Organic LETTERS

Letter

pubs.acs.org/OrgLett

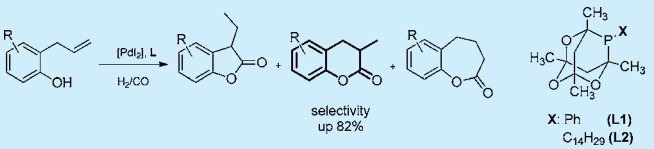
PdI_2-Catalyzed Regioselective Cyclocarbonylation of 2-Allyl Phenols to Dihydrocoumarins

Manuel Amézquita-Valencia and Howard Alper*

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario K1N 6N5, Canada

Supporting Information

ABSTRACT: A simple, efficient, and regioselective synthesis of 3-methyl-3,4-dihydrocoumarins is reported. The reaction of 2-allyl phenols with synthesis gas was catalyzed by PdI_2, and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (**L1**) and 1,3,5,7-tetramethyl-6-tetradecyl-2,4,8-trioxa-6-phosphaadamantane (**L2**) were effective as ligands, affording good product selectivity in all cases.



Coumarins and their derivatives are compounds that occur in a number of natural products and are key intermediates for the synthesis of biologically active molecules.[1] As an important subset, 3,4-dihydrocoumarins exhibit some interesting biological activities; their therapeutic properties include inhibition of sir2 as well as immunomodulatory and estrogenic activity.[2] Owing to the importance of these molecules, different synthetic approaches have been reported which include enzymatic synthesis,[3] [4 + 2] cycloaddition using silyl ketene acetals,[4] organocatalysts,[5] and transition-metal-catalyzed reactions.[6] Despite these examples, there are few methods to synthesize 3-methyl-3,4-dihydrocoumarins.[3b,6a,7] Metal-catalyzed cyclocarbonylation is an attractive approach for the preparation of a variety of cyclic compounds,[8] such as five-, six-, or seven-membered ring lactones and lactams.[9]

We have previously reported that the regioselectivity for the cyclocarbonylation of 2-allyl phenols is dependent on the reaction conditions. Our earlier publication noted that using $[Pd(PCy_3)_2(H)(H_2O)]^+BF_4^-$ or $[Pd(OAc)_2]$ as the catalyst and the bidentate ligand (dppb) gave fine selectivity for the formation of seven-membered ring heterocycles from 2-allyl phenols.[9] Similar results were observed using immobilized palladium catalysts such as Pd-clays and a recyclable system in ionic liquids.[10] In general, the product distribution was related to the extent of isomerization of the allyl substrate, and the selectivity was influenced by the metal precursor, solvent relative pressures of gases, and the ligand. Bidentate ligands are excellent for the cyclocarbonylation reactions. We reasoned that the use of an appropriate monodentate ligand could change the selectivity of this reaction. This concept is supported by the good results obtained working with a monodentate ligand for the cyclocarbonylation of 2-vinylphenol and allyl aniline.[9] Herein we report a highly selective process to form six-membered ring 3-methyl-3,4-dihydrocoumarins. The cycloisomerization of allyl phenols proceeded by employing PdI_2 and CYTOP ligands (**L1** and **L2**, Figure 1).

Initially, 2-allyl phenol **1a** was chosen as the model substrate, and extensive investigations were carried out to define the optimal reaction conditions (Table 1). As a starting point, intramolecular cyclocarbonylation experiments were performed with a 1:1 H_2/CO mixture (600 psi) for 20 h at 90 °C, using 2 mol % of different palladium precursors and CYTOP 292 (**L1**) as the ligand in dichloromethane (DCM). Although the cyclocarbonylation reaction is effective with different palladium sources such as $Pd(OAc)_2$, $Pd(tfa)_2$, $Pd(cod)_2Cl_2$, $Pd(MeCN)_2Cl_2$, and $Pd(acac)_2$, giving 100% conversion, our studies show that $Pd_2(dba)_3$ and PdI_2 are more selective than other palladium catalysts to form the six-membered ring 2,3-dihydrocoumarin **3a** (Table 1, entries 1−8). The best solvent is toluene (entry 13). The use of coordinating solvents such as tetrahydrofuran (THF) and acetonitrile (MeCN) resulted in reduced reactivity (entries 9−12). The analogous reaction with $Pd_2(dba)_3$ gave only traces of the desired products **2**/**3**/**4** (entry 14). When the reaction temperature was increased to 120 °C the selectivity increased (entries 15−20).

