

Pd(0)-Catalyzed Coupling–Cyclization of 2-(2',3'-Allenyl)acetylacetates and Organic Halides: An Efficient Synthesis of 4,5-Dihydrofuran Derivatives

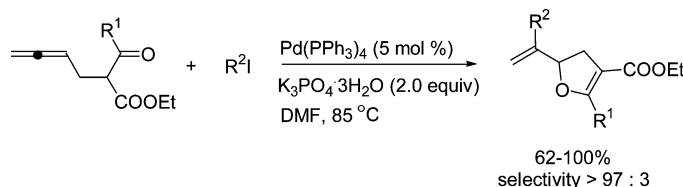
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ABSTRACT



Highly chemo- and regioselective Pd(0)-catalyzed coupling–cyclization of 2-(2',3'-allenyl)acetylacetates with organic halides using K_3PO_4 as base in DMF efficiently afforded 4,5-dihydrofuran derivatives in moderate to excellent yields, with a selectivity of >97:3.

The development of new chemical processes for producing elaborate and important heterocyclic structures in an efficient manner has become an important area of research in organic chemistry due to the importance of heterocyclic compounds.¹ Among heterocyclic compounds, dihydrofuran derivatives are intensively studied. They are important subunits in many biologically active compounds² and are also important intermediates in organic synthesis.³ Thus, much attention has been paid to the development of new methods for the synthesis of furans and dihydrofurans.⁴

Recently, we and others have shown that functionalized allenes can be facile starting materials for the preparation

of carbocycles and heterocycles.^{5,6} Especially, 2-(2',3'-allenyl)malonates could afford carbocycles, i.e., vinylic cyclopropane^{7a} and cyclopentene^{7b} derivatives, highly selectively by tuning the solvent and base used; the reaction of 1,2-allenyl ketones and organic halides in toluene using Et_3N as the base affords polysubstituted furans by the catalysis of Pd(0) and Ag_2CO_3 .^{7c–e} 2,5-dihydrofurans and 5,6-dihdropyrans can be synthesized via the Pd(II)-catalyzed coupling–cyclization of allylic halides with 2,3- or 3,4-allenols, respectively.^{7f,g} The reaction of 3,4-allenols with aryl iodides afforded 2,3-dihydrofurans via the oxidative addition–*exo*-mode oxypalladation–reductive elimination sequence.^{7h} Based on these observations, we envisioned that a Pd(0)-catalyzed cyclization of an organic halide with

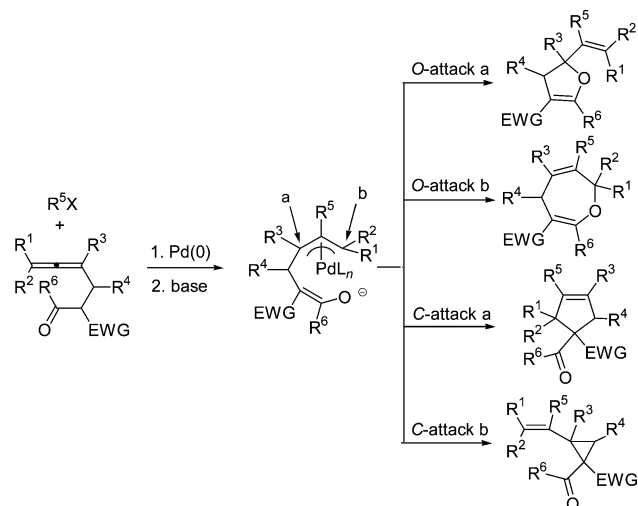
(1) For recent reviews on transition metal-catalyzed reactions for synthesis heterocyclic compounds, see: (a) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2285. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (d) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239.

(2) (a) Sasaki, T.; Yamakoshi, J.; Saito, M.; Kasai, K.; Matsudo, T. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1865. (b) Ottinger, H.; Soldo, T.; Hofmann, T. *J. Agric. Food Chem.* **2001**, *49*, 5383. (c) Vahtinen, S.-L.; Komulainen, H.; Kosma, V.-M.; Julkunen, A.; Maeki-Paakkanen, J. *Food Chem. Toxicol.* **1995**, *33*, 1027. (d) Moh, J. H.; Kim, J. K.; Jeong, Y. S.; Kim, J. Y.; Choi, Y. H.; Koh, H.-J. *J. Med. Chem.* **2004**, *47*, 792. (e) Vleet, T. R. V.; Klein, P. J.; Coulombe, R. A. *J. Toxicol. Environ. Health* **2002**, *65*, 853.

