JOC Article

Efficient Synthesis of 3-Chloromethyl-2(5*H*)-furanones and 3-Chloromethyl- 5,6-dihydropyran-2-ones via the $PdCl_2$-Catalyzed Chlorocyclocarbonylation of 2,3- or 3,4-Allenols

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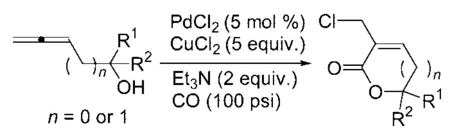

A mild and efficient methodology involving $PdCl_2$-catalyzed chlorocyclocarbonylation of 2,3- or 3,4-allenols with $CuCl_2$ for the synthesis of 3-chloromethyl-2(5*H*)-furanones and 3-chloromethyl-5,6-dihydropyran-2-ones was developed. This reaction proceeded in a highly regioselective manner, i.e., the chlorine atom was introduced to the terminal position of the allene moiety while the lactone linkage was formed between the center carbon atom of the allene moiety and the hydroxyl oxygen, which was established by the X-ray single crystal diffraction study of γ-lactone **3p**. The highly optically active 3-chloromethyl-2(5*H*)-furanones could be easily prepared from the readily available optically active 2,3-allenols. A mechanism for this reaction was proposed.

Introduction

2(5*H*)-Furanones and 5,6-dihydropyran-2-ones, important classes of oxygen-containing heterocyclic compounds, are common structural units in natural products[1] and important intermediates in organic synthesis.[2] 2(5*H*)-Furanone-containing compounds have been considered as potential insecticides, bactericides, fungicides, antibiotics, anticancer agents, antiinflammatories, allergy inhibitors, antisoriasis agents, cyclooxygenase inhibitors, phospholipase A_2 inhibitors, etc.[3] Thus, much attention has been focused on the efficient and diverse synthesis of 2(5*H*)-furanones[4] and 5,6-dihydropyran-2-ones.[5] Our group has also reported some methods for the synthesis of substituted 2(5*H*)-furanones based on the transition metal-promoted or

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(1) (a) Abida, L.; Mahendras, A.; Nilb, R. A. *J. Nat. Prod.* **1984**, *47*, 648. (b) Cambie, R. C.; Bergquist, P. R.; Karuso, P. *J. Nat. Prod.* **1988**, *51*, 1014. (c) De Guzman, F. S.; Schmitz, F. J. *J. Nat. Prod.* **1990**, *53*, 926. (d) Evidente, A.; Sparapano, L. *J. Nat. Prod.* **1994**, *57*, 1720. (e) Gloriam, B.; Gil, R.; Obert, C. *J. Nat. Prod.* **1995**, *58*, 70–5. (f) Syah, Y. M.; Ghisalberti, E. L.; Skelton, B. W.; White, A. H. *J. Nat. Prod.* **1997**, *60*, 49. (g) Ishikawa, T.; Nishigaya, K.; Uchikoshi, H.; Chen, I.-S. *J. Nat. Prod.* **1998**, *61*, 534. (h) Guo, Y.-W.; Gavagnin, M.; Mollo, E.; Trivellone, E.; Cimino, G. *J. Nat. Prod.* **1999**, *62*, 1194. (i) Mukku, V. J. R. V.; Speitling, M.; Laatsch, H.; Helmke, E. *J. Nat. Prod.* **2000**, *63*, 1570. (j) Murakami, T.; Morikawa, Y.; Hashimoto, M.; Okuno, T.; Harada, Y. *Org. Lett.* **2004**, *6*, 157. (k) Vaz, B.; Alvarez, R.; Brückner, R.; de Lera, A. R. *Org. Lett.* **2005**, *7*, 545. (l) De Fatima, A.; Kohn, L. K.; Antonio, M. A.; De Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2006**, *14*, 622. (m) Juan Hikawczuk, V. E.; Roberto Saad, J.; Giordano, O. S.; García, C.; Martín, T.; Martín, V. S.; Sosa, M. E.; Tonn, C. E. *J. Nat. Prod.* **2008**, *71*, 190.

(2) (a) Sánchez-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209. (b) Rabiczko, J.; Chmielewski, M. *J. Org. Chem.* **1999**, *64*, 1347. (c) Koulocheri, S. D.; Haroutounian, S. A.; Apostolopoulos, C. D.; Chada, R. K.; Couladouros, E. A. *Eur. J. Org. Chem.* **1999**, 1449. (d) Socha, D.; Jurczak, M.; Frelek, J.; Klimek, A.; Rabiczko, J.; Urbańczyk-Lipkowska, Z.; Suwińska, K.; Chmielewski, M.; Cardona, F.; Gotic, A.; Brandic, A. *Tetrahedron Asymmetry* **2001**, *12*, 3163. (e) Calvet, S.; Courillon, C.; Malacria, M. *Arkivok* **2002**, *part v*, 189. (f) Donate, P. M.; Frederico, D.; Da Silva, R.; Constantino, M. G.; Ponteb, G. D.; Bonattob, P. S. *Tetrahedron: Asymmetry* **2003**, *14*, 3253. (g) De March, P.; Figueredo, M.; Font, J.; Raya, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **2003**, *68*, 2437. (h) Blazecka, P. G.; Belmont, D.; Curran, T.; Pflum, D.; Zhang, J. *Org. Lett.* **2003**, *5*, 5015. (i) Aurrecoechea, J. M.; Suero, R.; De Torres, E. *J. Org. Chem.* **2006**, *71*, 8767. (j) Kong, K.; Romo, D. *Org. Lett.* **2006**, *8*, 2909. (k) Das Sarma, K.; Zhang, J.; Curran, T. T. *J. Org. Chem.* **2007**, *72*, 3311. (l) Stecko, S.; Pasniczek, K.; Jurczak, M.; Urbańczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1085.

