Palladium-Catalyzed Heteroannulation of 1,3-Dienes To Form α-Alkylidene-γ-butyrolactones

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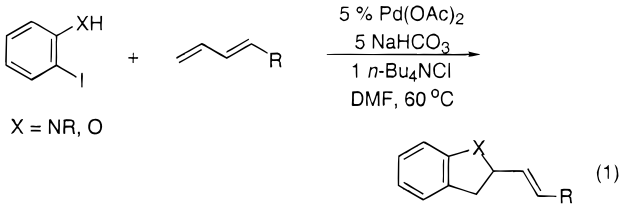
α-Alkylidene-γ-butyrolactones are readily prepared by the palladium-catalyzed heteroannulation of a variety of 1,3-dienes by α-iodo and α-bromo acrylic acids. The best results are obtained by employing a catalytic amount of the sterically hindered chelating alkyl phosphine D-*t*-BPF [(di-*tert*-butylphosphino)ferrocene]. In most cases, this process is highly regioselective. The reaction is believed to proceed via (1) oxidative addition of the vinylic halide to Pd(0), (2) organopalladium addition to the less hindered end of the 1,3-diene to form a π-allylpalladium intermediate, and (3) nucleophilic displacement of the palladium by the carboxylate ion.

Introduction

The synthesis of α-methylene-γ-lactone derivatives has been of great interest due to their biological activity and occurrence in numerous natural products.[1−3] Several of these compounds display antiinflammatory activity, as well as prostaglandin synthetase inhibitory activity.[2] Past progress in the synthesis of these heterocycles has involved multistep procedures,[4,5] which in some cases involves preparing the γ-lactone first, before transforming it into the corresponding α-methylene- or α-alkylidene-γ-lactone.[6−8]

Recently, it has been shown that palladium is an efficient catalyst for the heteroannulation of 1,3-dienes (eq 1).[9−11] This process proceeds through a π-allylpalladium intermediate, which is formed by the addition of an arylpalladium complex to the 1,3-diene. This π-allylpalladium intermediate closes to the five-membered ring by an internal nucleophilic attack on the π-allyl system. It has been observed, however, that these palladium conditions are ineffective for annulation with α-iodo or α-bromo acrylic acids. Possible problems with this system are the low reactivity of these vinylic halides toward oxidative addition and the possibility that the vinylpalladium species may coordinate too strongly with the neighboring carboxylate. This coordination could deactivate the vinylpalladium intermediate toward diene addition.

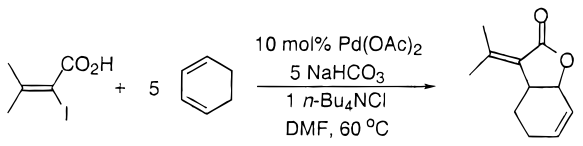


(1)

In congruence with our effort to prepare α-alkylidene-γ-butyrolactones through a palladium-catalyzed heteroannulation of 1,3-dienes by α-iodo and α-bromo acrylic acids, an Indian group published a communication that reported a few examples of this type of annulation, which resulted in modest to poor yields.[12] It is not clear form this work what reaction conditions were actually utilized or whether catalytic amounts of palladium were even employed. In this paper, we report reaction conditions under which the palladium-catalyzed regioselective heteroannulation of 1,3-dienes by α-iodo and α-bromo acrylic acids provides α-alkylidene-γ-butyrolactones in good yields. The major advantages that our system offers over recently reported results are improved yields and the use of catalytic amounts of palladium.

Results and Discussion

Our initial work was aimed at developing a set of palladium conditions that would work well for a variety of substrates in the production of α-alkylidene-γ-butyrolactones. The original optimized conditions for this system included $Pd(OAc)_2$ (0.05 mmol), vinylic halide (0.5 mmol), diene (2.5 mmol), $NaHCO_3$ (2.5 mmol), *n*-Bu_4NCl (0.5 mmol), and DMF (2 mL) as the solvent, a 60 °C reaction temperature, and a 3 day reaction time (eq 2).



