

SYNTHESIS OF VINYLIC LACTONES VIA PALLADIUM-CATALYZED COUPLING OF
 VINYLIC HALIDES OR TRIFLATES AND UNSATURATED CARBOXYLIC ACIDS

Richard C. Larock* and David J. Leuck

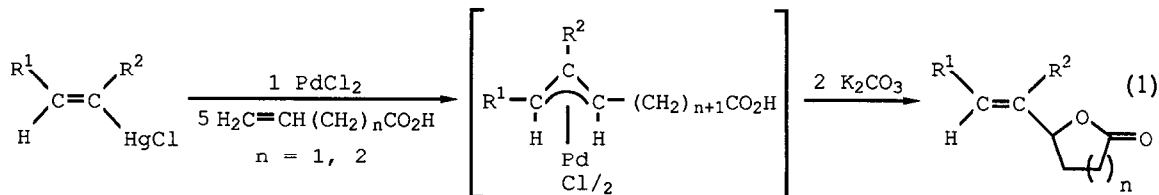
Department of Chemistry, Iowa State University, Ames, Iowa 50011
 and

L. Wayne Harrison

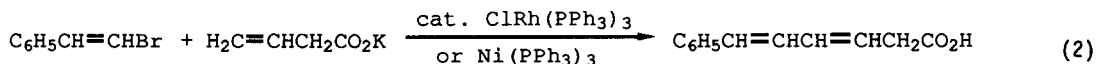
Department of Chemistry, Wilson College, Chambersburg, Pennsylvania 17201

Summary. Vinyllic halides or triflates react with 3-butenic or 4-pentenoic acids in the presence of 5% Pd(OAc)₂ or Pd(dba)₂, n-Bu₄NCl, i-PrNEt₂ and either acetonitrile or N,N-dimethylformamide at 80-100°C to afford the corresponding γ-alkenyl-γ-butyro- or δ-alkenyl-δ-valerolactones respectively by an intramolecular π-allylpalladium displacement process.

γ-Alkenyl-γ-butyrolactones and δ-alkenyl-δ-valerolactones are present in nature and have proven useful as intermediates in organic synthesis.¹⁻⁷ We recently reported a convenient new approach to such lactones using vinyllic mercurials, unsaturated carboxylic acids and palladium chloride in a two step process proceeding through intermediate π-allylpalladium compounds (eq. 1).⁸ Unfortunately, the limited availability of vinyllic mercurials and the use of stoichiometric amounts of palladium chloride detract from this procedure.



In theory one ought to be able to effect a similar transformation using vinyllic halides and only catalytic amounts of palladium according to Scheme I. However, analogous palladium-catalyzed vinyllic halide-alkene coupling reactions are well known to afford conjugated dienes,⁹ and nickel- or rhodium-catalyzed versions of the desired process have been reported to afford the conjugated diene as the sole product (eq. 2).¹⁰ One must also be concerned



about the thermal stability and base sensitivity of the various anticipated organopalladium intermediates, particularly the palladium hydride π-complex assumed to be involved in the rearrangement of intermediate 1 to 2.^{8,11}

Nevertheless, we are pleased at this time to report that by the appropriate choice of reaction conditions, one can effect the catalytic cross-coupling of vinyllic halides or triflates and unsaturated carboxylic acids using only 5% Pd(OAc)₂ (eq. 3, Table I). Best

