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Ruthenium-Catalyzed Cycloisomerization−Oxidation of Homopropargyl Alcohols. A New Access to γ-Butyrolactones

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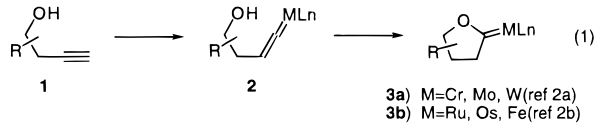
Abstract: Vinylidenemetal species, which readily form from terminal alkynes under mild conditions, have rarely been utilized as reactive intermediates in a catalytic cycle. The conversion of homopropargyl alcohols via such intermediates to metal-complexed oxacarbenes led to the development of an "oxidant" compatible with a ruthenium complex capable of performing the cycloisomerization, that would convert them to lactones. None of the oxidants known to stoichiometrically convert isolated metallooxacarbenes to esters are effective. The unconventional "oxidants", *N*-hydroxyimides, proved to be capable of effecting the desired transformation, with *N*-hydroxysuccinimide being the "oxidant" of choice. The procedure of choice employs cyclopentadienyl (1,4-cyclooctadiene) ruthenium chloride and trifuryl phosphine as the precatalyst in the presence of tetra-*n*-butylammonium bromide or hexafluorophosphate with *N*-hydroxysuccinimide as the oxidant in DMF−water at 95°. In this way, a wide diversity of homopropargyl alcohols were converted to γ-butyrolactones with excellent chemoselectivity. Lactones synthesized include an intermediate toward a platelet aggregation inhibitor, a fruit flavor principle, an inhibitor of binding of phorbol esters to PKC-α, a tobacco constituent, a wood constituent (quercus lactone), an aldosterone antagonist (spironolactone) precursor, and an acetogenin known for pesticidal and antitumor activities (muricatacin).

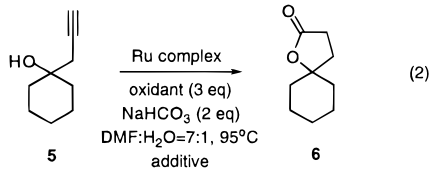
Organometallic vinylidene complexes derived from acetylenic compounds have been widely studied, but few catalytic cycles have evolved.[1−4] The facility by which such complexes are generated makes them attractive targets for development of more atom economical methodology. The importance of five-membered ring oxygen heterocycles directed our attention to the facility by which homopropargylic alcohols **1** react with a ruthenium complex to form an oxacarbene species **3**, presumably via nucleophilic addition to a vinylidene carbene intermediate **2** (eq 1).[2b] Release of the tetrahydrofuran moiety is required in order to convert this cycloisomerization into a catalytic cycle. The potential susceptibility of carbene intermediates toward nucleophilic addition and the importance of γ-butyrolactones led us to consider a catalytic cycle as outlined in Scheme 1. Such a task appeared daunting because extensive efforts toward stoichiometric decomplexation of the intermediate proved



(1)

fruitless.[5] Nevertheless, oxidation with strong oxidants such as ceric ammonium nitrate and dimethyldioxirane has been reported.[3] The critical issue is to discover an oxidant that will maintain the catalytic activity of the ruthenium for the cycloisomerization. We wish to report a mild oxidative cyclization of homopropargylic alcohols to γ-butyrolactones, catalyzed by a ruthenium complex.

To investigate the feasibility of the process, the transformation illustrated in eq 2 was pursued. We initiated our studies of the



(2)

oxidative cyclization of homopropargyl alcohol **5**[6] with the ruthenium complex **4** based upon Bruce's work[2b] and the use of a polar medium such as DMF−water to promote ionization of the catalyst. With conventional oxidants (hydrogen peroxide, *tert*-butyl hydroperoxide, MCPBA, pyridine *N*-oxide, DMSO), only starting material **5** was recovered. On the other hand, the unconventional "oxidant", *N*-hydroxyphthalimide (**7**), did give some of the desired lactone **6**[7] (Table 1, entry 1). A conversion

(1) For reviews, see: Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59. Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311.

(2) (a) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648 and references therein. (b) Bruce, M. I.; Swincer, A. G.; Thomson, B. J.; Wallis, R. C. *Aust. J. Chem.* **1980**, *33*, 2605.