(3) (a) Larock, R. D.; Riefling, B.; Fellows, C. A. *J. Org. Chem.* **1978**, *43*, 131, and references cited therein. (b) Brima, T. S. *Chem. Abstr.* **1991**, *114*, 185246y; U.S. patent 4,968,817, 1990. (c) Tanabe, A. *Chem. Abstr.* **1989**, *110*, 94978q; Jpn. Kokai Tokyo Koho JP 63,211,276 [88,211,276], 1988. (d) Lee, G. C. M. *Chem. Abstr.* **1990**, *113*, 191137j; Eur. Pat. Appl. EP 372,940, 1990. (e) Ducharme, Y.; Gauthier, J. Y.; Prasit, P.; Leblanc, Y.; Wang, Z.; Leger, S.; Therien, M. *Chem. Abstr.* **1996**, *124*, 55954y; PCT Int. Appl. WO 95 00,501, 1995. (f) Lee Gary, C. M.; Garst, M. E. *Chem. Abstr.* **1992**, *116*, 59197m; PCT Int. Appl. WO 91 16,055, 1991. (g) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090.

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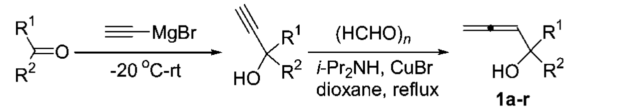
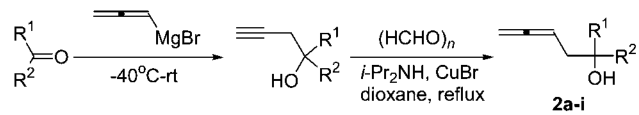
-catalyzed cyclization reactions of 2,3-allenoic acids/esters.[6] In addition, transition metal-catalyzed cyclocarbonylative cyclization reactions of (*Z*)-3-iodo-2-alkenols,[7] 2-bromoenals,[8] (*Z*)-2-iodoalkenyl aryl or alkyl ketones,[9] terminal or internal propargylic alcohols,[10] 3-aryl-2-alkynones,[11] 1,6-alkynals or hex-5-ynoic acid pyridin-2-yl esters,[12] terminal alkynes/H_2O,[13] and 4,6-di-*tert*-butylbenzofuran-2,3-dione/alkynes[14] prove to be effective in constructing 2(5*H*)-furanones. However, reports concerning the synthesis of 5,6-dihydropyran-2-ones through metal-catalyzed cyclocarbonylation reactions are rare.[15,16] In 2000, Takahashi et al.[16] reported a successful cyclocarbonylation of 2,3- or 3,4-allenols to form 2(5*H*)-furanones and 5,6-dihydropyran-2-ones using a ruthenium catalyst. On the other hand, we recently described a $PdCl_2$-catalyzed chlorocyclocarbonylation of 2-alkynols for the efficient synthesis of (*Z*)-α-chloroalkylidene-*β*-lactones.[17] On the basis of these results, we present here the regioselective chlorocyclocarbonylation of 2,3-

SCHEME 1



1a R^1 = n-C_8H_{17}, R^2 = H (76%)
1b R^1 = n-C_7H_{15}, R^2 = H (75%)
1c R^1 = n-C_6H_{13}, R^2 = H (67%)
1d R^1 = n-C_5H_{11}, R^2 = H (69%)
1e R^1 = $PhCH_2CH_2$, R^2 = H (68%)
1f R^1 = $PhCH_2$, R^2 = H (69%)
1g R^1 = cyclohexyl, R^2 = H (65%)
1h R^1 = Ph, R^2 = H (67%)
1i R^1 = 4-FC_6H_4, R^2 = H (60%)
1j R^1 = 4-ClC_6H_4, R^2 = H (66%)
1k R^1 = 4-BrC_6H_4, R^2 = H (65%)
1l R^1 = 1-naphthyl, R^2 = H (72%)
1m R^1 = 2-ClC_6H_4, R^2 = H (74%)
1n R^1 = 2,6-$Cl_2C_6H_3$, R^2 = H (58%)
1o R^1 = 4-EtC_6H_4, R^2 = H (72%)
1p R^1, R^2 = $(CH_2)_5$ (71%)
1q R^1, R^2 = $(CH_2)_4$ (51%)
1r R^1 = Ph, R^2 = Me (52%)

SCHEME 2



2a R^1 = Ph, R^2 = H (34%)
2b R^1 = 4-EtC_6H_4, R^2 = H (45%)
2c R^1 = 4-ClC_6H_4, R^2 = H (44%)
2d R^1 = 2-ClC_6H_4, R^2 = H (54%)
2e R^1 = 4-BrC_6H_4, R^2 = H (43%)
2f R^1 = 4-$Pr^iC_6H_4$, R^2 = H (46%)
2g R^1 = 1-naphthyl, R^2 = H (47%)
2h R^1 = n-C_8H_{17}, R^2 = H (47%)
2i R^1 = n-C_5H_{11}, R^2 = H (47%)

SCHEME 3

1s R^1 = n-C_6H_{13}, R^2 = Me
1t R^1 = n-C_5H_{11}, R^2 = 4-ClC_6H_4 (75%)

or 3,4-allenols affording 3-chloromethyl-2(5*H*)-furanones and 3-chloromethyl-5,6-dihydropyran-2-ones, respectively.

