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A New Approach to Macrocyclization via Alkene Formation in Catalytic Diazo Decomposition. Synthesis of Patulolides A and B

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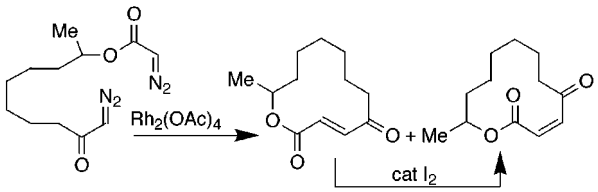
ABSTRACT



Effective synthetic uses of bisdiazocarbonyl compounds for the selective construction of diverse macrocycles, including the synthesis of patulolides A and B, by catalytic "carbene dimer" formation are reported. Control of stereochemistry and efficient methods for product isomerization or kinetic isomer differentiation have been achieved.

The formation of alkenes from diazocarbonyl compounds by so-called "carbene dimer" formation is a well-known process that has been overlooked as a viable synthetic transformation.[1,2] Its potential in intermolecular coupling from diazo ketones has been reported with copper catalysts,[3,4] and the stereochemical outcome of these reactions as a function of catalyst and substrate substituent effects has been reported.[5,6] Only two publications have described intramolecular applications,[7,8] although one of them reported the formation of cycloalkenediones from α,ω-bisdiazoketones with up to a 20-carbon ring in modest yields.[8] Convinced from prior investigations of addition reactions (cyclopropanation, cyclopropenation, aromatic cycloaddition) with the high potential of catalytic metal carbene processes for macrocyclic ring formation,[9−11] we set out to demonstrate the suitability of the so-called "carbene dimer" formation process for macrocycle syntheses.[12] We now report that

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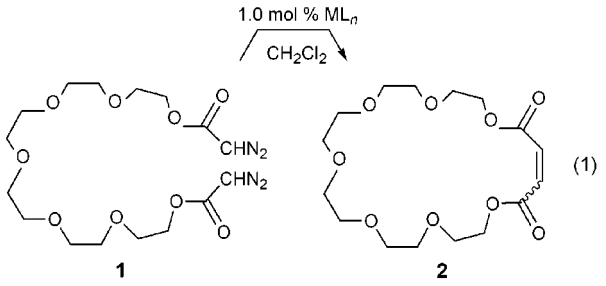
stereochemical control in macrocyclic formation can be achieved by specific catalyst selection and that this methodology can be effectively employed for the synthesis of patulolide A and patulolide B.

The bisdiazoacetate of hexaethylene glycol (**1**) was prepared from hexaethylene glycol by conventional methods in 58% overall yield. Addition of this diazo ester to a refluxing dichloromethane solution of catalyst produced macrocycle **2** (eq 1) in amounts and stereochemistry that

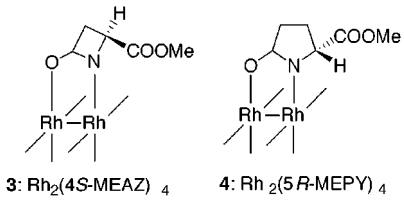


were dependent on the catalyst employed (Table 1). The major competing process was intermolecular oligomerization; intramolecular insertion into an ether oxygen-activated carbon−hydrogen bond, a highly favorable process with dirhodium(II) catalysis,[13] was not visibly productive. What is perhaps most surprising about the data in Table 1 is the extent of stereocontrol that could be achieved. With Cu(MeCN)$_4$PF$_6$ as the catalyst, **2** was obtained with a greater than 4:1 *E*:*Z* ratio. The use of rhodium acetate changes this stereoisomer ratio but not enough to be synthetically relevant. In contrast, chiral dirhodium(II) carboxamidates, either Rh$_2$(4*S*-MEAZ)$_4$ (**3**)[14] or, preferably, Rh$_2$(5*R*-MEPY)$_4$ (**4**),[15] cause predominant formation of the *Z*-isomer, presumably due to steric effects during dinitrogen loss from the coupled intermediate.[6]

