **2:3:4**, and **2** was separable from **3/4** by chromatography. This reaction was remarkably free of byproducts including those from addition/substitution to the original benzenedimethanol unit or C−H insertion into the oxygen-activated[11] benzylic position. The *p*-methoxybenzyl analog of **1** underwent $Rh_2(pfb)_4$-catalyzed diazo decomposition to give two aromatic cycloaddition products (eq 2) in 85% isolated yield, the major isomer of which (**6**, 87%) was that from addition to the 3,4-position of the benzylic group. This regiochemical preference is consistent with that of intermolecular aromatic cycloaddition to *p*-disubstituted benzene derivatives[4,5] and suggests its suitability as a synthetic methodology for remote functionalization. The structures of these compounds were elucidated by NMR spectroscopy using coupling constants from ^1H spectra and 2D methods.







With the analogous *cis*-2-buten-1,4-diyl derivative **8**, $Rh_2(pfb)_4$-catalyzed diazo decomposition produces modest amounts (47% yield) of three cycloheptatriene products, one each from addition to the 1,2-, 2,3-, and 3,4-positions of the benzene ring (eq 3). The product ratio, **9:10:11** = 31:21:48, is remarkably close to that obtained for intermolecular aromatic cycloaddition of ethyl diazoacetate to toluene catalyzed by dirhodium(II) trifluoroacetate (18:24:58) and suggests a conformational freedom for carbene addition in the intramolecular reaction that parallels that for the intermolecular reaction. Surprisingly, cyclopropanation of the allylic double bond did not occur in reactions catalyzed by $Rh_2(pfb)_4$, but this was the sole pathway for the dirhodium(II) caprolactamate, $Rh_2(cap)_4$, catalyzed reaction (eq 4). With $Rh_2(OAc)_4$ neither **9−11** nor **12** was formed, and oligomer formation was the assumed outcome. The influence of catalyst ligand on chemoselectivity can be understood through comparative reference to charge and frontier

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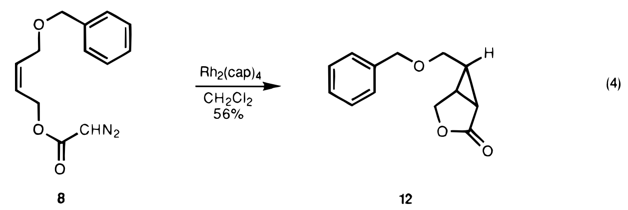
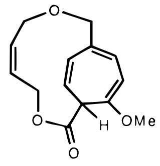


orbital properties of the catalysts.[12] With the *p*-methoxybenzyl analog of **8**, both the product from aromatic cycloaddition to the 3,4-position (**13**) and that from cycloaddition to the 1,2-position (**14**) were formed in the Rh$_2$(pfb)$_4$-catalyzed reaction (32% yield), but **13** was the major product (**13:14** = 87:13).



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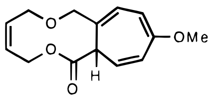

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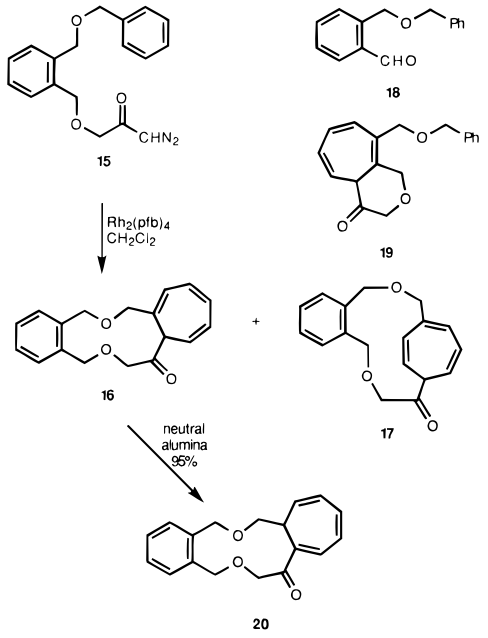
Diazo ketones have been even more widely employed than diazo esters for intramolecular aromatic cycloaddition reactions, and their utilization for the formation of bicyclo[5.3.0]decane and bicyclo[5.4.0]undecane substrates is well documented.[1−3,6−9,13] To evaluate the suitability of diazo ketones for macrocyclic aromatic cycloaddition, we selected **15** that with dirhodium(II) perfluorobutyrate yields aromatic cycloaddition products **16** and **17** in 30% and 9% isolated yields, respectively (Scheme 1). Minor products were those formed from intramolecular hydride abstraction from a benzylic position of **15** (**18**, 5% yield)[14] and from aromatic cycloaddition onto the disubstituted aromatic ring (**19**, 8% yield). Although **16** could be isolated by rapid flash chromatography on silica, it was sensitive to prolonged contact with silica which converted it into a mixture of products presumed to be the result of aromatization; compound **16** was also very sensitive to protonic acids. When **16** was placed in contact with neutral alumina, however, bond migration to **20** occurred. The 1,4-isomer **17** was inert to rearrangement on both silica and alumina. Similar macrocyclic aromatic cycloaddition did not occur with the *cis*-2-buten-1,4-diyl analog of **15**.

Scheme 1



The ability to formally connect a carbene to a remote aromatic ring offers new opportunities for the construction of macrocyclic compounds. Efforts are continuing in our laboratories to develop this methodology.

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Supporting Information Available: Experimental details for the synthesis and diazo decomposition of diazo compounds and product characterization (11 pages). See any current masthead page for ordering and Internet access instructions.

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