Pure & Appl. Chem., Vol. 60, No. 1 pp. 27–34, 1988.
Printed in Great Britain.

Metal mediated routes to 5-membered rings

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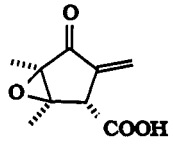
Abstract - New methods for the synthesis of functionalized alkylidene cyclopentenone and alkylidene indanone derivatives are described. The first, a method based on the reaction of cationic stoichiometric maleoylcobalt complexes with terminal alkynes, allows the synthesis of 5-alkylidene cyclopent-2-ene-1,4-diones by reaction with terminal alkynes. The formation of the alkylidene cyclopentenedione ring system is presumed to arise via the intermediacy of a cationic vinylidene complex formed via tautomerization of the terminal alkyne within the coordination sphere of the cobalt. A more practical process for the preparation of alkylidene cyclopentenediones and 2-alkylidene indan-1-ones was developed based on the palladium(II) induced electrophilic ring expansion of 4-(1-alkynyl)-4-hydroxycyclobut-2-en-1-one, 2-(1-alkynyl)-2-hydroxy benzocyclobutenone, and various derivatives. Some of the compounds prepared were assayed for in vitro antitumor activity.

Natural products containing or derived from an alkylidene cyclopentenone substructure show significant biological activity. For example, there is a growing class of cyclopentanoid antibiotics[2] such as methylenomycin A and B,[3] 1 and 2, the pentenomycins,[4] 3, xanthocidin,[5] 4, and the known antitumor agent sarcomycin,[6] 5. More recently, a series of marine eicosanoids related to the prostaglandins, such as the clavulones[7] (claviridenones[8]) 6, chloro[9]-bromo- and indovulones[10] 7, and the punaglandins[11] 8, have been reported to possess remarkable cytotoxicity in both in vitro and in vivo studies.[12] In fact, the non-naturally occurring arylidene cyclopentenediones 9 also show reasonable in vitro antitumor activity.[13]

The significant biological activity of the alkylidene cyclopentenone natural and non-natural products has prompted the development of numerous methods for the synthesis of this class of compounds.[14] We describe herein new methods for the preparation of functionalized alkylidene cyclopentenones and alkylidene indanones.



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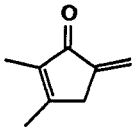

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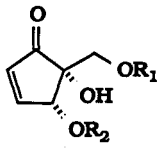
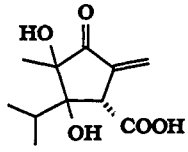


3

$R_1 = H; R_2 = H$
$R_1 = H; R_2 = Ac$
$R_1 = Ac; R_2 = H$



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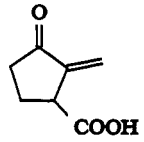

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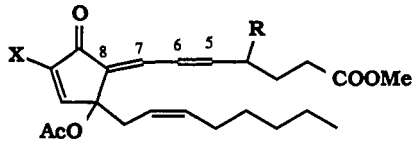
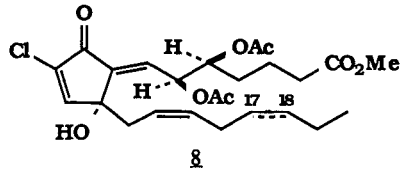


6

Clavulone I: X=H; R=OAc; 5,6-Z; 7,8-E
Clavulone II: X=H; R=OAc; 5,6-E; 7,8-E
Clavulone III: X=H; R=OAc; 5,6-E; 7,8-Z

7

Chlorovulone I: X=Cl; R=H; 5,6-Z; 7,8-E
Chlorovulone II: X=Cl; R=H; 5,6-E; 7,8-E
Chlorovulone III: X=Cl; R=H; 5,6-E; 7,8-Z
Bromovulone: X=Br; R=H; 5,6-Z; 7,8-E
Iodovulone: X=I; R=H; 5,6-Z; 7,8-E



