Pergamon

Tetrahedron Letters, Vol. 37, No. 16, pp. 2749-2752, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00421-2

CATALYTIC COBALT-MEDIATED REDUCTIVE CARBOCYCLIZATIONS

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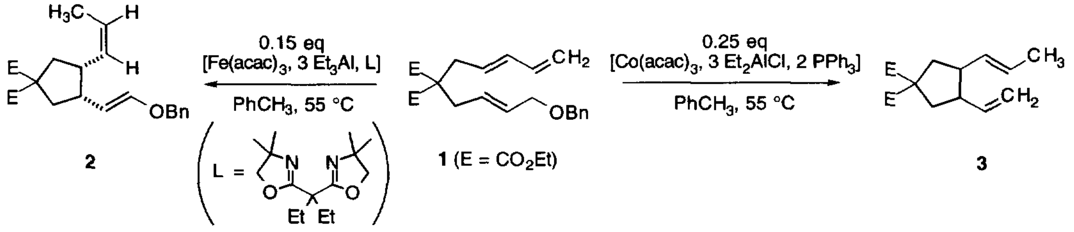
Summary: The cobalt-catalyzed cyclization of certain acyclic enediene substrates proceeds stereoselectively to afford substituted divinyl cyclopentanes and cyclohexanes in good yield. A variation, involving a substrate wherein a suitably disposed alkyne separates the reacting alkene and 1,3-diene partners, affords a novel cascade cyclization product. Copyright © 1996 Elsevier Science Ltd

We previously reported developmental studies[1,2] and synthetic applications[3,4] of a stereoselective iron-catalyzed carbocyclization of enediene substrates. The cyclization is illustrated by the conversion of triene **1** to the divinylcyclopentane derivative **2** upon treatment by a reduced iron catalyst system. The catalyst is generated by the in situ reduction of iron(III) 2,4-pentanedionate by triethylaluminum (3 equivalents) and modified by a 1,3-bisoxazoline or bipyridine ligand (1 equivalent). This transformation can be thought of as the operational equivalent of a [4+4]-ene cyclization, wherein the allylic hydrogen is transferred intramolecularly to the terminus of the diene moiety. While the iron-catalyzed cyclization is quite efficient in a variety of five- and six-membered ring forming reactions, enedienes bearing alkyl-substituted diene or alkene moieties are generally poor substrates. This is perhaps not surprising. The combination of a reduced iron center (presumably, iron(0)) and a bidentate nitrogen ligand should afford an electron rich iron complex, one that is likely to exhibit low binding affinity for an electron rich diene- or alkene-bearing substrate. We reasoned that an isoelectronic Co(I)-based catalyst system might effect the same transformation (*i.e.*, **1** to **2**), and yet, be better suited for those substrates bearing electron rich functionalities. We now describe results from our preliminary investigations directed toward that goal.



2

1 ($E = CO_2Et$)

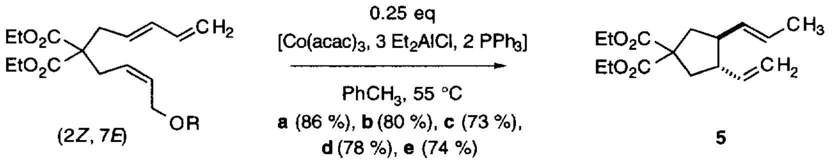
3

Cobalt catalyst systems are particularly valuable reagents for effecting [2+2+2]-cycloisomerization reactions; for example, in acetylene and related cyclotrimerizations,[5] Pauson-Khand cyclization,[6] and homo-Diels-Alder cycloaddition.[7,8] We began our investigation by treating enediene **1** with a catalyst system that has proven useful for homo-Diels-Alder cycloadditions, a catalyst generated in situ via the reduction of $Co(acac)_3$ with diethylaluminum chloride. Expecting enol ether **2**, we were surprised to find a product of apparent reductive cyclization possessing the skeleton shown in **3**. A number of synthetically interesting catalytic metal-mediated reductive cyclizations have recently been defined, including cyclizations of enynes, diynes, and bisdienes using nickel and palladium catalysts,[9-11] so we decided to pursue the cobalt-catalyzed cyclization further.