(2)

Unfortunately, these conditions only produced the desired γ-lactones in modest yields (30−40%). Further optimization was carried out focusing on the use of various phosphine ligands. Triphenylphosphine was explored

(1) Grieco, P. A. *Synthesis* **1975**, 67−82.
(2) Katsumi, I.; Kondo, H.; Yamashita, K.; Hidaka, T.; Hosoe, K.; Yamashita, T.; Watanabe, K. *Chem. Pharm. Bull.* **1986**, *34*, 121−129.
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(6) Murray, A. W. *J. Chem. Soc., Chem. Commun.* **1984**, 132−133.
(7) Larson, G. L.; Betancourt de Perez, R. M. *J. Org. Chem.* **1985**, *50*, 5257−5260.
(8) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967−5971.
(9) Larock, R. C.; Berrios-Pena, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447−3450.
(10) Larock, R. C.; Guo, L. *Synlett* **1995**, 465−466.
(11) O'Connor, J. M.; Stallman, B. J.; Clark, W.; Shu, A.; Spada, R.; Stevenson, T.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807−809.
(12) Iyer, S.; Ramesh, C. *Tetrahedron Lett.* **1999**, *40*, 4719−4720.

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Table 1. Effect of Phosphine Ligands[a]

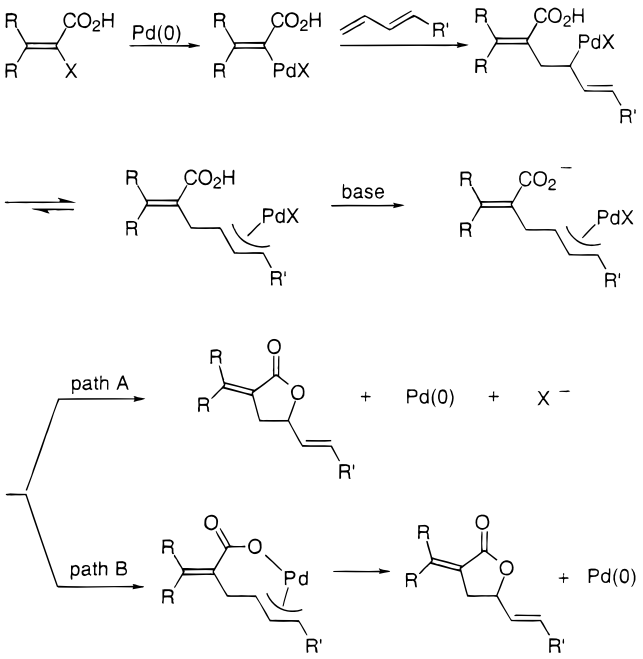
entry	ligand	time (h)	% yield
1	20 mol % PPh_3	72	31
2	10 mol % DPPE	72	5
3	10 mol % DPPF	24	20
4	20 mol % DPPF	24	46
5	20 mol % P(*t*-Bu)$_3$	72	0
6	20 mol % D-*t*-BPF	24	70

[a] Conditions are the same as those in eq 2.

first, because of its availability and success in other organopalladium transformations (entry 1, Table 1). However, this ligand, as well as some bidentate derivatives (entries 2−4), did not appear to improve the reaction significantly. Recently, there have been reports of the use of more hindered and electron-rich phosphine ligands, such as P(*t*-Bu)$_3$, PCy_3, D-*t*-BPF, and bis(di-*tert*-butylphosphino)ferrocene, activating aryl chlorides in palladium-catalyzed processes.[13−15] When P(*t*-Bu)$_3$ was employed in our system, there was no evidence of the desired lactone. However, since P(*t*-Bu)$_3$ is highly reactive toward oxygen, it is possible that the ligand could have been oxidized to the corresponding phosphine oxide along the way. Hartwig et al. have shown that mono- and diphosphine-substituted ferrocene derivatives accelerate the arylation of ketones and malonates with bromo- and chloroarenes as effectively as P(*t*-Bu)$_3$.[16,17] Therefore, D-*t*-BPF [(di-*tert*-butylphosphino)ferrocene] was prepared by monolithiation of ferrocene, followed by quenching with ClP(*t*-Bu)$_2$.[18] This ligand is less oxygen sensitive and can easily be handled in the presence of air for fairly long periods of time. When 20 mol % D-*t*-BPF was added to the previously optimized palladium conditions for the synthesis of α-alkylidene-γ-butyrolactones, the yields were increased greatly and the reaction times were reduced to 24 h. The D-*t*-BPF offers two advantages. First, because alkylphosphines bind more strongly to palladium than aryl phosphines, the electron density at the metal center is increased, which may accelerate the reaction rate. Second, this sterically hindered ligand may help break up any unwanted coordination of the vinylpalladium species and the neighboring carboxylic acid. Therefore, our best present reaction conditions for the preparation of α-alkylidene-γ-butyrolactones are found in eq 2, with the addition of 20 mol % D-*t*-BPF.