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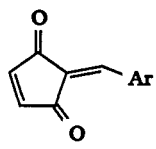
Punaglandin 3: 17,18-dehydro
Punaglandin 4: 17,18-dihydro



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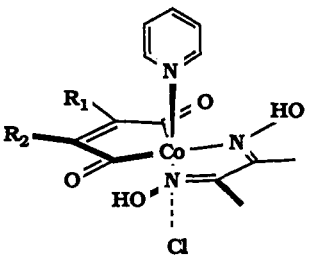
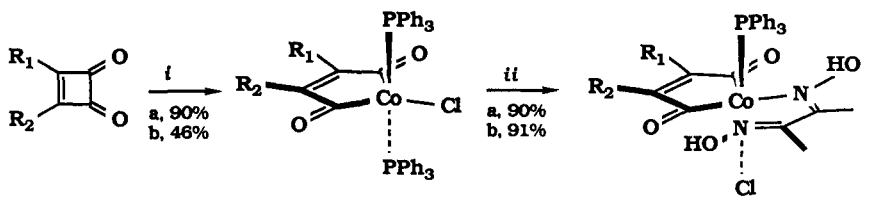


10

Maleoylcobalt complexes of general structure 10 were developed in our laboratory for the synthesis of quinones by reaction with alkynes.[15] During an investigation of various ligand effects on the quinone synthesis, we had occasion to prepare 11a, the triphenylphosphine analog of 10 (eq.1). Complex 11a proved unreactive toward terminal alkynes under conditions which provided quinones from 10, so we increased the reactivity of 11a toward alkynes by removal of the chloride ligand with $AgBF_4$ in CH_3CN (eq.2). The resulting cation, 12a, on reaction with terminal alkynes (1.5 equivalents) in dichloroethane at 70°C for 36 h, produced only very low yields of quinones; instead, transformation to the alkylidene cyclopentenediones 13 occurred in good to modest yields (Table 1). The reaction proceeded with a range of terminal alkynes and was compatible with propargyl ether and CN, OAc, and Cl functionality, however, best yields were obtained with simple aliphatic terminal alkynes. Using an unsymmetrically substituted maleoylcobalt complex, 12b, alkylidene cyclopentenediones were formed as 1 : 1 mixtures of stereoisomers. Attempts to extend the reaction to 1-trimethylsilyl substituted alkynes, via silatropic rearrangement, and to enynes and diynes were not successful. If there is any trend noted from the results of Table 1 it is that electron withdrawing substituents seem to lead to lower yields of product.



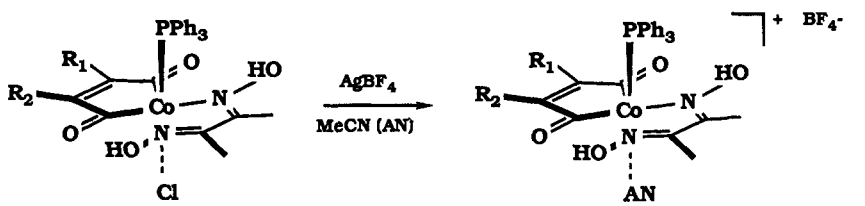
(eq. 1)

i: $ClCo(PPh_3)_3$/PhH

ii: dimethylglyoxime/acetonitrile

11a $R_1=R_2=Me$

11b R_1=i-Pr; R_2=OMe



(eq.2)