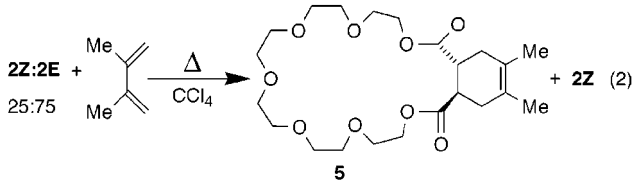
Table 1. Catalyst Dependence for Yield and *Z*/*E* Ratio of **2**[a]

catalyst	yield, %[b]	2*Z*:2*E*
Cu(MeCN)$_4$PF$_6$	73	18:82
Cu(PhCOCHCOCH$_3$)$_2$	40	32:68
Rh$_2$(OAc)$_4$	43	39:61
Rh$_2$(pfb)$_4$[c]	35	46:54
Rh$_2$(4*S*-MEAZ)$_4$	62	73:27
Rh$_2$(5*R*-MEPY)$_4$	75	74:26

[a] Reaction performed in refluxing dichloromethane; diazo ester was added to the catalyst (1.0 mol %) solution via a syringe pump. [b] Yield (unoptimized) of **2** after chromatography on silica gel. [c] Rhodium(II) perfluorobutyrate.



Treatment of a 25:75 mixture of **2Z**:**2E** with 2,3-dimethyl-1,3-butadiene (10 molar equiv) in carbon tetrachloride at reflux gave, after 48 h, complete consumption of **2E** without any observable reaction of **2Z** (eq 2). This outcome was



surprising since relative reactivities of geometrical isomers were not anticipated to differ to such a level in Diels−Alder chemistry. For comparison, we reacted a mixture of dimethyl maleate and fumarate under the same conditions and found that the fumarate ester was also at least 50 times more reactive than the maleate ester toward 2,3-dimethyl-1,3-butadiene. The overall outcome is an effective kinetic isomer differentiation, with the trans isomer reacting first followed by a very slow cycloaddition of the cis dienophile. The implications of these constructions for the design and applications of crown ethers are under investigation.

A broad selection of bisdiazoacetates, including those from diethylene glycol and tetraethylene glycol, have been treated with dirhodium(II) catalysts, and the coupling products are the only ones observed (from 96:4 to 88:12 *Z*:*E* ratios). Other systems capable of addition, insertion, or ylide reactions, namely bidsiazoacetates from *cis*-2-butene-1,4-diol, isomannide, and 1,4-butanediol, give coupling product (*Z* only) exclusively. Thus, as previously suggested by data from McKervey for bisdiazoketones,[8] this coupling reaction is general for the formation of medium rings to macrocycles and occurs exclusively even when alternative addition, insertion, or ylide transformations might also be favorable.

Patulolides A and B (**6** and **7**) are macrocyclic lactones that, since their isolation from *Penicillium urticae* mutant S11R59,[16] have been shown to have antifungal, antibacterial, and antiinflammatory activities.[16,17] Multistep syntheses of