We have not yet carried out extensive studies to optimize the catalyst and conditions, but we find that: (a) the hydride apparently comes from diethylaluminum chloride and using approximately three equivalents relative to cobalt affords the best yield and cleanest product; (b) diethylaluminum chloride is a better reducing agent than ethylaluminum dichloride, triethylaluminum, or $NaBH_4$; (c) $Co^{III}(acac)_3$ is a better catalyst precursor than $Co^{II}(acac)_2$ or $Co^{II}Cl_2$; and (d) the cyclizations can be run in toluene, dichloromethane or THF with comparable results. Our typical reaction conditions employ the catalyst system [$Co^{III}(acac)_3$ / 2 Ph_3P / 3 Et_2AlCl] in toluene (ca 55 °C), and under these conditions, (2*E*,7*E*)-enediene **1** affords the divinylcyclopentane **3** in 77 % chemical yield. The product obtained is a 6.3:1 *trans:cis* mixture of cyclopentane diastereomers. Each diastereomer bears the propenyl side chain with predominantly the E geometry (>15:1 *E:Z*); that is, the major product obtained from enediene **1** is diastereomer **5**, *vide infra.*

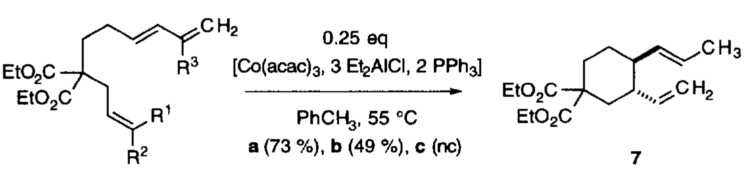
We find that the isomeric (2*Z*,7*E*)-enediene is a better substrate for this cobalt catalyst system. Compared to the (2*E*,7*E*) isomer, (2*Z*,7*E*)-**4a** affords the *trans*-divinylcyclopentane **5** in higher yield (86 % versus 77 %) and better diastereoselectivity (25:1 versus 6.3:1 *trans:cis* and >20:1 *E:Z*). To examine the influence of the allylic leaving group, cyclizations of several other alcohol derivatives were carried out. The benzyl group is not required for efficient cyclization. The corresponding silyl ethers **4b** and **4c** afford product **5** in 80 % and 73 % yield, respectively. Surprisingly, the allylic acetate **4d** and the allylic carbonate **4e** are also good substrates. In a direct competition experiment, the allylic acetate **4d** is consumed approximately one and one-half times faster than benzyl ether **4a**.

4a (R = CH_2Ph)
b (R = $Si(i\text{-}Pr)_3$)
c (R = $Si(t\text{-}Bu)Me_2$)
d (R = $C(O)CH_3$)
e (R = CO_2Et)



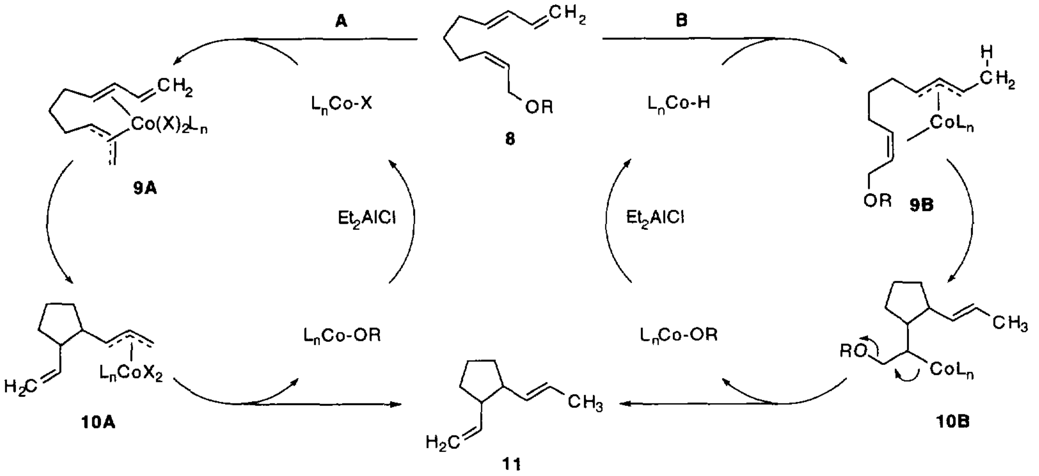
The (2*Z*,8*E*)-enediene **6a** undergoes cobalt-catalyzed cyclization to afford the *trans*-divinylcyclohexane **7** in 73 % yield and high isomeric purity (50:1 *trans:cis*, 15:1 *E:Z*). Again, the (2*Z*)-isomer is a better substrate than the corresponding (2*E*)-isomer. The latter substrate, (2*E*,8*E*)-enediene **6b**, affords **7** in only 49 % yield. An additional substituent on the 1,3-diene moiety hinders the reaction, and enediene **6c** failed to cyclize under the standard conditions.