TABLE I. SYNTHESIS OF VINYLIC LACTONES^a

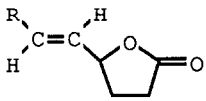
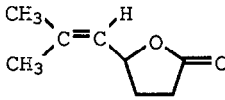
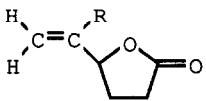
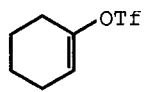
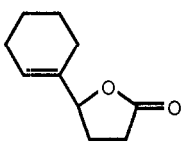
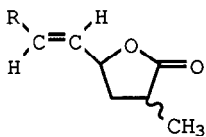
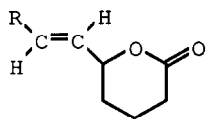
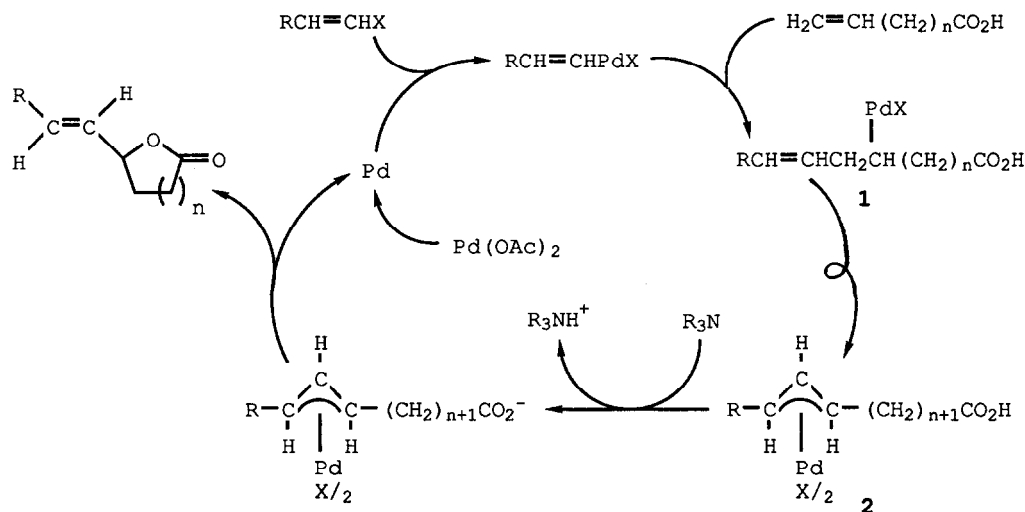
Entry	Unsaturated Acid	Alkenyl Halide or Triflate	Lactone	% Isolated Yield
	$\text{H}_2\text{C}=\text{CHCH}_2\text{CO}_2\text{H}$			
			R	
1	<i>E</i> - $n\text{-C}_4\text{H}_9\text{CH}=\text{CHI}$	$n\text{-C}_4\text{H}_9$	$n\text{-C}_4\text{H}_9$	66, 73 ^b
2	<i>Z</i> - $n\text{-C}_4\text{H}_9\text{CH}=\text{CHI}$	$n\text{-C}_4\text{H}_9$	$n\text{-C}_4\text{H}_9$	59
3	<i>E</i> - $n\text{-C}_4\text{H}_9\text{CH}[\text{OSiMe}_2(\text{t-Bu})]\text{CH}=\text{CHI}$	$n\text{-C}_4\text{H}_9\text{CHOSiMe}_2(\text{t-Bu})$	$n\text{-C}_4\text{H}_9\text{CHOSiMe}_2(\text{t-Bu})$	41
4	<i>E</i> - $(\text{CH}_3)_3\text{CCH}=\text{CHI}$	$(\text{CH}_3)_3\text{C}$	$(\text{CH}_3)_3\text{C}$	60
5	<i>E</i> - $\text{C}_6\text{H}_5\text{CH}=\text{CHI}$	C_6H_5	C_6H_5	49, 54 ^b
6	<i>E</i> - $\text{C}_6\text{H}_5\text{CH}=\text{CHBr}$	C_6H_5	C_6H_5	53 ^c
7	$(\text{CH}_3)_2\text{C}=\text{CHI}$			61
				
			R	
8	$\text{H}_2\text{C}=\text{CBrC}_6\text{H}_5$	C_6H_5	C_6H_5	25 ^c
9	$\text{H}_2\text{C}=\text{CI}(\text{CH}_2)_3\text{CH}_3$	$n\text{-C}_4\text{H}_9$	$n\text{-C}_4\text{H}_9$	30
10				58 ^c
	$\text{H}_2\text{C}=\text{CH}(\text{CH}_3)\text{CHCO}_2\text{H}$			
			R	
			<i>trans/cis</i>	
11	<i>E</i> - $n\text{-C}_4\text{H}_9\text{CH}=\text{CHI}$	$n\text{-C}_4\text{H}_9$	$n\text{-C}_4\text{H}_9$ 2.6/1	59
12	<i>E</i> - $\text{C}_6\text{H}_5\text{CH}=\text{CHBr}$	C_6H_5	C_6H_5 2.3/1	55
	$\text{H}_2\text{C}=\text{CH}(\text{CH}_2)_2\text{CO}_2\text{H}$			
			R	
13	<i>E</i> - $n\text{-C}_4\text{H}_9\text{CH}=\text{CHI}$	$n\text{-C}_4\text{H}_9$	$n\text{-C}_4\text{H}_9$	61 ^d
14	<i>E</i> - $n\text{-C}_4\text{H}_9\text{CH}[\text{OSiMe}_2(\text{t-Bu})]\text{CH}=\text{CHI}$	$n\text{-C}_4\text{H}_9\text{CHOSiMe}_2(\text{t-Bu})$	$n\text{-C}_4\text{H}_9\text{CHOSiMe}_2(\text{t-Bu})$	39 ^d
15	<i>E</i> - $(\text{CH}_3)_3\text{CCH}=\text{CHI}$	$(\text{CH}_3)_3\text{C}$	$(\text{CH}_3)_3\text{C}$	63 ^d

TABLE I. CONTINUED

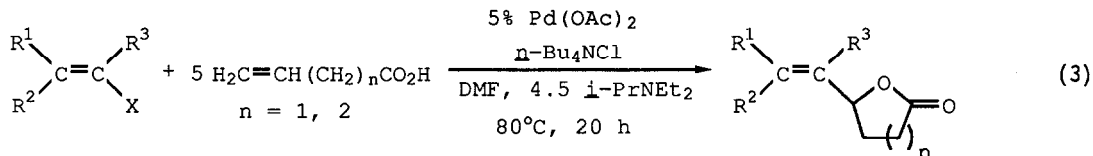
Entry	Unsaturated Acid	Alkenyl Halide or Triflate	Lactone	% Isolated Yield
16		E- C ₆ H ₅ CH=CHI	C ₆ H ₅	21 ^d
17		E- C ₆ H ₅ CH=CHBr	C ₆ H ₅	26 ^d , 27 ^{c,d}

^aAll reactions were run by heating the alkenyl halide or triflate (0.5 mmol), the unsaturated acid (2.5 mmol), *n*-Bu₄NCl (0.5 mmol), *i*-PrNEt₂ (2.25 mmol) and Pd(OAc)₂ (0.025 mmol) in 2 ml of DMF at 80°C for 20 h in a sealed vial unless otherwise specified. ^bReaction run on a 1.0 mmole scale. ^cReaction run at 100°C. ^dReaction run in acetonitrile using 5% Pd(dba)₂.

