

A Palladium-Catalyzed Regioselective Hydroesterification of Alkenylphenols to Lactones with Phenyl Formate as CO Source

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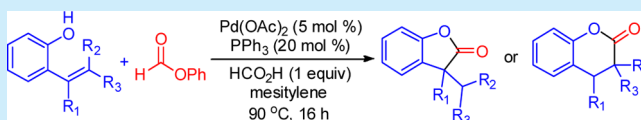
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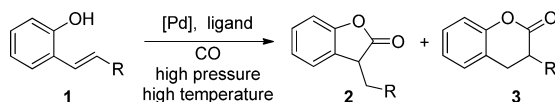
S Supporting Information

ABSTRACT: An effective Pd(OAc)₂-PPh₃ catalyzed hydroesterification of alkenylphenols with phenyl formate as CO surrogate is described. A variety of lactones are obtained in generally high yields with high regioselectivities. In one case, 76% ee is obtained with a chiral ligand.



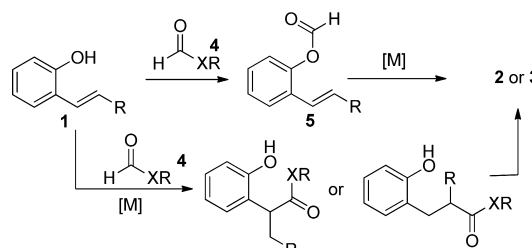
Lactones such as benzofuran-2(3H)-ones (**2**) and 3,4-dihydrocoumarins (**3**) are important functional moieties present in a wide variety of biologically significant compounds¹ and materials.² Among various methods toward this class of molecules,³ the Reppe-type cyclocarbonylation process presents an attractive approach (Scheme 1).^{3a,b,4–10} However, these

Scheme 1



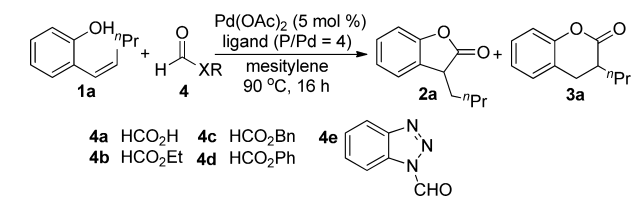
types of processes have been typically carried out under high pressure of toxic CO at high temperature, which sometimes makes them inconvenient to be used and explored in laboratories. In recent years, there has been a growing trend in using various CO surrogates in carbonylation processes to circumvent the use of external CO.¹¹ A number of metal-catalyzed hydroesterification methods with formates and related compounds have been reported, mostly with Ru₃(CO)₁₂ as catalyst.^{12,13} However, the palladium-catalyzed process is less well explored with only limited olefin examples being reported.^{13m} Furthermore, little has been reported for metal-catalyzed asymmetric hydroesterification without the use of external CO gas. In general, lactones **2** and **3** can be formed via an intramolecular hydroesterification of formate **5**^{3g} or an intermolecular hydroesterification and subsequent lactonization¹⁴ (Scheme 2). As part of our general interest in olefin functionalization,¹⁵ we have investigated palladium-catalyzed hydroesterification of alkenylphenols to lactones using phenyl formate as CO source and have found that the reaction can proceed efficiently and regioselectively. Moreover, the enantioselective process is shown to be feasible. Herein, we wish to report our preliminary results on this subject.

Scheme 2



(Z)-2-(Pent-1-enyl)phenol (**1a**) was used as the test substrate. Formic acid and its derivatives were initially examined for the reaction with Pd(OAc)₂-PPh₃ catalyst in mesitylene at 90 °C (Table 1, entries 1–5). While few lactones were obtained with HCO₂H, HCO₂Et, and HCO₂Bn (Table 1, entries 1–3), the desired benzofuran-2(3H)-one (**2a**) was obtained as essentially one regioisomer in 86% yield in the presence of HCO₂Ph (Table 1, entry 4). The reaction also proceeded well with *N*-formylbenzotriazole (**4e**), giving lactone **2a** in 79% yield (Table 1, entry 5). Studies showed that Pd(OAc)₂ was a more effective catalyst than other palladium species, such as Pd(dba)₂, PdCl₂, and PdCl₂(CH₃CN)₂ (Table 1, entries 6–8). Comparable results were obtained with bidentate phosphines such as dppp, dppb, and dppf (Table 1, entries 10–12). No product was obtained without ligand added (Table 1, entry 13). The reaction was further improved by adding formic acid, giving lactone **2a** in essentially quantitative yield (Table 1, entry 14).¹⁶ Acetic acid was also found to be beneficial to the reaction (Table 1, entry 15). However, TsOH and Et₃N were found to be detrimental to the reaction (Table 1, entries 16 and 17).