6a (R^1 = CH_2OBn, R^2, R^3 = H)
b (R^1 = H, R^2 = CH_2OBn, R^3 = H)
c (R^1 = CH_2OBn, R^2 = H, R^3 = CH_3)



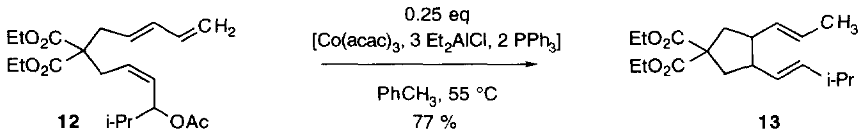
Scheme I illustrates two models for the possible catalytic cycle. Pathways **A** and **B** differ in the manner by which an initial π-allylcobalt species **9** is generated. Path **A** proceeds via initial insertion into the allylic C-O bond, a feature that is supported by the observed rate difference between substrates **4a** and **4d**. Recall that the substrate bearing the better leaving group, the allylic acetate **4d**, reacts about one and one-half times faster. However, enediene **6c** bears the same allylic leaving group as **6a**. Its failure to cyclize argues against pathway **A**.

Scheme I. Two models for the cobalt-catalyzed reductive cyclization of enedienes.



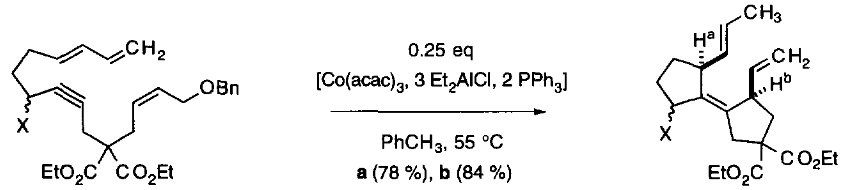
We currently prefer the alternative path **B** as our working model. Pathway **B** proceeds via the addition of cobalt hydride across the 1,3-diene moiety. The formation of a π-allylcobalt complex via the addition of Co-H to a 1,3-diene has been implicated in a variety of intermolecular cobalt-catalyzed coupling reactions, including diene dimerization,[12] diene-to-alkene cross coupling,[13] and diene-to-alkyne cross coupling reactions.[14] The resulting π-allylcobalt species **9B** could undergo cycloisomerization via insertion of the pendant alkene[2] to afford the alkylcobalt species **10B**. Cleavage of the cobalt-carbon σ-bond with loss of the β-alkoxide leaving group accounts for the observed product **11**. Reduction of the resulting cobalt alkoxide by diethylaluminum chloride would regenerate the requisite cobalt hydride catalyst.

The effect of alkyl substitution at the allylic position gives additional insight into the cyclization reaction. Substrate **12** undergoes facile cyclization and affords divinylcyclopentane **13** in 77 % yield. The two new disubstituted alkenes within structure **13** are formed with predominantly the E geometry, each >20:1 *E:Z*. However in contrast to the cyclization of **4**, which proceeds with high *trans:cis* diastereoselectivity, divinylcyclopentane **13** is formed as a near 1:1 *trans:cis* mixture.



One possible explanation for the formation of a substantial fraction of the *cis*-divinylcyclopentane from enediene **12** is consistent with the model outlined in pathway **B** (Scheme I). Addition of Co-H to the chiral enediene **12** should afford two diastereomeric complexes akin to **9b**. It is reasonable to assume that both the cycloisomerization step (*i.e.*, **9B** to **10B**) and the elimination step (*i.e.*, **10B** to **11**) proceed stereospecifically. Since the nature of the allylic leaving group affects the rate of the cyclization, the cycloisomerization of **9B** to **10B** in this model must be fast relative to the elimination of **10B** to **11**. To establish the correct relative stereochemistry between the vicinal C-O and C-Co bonds as required for stereospecific elimination to the (*E*) *iso*-propyl-substituted alkene, one of the diastereomeric complexes of **9B** must react via the *cis*-diastereomer of **10B**.

This cobalt-catalyzed reductive cyclization is also applicable to certain cascade cyclizations. For example, cyclization of **14a** affords the unusual bicyclic triene **15a** in 78 % yield as a 4:1 mixture of diastereomers. The results of nOe studies on **15a**, particularly the strong nOe from observed H^a to H^b (11 %), are consistent with the cis relationship between the pendant alkene groups. The related substrate **14b** cyclizes similarly (84 % yield).



14a (X = H); **b** (X = OTBDMS)

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In summary, we have uncovered a novel cobalt-catalyzed cyclization that complements the known iron-[2] and palladium-catalyzed[15] cycloisomerizations of enediene substrates. Further investigations are in progress.

Acknowledgments. Financial support of this work by the National Institutes of Health (GM34927) is gratefully acknowledged. We thank the NIH (SIG 1-S10-RR06301) for NMR instrumentation funding, the NSF (CHE-93000831) for GC-MS instrumentation funding, and Dr. Richard Shoemaker for technical assistance.

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(*Received in USA* 9 *January* 1996; *accepted* 29 *February* 1996)