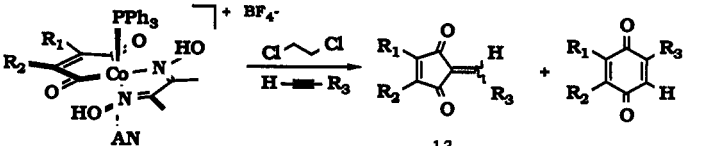
12a $R_1=R_2=Me$

12b R_1=i-Pr; R_2=OMe

It is curious that the simple substitution of PPh_3 for pyridine in complex 10 causes, what appears to be, a major change in the path of the reaction, both in terms of the reactivity of the complex toward alkynes and in the formation of the alkylidene cyclopentenedione product. How can we account for this behavior? Complex 10 seems to react with alkynes to give quinones by first dissociating the axial chlorine, which allows the alkyne to coordinate to the cobalt.[15d,e] After this requisite prior coordination, it is possible that quinone formation occurs by means of insertion of the alkyne into one of the cobalt acyl bonds followed by reductive elimination to give the quinone (Scheme 1). It logically follows that any phenomenon that retards chloride ligand dissociation could slow down the rate of reaction of the dimethylglyoxime based complexes with alkynes. Substitution of pyridine with PPh_3 seems to do just that, since ionization to a cationic maleoylcobalt complex should be more facile (better stabilization of the cation) in the pyridine system than with the PPh_3 complexes.

The formation of alkylidene cyclopentenediones can be rationalized as occurring through the cationic vinylidene cobalt intermediate 14 (eq.3). Tautomerization of terminal alkynes to vinylidenes, stabilized by coordination to a metal complex, is a well precedented transformation in organometallic chemistry.[16] In comparing the reactivity of the pyridine complex 10 and PPh_3 system 11 toward a coordinated alkyne, the observed product distribution suggests that the rate of vinylidene formation is faster than migratory insertion in the

Table 1. Formation of 5-Alkylidene Cyclopentenediones From Maleoylcobalt Complexes 12a and 12b and Terminal Alkynes

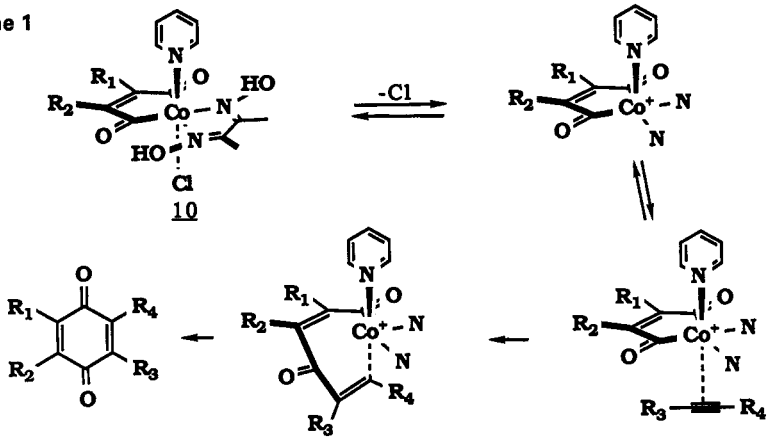


12a R_1=R_2=Me

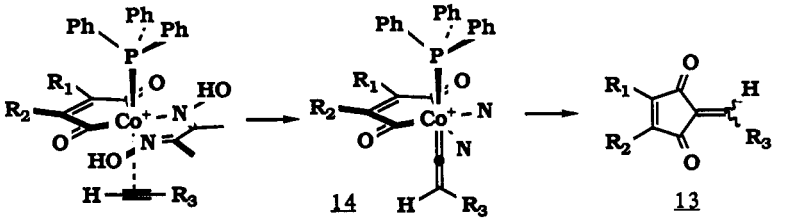
12b R_1=i-Pr; R_2=OMe

ENTRY	COMPLEX	ALKYNE R_3	PRODUCT YIELD, %	QUINONE YIELD, %
1	12a	n-Bu	66	08
2	12a	$(CH_2)_3Cl$	44	08
3	12a	CH_2OCH_3	34	14
4	12a	$(CH_2)_3CN$	41	09
5	12a	Ph	23	13
6	12a	CH_2OAc	30	00
7	12a	CH_6H_{11}	80	00
8	12a	$(CH_2)_{12}CH_3$	74	10
9	12b	n-Bu	72	00
10	12b	C_6H_{11}	75	04