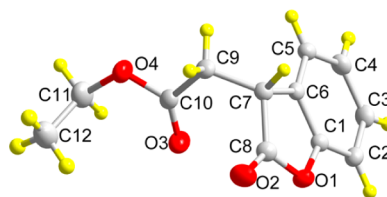
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Table 1. Screening of Reaction Conditions^a

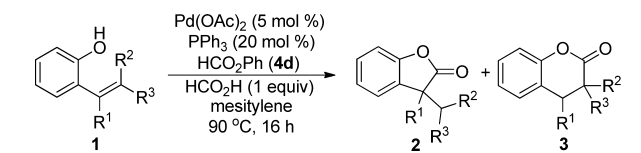
entry	4	Pd	ligand	additive	2a:3a ^b	yield (%) ^c
1	4a	Pd(OAc) ₂	PPh ₃			0
2	4b	Pd(OAc) ₂	PPh ₃			0
3	4c	Pd(OAc) ₂	PPh ₃			0
4	4d	Pd(OAc) ₂	PPh ₃		>99:1	86
5	4e	Pd(OAc) ₂	PPh ₃		>99:1	79
6	4d	Pd(dba) ₂	PPh ₃		>99:1	12
7	4d	PdCl ₂	PPh ₃			0
8	4d	PdCl ₂ (CH ₃ CN) ₂	PPh ₃			0
9	4d	Pd(OAc) ₂	dppe		89:11	38
10	4d	Pd(OAc) ₂	dppp		94:6	77
11	4d	Pd(OAc) ₂	dppb		98:2	85
12	4d	Pd(OAc) ₂	dppf		>99:1	80
13	4d	Pd(OAc) ₂				0
14	4d	Pd(OAc) ₂	PPh ₃	HCO ₂ H	>99:1	99
15	4d	Pd(OAc) ₂	PPh ₃	AcOH	>99:1	93
16	4d	Pd(OAc) ₂	PPh ₃	TsOH		0
17	4d	Pd(OAc) ₂	PPh ₃	Et ₃ N		0

^aThe reactions were carried out with **1a** (0.50 mmol), **4** (0.60 mmol), [Pd] (0.025 mmol), and ligand (0.05 or 0.10 mmol, P/Pd = 4/1) in mesitylene (0.5 mL) at 90 °C for 16 h unless otherwise stated. For entries 14–17, additive (1 equiv) was used. ^bThe ratio was determined by ¹H NMR analysis of the crude reaction mixture. ^cIsolated yield.

The hydroesterification can be extended to a wide variety of alkenylphenols to give the corresponding lactones in 47–99% yields (Table 2). Both *cis* and *trans* disubstituted alkenylphenols were effective substrates, giving five-membered lactones as major products (Table 2, entries 1–6) (the X-ray structure of **2d** is shown in Figure 1). The regioselectivity was generally

Figure 1. X-ray structure of compound **2d**.

high except for phenyl-substituted olefin **1f** (Table 2, entry 6). Trisubstituted and monosubstituted terminal olefins also gave five-membered lactones as essentially single regioisomers in high yields (Table 2, entries 7–9). The regioselectivity was reversed for 1,1-disubstituted olefins, predominantly giving six-membered lactones in high yields (Table 2, entries 10–13) (the X-ray structure of **3j** is shown in Figure 2). In the case of 2-allylphenol (**1n**), the five-membered lactone was obtained in 99% yield (Table 2, entry 14). It is likely that the double bond underwent isomerization under the reaction conditions. For substrate **1o** in which the double bond isomerization was blocked by the two methyl groups, seven-membered lactone **3o** was obtained as major regioisomer in 47% yield (Table 2, entry 15). 2-Vinylbenzyl alcohol (**1p**) was also an effective substrate,