Upon examining the heteroannulation of a variety of 1,3-dienes under our optimized conditions (Table 2), it was found that the best results were obtained using acyclic dienes, bearing a monosubstituted terminal double bond (entries 2−6, 13, 14, and 16). This can be explained by steric arguments and the ability of the palladium catalyst to coordinate to the terminal double bond of the diene. When the single substituent on the diene is small, such as a methyl or methoxy group, the product was obtained as a mixture of cis and trans isomers (entries 2, 3, 6, and 13). When the terminal group is larger and aryl, such as a phenyl or furyl group, only the trans isomer was obtained (entries 4, 5, 14, and 16). Dienes that are substituted in the 3-position also give good yields (entries 7, 8, and 12). However, when isoprene was used, a mixture of regioisomers were obtained arising from vinylpalladium addition to both ends of the diene (entries 7 and 12). Surprisingly, 1,3-dienes that were substituted in both of the internal positions, 2,3-dimethyl-1,3-butadiene and 2,3-dimethoxy-1,3-butadiene, did not afford good yields of lactone. Simple cyclic dienes, such as 1,3-cyclohexadiene, produced the desired lactone in modest to good yields (entries 1, 9−11, and 15).

Scheme 1



A variety of acrylic acids were used in this study to better determine the scope and limitations of this annulation. It was first discovered that acrylic acids with alkyl substituents in the β-position reacted in a fashion similar to those with aryl substituents. However, acid **20**, which has a 2-furyl group cis to the bromine, produces lower yields than acid **14**, which has a phenyl group cis to the bromine. A possible explanation for the difference in yields is that the furyl group is coordinating to the vinylpalladium species, thus reducing its reactivity toward diene addition. It has also been discovered that vinylic bromides are as reactive as vinylic iodides. This result is somewhat surprising in that previous work has generally shown that vinylic and aryl iodides are much more reactive than the corresponding bromides. However, it should be noted that the ligand used in this palladium-catalyzed reaction was originally designed to activate aryl chlorides and bromides toward oxidative addition by palladium(0).[16,17]

This heteroannulation process most likely proceeds through a π-allylpalladium intermediate as shown in Scheme 1. The key steps are (1) Pd(OAc)$_2$ reduction to the active palladium(0) catalyst, (2) oxidative addition of the vinylic iodide or bromide to Pd(0), (3) organopalladium addition to the less hindered end of the 1,3-diene to form a π-allylpalladium intermediate, and (4) displacement of palladium by the neighboring carboxylate ion. The exact nature of this substitution process for acyclic dienes is uncertain. The carboxylate ion could effect direct backside displacement of palladium (path A). Alterna-

(13) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387−3388.
(14) Aranyos, A.; Old, D. W.; Ayumu, K.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378.
(15) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11.
(16) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370.
(17) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478.
(18) The procedure for D-*t*-BPF was provided by Grace Mann of the Hartwig group at Yale University.

Table 2. Synthesis of α-Alkylidene-γ-butyrolactones

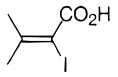
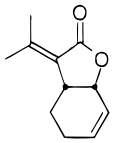
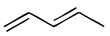
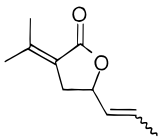
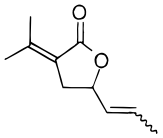
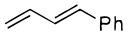
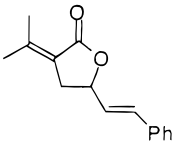
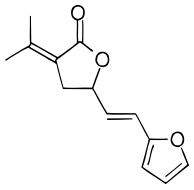
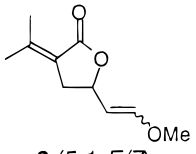
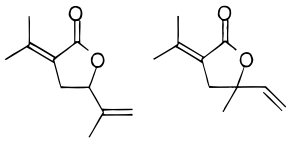
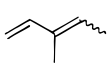
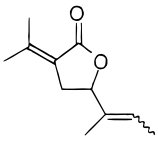
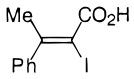
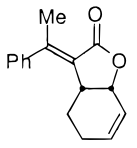
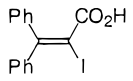
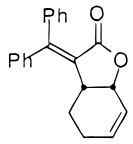
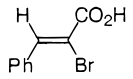
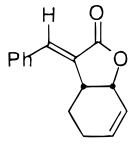
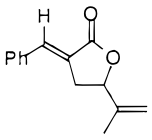
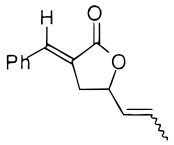
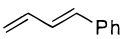
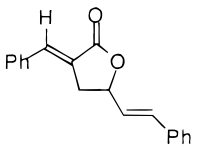
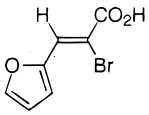
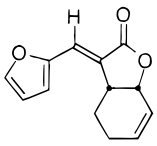
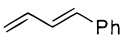
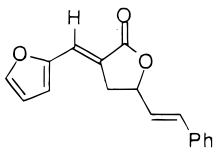
entry	carboxylic acid	diene	products	% yield
1	 **1**		 **2**	70
2			 **3** (9:1 *E/Z*)	96
3			 **3** (9:1 *E/Z*)	99
4			 **4**	74
5		 1:1 *E/Z*	 **5**	73
6		 3:1 *E/Z*	 **6** (5:1 *E/Z*)	74
7			 **7** **8**	70 (10:1)
8		 2:1 *E/Z*	 **9** (2.4:1 *E/Z*)	66
9	 **10**		 **11**	65