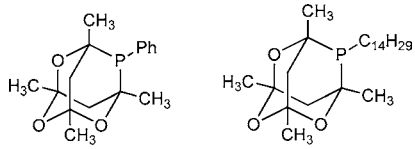


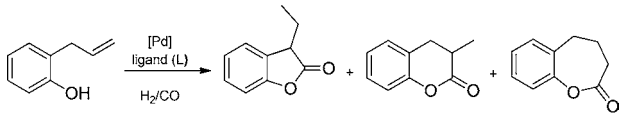
Figure 1. CYTOP ligands used. 1,3,5,7-Tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (**L1**) and 1,3,5,7-tetramethyl-6-tetradecyl-2,4,8-trioxa-6-phosphaadamantane (**L2**).

Finally, the best results were obtained using PdI_2 in toluene at 120 °C for 20 h to form the corresponding 3-methyl-3,4-dihydrocoumarin **3a** in 82% selectivity (entry 21), accompanied by smaller amounts of five- and seven-membered ring lactones (**2a** and **4a**). In contrast, poor selectivity was obtained using $PdCl_2$ under the same reaction conditions (entry 22). No

Received: October 2, 2014
Published: November 11, 2014

dx.doi.org/10.1021/ol5029157 | *Org. Lett.* 2014, 16, 5827−5829

Table 1. Screening of Reaction Conditions[a]

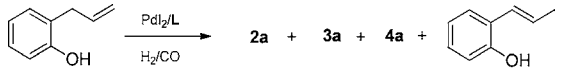


1a 2a 3a 4a

entry	[Pd]	solvent	conv (%)[b]	2a:3a:4a (%)[b]
1	$Pd_2(dba)_3$	DCM	100	12:39:49
2	$Pd(OAc)_2$	DCM	100	20:20:60
3	$Pd(tfa)_2$	DCM	100	18:30:52
4	$Pd(cod)Cl_2$	DCM	100	26:26:48
5	$Pd(MeCN)_2Cl_2$	DCM	100	24:38:38
6	$Pd(acac)_2$	DCM	100	21:36:43
7	$PdCl_2$	DCM	100	31:35:34
8	PdI_2	DCM	100	16:54:30
9	$Pd_2(dba)_3$	THF	NR[c]	—
10	$Pd_2(dba)_3$	MeCN	NR[c]	—
11	PdI_2	MeCN	NR[c]	—
12	PdI_2	THF	NR[c]	—
13	PdI_2	PhMe	100	20:58:22
14	$Pd_2(dba)_3$	PhMe	NR[c]	—
15[d]	$Pd_2(dba)_3$	DCM	NR[c]	—
16[d]	$Pd(OAc)_2$	DCM	98	16:50:34
17[d]	$Pd(cod)Cl_2$	DCM	99	36:48:16
18[d]	$Pd(MeCN)_2Cl_2$	DCM	99	23:45:32
19[d]	$Pd(MeCN)_2Cl_2$	PhMe	100	9:44:47
20[d]	$Pd(cod)Cl_2$	PhMe	100	27:28:45
21[d]	**PdI_2**	**PhMe**	**100**	**10:82:8**
22[d]	$PdCl_2$	PhMe	100	35:32:33
23[d,e]	PdI_2	PhMe	0	—

[a]Reactions were carried out with **1a** (3.8 mmol), 2 mol % [Pd] (0.076 mmol), ligand **L1** (0.152 mmol), CO (300 psi), and H_2 (300 psi) at 90 °C in 10 mL of solvent. [b]The conversion and the ratio of **2**/**3**/**4** were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]No reaction. [d]Reaction at 120 °C. [e]Reaction without ligand.

Table 2. Cyclocarbonylation of 1a Using Different Ligands[a]



1a 5a

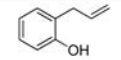
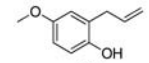
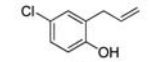
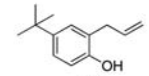
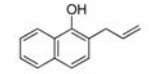
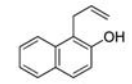
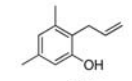
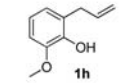
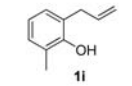
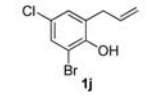
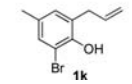
entry	ligand (**L**)	conversion (%)[b]	2a:3a:4a:5a[c] (%)[b]
1	PPh_3	100	14:48:15:23
2	$(p\text{-Tolyl})_3P$	100	6:40:10:44
3	PCy_3	0	–
4	dppp	5	traces
5	dppb	3	traces
6	**L2**	100	10:80:10:0

[a]Reactions were carried out with **1a** (3.8 mmol), 2 mol % PdI_2 (0.076 mmol), ligand **L** (0.152 mmol), CO (300 psi), and H_2 (300 psi) at 120 °C in 10 mL of toluene. [b]The conversion and the ratio of **2**/**3**/**4**/**5** were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]Isomerization product.

products were observed without added ligand and the starting material was recovered (entry 23).