(3) (a) Gottlieb, O. R. *New Natural Products and Plant Drugs with Pharmacological, Biological, or Therapeutic Activity*; Springer-Verlag: Berlin-Heidelberg, Germany, 1987; p 227. (b) Ward, R. S. *Tetrahedron* **1990**, *46*, 5029. (c) Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 217. (d) Merrit, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243. (e) Moody, C. J.; Davies, M. *Stud. Nat. Prod. Chem.* **1992**, *10*, 201. (f) Koert, U. *Synthesis* **1995**, 115. (g) Benassi, R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scrivan, E. F. V., Bird, C. W., Eds.; Elsevier: Oxford, U.K. 1996; Vol. 2, p 259. (h) Koch, S. S. C.; Chamberlin, A. R. *Stud. Nat. Prod. Chem.* **1995**, *16*, 687. (i) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75.

2-(2',3'-allenyl)acetylacetates may form 4,5-dihydrofurans, 2,5-dihydroxepines, cyclopentenones, or cyclopropanes with the intramolecular attack of the enolate intermediate (Scheme 1). In this paper, we report a highly selective formation of

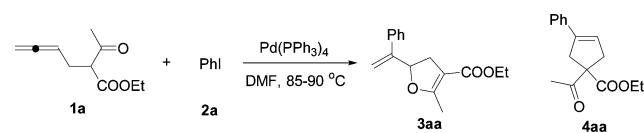
Scheme 1



4,5-dihydrofurans from organic halides and 2-(2',3'-allenyl)-acetylacetates.

At first, a mixture of 2-(2',3'-allenyl)acetylacetate **1a**, PhI, and LiOH in DMF was stirred in the presence of Pd(PPh₃)₄ at 85 °C for 7 h to afford the expected product **3aa** in 63% yield together with the formation of the five-membered carbocycle **4aa** in 15% yield (entry 1, Table 1). To improve the selectivity and yield, the base effect was studied (Table 1). With the addition of LiOH, *t*-BuOK, or NaOH, the reaction afforded a mixture of **3aa** and **4aa** (entries 1–3, Table 1). Using bases such as NaH (entry 4, Table 1), K₂-

Table 1. Effect of Base on the Pd(0)-Catalyzed Coupling–Cyclization of 2-(2',3'-Allenyl)acetylacetate **1a** and PhI^a



entry	base	time (h)	isolated yield of 3aa (4aa) (%)	ratio 3aa : 4aa ^b
1	LiOH	7	63 (15)	81:19
2	<i>t</i> -BuOK	8	54	91:9
3	NaOH	8	68	99:1
4	NaH	7	45	100:0
5	K ₂ CO ₃	8	68	100:0
6	Et ₃ N	7	73	100:0
7	KOH	8	68	100:0
8		8	13 ^c	100:0
9	K ₃ PO ₄ ·3H ₂ O	8	100	100:0

^a The reaction was conducted using **3aa** (0.15 mmol), Pd(PPh₃)₄ (5 mol %), PhI (1.2 equiv), and base (2.0 equiv) in DMF. ^b Determined by NMR analysis. ^c 71% of **1a** was recovered.

CO₃ (entry 5, Table 1), Et₃N (entry 6, Table 1), KOH (entry 7, Table 1), or K₃PO₄ (entry 9, Table 1), the reaction afforded **3aa** as the only product. Without base, the reaction is also highly selective, but product **3aa** was formed in only 13% isolated yield (entry 8, Table 1). K₃PO₄ turned out to be the best base, affording **3aa** in a quantitative yield.

The solvent effect using K₃PO₄ as base was then studied. THF (entry 2, Table 2) and CH₃CN (entry 3, Table 2) formed product **3aa** together with 2–3% of **4aa**. Toluene (entry 4, Table 2), DMSO (entry 5, Table 2), 1,4-dioxane (entry 6, Table 2), or CH₂Cl₂ (entry 7, Table 2) afforded product **3aa** as the only product in relative low yields. The reaction in CH₃OH (entry 8, Table 2) failed to afford the products. DMF is the best solvent (entry 1, Table 2).