Results and Discussion

Preparation of the Starting Materials. All of the terminal 2,3- or 3,4-allenols (**1a**−**r** or **2a**−**i**) were synthesized by the Crabbé homologation of the corresponding terminal alkynols,[18] which were easily obtained via the Grignard reaction of ethynyl magnesium bromide[19] or allenyl magnesium bromide[20] with carbonyl compounds (Schemes 1 and 2). 2,3-Allenols **1s**,**t** were prepared from the reaction of the corresponding propargylic bromides with aldehydes in the presence of NaI and $SnCl_2$ (Scheme 3).[21] 2-Methyl-4-phenylbuta-2,3-dienol (**1u**) was prepared by reduction of ethyl 2-methyl-4-phenyl-2,3-butadienoates with DIBAL-H.[22]

Optically active (*R*)- or (*S*)-**1a**−**d** were also prepared via the Crabbé reaction of the corresponding (*R*)- or (*S*)-propargylic

(4) For reviews, see: (a) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353. (b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (c) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. (d) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377. For some of the most recent examples, see: (e) Renurd, M.; Ghosez, L. A. *Tetrahedron* **2001**, *57*, 2597. (f) Concellón, J. M.; Riego, E.; Bernad, P. L. *Org. Lett.* **2002**, *4*, 1303. (g) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (h) Linclau, B.; Boydell, A. J.; Clarke, P. J.; Horan, R.; Jaequet, C. *J. Org. Chem.* **2003**, *68*, 1821. (i) Zhang, J.; Das Sarma, K.; Curran, T. T.; Belmont, D. T.; Davidson, J. G. *J. Org. Chem.* **2005**, *70*, 5890. (j) Sheng, S.-R.; Xu, L.; Zhang, X.-L.; Liu, X.-L.; Wei, M.-H. *J. Comb. Chem.* **2006**, *8*, 805. (k) Maulide, N.; Markó, I. E. *Org. Lett.* **2006**, *8*, 3705. (l) Patil, S. N.; Liu, F. *Org. Lett.* **2007**, *9*, 195.

(5) For reviews, see: (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377. (b) Boucard, V.; Broustal, G.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 225. For some of the most recent examples, see: (c) Bai, T.; Ma, S.; Jia, G. *Tetrahedron* **2007**, *63*, 6210. (d) Tiseni, P. S.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 5325. (e) You, Z.-W.; Jiang, Z.-X.; Wang, B.-L.; Qing, F.-L *J. Org. Chem.* **2006**, *71*, 7261. (f) Hopkins, C. D.; Guan, L.; Malinakova, H. C. *J. Org. Chem.* **2005**, *70*, 6848. (g) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2004**, *6*, 2221. (h) Marco, J. A.; Carda, M.; Rodríguez, S.; Castillo, E.; Kneeteman, M. N. *Tetrahedron* **2003**, *59*, 4085. (i) Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. *Org. Lett.* **2001**, *3*, 3807.

(6) For an account see: (a) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (b) Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387. (c) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393. (d) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *55*, 12137. (e) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314. (f) Ma, S.; Duan, D.; Shi, Z. *Org. Lett.* **2000**, *2*, 1419. (g) Ma, S.; Wu, S. *Chem. Commun.* **2001**, 441. (h) Ma, S.; Shi, Z. *Chin. J. Chem.* **2001**, *19*, 1280. (i) Ma, S.; Shi, Z.; Wu, S. *Tetrahedron: Asymmetry* **2001**, *12*, 193. (j) Ma, S.; Yu, Z.; Wu, S. *Tetrahedron* **2001**, *57*, 1585. (k) Ma, S.; Duan, D.; Wang, Y. *J. Comb. Chem.* **2002**, *4*, 239. (l) Ma, S.; Shi, Z. *Chem. Commun.* **2002**, 540. (m) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1775. (n) Ma, S.; Yu, Z. *J. Org. Chem.* **2003**, *68*, 6149. (o) Ma, S.; Wu, B.; Shi, Z. *J. Org. Chem.* **2004**, *69*, 1429. (p) Ma, S.; Yu, Z. *Chem. Eur. J.* **2004**, *10*, 2078.

(7) (a) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. (b) Qing, F.-L.; Jiang, Z.-X. *Tetrahedron Lett.* **2001**, *42*, 5933.

(8) Choa, C. S.; Shim, H. S. *Tetrahedron Lett.* **2006**, *47*, 3835.

(9) Copéret, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 3422.

(10) (a) Ali, B. E.; Alper, H. *J. Org. Chem.* **1991**, *56*, 5357. (b) Xiao, W.; Alper, H. *J. Org. Chem.* **1997**, *62*, 3422. (c) Yu, W.; Alper, H. *J. Org. Chem.* **1997**, *62*, 5684. (d) Fukuta, Y.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* **2001**, *42*, 1301–147. (e) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387.

(11) Van den Hoven, B. G.; Ali, B. E.; Alper, H. *J. Org. Chem.* **2000**, *65*, 4131.

(12) (a) Chatani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335. (b) Harada, Y.; Fukumoto, Y.; Chatani, N. *Org. Lett.* **2005**, *7*, 4385.

(13) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1999**, *40*, 989.

(14) Chatani, N.; Amako, K.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **2003**, *68*, 1591.

(15) (a) Dupont, J.; Donato, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 949. (b) Pommier, A.; Stepanenko, V.; Jarowicki, K.; Kocienski, P. J. *J. Org. Chem.* **2003**, *68*, 4008.