To explore the efficiency of the PdI_2/CYTOP 292 catalytic system further, we worked with different commercial phosphine ligands (Table 2). Under the above optimized conditions, the use of monodentate phosphines such as PPh_3 or $(p\text{-Tolyl})_3P$ resulted in excellent conversion, but poor selectivity, and also included the formation of **5a** in some instances, corresponding

Table 3. Cyclocarbonylation of Different Allyl Phenols Using PdI_2 and L1 or L2 as the Ligand[a]

entry	substrate	ligand	distribution products %[b] 2	3	4
1	 1a	**L1**	10	82(79)[c]	8
		L2	10	80(78)[c]	10
2	 1b	**L1**	14	73	13
		L2	14	75(70)[c]	11
3	 1c	**L1**	12	74(71)[c]	14
		L2	11	74	15
4	 1d	**L1**	13	75(71)[c]	12
5	 1e	**L1**	8	75(70)[c]	17
6	 1f	**L1**	4	80	16
		L2	9	80(77)[c]	11
7	 1g	**L1**	9	78(75)[c]	13
		L2	10	76	14
8	 1h	**L1**	13	77	9
		L2	11	79(75)[c]	10
9	 1i	**L1**	14	76(70)[c]	10
10	 1j	**L1**	18	74(70)[c]	8
11	 1k	**L1**	18	73(70)[c]	9

[a]Reactions were carried out with **1** (3.8 mmol), 2 mol % of PdI_2 (0.076 mmol), and CYTOP 292 (**L1**) or **L2** ligand (0.152 mmol) in 10 mL of toluene at 120 °C for 20 h. [b]The product distribution and the ratio of **2**/**3**/**4** were determined by ^{1}H NMR analysis of the crude reaction mixture. [c]The isolated yield after column chromatography is shown in brackets.

to isomerization of the double bond in the substrate (entries 1 and 2). Moreover, no catalytic activity was observed using PCy_3 (entry 3). The use of dppp or dppb as ligands gave only 5% and 3% conversion, respectively, with traces of the desired products (entries 4 and 5). However, another ligand with the phosphaadamantane framework (**L2**) afforded similar results to that of **L1** (entry 6).

Having established the optimal reaction conditions, the intramolecular cyclocarbonylation was then applied to a variety of 2-allyl phenols. All reactions proceeded to full conversion with excellent regioselectivity, giving the six-membered ring 3-methyl-3,4-dihydrocoumarins as major products (from 73% to 82% yields), and the results are summarized in Table 3. The electronic nature of the substituent on the aryl ring of the

dx.doi.org/10.1021/ol5029157 | Org. Lett. 2014, 16, 5827–5829

substrates had little influence on the product selectivity. For example, substrates bearing both *para*-substituted electron-donating and -withdrawing substituents gave comparable selectivity for the six-membered ring heterocycles (**3a**−**c**) (entries 1−3). An allyl phenol bearing a sterically bulky *p*-*tert*-butyl group (**1d**) gave the desired product (**3d**) in good selectivity (entry 4), as did substrates with an α-naphthyl group (entries 5 and 6).

Good regioselectivity was also realized for *meta*-substituted reactants forming six-membered ring dihydrocoumarins in good yields (entry 7). The same selectivity occurred when the reaction was carried out with *o*-methoxy and *o*-methyl groups on the aromatic ring (entries 8 and 9). Substrates with two different substituents (**1j**−**k**) also experienced cyclocarbonylation to form six-membered ring lactones in excellent regioselectivity (entries 10 and 11). Clearly, these results show that the cyclocarbonylation using the PdI_2/**L1** or **L2** catalytic system is not sensitive to electronic or steric effects.

In conclusion, we have developed an efficient regioselective cyclocarbonylation of 2-allyl phenols using a combination of PdI_2 as the metal catalyst source and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (**L1**) or 1,3,5,7-tetramethyl-6-tetradecyl-2,4,8-trioxa-6-phosphaadamantane (**L2**) as a ligand. This method provides facile access to a variety of 3-methyl-3,4-dihydrocoumarins in excellent regioselectivity and good yields.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: howard.alper@uottawa.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Cytec Canada, Inc. and to the Natural Sciences and Engineering Research Council (NSERC) for support of this work. This paper is dedicated to the memory of Prof. Dr. Armando Cabrera (1944−2014).