Table 2 (Continued)

entry	carboxylic acid	diene	products	% yield
10	 **12**		 **13**	60
11	 **14**		 **15**	85
12			 **16** **17**	66 (3:1)
13			 **18** (10:1 *E/Z*)	78
14			 **19**	99
15	 **20**		 **21**	64
16			 **22**	50

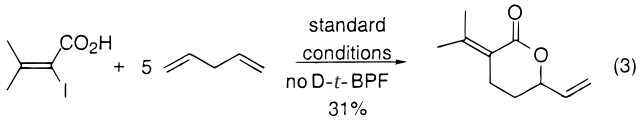
tively, the carboxylate ion could proceed through frontside attack on palladium to produce a palladacycle that subsequently undergoes reductive elimination to the five-membered ring lactone. Since the annulation onto 1,3-cyclohexadiene produces only the cis ring fusion, pathway B is believed to be the dominant process at least with cyclic dienes.

The annulation of acyclic dienes produces primarily the trans stereoisomer. This can be easily explained by the π-allylpalladium intermediate conforming mainly to the more stable *syn*-η^3-allyl complex.[19] *cis*- and *trans*-1,3-pentadiene both produce the same mixture of lactones in a 9:1 *E*/*Z* ratio. Dienes that have a bulkier substituent in the 1-position, such as 1-phenyl-1,3-butadiene and 2-(1,3-butadienyl)furan, only produce the trans isomer.

In an attempt to broaden the scope of this chemistry, similar heteroannulations were performed on 1,4-dienes.

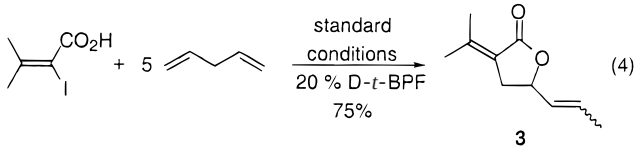
(19) Maitlis, P. M.; Espinet, P.; Russell, M. J. H. *Compr. Organomet. Chem.* **1982**, *6*, 385.

When carboxylic acid **1** was reacted with 1,4-pentadiene using the optimized palladium conditions excluding D-*t*-BPF, the predicted six-membered ring lactone was obtained in a 31% yield (eq 3). However, it was discovered



(3)

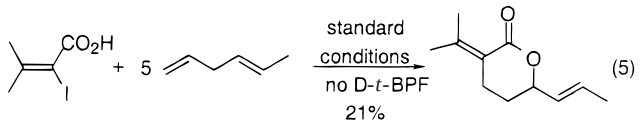
that reactions that contained D-*t*-BPF apparently isomerize the 1,4-diene to the corresponding 1,3-diene. When 20 mol % of D-*t*-BPF was added to the palladium reaction, the five-membered ring lactone **3** was recovered in a 75% yield as a 9:1 cis/trans mixture (eq 4). The production of



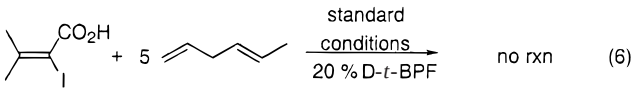
(4)

3

the five-membered ring lactone can be explained by isomerization of the 1,4-pentadiene to 1,3-pentadiene and subsequent annulation. When 1,4-hexadiene and no D-*t*-BPF are utilized, the anticipated six-membered ring lactone is obtained in a 21% yield (eq 5). However, in the presence of 20 mol % D-*t*-BPF, no annulation product was observed (eq 6). This occurs because the corresponding isomerized 2,3-hexadiene is sterically hindered at both ends and is less reactive toward vinylpalladium addition.