(16) (a) Yoneda, E.; Kaneko, T.; Zhang, S.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441. (b) Yoneda, E.; Zhang, S.; Zhou, D.; Onitsuka, K.; Takahashi, S. *J. Org. Chem.* **2003**, *68*, 8571.

(17) (a) Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* **2003**, *5*, 4429. (b) Ma, S.; Wu, B.; Jiang, X.; Zhao, S. *J. Org. Chem.* **2005**, *70*, 2568.

(18) (a) Crabbé, P.; Nassim, B.; Robert-Lopes, M.-T. *Org. Synth.* **1985**, *63*, 203. (b) Ma, S.; Hou, H.; Zhao, S.; Wang, G. *Synthesis* **2002**, 1643.

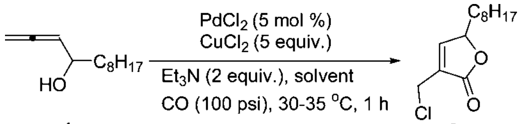
(19) Brandsma, L. In *Synthesis of acetylenes, allenes, and cumulenes: methods and techniques*; Elsevier: Bilthoven, The Netherlands, 2004.

(20) (a) Hashmi, A. S. K.; Ruppert, T. L.; Knöfel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295. (b) Ma, S.; Yu, S.; Yin, S. *J. Org. Chem.* **2003**, *68*, 8996.

(21) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 621.

(22) Yin, S.; Ma, S.; Jiao, N.; Tao, F. *Chin. J. Chem.* **2002**, *20*, 707.

TABLE 1. $PdCl_2$-Catalyzed Chlorocyclocarbonylation of 1,2-Dodecadien-4-ol 1a with $CuCl_2$

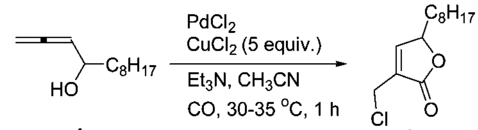


1a 3a

entry	solvent	isolated yield of **3a** (%)
1	dioxane	18
2	toluene	19
3	benzene	trace
4	DMF	0
5	CH_2Cl_2	57
6	THF	65
7	CH_3CN	66
8	THF[a]	66
9	CH_3CN[a]	70

[a] 0.5 equiv of benzoquinone was added.

TABLE 2. $PdCl_2$-Catalyzed Chlorocyclocarbonylation of 1,2-Dodecadien-4-ol 1a with $CuCl_2$ in MeCN under Different Pressures of CO Using Different Amounts of $PdCl_2$ and Et_3N

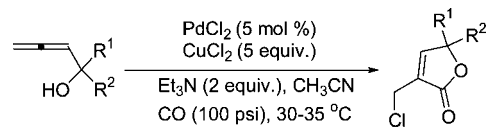


1a 3a

entry	$PdCl_2$ (mol %)	Et_3N (equiv)	CO (psi)	isolated yield of **3a** (%)
1	3	2	100	60
2	10	2	100	63
3	5	2	1 atm[a]	55
4	5	2	200	61
5	5	1	100	59
6	5	3	100	52

[a] This reaction was conducted with a balloon of CO.

TABLE 3. $PdCl_2$-Catalyzed Chlorocyclocarbonylation of Various 2,3-Allenols with $CuCl_2$



1 3

entry	substrate **1**	R^1	R^2	time (h)	isolated yield of **3**[a] (%)
1	**1a**	n-C_8H_{17}	H	1	66 (**3a**)
2	**1b**	n-C_7H_{15}	H	1	65 (**3b**)
3	**1c**	n-C_6H_{13}	H	1	66 (**3c**)
4	**1d**	n-C_5H_{11}	H	1	69 (**3d**)
5	**1e**	$PhCH_2CH_2$	H	1	74 (**3e**)
6	**1f**	$PhCH_2$	H	1	70 (**3f**)
7	**1g**	cyclohexyl	H	1	70 (**3g**)
8	**1h**	Ph	H	0.5	62 (**3h**)
9	**1i**	4-FC_6H_4	H	0.5	66 (**3i**)
10	**1j**	4-ClC_6H_4	H	0.5	67 (**3j**)
11	**1k**	4-BrC_6H_4	H	0.5	69 (**3k**)
12	**1*l***	1-naphthyl	H	0.5	70 (**3*l***)
13	**1m**	2-ClC_6H_4	H	0.5	65 (**3m**)
14	**1n**	2,6-$Cl_2C_6H_3$	H	0.5	66 (**3n**)
15	**1o**	4-EtC_6H_4	H	0.5	50 (**3o**)
16	**1p**	$-(CH_2)_5-$		1	59 (**3p**)
17	**1q**	$-(CH_2)_4-$		1	24 (**3q**)
18	**1r**	Ph	Me	1	42 (**3r**)

[a] For entries 1−7 and 16−18 the eluent = petroleum ether and ethyl ether or ethyl acetate (10:1); for entries 8−15 the eluent = dichloromethane and petroleum ether (5:1).

alcohols,[18b] which are easily available from the kinetic enzymatic resolution of the corresponding racemic terminal propargylic alcohols.[23]