Table 2. Hydroesterification of Alkenylphenols^a

entry	1	product	yield (%) (2:3) ^c
1			99
2	X = H, R ² = ⁿ Pr 1a	2a	89 (95:5)
3	X = Cl, R ² = ⁿ Pr 1b	2b	94
	X = H, R ² = ⁱ Pr 1c	2c	
4			79 (87:13)
5			90
6			92 ^d (74:26)
7			91
8			87
9			88
10 ^b	X = H, R ¹ = Ph 1j		80
11	X = H, R ¹ = 4-F-Ph 1k		87
12	X = H, R ¹ = Me 1l		91 (2:98)
13	X = Cl, R ¹ = Me 1m		90
14			99
15			47 (10:90)
16			73

^aThe reactions were carried out with **1** (0.50 mmol), **4d** (0.60 mmol), Pd(OAc)₂ (0.025 mmol), PPh₃ (0.10 mmol), and HCO₂H (0.50 mmol) in mesitylene (0.5 mL) at 90 °C for 16 h unless otherwise stated. ^bFor 24 h. ^cIsolated yield for the major product. For entries 2, 4, 6, 12, and 15, the ratio of two regioisomers was determined by ¹H NMR analysis of the crude reaction mixture. In other cases, the other regioisomer was barely detectable if there was any. ^dCombined yield of **2f** and **3f**.

giving 6-*exo* product **2p** as essentially one regioisomer in 73% yield (Table 2, entry 16).

No significant amounts of formate **5a** were detected by ¹H NMR spectroscopic analysis of the crude reaction mixture with

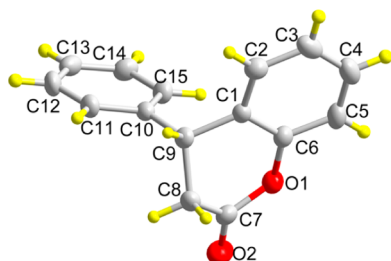
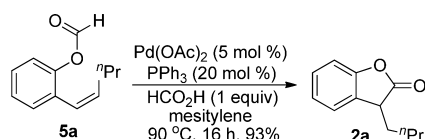


Figure 2. X-ray structure of compound 3j.

(*Z*)-2-(pent-1-enyl)phenol (**1a**) as substrate. When preformed formate **5a** was subjected to the reaction conditions without phenyl formate, lactone **2a** was obtained in 93% yield (Scheme 3). At this moment, it is not clear if formate **5a** is a possible

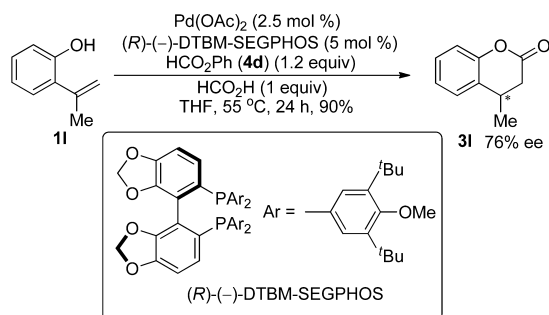
Scheme 3



reaction intermediate. Alternatively, the reaction could also proceed via an intermolecular hydroesterification and subsequent lactonization (Scheme 2). At the current stage, it is not clear whether the reaction proceeded directly with phenyl formate or with CO generated *in situ* from phenyl formate. A precise understanding of the reaction mechanism awaits further study.