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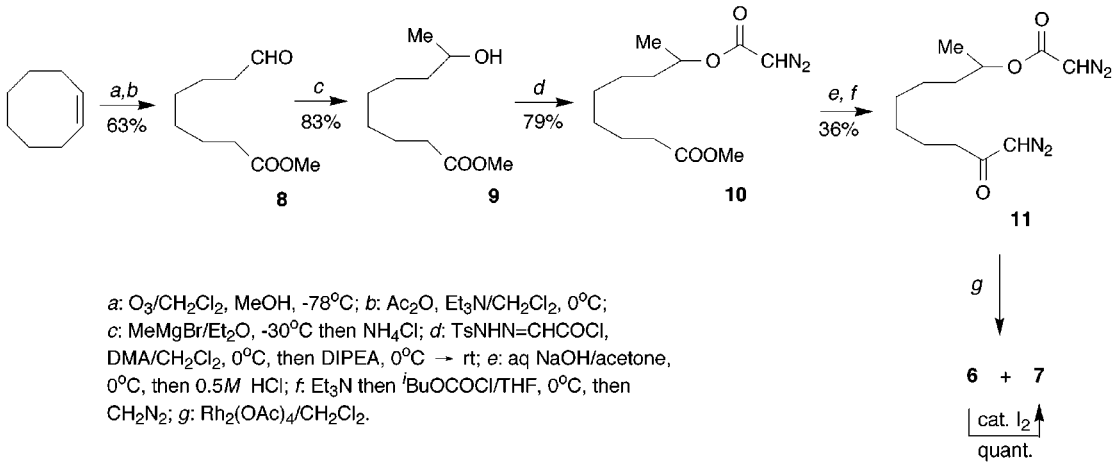
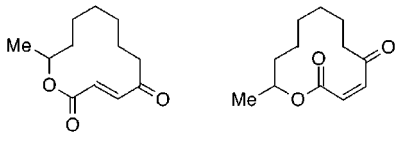
Scheme 1



a: O_3/CH_2Cl_2, MeOH, -78°C; *b*: Ac_2O, Et_3N/CH_2Cl_2, 0°C; *c*: MeMgBr/Et_2O, -30°C then NH_4Cl; *d*: TsNHN=CHCOCl, DMA/CH_2Cl_2, 0°C, then DIPEA, 0°C → rt; *e*: aq NaOH/acetone, 0°C, then 0.5*M* HCl; *f*: Et_3N then ^{t}BuOCOCl/THF, 0°C, then CH_2N_2; *g*: $Rh_2(OAc)_4/CH_2Cl_2$.

these lactones have been reported,[18−21] most of which having employed esterification as the ring-closing step.



In the synthetic approach to **6** and **7** that we now report (Scheme 1), two previously unexplored processes—the sequential construction of a diazo ester and a diazo ketone and the coupling of this mixed diazo compound—were employed. Accordingly, because of the known relative reactivities of diazo ketones and diazo esters,[1] bisdiazocarbonyl compound **11** was constructed by initially preparing diazo ester **10**[22] and then preparing diazo ketone **11**.[23] Treatment of **11** with a catalytic amount of $Rh_2(OAc)_4$ produced a 1:1 mixture of **6** and **7**, each of which was isolated in chromatographically pure form (15% **6** + 15% **7**). With $Cu(MeCN)_4PF_6$ as the catalyst, a 1:2 ratio of **6**:**7** was formed but in only 11% isolated yield.

Copper catalysts normally exhibit a preference for formation of the *E*-isomer in these coupling transformations,[3−5,8] so the reverse preference from the $CuPF_6$-catalyzed reaction was surprising. Furthermore, computational analysis (SPARTAN SGI version 5.1.1) suggested that **6** was more stable than **7**. However, treatment of **6** with a catalytic amount of iodine quantitatively converted **6** to **7**. This observation, and the probable thermodynamic stability of **7** relative to **6**, also explains the serendipitous discovery by Mori and Sakai[21] of double bond isomerization during pyridinium chlorochromate oxidation of patulolide C, the γ-hydroxyenoate analogue of **6**. The simple isomerization of patulolides A to B renders all previous syntheses of patulolide A as de facto syntheses of patulolide B. Overall, the synthesis presented in Scheme 1 is the most efficient and economical yet designed for the construction of patulolide B.

Further optimizations of these processes are possible, both in the synthesis of bisdiazocarbonyl compounds and in yields and selectivities from coupling reactions. However, the present results demonstrate a synthetically viable approach to a broad range of macrocycles.

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Supporting Information Available: Experimental and spectral data that include the synthesis and reactions of diazo compounds and characterization of reaction products. This information is available free of charge via the Internet at http://pubs.acs.org.

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