Synthesis of 3-Chloromethyl-2(5*H*)-furanones via the $PdCl_2$-Catalyzed Chlorocyclocarbonylation of 2,3-Allenols. In our initial try, the reaction of 2,3-allenol **1a** failed to afford the chlorocarbonylative cyclization reaction under the same reaction conditions reported previously for the chlorocyclocarbonylation of 2-alkynols (10 mol % of $PdCl_2$ and 5 equiv of $CuCl_2$).[17] To our delight, when 2 equiv of Et_3N were used as the base, 18% of chlorocarbonylative cyclization product 3-chloromethyl-5-octyl-2(5*H*)-furanone **3a** was isolated under the action of 5 mol % of $PdCl_2$ and 5 equiv of $CuCl_2$ in dioxane (entry 1, Table 1). The reaction is highly regioselective with the chlorine being introduced to the terminal position of the allene moiety and the lactone linkage being formed between the center carbon atom of the allene moiety and the hydroxyl oxygen. Further studies indicated that toluene, benzene, and DMF are poor solvents for this reaction (entries 2−4, Table 1). However, CH_2Cl_2, THF, or CH_3CN all provided the product **3a** in 57−66% yields (entries 5−7, Table 1). The addition of 0.5 equiv of benzoquinone[24] did not improve the yield of **3a** dramatically (entries 8 and 9, Table 1).

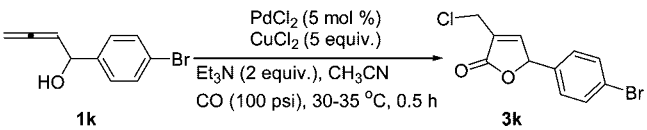
The effects of the loading of $PdCl_2$, the amount of Et_3N, and the pressure of CO were also examined (Table 2). The results indicated that 5 mol % of $PdCl_2$, 2 equiv of Et_3N, and 100 psi of CO are the best reaction conditions for this reaction (compare the results of Table 2 with entry 7, Table 1).

Therefore, we defined Conditions A (5 mol % of $PdCl_2$, 5 equiv of $CuCl_2$, 2 equiv of Et_3N, 100 psi of CO, CH_3CN, 30−35 °C) for the chlorocyclocarbonylation of 2,3-allenols (entry 7, Table 1). It should be noted that the reaction did not afford other cyclization products as judged from the ^1H NMR spectrum of the crude reaction mixture under the standard conditions.

To investigate the scope of the reaction, the chlorocyclocarbonylation of various 2,3-allenols **1** was conducted under Conditions A and the results are summarized in Table 3. Both secondary and tertiary alcohols afforded the products in moderate to good yields with the 2- and 4-position substituents all being hydrogen. R^1 may be an alkyl group, benzyl, or an aryl group and R^2 can be hydrogen or an alkyl group. To our disappointment, under identical conditions, 2-substituted, 4-nonsubstitued, or 2,4-disubstituted 2,3-allenols such as **1s−u** failed to undergo this transformation although the starting materials were completely consumed. It should be pointed out that the yields of products **3h−o** with R^1 = aryl and R^2 = hydrogen were dramatically decreased when petroleum ether and ethyl ether or ethyl acetate (10:1) were used as the eluents for flash chromatography on silica gel. However, when a mixture of CH_2Cl_2 and petroleum ether was used as the eluent, the isolated yield of **3k** was improved (Table 4). Compounds **3a−g** and **3p−r** were isolated by using petroleum ether and ethyl ether or ethyl acetate (10:1) as the eluents for flash chromatography without any difficulty. In addition, the substrate **1o** having an electron-donating ethyl group at the para position of the aromatic ring afforded the corresponding product **3o** in somewhat lower

(23) (a) Xu, D.; Li, Z.; Ma, S. *Chem. Eur. J.* **2002**, *21*, 5012. (b) Xu, D.; Li, Z.; Ma, S. *Tetrahedron: Asymmetry* **2003**, *14*, 3657. (c) Xu, D.; Li, Z.; Ma, S. *Tetrahedron Lett.* **2003**, *44*, 6343. (d) Xu, D.; Lu, Z.; Li, Z.; Ma, S. *Tetrahedron* **2004**, *60*, 11879.
(24) (a) Grennberg, H.; Gogoll, A.; Bäckvall, J. E. *Organometallics* **1993**, *12*, 1790. (b) Jia, C.; Lu, W.; Kitamura, T.; Fijiwara, Y. *Org. Lett.* **1999**, *1*, 2097.

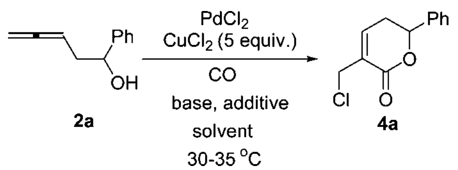
TABLE 4. $PdCl_2$-Catalyzed Chlorocyclocarbonylation of 1k with $CuCl_2$ Using Different Eluents for Flash Chromatography



entry	eluent for flash chromatography	isolated yield of **3k** (%)
1[a]	DCM/PE=1:1	34
2[b]	DCM/PE=2:1	53
3[b]	DCM/PE=3:1	64
4[b]	DCM/PE=4:1	68
5[b]	DCM/PE=5:1	69
6[b]	DCM/PE=6:1	68

[a] Reaction mixture was filtrated through a short column of silica gel before being subjected to flash chromatography on silica gel. [b] Reaction mixture was evaporated directly before being subjected to flash chromatography on silica gel.