Encouragingly, preliminary studies showed that the asymmetric hydroesterification is also feasible. For example, when (*R*)-(-)-DTBM-SEGPHOS¹⁷ was used as chiral ligand, lactone **3l** was obtained in 90% yield and 76% ee (Scheme 4).¹⁸

Scheme 4



In summary, we have developed an efficient Pd(OAc)₂-PPh₃ catalyzed hydroesterification of alkenylphenol using phenyl formate as CO source. A wide variety of lactones have been obtained in generally high yields (up to 99%) with high regioselectivity. The current process provides a viable approach to synthesize benzofuran-2(3*H*)-ones and 3,4-dihydrocoumarins, which are present in many biologically and chemically important compounds. Studies have shown that asymmetric hydroesterification is also feasible with chiral ligand. Further efforts will be devoted to understanding the reaction mechanism, expanding the substrate scope, and developing a more effective asymmetric process.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, characterization data, X-ray structures, data for the determination of enantiomeric excess, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For leading references, see: (a) Closse, A.; Haeflinger, W.; Hauser, D.; Gubler, H. U.; Dewald, B.; Baggolini, M. *J. Med. Chem.* **1981**, *24*, 1465. (b) Chakrabarti, J. K.; Eggleston, R. J.; Gallagher, P. T.; Harvey, J.; Hicks, T. A.; Kitchen, E. A.; Smith, C. W. *J. Med. Chem.* **1987**, *30*, 1663. (c) Phillips, W. R.; Baj, N. J.; Gunatilaka, A. A. L.; Kingston, D. G. I. *J. Nat. Prod.* **1996**, *59*, 495. (d) Posakony, J.; Hirao, M.; Stevens, S.; Simon, J. A.; Bedalov, A. *J. Med. Chem.* **2004**, *47*, 2635. (e) Rizzi, E.; Dallavalle, S.; Merlini, L.; Beretta, G. L.; Pratesi, G.; Zunino, F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4313. (f) Kumar, A.; Singh, B. K.; Tyagi, R.; Jain, S. K.; Sharma, S. K.; Prasad, A. K.; Raj, H. G.; Rastogi, R. C.; Watterson, A. C.; Parmar, V. S. *Bioorg. Med. Chem.* **2005**, *13*, 4300. (g) Roelens, F.; Huvaere, K.; Dhooze, W.; Cleemput, M. V.; Comhaire, F.; Keukeleire, D. D. *Eur. J. Med. Chem.* **2005**, *40*, 1042. (h) Zhang, X.; Wang, H.; Song, Y.; Nie, L.; Wang, L.; Liu, B.; Shen, P.; Liu, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 949. (i) Morales-Escobar, L.; Braca, A.; Pizzi, C.; De Tommasi, N. *ARKIVOC* **2007**, *vii*, 349. (2) For leading references, see: (a) Lundgren, C. V.; Koner, A. L.; Tinkl, M.; Pischel, U.; Nau, W. M. *J. Org. Chem.* **2006**, *71*, 1997. (b) Meng, X.; Xin, Z.; Li, Y.; Cai, Z. *Polym. Degrad. Stab.* **2007**, *92*, 184. (3) For leading references, see: (a) Dong, C.; Alper, H. *J. Org. Chem.* **2004**, *69*, 5011. (b) Ye, F.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 1855. (c) Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086. (d) Azzena, U.; Pisano, L.; Pittalis, M. *Appl. Organomet. Chem.* **2008**, *22*, 523. (e) Kim, H.; Yun, J. *Adv. Synth. Catal.* **2010**, *352*, 1881. (f) Gu, Y.; Xue, K. *Tetrahedron Lett.* **2010**, *51*, 192. (g) Konishi, H.; Ueda, T.; Muto, T.; Manabe, K. *Org. Lett.* **2012**, *14*, 4722. (h) Lee, J. W.; List, B. *J. Am. Chem. Soc.* **2012**, *134*, 18245. (4) For leading reviews on Pd-catalyzed carbonylation, see: (a) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435. (b) Barnard, C. F. *J. Organometallics* **2008**, *27*, 5402. (c) Brennfuehrer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, *1*, 28. (d) Wu, X.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. (5) For a leading review on Pd-catalyzed hydrocarboxylation, see: Ali, B. E.; Alper, H. in *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons, Inc.: New York, 2002; pp 2333–2349. (6) For a leading review on Pd-catalyzed carbonylative lactonization and lactamization, see: Farina, V.; Eriksson, M. in *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons, Inc.: New York, 2002; pp 2351–2375. (7) For leading reviews on Pd-catalyzed asymmetric hydroesterification in the presence of CO gas, see: (a) Claver, C.;

Godard, C.; Ruiz, A.; Pàmies, O.; Diéguez, M. in *Modern Carbonylation Methods*; Kollar, L., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2008; pp 65–92. (b) Godard, C.; Munoz, B. K.; Ruiz, A.; Claver, C. *Dalton Trans.* **2008**, 853.