(5)



(6)

Conclusion

The palladium-catalyzed heteroannulation of acyclic and cyclic 1,3-dienes by α-iodo and α-bromo acrylic acids has been proven to be a useful route for the synthesis of α-alkylidene-γ-butyrolactones. For most substrates, this process is highly regio- and stereoselective. Annulation predominately occurs at the less hindered end of the diene, and with acyclic dienes the *E* isomer is the major product. The success of this process is dependent upon the use of the sterically hindered, electron-rich phosphine ligand D-*t*-BPF. The exact role of this ligand is uncertain, but it is likely breaking up any unwanted coordination between the vinylpalladium species and the neighboring carboxylic acid.

Experimental Section

General Procedures. All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica plates (Whatman K6F), and visualization was effected with short-wavelength UV light (254 nm) or basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL H_2O].

Reagents. All reagents were used directly as obtained commercially unless otherwise stated. $KMnO_4$, K_2CO_3, NaOH, $NaHCO_3$, and *N*,*N*-dimethylformamide were obtained from Fischer Scientific. Anhydrous *n*-Bu_4NCl was purchased from Lancaster Synthesis, Inc. Palladium acetate was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. Isoprene, 1,3-cyclohexadiene, (*E*/*Z*)-1,3-pentadiene, 3-methyl-1,3-pentadiene, and 1-methoxy-1,3-butadiene were purchased from Aldrich Chemical Co., Inc. (*E*)-1-Phenyl-1,3-butadiene,[20] 2-(1,3-butadienyl)furan,[21] 2-bromo-3-(furan-2-yl)-acrylic acid,[22] and 2-bromo-3-phenylacrylic acid[23] were prepared according to previous literature procedures.

(Di-*tert*-butylphosphino)ferrocene. (Di-*tert*-butylphosphino)ferrocene was prepared by a procedure provided by the Hartwig group.[18] Into a 250 mL Schlenk flask under Ar were added ferrocene (50 mmol) and THF (25 mL). *tert*-Butyllithium (95 mmol) was added dropwise into the Schlenk flask via an addition funnel. After the addition (ca. 30 min), the reaction was allowed to stir at room temperature for 2 h, and an orange precipitate collected at the bottom of the flask. Di(*tert*-butyl)-chlorophosphine (132 mmol) was added dropwise to the reaction mixture at room temperature via an addition funnel. After 4 h, MeOH (6 mL) was added to the flask, and the mixture was allowed to stir for 0.5 h. The solvent was removed under vacuum, the resulting deep orange solid was dissolved in pentane (75 mL), and the mixture was filtered through a medium fritted funnel. The orange solution was concentrated under vacuum and cooled to −35 °C overnight. An orange solid was obtained, which was sublimed twice, to give the product in a 51% yield: ^{1}H NMR (^{31}P decoupled, $CDCl_3$) δ 1.23 (s, 18 H, 4.04 (s, 5 H), 4.09 (s, 2 H), 4.09 (s, 2 H).

General Procedure for the Palladium-Catalyzed Reactions. $Pd(OAc)_2$ (0.05 mmol), *n*-Bu_4NCl (0.5 mmol), $NaHCO_3$ (2.5 mmol), D-*t*-BPF (0.01 mmol), diene (2.5 mmol), vinyl iodide or bromide (0.5 mmol), and DMF (2 mL) were added to an argon flushed 2 dram vial. The vial was flushed further with argon for 2 min and heated at 60 °C for 24 h. The reaction mixture was cooled, diluted with saturated NH_4Cl, extracted with ether, dried over anhydrous $MgSO_4$, and filtered. The organic solvent was evaporated in vacuo, and the product was isolated by flash chromatography (10:1 hexanes/EtOAc) on a silica gel column. The following compound was prepared by the above procedure, and the results are summarized in Table 2.

***cis*-3-Isopropylidene-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one (2)** (entry 1, Table 2): slightly yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.27 (dq, J = 12.8, 4.4 Hz, 1 H), 1.76−1.82 (m, 1 H), 1.93 (s, 3 H), 1.96−2.04 (m, 1 H), 2.11−2.19 (m, 1 H), 2.24 (s, 3 H), 2.99 (dt, J = 12.8, 5.6 Hz, 1 H), 4.56 (m, 1 H), 5.95 (dt, J = 10, 2.8 Hz, 1 H), 6.17 (t, J = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.09, 23.56, 23.74, 38.98, 71.23, 123.20, 125.98, 134.36, 149.78, 169.89 (one sp^3 carbon missing due to overlap); IR (neat) 3034, 2926, 1747 (C=O) cm^{-1}; HRMS for $C_{11}H_{14}O_2$ calcd 178.0994, found 178.0997.

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Supporting Information Available: Characterization, including ^{1}H and ^{13}C NMR spectra, for all lactone products in Table 2 and preparative procedures and characterization for vinylic iodides **1**, **10**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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