TABLE 5. $PdCl_2$-Catalyzed Chlorocyclocarbonylation of 1-Phenyl-3,4-pentadien-1-ol 2a with $CuCl_2$



entry	$PdCl_2$ (mol %)	CO (psi)	base (equiv)	additive (equiv)	solvent	time (h)	isolated yield of **4a** (%)
1	10	300			THF	4	complicated
2	5	100	Et_3N (2)		CH_3CN	1	35
3	5	60	NaOAc (3)		CH_3CN	2	35
4	10	60	NaOAc (3)		HOAc	3	33
5[a]	10	60	NaOAc (3)		dioxane	2	NR
6[b]	10	60	NaOAc (3)		DMF	2	0
7[a]	10	60			Et_3N	2	NR
8	5	100	Et_3N (2)		THF	1	48
9	5	100	Et_3N (2)	BQ[c] (0.1)	THF	1	50
10	5	100	Et_3N (2)	BQ (0.5)	THF	1	53
11	5	100	Et_3N (2)	BQ (1.0)	THF	1	53

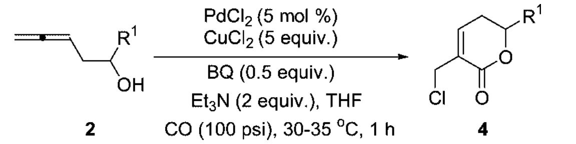
[a] Compound **2a** was not completely consumed. [b] No **2a** was left. [c] BQ is an abbreviation for benzoquinone.

yield (entry 15, Table 3) as compared to substrates **1h**−**n** (entries 8−14, Table 3). The reaction of **1q** with a five-membered ring afforded the corresponding product **3q** in 24% yield probably due to its instability. The butenolide structures of products **3** and the regioselectivity were established by the single crystal X-ray diffraction study of **3p** (see Figure S6 in the Supporting Information).[25]

Synthesis of 3-Chloromethyl-5,6-dihydropyran-2-ones via the $PdCl_2$-Catalyzed Chlorocyclocarbonylation of 3,4-Allenols. Stimulated by the above successful results, we wanted to expand the current reaction from 2,3-allenols to 3,4-allenols. Again, the reaction of 3,4-allenol **2a** failed to afford the chlorocarbonylative cyclization reaction under the same reaction conditions reported previously for the chlorocyclocarbonylation of 2-alkynols (entry 1, Table 5).[17] Gratifyingly, under Conditions A successfully applied for the 2,3-allenols, pyran-2-one **4a** was obtained in 35% yield (entry 2, Table 5). No improvement of yield was observed when NaOAc was used as the base instead of Et_3N (entry 3, Table 5). When HOAc was used instead of CH_3CN as the solvent, the yield dropped slightly (entry 4, Table 5). Further studies showed that dioxane, DMF, and Et_3N are all poor solvents for this reaction (entries 5−7, Table 5). When THF was used as the solvent, the yield was improved to 48% (entry 8, Table 5). When benzoquinone (0.5 equiv.), which has been extensively used for the oxidation of Pd(0) to Pd(II) under acidic conditions,[24] was added to the reaction mixture, the yield of product was slightly improved to 53% (compare entry 10 with entry 8, Table 5). With more benzoquinone no further improvement of the yield was observed (entry 11, Table 5). Thus, we defined Conditions B (5 mol % of $PdCl_2$, 5 equiv of $CuCl_2$, 2 equiv of Et_3N, 100 psi of CO, 0.5 equiv of benzoquinone, THF, 30−35 °C) for the chlorocyclocarbonylation of 3,4-allenols (entry 10, Table 5). It should be noted that the reaction did not afford other cyclization products as judged from the ^1H NMR spectrum of the crude reaction mixture under the standard conditions.

(25) For the crystal data and ORTEP representation of compound **3p**, see the Supporting Information.

TABLE 6. $PdCl_2$-Catalyzed Chlorocyclocarbonylation of Various 3,4-Allenols with $CuCl_2$



entry	substrate **2**	R^1	product **4**	isolated yield (%)
1	**2a**	Ph	**4a**	53
2	**2b**	4-EtC_6H_4	**4b**	46
3	**2c**	4-ClC_6H_4	**4c**	55
4	**2d**	2-ClC_6H_4	**4d**	54
5	**2e**	4-BrC_6H_4	**4e**	55
6	**2f**	4-$Pr^iC_6H_4$	**4f**	43
7	**2g**	1-naphthyl	**4g**	53
8	**2h**	*n*-C_8H_{17}	**4h**	30
9	**2i**	*n*-C_5H_{11}	**4i**	23

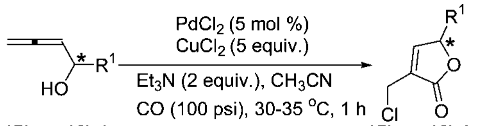
Some typical results for the chlorocyclocarbonylation of 3,4-allenols are listed in Table 6. Similar to the results of 2,3-allenols, 1-substituted 3,4-allenols **2a**−**i** underwent the cyclocarbonylation smoothly and highly regioselectively to afford 3-chloromethyl-5,6-dihydropyran-2-ones **4a**−**i** in moderate yields (entries 1−9, Table 6). The substrates **2h**,**i** having alkyl groups at the 1-position afforded the corresponding products **4h**,**i** in much lower yields as compared to the reaction of substrates **2a**−**g** with aryl groups at the same position.