Scheme 1



PPh_3 system, while the opposite must hold for the pyridine complex. The precise reasons for the change in rates of these reactions is not known, but the rate difference might be rationalized qualitatively by considering the sigma donor effects of PPh_3 versus pyridine which suggest that the cationic PPh_3 complex would be more electrophilic than the pyridine cation. Thermodynamic considerations aside, if migratory insertion is dependent on the availability of electron density at the migrating locus, it is possible that migratory insertion is retarded for the complex containing PPh_3 relative to that with pyridine. Using similar arguments, one can rationalize the vinylidene formation as proceeding via nucleophilic attack of the alkyne π-electrons on the cationic metal complex. The more electrophilic the metal complex, the more facile the vinylidene formation. In accord with these qualitative rationalizations we note that using the more basic phosphine, PCy_3, in place of PPh_3, shifted the product formation in favor of quinone in a single experiment where the more basic phosphine was used.



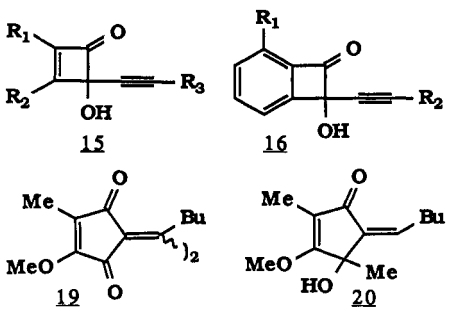
(eq. 3)

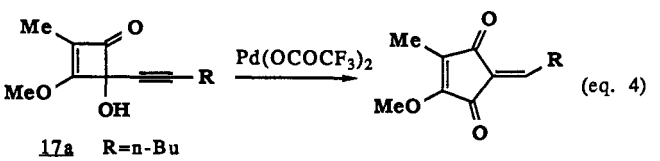
Table 2. In Vitro Antitumor Assay of Alkylidene Cyclopentenediones 13 (R_1, R_2=Me; R_3=n-C_4H_9 and $(CH_2)_3Cl$) Compared With Cisplatin and Mitomycin C (IC_{50}, μg/mL).

Cell Line	Cisplatin	Mitomycin C 13, R_3=n-C_4H_9	13, R_3=$(CH_2)_3Cl$
murine melanoma	7.7	2.5	15.1	11.1
human colon (HCT-116)	4.5	0.50	15.2	15.0
human nasopharyngyl	2.6	0.69	18.6	6.4
human colon (Moser)	6.3	2.2	15.2	17.4
murine lung	7.0	0.75	14.4	17.0

Given the pronounced antitumor activity of a number of alkylidene cyclopentenone derivatives (see above), we submitted two of the compounds prepared above for in vitro antitumor assay.[17] The results listed in Table 2 demonstrate that the alkylidene cyclopentenediones show significant cytotoxicity towards a number of tumor cell lines.

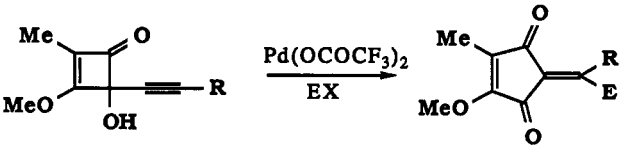
Having discovered a stoichiometric transition metal based route to functionalized alkylidene cyclopentenone derivatives, we considered finding a metal catalyzed entry to these compounds in order to increase the practicality of the method. 4-Alkynyl-4-hydroxycyclobutenones 15 and 2-alkynyl-2-hydroxybenzocyclobutenones 16 are derived from cyclobutenediones and benzocyclobutenediones, respectively, by the high yield addition of alkynyl anions, and the reactions occur with good regioselectivity with a number unsymmetrically substituted substrates.[18] Treatment of 4-(1-hexynyl)-4-hydroxy-3-methoxy-2-methylcyclobut-2-enone 17a with 10 mole % $Pd(OCOCF_3)_2$ in THF at 60°C for 1 hr induced a clean rearrangement leading to E-alkylidene cyclopentenedione 18a isolated together with the Z-stereoisomer in a 12:1 ratio in 45% yield (eq.4). The other major product in this reaction was 19 (28% yield-mixture of stereoisomers), a dimer of 18a, presumably formed by reaction of the vinyl palladium intermediate with protonated product 18a in a Heck type reaction.[19] Confirmation of structure 18a as the major stereoisomer was arrived at in the following fashion. Palladium induced ring expansion of 17 could have occurred to form the proposed 5-alkylidene cyclopent-2-ene-1,4-dione or a 5-alkylidene cyclopent-3-ene-1,2-dione.