(8) For leading references on Pd-catalyzed asymmetric hydroesterification in the presence of CO gas, see: (a) Botteghi, C.; Consiglio, G.; Pino, P. *Chimia* **1973**, 27, 477. (b) Consiglio, G. *Helv. Chim. Acta* **1976**, 59, 124. (c) Consiglio, G. *J. Organomet. Chem.* **1977**, 132, C26. (d) Hayashi, T.; Tanaka, M.; Ogata, I. *Tetrahedron Lett.* **1978**, 41, 3925. (e) Becker, Y.; Eisenstadt, A.; Stille, J. K. *J. Org. Chem.* **1980**, 45, 2145. (f) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, 112, 2803. (g) Zhou, H.; Lu, S.; Hou, J.; Chen, J.; Fu, H.; Wang, H. *Chem. Lett.* **1996**, 339. (h) Zhou, H.; Hou, J.; Cheng, J.; Lu, S.; Fu, H.; Wang, H. *J. Organomet. Chem.* **1997**, 543, 227. (i) Nozaki, K.; Kantam, M.; Horiuchi, L. T.; Takaya, H. *J. Mol. Catal.* **1997**, 118, 247. (j) Oi, S.; Nomura, M.; Aiko, T.; Inoue, Y. *J. Mol. Catal.* **1997**, 115, 289. (k) Yu, W.; Bensimon, C.; Alper, H. *Chem.—Eur. J.* **1997**, 3, 417. (l) Wang, L.; Kwok, W. H.; Chan, A. S. C.; Tu, T.; Hou, X.; Dai, L. *Tetrahedron: Asymmetry* **2003**, 14, 2291. (m) Kawashima, Y.; Okano, K.; Nozaki, K.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, 77, 347. (n) Guiu, E.; Caporali, M.; Muñoz, B.; Müller, C.; Lutz, M.; Spek, A. L.; Claver, C.; van Leeuwen, P. W. N. M. *Organometallics* **2006**, 25, 3102. (o) Konrad, T. M.; Fuentes, J. A.; Slawin, A. M. Z.; Clarke, M. L. *Angew. Chem., Int. Ed.* **2010**, 49, 9197. (p) Konard, T. M.; Durrani, J. T.; Cobley, C. J.; Clarke, M. L. *Chem. Commun.* **2013**, 49, 3306. (q) Reference 3a.

(9) For leading references on Pd-catalyzed hydroesterification in the presence of CO gas, see: (a) Tamaru, Y.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1987**, 28, 325. (b) Alper, H.; Hamel, N. *Chem. Commun.* **1990**, 135. (c) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1991**, 56, 1099. (d) Ali, B. E.; Alper, H. *J. Org. Chem.* **1991**, 56, 5357. (e) Brunner, M.; Alper, H. *J. Org. Chem.* **1997**, 62, 7565. (f) Ogawa, A.; Kuniyasu, H.; Sonoda, N.; Hirao, T. *J. Org. Chem.* **1997**, 62, 8361. (g) Tezuka, K.; Ishizaki, Y.; Inoue, Y. *J. Mol. Catal.* **1998**, 129, 199. (h) Troisi, L.; Vasapollo, G.; El Ali, B.; Mele, G.; Florio, S.; Capriati, V. *Tetrahedron Lett.* **1999**, 40, 1771. (i) Akao, M.; Sugawara, S.; Amino, K.; Inoue, Y. *J. Mol. Catal.* **2000**, 157, 117. (j) Seayad, A.; Jayasree, S.; Damodaran, K.; Toniolo, L.; Chaudhari, R. V. *J. Organomet. Chem.* **2000**, 601, 100. (k) Ooka, H.; Inoue, T.; Ituno, S.; Tanaka, M. *Chem. Commun.* **2005**, 1173. (l) Estorach, C. T.; Masdeu-Bultó, A. M. *Catal. Lett.* **2008**, 122, 76. (m) Yang, J.; Yuan, Y. *Catal. Lett.* **2009**, 131, 643. (n) Kuniyasu, H.; Yoshizawa, T.; Kambe, N. *Tetrahedron Lett.* **2010**, 51, 6818.