(3) (a) Quayle, P.; Rahman, S.; Ward, E. L. M. *Tetrahedron Lett.* **1994**, *35*, 3801. Quayle, P.; Rahman, S. *Tetrahedron Lett.* **1995**, *36*, 8087. (b) Gilbert, M.; Ferrer, M.; Lluch, A.-M.; Sanchez-Baeza, F.; Messeguer, A. *J. Org. Chem.* **1999**, *64*, 1591. (c) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990,** *112*, 3642.

(4) (a) For a recent general review for ruthenium catalyzed reactions, see: Murahashi, S.-I.; Takaya, H.; Naota, T. *Chem. Rev.* **1998**, *98*, 2599. (b) For examples of catalytic reactions of terminal acetylenes via vinylidene intermediates, see: Mahé, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1989**, *54*, 1518. Trost, B. M.; Dyker, G.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 7809. Wakatsuki, Y.; Yamazaki, H.; Kumegawa, N.; Satoh, T.; Satoh, J. Y. *J. Am. Chem. Soc.* **1991**, *113*, 9604. Murakami, M.; Ubukata, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 7361. Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319. Gemel, C.; Trimmel, G.; Slugovc, C.; Kremel, S.; Mereiter, K.; Schmid, R.; Kirchner, K. *Organometallics* **1996**, *15*, 3998.

(5) For unsuccessful examples, see: Davies, G.; McNally, J. P.; Smallridge, A. J. *Adv. Organomet. Chem.* **1990**, *30*, 1 and references therein.

(6) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870.

(7) Olivier, P. *Tetrahedron* **1994**, *50*, 13687.

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Scheme 1. Proposed Catalytic Cycle

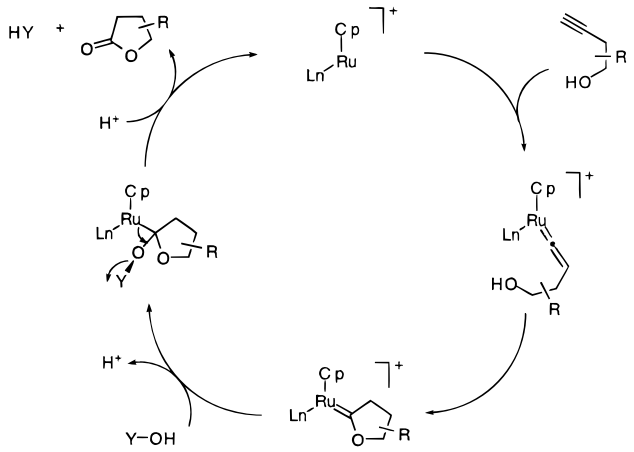
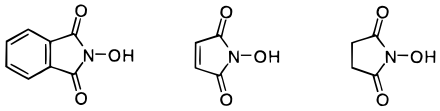


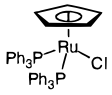
Table 1. Variation of the Oxidants Using Precatalyst **4**[a]



7 **8** **9**

entry	oxidant	additive	concn (M)	time (h)	convrsn (%)[b]	yield[b] (%)	brsm[c] (%)
1	**7**		0.1	72	33	17	52
2	**8**		0.1	72	58	38	65
3	**9**		0.1	72	97	61	63
4	**9**		0.4	42	96	61	63
5	**9**	Bu_4NBr	0.4	22	100	66 (59[d])	66
6	**9**	Bu_4NBr	0.8	22	100	45	45
7	**9**	Bu_4NCl	0.4	22	100	64	64
8	**9**	Bu_4NHSO_4	0.4	22	100	60	60
9	**9**	$C_{16}H_{33}(Me)_3NBr$	0.4	22	72	49	68
10	**9**	$(CH_3)_4NBr$	0.4	22	71	41	58
11[e]	**9**	Bu_4NPF_6	0.4	28	100	71 (65[d])	71

[a] Reaction performed as outlined in eq 2 with Ru complex **4** (15 mol %) as precatalyst and 45 mol % of any additive. [b] Determined by GC using tetradecane as an internal standard. [c] Yield based upon reacted starting material. [d] Isolated yield. [e] In this run, 18 mol % Ru complex **4** employed.



4

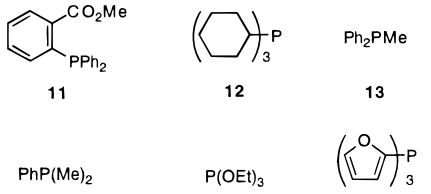
problem was apparent. Using a sterically less demanding imide, the maleimide **8**, did improve the conversion (entry 2). The best result was obtained with the more nucleophilic *N*-hydroxysuccinimide (**9**) (entry 3), although, in principle, it should be the poorer oxidant (i.e., stronger N−O bond).