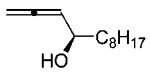
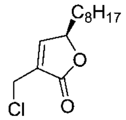
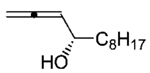
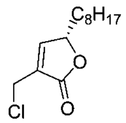
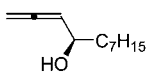
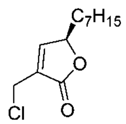
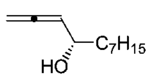
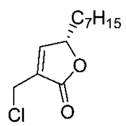
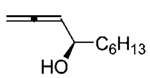
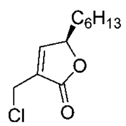
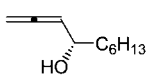
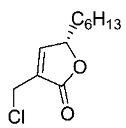
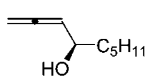
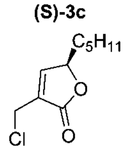
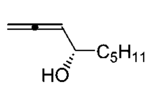
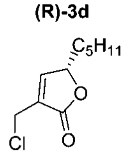
Preparation of Optically Active 3-Chloromethyl-2(5*H*)-furanones. With the successful chlorocyclocarbonylation protocol for the synthesis of 3-chloromethyl-2(5*H*)-furanones in hand, further studies were conducted to see the possibility of synthesizing optically active 3-chloromethyl-2(5*H*)-furanones under the established Conditions A. Some typical results are summarized in Table 7. From Table 7, it can be concluded that racemization of the chiral center in (*R*)- or (*S*)-**3** was not observed with the yields ranging from 64% to 70%.

NMR Spectra. In the light of X-ray single crystal diffraction analysis of compound **3p**, we established the structure of the products obtained from this $PdCl_2$-catalyzed chlorocyclocarbonylation of 2,3- or 3,4-allenols. However, there are some noteworthy characteristics in the NMR spectra of products **3** and **4**. The related information is available in the Supporting Information.

Mechanistic Considerations. A rationale for the $PdCl_2$-catalyzed regioselective chlorocyclocarbonylation of 2,3- or 3,4-allenols is shown in Scheme 4. The selective coordination of the terminal double bond in **1** or **2** with $PdCl_2$ gives coordination

TABLE 7. Synthesis of Optically Active 3-Chloromethyl-5*H*-furan-2-ones

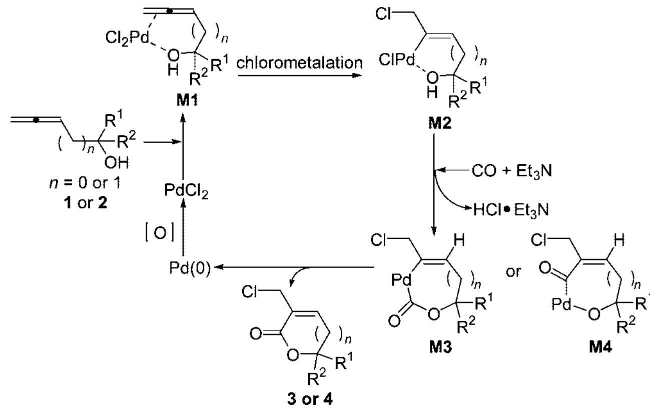


entry	substrate	product 3	yield (%) of 3[a]	ee (%) of 3[b]
1	 (R)-1a, >99% ee	 (R)-3a	70	99
2	 (S)-1a, 97% ee	 (S)-3a	69	97
3	 (R)-1b, >99% ee	 (R)-3b	68	99
4	 (S)-1b, 99% ee	 (S)-3b	69	99
5	 (R)-1c, >99% ee	 (R)-3c	69	99
6	 (S)-1c, 96% ee	 (S)-3c	69	96
7[c]	 (R)-1d, >99% ee	 (R)-3d	64	99
8	 (S)-1d, 93% ee	 (S)-3d	70	93

[a] Isolated yield. [b] ee value was determined by HPLC. [c] The reaction was carried out under Conditions B.

complex **M1**, which is followed by the highly regioselective chlorometalation to give the cyclic vinylic intermediate **M2** by introducing the chlorine atom to the terminal position of the allene moiety.[26] Subsequent coordination and insertion of CO affords metallocyclic intermediates **M3** or **M4**. Reductive

SCHEME 4



elimination of **M3** or **M4** affords **3** or **4** and Pd(0), which is oxidized with oxidant to regenerate the catalytically active species $PdCl_2$.

Conclusion

In summary, we have developed a mild and efficient methodology for the regioselective synthesis of 3-chloromethyl-2(5*H*)-furanones and 3-chloromethyl-5,6-dihydropyran-2-ones in moderate to good yields. The key step of this reaction may involve the highly regioselective chlorometalation of $PdCl_2$ with the terminal double bond in allenols by introducing the chlorine atom to the terminal position of the allene moiety, which has similar regioselectivity as in the copper(I) chloride-mediated carbometalation of 2,3-allenols with Grignard reagents reported recently by our group.[26c] Highly optically active 3-chloromethyl-2(5*H*)-furanones can be easily formed from the readily available optically active 2,3-allenols. Further studies in this area are being conducted in our laboratory.