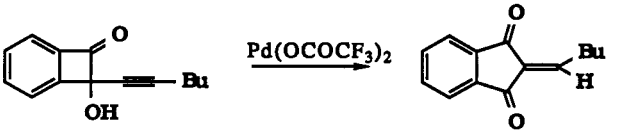
The latter ring system appears to be unknown, and it is unlikely that the palladium catalyzed ring expansion produced this isomer for a number of reasons. First, the 5-alkylidene cyclopent-2-end-1,4-dione ring system shows a strong ν_{CO} near 1690cm^{-1} in the IR (in addition to a weak absorbance near 1730 cm^{-1}); we have prepared and rigorously characterized a number of 5-alkylidene cyclopent-2-ene-1,4-diones by the chemistry described in the first part of this manuscript, and the spectroscopic data obtained for the products of the palladium catalyzed reaction are in complete accord with the structures proposed here. Second, in the reaction reported in equation 6 (see below), ring expansion of the benzocyclobutenone system gives a compound with ν_{CO} at 1690cm^{-1} in the IR (with a weak absorbance at 1725 cm^{-1}) and with only one carbonyl absorbance in the ^{13}C NMR. We observed no stereoisomers in this reaction. The 2-alkylidene indane-1,3-dione would be symmetrical relative to isomerization about the alkylidene double bond, while the isomeric 3-alkylidene-indane-1,2-dione would exist as a mixture of two double stereoisomers. We can observe, by spectroscopic means, both alkylidene isomers in all cases where they exist, but we can detect no absorbances indicating a double bond isomer in the ^1H NMR spectrum of the crude product of equation 6. Spectroscopic arguments were used to deduce the products formed in the other palladium induced ring expansions described in the paper. Finally, the stereochemistry about the alkylidene double bond was confirmed by the reaction of 18a with MeLi to give 20 in 80% yield. Since addition of MeLi to the more reactive ketone was anticipated, the observation of ^1H NMR vinyl hydrogen absorptions at δ6.06 for the major isomer and δ6.45 for the minor isomer dictate assignment of the stereochemistry shown in 20 to the major stereoisomer (vinyl H anti to deshielding carbonyl).

In order to maximize the formation of the protonated product 18a, further reaction of 18a with the vinyl palladium intermediate must be inhibited. Although increasing the amount of acid present in the reaction medium did not significantly improve the yield of 18a, we did notice a variation in the 18/19 ratio with the structure of the 4-(1-alkynyl) -hydroxy-3-methoxy-2-methylcyclobut-2-enone. 4-Phenyl-4-hydroxy-3-methoxy-2-methylcyclobut-2-enone, 17b, possesses a sterically demanding substituent at the vinyl carbon, and it underwent palladium catalyzed rearrangement (10% $Pd(OCOCF_3)_2$ in THF at 40°C for 5 h) to give the alkylidene cyclopentenedione 18b in 40% yield with no trace of the corresponding dimer observed (eq.4). Of interesting synthetic potential, we discovered that efficient trapping of the vinyl palladium intermediate could be effected by inhibiting the protonation with an acid scavenger (propylene oxide) and conducting the ring expansion reaction with 5% $Pd(OCOCF_3)_2$ in the presence of allyl bromide or NBS to provide the tetrasubstituted alkylidene cyclopentenones, 21, shown in eq.5. In the former case a 73% yield of the tetrasubstituted alkylidene cyclopentenedione 21a was produced with a stereoisomer ratio of >20 : 1, while NBS efficiently gave the vinyl bromide 21b as a 13 : 1 mixture of stereoisomers in 77% yield. Assignment of stereochemistry to 21a and 21b is presumed to follow that deduced for the protonated analog 18a.