■ REFERENCES

(1) (a) *Coumarins: Biology, Applications and Mode of Action*; O'Kennedy, R., Thornes, R., Eds.; John Wiley & Sons: New York, 1997. (b) Fedorov, A. Y.; Nyuchev, A. V.; Beletskaya, I. P. *Chem. Heterocycl. Compd.* **2012**, *48*, 166−178. (c) Ferguson, J.; Zeng, F.; Alper, H. *Org. Lett.* **2012**, *14*, 5602−5605.

(2) (a) Bedalov, A.; Gatbonton, T.; Irvine, W. P.; Gottschling, D. E.; Simon, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 15113−15118. (b) Posakony, J.; Hirao, M.; Stevens, S.; Simon, J. A.; Bedalov, A. *J. Med. Chem.* **2004**, *47*, 2635−2644. (c) Zhang, X.-f.; Wang, H.-m.; Song, Y.-l.; Nie, L.-h.; Wang, L.-f.; Liu, B.; Shen, P.-p.; Liu, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 949−953. (d) Roelens, F.; Huvaere, K.; Dhooge, W.; Van Cleemput, M.; Comhaire, F.; De Keukeleire, D. *Eur. J. Med. Chem.* **2005**, *40*, 1042−1051.

(3) (a) Mangas-Sánchez, J.; Busto, E.; Gotor, V.; Gotor-Fernández, V. *Org. Lett.* **2013**, *15*, 3872−3875. (b) Rioz-Martínez, A.; de Gonzalo, G.; Torres Pazmiño, D. E.; Fraaije, M. W.; Gotor, V. *J. Org. Chem.* **2010**, *75*, 2073−2076. (c) Mangas-Sanchez, J.; Busto, E.; Gotor-Fernandez, V.; Gotor, V. *Catal. Sci. Technol.* **2012**, *2*, 1590−1595.

(4) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10*, 4951−4953.

(5) (a) Peng, S.; Wang, L.; Guo, H.; Sun, S.; Wang, J. *Org. Biomol. Chem.* **2012**, *10*, 2537−2541. (b) Lu, D.; Li, Y.; Gong, Y. *J. Org. Chem.* **2010**, *75*, 6900−6907. (c) Hong, B.-C.; Kotame, P.; Lee, G.-H. *Org. Lett.* **2011**, *13*, 5758−5761.

(6) (a) Aspin, S.; López-Suárez, L.; Larini, P.; Goutierre, A.-S.; Jazzar, R.; Baudoin, O. *Org. Lett.* **2013**, *15*, 5056−5059. (b) Wang, H.; Dong, B.; Wang, Y.; Li, J.; Shi, Y. *Org. Lett.* **2013**, *16*, 186−189. (c) Barluenga, J.; Andina, F.; Aznar, F. *Org. Lett.* **2006**, *8*, 2703−2706. (d) Konishi, H.; Ueda, T.; Muto, T.; Manabe, K. *Org. Lett.* **2012**, *14*, 4722−4725. (e) Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086−12087.

(7) Murakata, M.; Tsutsui, H.; Takeuchi, N.; Hoshino, O. *Tetrahedron* **1999**, *55*, 10295−10304.

(8) (a) Nagy, E. E.; Hyatt, I. F. D.; Gettys, K. E.; Yeazell, S. T.; Frempong, S. K.; Croatt, M. P. *Org. Lett.* **2013**, *15*, 586−589. (b) Cao, H.; Vieira, T. O.; Alper, H. *Org. Lett.* **2010**, *13*, 11−13. (c) Zheng, Z.; Alper, H. *Org. Lett.* **2009**, *11*, 3278−3281. (d) Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 5567−5569. (e) Chouhan, G.; Alper, H. *Org. Lett.* **2009**, *12*, 192−195. (f) Schranck, J.; Wu, X.-F.; Tlili, A.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2013**, *19*, 12959−12964. (g) Guan, Z.-H.; Chen, M.; Ren, Z.-H. *J. Am. Chem. Soc.* **2012**, *134*, 17490−17493.

(9) El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264−4270.

(10) (a) Chanthateyanonth, R.; Alper, H. *Adv. Synth. Catal.* **2004**, *346*, 1375−1384. (b) Touzani, R.; Alper, H. *J. Mol. Catal. A* **2005**, *227*, 197−207. (c) Orejon, A.; Alper, H. *J. Mol. Catal. A* **1999**, *143*, 137−142. (d) Ye, F.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 1855−1861.