Since nucleophilicity seems to be a significant factor, modifying the counterion was examined. Use of a tetra-*n*-butylammonium salt significantly shortened the reaction time (entries 5−8). No apparent dependence on the nature of the anion associated with the tetra-*n*-butylammonium salt was noted (entries 5−8). On the other hand, the structure of the ammonium ion did have a significant effect (entries 9 and 10). Performing the reaction in air has no effect. Using the conditions of entry 5, a 59% isolated yield of lactone **6** was obtained within 1 day.

To explore the effect of a phosphine ligand, we switched to complex **10** as the precatalyst.[8] Better conversions were obtained by using less than 2 phosphines per ruthenium. Using 1.5 phosphines per ruthenium allowed reaction to proceed to completion after 17 h. As summarized in Table 2, bulkier as well as less bulky[9] and more electron rich[10] phosphines gave poorer results (entries 2−5). A phosphite ligand gave poorer conversions, although the yield based upon recovered starting material was nearly unchanged (entry 6). On the other hand, trifurylphosphine (**16**), a small and electron-poor ligand,[11] gave somewhat improved results (entry 7). Interestingly, decreasing the amount of the catalyst increased the yield somewhat (entries 8 and 9). Dropping the catalyst loading below 5% still maintained good yields but saw the conversion drop somewhat (entry 10). These results are consistent with the nucleophilic addition step being product (rate?) determining; therefore, increasing the electrophilicity of the ruthenium[12] and minimizing steric hindrance increases the reactivity of the catalyst.

Using the conditions of 5−10% of ruthenium complex **10** in the presence of trifurylphosphine and tetra *n*-butylammonium bromide with sodium bicarbonate as base and **9** as oxidant, a wide range of homopropargylic alcohols was converted to their corresponding γ-butyrolactones (see Table 3).[13] The substrates

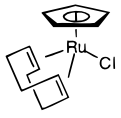
Table 2. Variation of the Ligand System[a]



11 **12** **13** **14** **15** **16**

entry	Ru amt (%)	ligand	ligand amt (%)	reaction time (h)	convrsn (%)[b]	yield[b] (%)	brsm[c] (%)
1	15	PPh_3	23	13	95	60	64
2	15	**11**	23	13	100	29	29
3	15	**12**	23	13	100	22	22
4	15	**13**	23	13	81	59	72
5	15	**14**	23	13	79	55	69
6	15	**15**	23	13	77	50	65
7	15	**16**	23	13	100	66	66
8	10	**16**	15	18	100	73	73
9	5	**16**	7.5	23	100	74 (63[d])	74
10	4	**16**	6	29	93	66	71

[a] Reaction performed as in eq 2 with *N*-hydroxysuccinimide (**9**) as oxidant and tetra-*n*-butylammonium bromide as additive. [b] Determined by GC using tetradecane as an internal standard. [c] Yield based upon reacted starting material. [d] Isolated yield.



10

(8) Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.

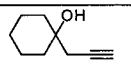
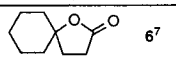
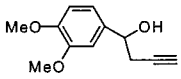
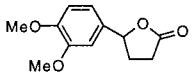
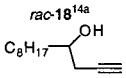
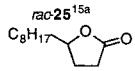
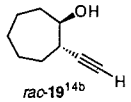
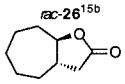
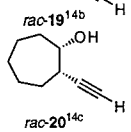
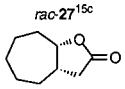
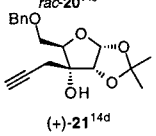
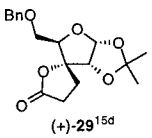
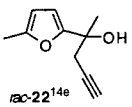
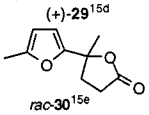
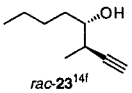
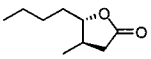
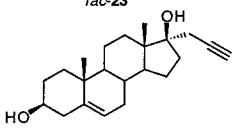
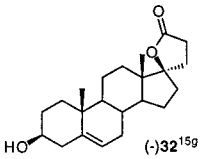
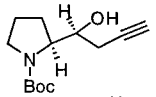
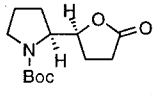
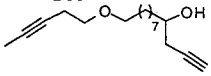
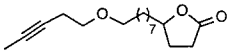
(9) (a) Cone angle data for the ligands: (i) PPh_3, 145°; (ii) **12**, 170°; (iii) **13**, 136°; (iv) **14**, 122°; (v) **15**, 109°. (b) For extensive compilation of cone angles of phosphine ligands, see: Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1.