21a E=allyl, 73%
21b E=Br, 77%

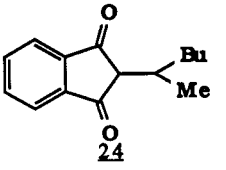
(eq. 5)



(eq. 6)

22 23

The ring expansion sequence was extended to 2-(1-hexynyl)-2-hydroxybenzocyclobutenone 22 (eq.6), prepared by addition of 1-lithiohexyne to benzocyclobutenedione. The product, 2-(1-pentylidene)indane-2,3-dione, 23, evidently formed in high yield as judged from the ^1H and ^{13}C NMR and IR spectra of the crude product, however, rapid decomposition occurred when purification was attempted on SiO_2 or other media. The existence of 23 was indirectly verified through reaction with MeLi which gave predominantly the stable 1,4-adduct, 24. To



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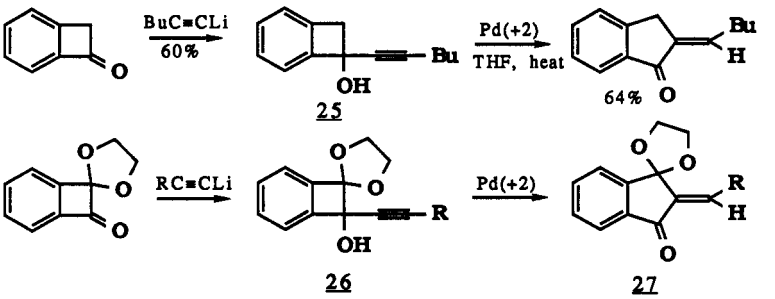
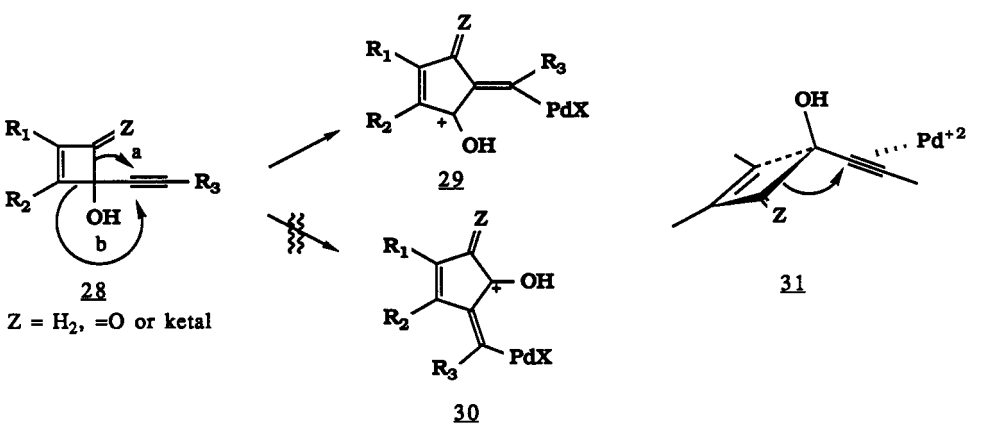
circumvent the reactivity of the 2-alkylidene indanediones, we explored the reactivity of the alkynyl adducts of both benzocyclobutenone[20] and the ethylene glycol monoketal of benzocyclobutenedione[21] (83% yield from benzocyclobutenone) and carried through the sequences shown in Scheme 2. All reactions occurred in high yield and the products were easily isolated and characterized. Again, as with the ring expansions shown above, the chemical shifts of the olefinic hydrogens observed for both isomers were used to establish the stereochemistry of the predominant regioisomer. Rearrangement of the benzocyclobutene derivative 25 occurred in good yield and stereoselectivity and established the potential of using the palladium catalyzed reaction for the synthesis of alkylidene indenones and possibly alkylidene cyclopentenones. Significantly, the ketal-protected benzocyclobutenone derivatives, 26, rearranged in excellent yield and stereoselectivity to give the monoketal derivatives of 2-alkylidene indane-1,3-diones, 27. In contrast to the highly sensitive 2-pentylidene indane-1,3-dione, 23, the monoketal derivatives are easily isolated, stable compounds. These molecules are perfectly functionalized for elaboration into benzo derivatives of natural products such as the clavulones, 6.