Experimental Section

$PdCl_2$-Catalyzed Chlorocyclocarbonylation of 2,3-Allenols in the Presence of $CuCl_2$. Preparation of 3-Chloromethyl-2(5*H*)-furanones 3a−g and 3p−r. Typical Procedure I (Conditions A): Synthesis of 3-Chloromethyl-5-octyl-2(5*H*)-furanone (3a). 2,3-Allenol **1a** (92 mg, 0.50 mmol), anhydrous $CuCl_2$ (336 mg, 2.50 mmol), $PdCl_2$ (5 mg, 0.028 mmol), CH_3CN (6 mL), and Et_3N (102 mg, 1.01 mmol) were added sequentially to a glass vessel containing a stirring bar placed in a stainless-steel autoclave with stirring. The autoclave was flushed three times with 150 psi of CO gas. The autoclave was then charged with 100 psi of CO gas. After the mixture was stirred for 1 h at 30−35 °C (oil bath), the excess CO gas was ventilated, and the residue was diluted with Et_2O. Filtration through a short column of silica gel, evaporation, and flash chromatography on silica gel (eluent: petroleum ether/ethyl ether = 10:1) afforded 82 mg (66%) of **3a**: liquid; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (q, J = 1.8 Hz, 1 H), 5.00−4.94 (m, 1 H), 4.22 (t, J = 1.8 Hz, 2 H), 1.80−1.69 (m, 1 H), 1.68−1.60 (m, 1 H), 1.49−1.16 (m, 12 H), 0.85 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.0, 152.0, 130.8, 81.6, 35.9, 33.0, 31.6, 29.2, 29.1, 29.0, 24.8, 22.5, 14.0; MS (EI) *m/z* (%) 246 (M^+(^{37}Cl), 2.10), 244 (M^+(^{35}Cl), 5.11), 57 (100); IR (neat) 2927, 1761, 1653, 1466, 1341, 1087 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{21}O_2{}^{35}Cl$ (M^+) 244.1230, found 244.1232.

Preparation of 3-Chloromethyl-2(5*H*)-furanones 3h−o. Compounds **3h−o** were synthesized following typical procedure I except that the reaction time was reduced to 0.5 h, the reaction mixture was evaporated directly before being subjected to flash chroma-

(26) (a) Lu, Z.; Ma, S. *J. Org. Chem.* **2006**, *71*, 2655. (b) Ma, S.; Lu, Z. *Adv. Synth. Catal.* **2006**, *348*, 1894. (c) Lu, Z.; Ma, S. *Adv. Synth. Catal.* **2007**, *349*, 1225. (d) Lu, Z.; Chai, G.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 14546.

tography on silica gel, and the eluent used for flash chromatography is a 5:1 mixture of dichloromethane and petroleum ether.

PdCl$_2$-Catalyzed Chlorocyclocarbonylation of 3,4-Allenols in the Presence of CuCl$_2$. Preparation of 3-Chloromethyl-5,6-dihydropyran-2-ones 4a−i. Typical Procedure II (Conditions B): Synthesis of 3-Chloromethyl-6-(2′-chlorophenyl)-5,6-dihydropyran-2-one (4d). 3,4-Allenol **2d** (197 mg, 1.01 mmol), anhydrous $CuCl_2$ (672 mg, 5.00 mmol), $PdCl_2$ (9 mg, 0.051 mmol), benzoquinone (54 mg, 0.50 mmol), THF (12 mL), and Et_3N (202 mg, 2.00 mmol) were added sequentially to a glass vessel containing a stirring bar placed in a stainless-steel autoclave with stirring. The autoclave was flushed three times with 150 psi of CO gas. The autoclave was then charged with 100 psi of CO gas. After the mixture was stirred for 1 h at 30−35 °C (oil bath), the excess CO gas was ventilated, and the residue was diluted with Et_2O. Filtration through a short column of silica gel, evaporation, and flash chromatography on silica gel (eluent: dichloromethane/petroleum ether = 1:1) afforded 141 mg (54%) of **4d**: solid; mp 102−104 °C (petroleum ether/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.5 and 1.5 Hz, 1 H), 7.40−7.28 (m, 3 H), 7.13−7.07 (m, 1 H), 5.84 (dd, J = 12.2 and 3.8 Hz, 1 H), 4.41 (dm, J = 13.0 Hz, 1 H), 4.34 (dm, J = 13.0 Hz, 1 H), 2.89 (ddd, J = 18.5, 6.3, and 3.8 Hz, 1 H), 2.56 (ddq, J = 18.5, 12.2, and 2.2 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 163.2, 142.4, 135.7, 131.2, 129.6, 129.5, 129.1, 127.34, 127.32, 76.0, 41.1, 30.5; MS (EI) m/z (%) 260 (M^+(2 × ^{37}Cl), 0.85), 258 (M^+(^{37}Cl, ^{35}Cl), 4.33), 256 (M^+(2 × ^{35}Cl), 6.40), 116 (100); IR (neat) 3066, 2964, 1728, 1596, 1574, 1479, 1378, 1234, 1122 cm^{-1}. Anal. Calcd for $C_{12}H_{10}O_2Cl_2$: C, 56.06; H, 3.92. Found: C, 55.94; H, 3.80.

Synthesis of (5*R*)-3-Chloromethyl-5-octyl-2(5*H*)-furanone ((5*R*)-(3a)) Following Typical Procedure I. The reaction of (*R*)-**1a** (182 mg, 1.00 mmol, >99% ee), anhydrous $CuCl_2$ (673 mg, 5.01 mmol), $PdCl_2$ (9 mg, 0.051 mmol), and Et_3N (202 mg, 2.00 mmol) in 12 mL of CH_3CN afforded 172 mg (70%) of (5*R*)-**3a** with 99% ee as determined by HPLC analysis (Chiralcel OJ-H, *n*-hexane:*i*-PrOH = 90:10, 0.7 mL/min, 214 nm), t_r 12.5 (minor), 14.0 (major); $[\alpha]^{20}_D$ −32.9 (c 1.05, $CHCl_3$).

Acknowledgment. Financial support from the Major State Basic Research Development Program (Grant No. 2006CB806105), National Natural Science Foundation of China (Nos. 20732005 and 20423001), and Shanghai Municipal Committee of Science and Technology is greatly appreciated.

Supporting Information Available: General procedures and analytical data for compounds **1**, **2**, **3**, and **4**, ^{1}H and ^{13}C NMR spectra of these compounds, and CIF file of **3p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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