(10) For quantitative data for electron density of phosphine ligands, see: Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(11) For the use of tri-*o*-furylphosphine in cross-coupling reactions, see: Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. Farina, V.; Baker, S. R.; Benigni, D. A.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 5739.

(12) For analogous discussion in the intermolecular reaction of methanol with Ru-vinylidene complexes, see ref 5. Also, see: Lagadec, R. L.; Roman, E.; Toupet, L.; Muller, U.; Dixneuf, P. H. *Organometallics* **1994**, *13*, 5030. Bozec, H. L.; Dixneuf, P. H. *Organometallics* **1991**, *10*, 2768.

Table 3. Representative Examples of Ru-Catalyzed Oxidative Cyclization of Homopropargyl Alcohols

Entry	Substrate	Product	Method[a]	Time(h)	Yield(%)[b]
1	 **5**[6]	 **6**[7]	A	23	63
			C	17	73–76[c]
2			B	39	48
	rac-**18**[14a]	*rac*-**25**[15a]	D	34	55
3			B	24	61
	rac-**17**[14d]	*rac*-**26**[15b]			
4			B	23	63
			E	20	74
	rac-**19**[14b]	*rac*-**27**[15c]			
5			B	18	61
			E	20	72
	rac-**20**[14c]	*rac*-**28**[15c]			
6			B	24	55
	(+)-**21**[14d]	(+)-**29**[15d]			
7			B	24	51
	rac-**22**[14e]	*rac*-**30**[15e]	D	25	49
8			A	21	63
	rac-**23**[14f]	*rac*-**31**[15f]	E	20	67
9			B	18	65
	(-)**24**[14g]	(-)**32**[15g]			
10			D	28	61
11			D	21	59

[a] Method A, as in eq 2 using 5% **10**, 7.5% **16**, 15% tetra-*n*-butylammonium bromide, and **9** as oxidant. Method B, as in eq 2 using 10% **10**, 15% **16**, 30% tetra-*n*-butylammonium bromide, and **9** as oxidant. Method C, as in eq 2 using 7% **10**, 10% **16**, 45% tetra-*n*-butylammonium hexafluorophosphate, and **9** as oxidant. Method D, as in eq 2 using 13% **10**, 20% **16**, 60% tetra-*n*-butylammonium hexaflurophosphate, and **9** as oxidant. Method E, as in eq 2 using 10% **10**, 15% **16**, 50% tetra-*n*-butylammonium hexafluorophosphate, and **9** as oxidant. [b] Isolated yields. [c] GC yield in this case is 84°).

are easily accessed by adding allenylmagnesium bromide to aldehydes or ketones (entries 1−3, 6, 7, 9−11) or by opening epoxides (entries 4, 5 (after alcohol inversion), and 8).[14] Excellent chemoselectivity is observed. Both *cis*- and *trans*-fused lactones are equivalently accessed. In many examples of formation of the vinylidene ruthenium complexes, ammonium hexafluorophosphate is employed.[1,4,16] To check whether the presence of hexafluorophosphate anion plays any role, the reaction of entry 1 was repeated using tetra-*n*-butylammonium hexafluorophosphate. Remarkably, the yield increased significantly. Using this latter quaternary salt did increase the yield in several additional cases (entries 2, 4, 5, and 8) but had no effect on entry 7. A number of the lactones in Table 3 are of significant interest, including **25**, an intermediate toward a platelet aggregation inhibitor;[15a] **26**, a fruit flavor principle; **29**, an inhibitor of binding of a phorbol ester to PKC-α; **30**, a

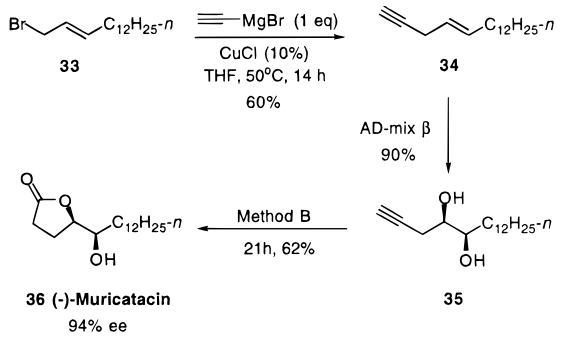
(13) For the discussion of biological activity of γ-butyrolactones, see: Chamberlin, R.; Koch, C. *J. Org. Chem.* **1993**, *58*, 2725 and references therein.