(10) For leading references on Rh-catalyzed hydroesterification in the presence of CO gas, see: (a) Yokota, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* **2003**, 5, 4329. (b) Inoue, S.; Yokota, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* **2006**, 8, 2519.

(11) For a review on carbonylations without the use of CO gas, see: Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, 43, 5580.

(12) For leading references on hydroesterification in the presence of formates and CO gas, see: (a) Isnard, P.; Denise, B.; Sneeden, R. P. A. *J. Organomet. Chem.* **1983**, 256, 135. (b) Mlekuz, M.; Joo, F.; Alper, H. *Organometallics* **1987**, 6, 1591. (c) Kondo, T.; Yoshii, S.; Tsuji, Y.; Watanabe, Y. *J. Mol. Catal.* **1989**, 50, 31. (d) Keim, W.; Becker, J. *J. Mol. Catal.* **1989**, 54, 95. (e) Suzuki, Y.; Katoh, H.; Ishii, Y.; Hidai, M. *J. Mol. Catal.* **1995**, 95, 129. (f) Lugan, N.; Lavigne, G.; Soulie, J. M.; Fabre, S.; Kalck, P.; Saillard, J. Y.; Halet, J. F. *Organometallics* **1995**, 14, 1712.

(13) For leading references on hydroesterification with formates in the absence of CO gas, see: (a) Ueda, W.; Yokoyama, T.; Morikawa, Y.; Moro-oka, Y.; Ikawa, T. *J. Mol. Catal.* **1988**, 44, 197. (b) Lin, I. J. B.; Alper, H. *J. Chem. Soc., Chem. Commun.* **1989**, 248. (c) Nahmed, E. M.; Jenner, G. *J. Mol. Catal.* **1990**, 59, L15. (d) Lavigne, G.; Lugan, N. *J. Am. Chem. Soc.* **1992**, 114, 10669. (e) Grevin, J.; Kalck, P. *J. Organomet. Chem.* **1994**, 476, C23. (f) Jenner, G.; Taleb, A. B. *J. Mol. Catal.* **1994**, 91, 31. (g) Legrand, C.; Castanet, Y.; Mortreux, A.; Petit, F. *J. Chem. Soc., Chem. Commun.* **1994**, 1173. (h) Fabre, S.; Kalck, P.; Lavigne, G. *Angew. Chem., Int. Ed.* **1997**, 36, 1092. (i) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, 124, 750. (j) Na, Y.; Ko, S.; Hwang, L. K.; Chang, S. *Tetrahedron Lett.* **2003**, 44, 4475. (k) Wang, L.;

Floreancig, P. E. *Org. Lett.* **2004**, 6, 4207. (l) Park, E. J.; Lee, J. M.; Han, H.; Chang, S. *Org. Lett.* **2006**, 8, 4355. (m) Katafuchi, Y.; Fujihara, T.; Iwai, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2011**, 353, 475. (n) Reference 3g.

(14) For a leading reference on Ru-catalyzed hydroesterification/lactonization of allylic and homoallylic alcohols, see ref 13k.

(15) (a) Shi, Y. *Acc. Chem. Res.* **2004**, 37, 488. (b) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, 129, 762. (c) Huang, D.; Liu, X.; Li, L.; Cai, Y.; Liu, W.; Shi, Y. *J. Am. Chem. Soc.* **2013**, 135, 8101.

(16) For leading references on using acid as additive, see: (a) Williams, D. B. G.; Shaw, M. L.; Green, M. J.; Holzapfel, C. W. *Angew. Chem., Int. Ed.* **2008**, 47, 560. (b) References 9j, 9k, 9m, and 12b.

(17) For a leading reference on DTBM-SEGPPOS, see: Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, 4, 4045.

(18) For a recent reference on asymmetric hydrocarbonylations of alkenes, see: Donets, P. A.; Cramer, N. *J. Am. Chem. Soc.* **2013**, 135, 11772.