How do we rationalize the exceptional stereoselectivity observed in the palladium induced ring expansions of 4-alkyl-4-hydroxycyclobutenones 15 and 2-alkyl-2-hydroxy benzocyclobutenones 16? Two factors seem to be operating to influence the stereochemical outcome of these reactions. First, it is apparent that only one of two possible bonds, a or b in 28, is migrating to the adjacent sp hybridized carbon. Ring expansions from 4 to 5 membered rings are very common, and a number of rationalizations for the selectivity of the ring expansions have been advanced.[22] In our examples, it appears that the non-vinyl or non-aryl carbon, a in 28, selectively migrates in every case. While the ability of the migrating group to stabilize positive charge could play a role in governing the selectivity of the reaction, we can explain the outcome of the ring expansion by postulating a reaction path that proceeds through the best stabilized cationic intermediate (28→29, not 30). Then, formation of the final product is concluded in a stereospecific fashion by trans addition across the alkyne bond as depicted in 31.

Scheme 2



R	yield 26	conditions	yield 27	isomer ratio
$n\text{-}C_4H_9$	92%	2.5% $Pd(OTf)_2$, 12h, rt	91%	36:1
$n\text{-}C_6H_{13}$	81%	2.5% $Pd(OTf)_2$, 24h, rt	51%	26:1
$c\text{-}C_6H_{11}$	97%	2.5% $Pd(OTf)_2$, 10h, rt	75%	>99:1
$SiMe_3$	84%	2.5% $Pd(OTf)_2$, 12h, rt	56%	20:1
Ph	92%	2.5% $Pd(OTf)_2$, 12h, rt	89%	20:1
CH_2OCH_3	90%	2.5% $Pd(OTf)_2$, 12h, rt	84%	>99:1
$CH(OTBDMS)CH_3$	97%	5.0% $Pd(OTf)_2$, 10h, rt	66%	18:1
$(CH_2)_2OTBDMS$	74%	5.0% $Pd(OTf)_2$, 12h, rt	75%	22:1



In conclusion, we have discovered two new transition metal based methods for the preparation of functionalized alkylidene cyclopentenones and alkylidene indanones. Using the palladium catalyzed ring expansion of 4-alkyl-4-hydroxycyclobutenones and 2-alkyl-2-hydroxybenzocyclobutenone ethylene glycol ketals, it is possible to control the stereochemistry about the alkylidene double bond. This chemistry should prove useful in the synthesis of cyclopentanoid natural products, but also holds promise as a method for the rapid construction of non-naturally occurring, bioactive cyclopentanoid derivatives. Since much of the molecular complexity of natural products may not be important for biological activity, the development of new synthetic methods that provide easy access to highly functionalized compounds will be important in defining the limiting structures necessary to support the sought after biological action. In this light, the unique ability of the palladium catalysts to form alkylidene cyclopentenones under neutral conditions at ambient temperatures from highly functionalized substrates could make this chemistry a powerful synthetic tool for structure-function studies.

Acknowledgement This investigation was supported by PHS grants number CA 40157 and CA 44404 awarded by the National Cancer Institute, DHHS.

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