(14) (a) Bieber, L. W.; Silva, M. F.; Costa, R. C.; Silva, L. O. *Tetrahedron Lett.* **1998**, *39*, 3655. (b) Fukuda, Y.; Matsubara, S.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 5812. (c) Murray, T. F.; Samsel, E. G.; Varma, V.; Norton, J. R. *J. Am. Chem. Soc.* **1981**, *103*, 7520. (d) Alper, B.; Hendrix, M.; Sears, P.; Wong, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 1965. (e) This compound was synthesized from commercially available 5-acetyl-2-methylfuran by treatment with propargylmagnesium bromide. (f) Hoffmann, R. W.; Giesen, V. F.; Fuest, M. *Liebigs Ann. Chem.* **1993**, *6*, 629. (g) Mauvais, A.; Burger, A.; Roussel, J. P.; Hetru, C.; Luu, B. *Bioorg. Chem.* **1994**, *22*, 36.

(15) (a) For the discussion of the usage of this compound, see: Vijay, N.; Jaya, P.; Tesmol, G. *Tetrahedron* **1998**, *53*, 15061. (b) Krief, A.; Rouvaux, A.; Tuch, A. *Tetrahedron* **1998**, *54*, 6903. (c) Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10. (d) Lee, J.; Marquez, V. E.; Lewin, N. E.; Blumberg, P. M. *Synlett* **1994**, 206. (e) Wahlberg, I.; Pettersson, T.; Eklund, A.-M. *J. Agric. Food Chem.* **1993**, *41*, 2097. (f) For other syntheses of Quercus lactone, see: Masuda, M.; Nishimura, K. *Chem. Lett.* **1981**, 133 and references therein. (g) An intermediate in the synthesis of spironolactone: Cella, J. A.; Brown, E. A.; Burtner, R. R. *J. Org. Chem.* **1959**, *24*, 743. For the discussion of the biological activity of spironolactone as an aldosterone antagonist, see: Sutter, J. L.; Lau, E. P. K. In *Analytical Profiles of Drug Substances*; Florez, K., Ed.; Academic: New York, 1975; Vol. 4, pp 431−451.

(16) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5579. Ruiz, N.; Péron, D.; Dixneuf, P. H. *Organometallics* **1995**, *14*, 1095.

Scheme 2. Sunthesis of (−)-Muricatacin



tobacco constituent; **31**, a wood constituent;[15f] and **32**,[15g] an intermediate toward spironolactone, an aldosterone antagonist. Entries 10 and 11 illustrate chemoselectivity issues. Finally, a concise synthesis of the acetogenin (−)-muricatacin,[17] compounds known for their pesticidal and antitumor activities, was accomplished as shown in Scheme 2 from the known bromide **33**.[18,19] The asymmetric dihydroxylation of enyne **34** proceeded in about 94% ee, established on the basis of the enantiomeric purity of the final product as determined by comparison of optical rotations. This example highlights the chemoselectivity—only the γ-butyrolactone is obtained, with no detectable amount of the corresponding six-membered ring lactone. Thus, free hydroxyl groups do not interfere.

The question of mechanism must be reserved until more detailed studies are performed. The working hypothesis presented in Scheme 1 appears consistent with our observations. The steric and electronic influences on the ruthenium that affect the nucleophilic addition appear to be quite significant. Further developments of this new catalytic lactone synthesis and its broader implications for additional catalytic cycles based upon the principles outlined in this scheme are the subject of future studies.

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Supporting Information Available: General procedure for the synthesis of γ-butyrolactones and characterization data for **25**−**32**, **36** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Enantiomeric excess of **36** was determined by the comparison of optical rotation data. See: Sharpless, K. B.; Zhang, X.-L.; Wang, Z.-M.; Keinan, E.; Sinha, S. *Tetrahedron Lett.* **1992**, *33*, 6407.