Scheme I



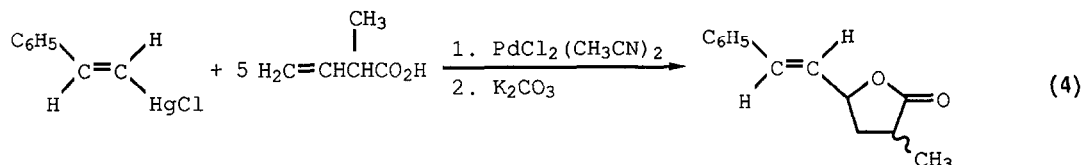
results have generally been obtained using reaction conditions similar to those we have successfully employed for the cross-coupling of aryl and vinylic halides with cyclic alkenes,^{12,13} except that tertiary amine bases give better results than Na₂CO₃, K₂CO₃ or



NaOAc. The carbonate bases on occasion give yields comparable to those of *i*-PrNEt₂, but the results are inconsistent perhaps due to solubility problems. Both NaOAc and *N,N,N',N'*-tetramethylethylenediamine gave very poor results in these reactions. Lowering the amount of base from 4.5 to 2 equivalents resulted in a significant decrease in yield. While better yields of butyrolactones were obtained using *N,N*-dimethylformamide (DMF) as the solvent, acetonitrile proved superior in the formation of valerolactones. For the preparation of valerolactones, comparable yields were obtained using either Pd(OAc)₂ or Pd(dba)₂ (dba = dibenzylideneacetone) as the catalyst, but the former reagent proved superior in the synthesis

of butyrolactones. Reducing the number of equivalents of unsaturated acid from 5 to 2 again resulted in a significant drop in yield.

A variety of unsaturated carboxylic acids can be employed in these reactions. 3-Butenoic acid, 4-pentenoic acid and 2-methyl-3-butenoic acid all afford comparable yields. Interestingly, the latter carboxylic acid shows a modest 2.3-2.6/1 selectivity for formation of the *trans* over the *cis* lactone (Entries 11 and 12), whereas the analogous reaction of styrylmercuric chloride gave a 45:55 *trans/cis* mixture (eq. 4).⁸



We have been successful in these lactone syntheses in employing vinylic iodides, bromides and triflates. The reactions of bromides and triflates require a higher temperature (100°C) however to reach completion in a comparable time. 1-Halo-1-alkenes give significantly higher yields than 2-halo-1-alkenes, perhaps due to steric hindrance to addition of the resulting vinylpalladium species to the carbon-carbon double bond of the unsaturated carboxylic acid. It is noteworthy that 1-iodo-1-hexene (Entry 2) affords only the lactone bearing a *trans* double bond. Presumably, the more stable syn π -allylpalladium intermediate 2 is being formed during the rearrangement of intermediate 1 to 2 (see Scheme 1).

In conclusion, the palladium-catalyzed cross-coupling of vinylic halides or triflates and unsaturated carboxylic acids provides a unique new route to vinylic lactones. We are presently examining the possibility of extending this approach to the synthesis of a wide variety of heterocycles and carbocycles.

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REFERENCES

1. Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* 1979, **101**, 6756.
2. Trost, B. M.; Klun, T. P. *J. Org. Chem.* 1980, **45**, 4256.
3. Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* 1981, **103**, 1864.
4. Mäcke, H.; Houlding, V.; Adamson, A. W. *J. Am. Chem. Soc.* 1980, **102**, 6891.
5. Fujisawa, T.; Sato, T.; Kawashima, M.; Naruse, K.; Tamai, K. *Tetrahedron Lett.* 1982, **23**, 3583.
6. Sato, T.; Naruse, K.; Fujisawa, T. *Tetrahedron Lett.* 1982, **23**, 3587.
7. Fujisawa, T.; Kawashima, M.; Ando, S. *Tetrahedron Lett.* 1984, **25**, 3213.
8. Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* 1987, **28**, 4977.
9. Heck, R. F. *Org. Reactions* 1982, **27**, 345.
10. Chiusoli, G. P.; Salerno, G.; Giroladini, W.; Pallini, L. *J. Organomet. Chem.* 1981, **219**, C16.
11. Larock, R. C.; Mitchell, M. A. *J. Am. Chem. Soc.* 1978, **100**, 180.
12. Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* 1988, **29**, 905.
13. Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* 1988, **29**, 2919.

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