By applying these standard reaction conditions, we studied the synthesis of 2-methyl-3-ethoxycarbonyl-5-vinyl-4,5-dihydrofuran from 2-(2',3'-allenyl)acetylacetate **1a** and different organic halides. The results are summarized in Table 3. From the results in the table, the following issues should

(4) (a) Dean, F. M.; Sargent, M. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4; pp 531–712. (b) Benassi, R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996, Vol. 2, pp 259–436. (c) Fuentes, L. M.; Larson, G. L. *Tetrahedron Lett.* **1982**, 23, 271. (d) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1371. (e) Pravia, K.; White, R.; Fodda, R.; Maynard, D. F. *J. Org. Chem.* **1996**, 61, 6031. (f) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1996**, 37, 2781. (g) Alonso, I.; Carretero, J. C.; Garrido, J. L.; Magro, V.; Pedregal, C. *J. Org. Chem.* **1997**, 62, 5682. (h) Garrido, J. L.; Alonso, I.; Carretero, J. C. *J. Org. Chem.* **1998**, 63, 9406. (i) Ichikawa, J.; Fujiwara, M.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **2000**, 1887. (j) Nguyen, V.-H.; Nishino, H.; Kurosawa, K. *Tetrahedron Lett.* **1996**, 37, 4949. (k) Garzino, F.; Meon, A.; Brun, P. *Tetrahedron Lett.* **2000**, 41, 9803. (l) Nair, V.; Mathew, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 187. (m) Lee, Y. R.; Kim, B. S. *Tetrahedron Lett.* **1997**, 38, 2095. (n) Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.* **1998**, 63, 2641. (o) Lund, E. A.; Kennedy, I. A.; Fallis, A. G. *Can. J. Chem.* **1996**, 74, 2401. (p) Schabbert, S.; Schauman, E. *Eur. J. Org. Chem.* **1998**, 1873. (q) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, 58, 6952. (r) Feldman, K. S.; Wroblewski, M. L. *J. Org. Chem.* **2000**, 65, 8659.

(5) For reviews, see: (a) Ma, S. *Acc. Chem. Res.* **2003**, 36, 701. (b) Ma, S. In *Topics in Organometallic Chemistry*; Tsuji, T., Ed.; Springer-Verlag: Berlin, Heidelberg, 2005; Vol. 14, pp 183–210. (c) Murakami, M.; Matsuda, T. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 727–815. (d) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, 44, 850.

(6) For most recent examples, see: carbocycles (a) Molander, G. A.; Cormier, E. P. *J. Org. Chem.* **2005**, 70, 2622. (b) Mukai, C.; Kuroda, N.; Ukon, R.; Itoh, R. *Heterocycles* **2005**, 70, 6282. (c) Ma, S.; Duan, D.; Shi, Z. *Org. Lett.* **2000**, 2, 1419. (d) Ma, S.; Xie, H. *Org. Lett.* **2000**, 2, 3801. (e) Hoffmann-Rolder, A.; Krause, N. *Org. Lett.* **2001**, 3, 2537. (f) Ma, S.; Gao, W. *Org. Lett.* **2002**, 4, 2989. (g) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, 42, 184. (h) Ma, S.; Yu, F.; Gao, W. *J. Org. Chem.* **2003**, 68, 5943. (i) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, 126, 9645. (j) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, 126, 8744. (k) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, 128, 9066. (l) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, 128, 10352. (m) Alcaide, B.; Almendros, P.; Campo, T. M. *Angew. Chem., Int. Ed.* **2006**, 45, 4501.

(7) (a) Ma, S.; Zhao, S. *Org. Lett.* **2000**, 2, 2495. (b) Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, 67, 2837. (c) Ma, S.; Li, L. *Org. Lett.* **2000**, 2, 941. (d) Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117. (e) Ma, S.; Zhang, J.; Lu, L. *Chem. Eur. J.* **2003**, 9, 2447. (f) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, 41, 8933. (g) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, 67, 6104. (h) Ma, S.; Gao, W. *Synlett* **2002**, 1, 65.

Table 2. Solvent Effect of Pd(0)-Catalyzed Coupling–Cyclization of 2-(2',3'-Allenyl)acetylacetate **1a** and PhI^a

entry	solvent	temp (°C)	time (h)	isolated yield of 3aa (%)	ratio 3aa:4aa
1	DMF	85	8	100	100:0
2	THF	reflux	8	81	100:0
3	CH ₃ CN	reflux	8	81	≥97:3
4	toluene	85	8	91	100:0
5	DMSO	85	8	82	100:0
6	dioxane	85	8	87	100:0
7	CH ₂ Cl ₂	reflux	6	78	100:0
8	CH ₃ OH	reflux	6	0	

^a The reaction was conducted using **1a** (0.15 mmol), Pd(PPh₃)₄ (5 mol %), PhI (1.2 equiv), and K₃PO₄ (2.0 equiv).

be noted: (i) the yields of this reaction range from moderate to excellent; (ii) electron-rich (entries 2 and 3, Table 3),

Table 3. Reaction of **1a** with Different Organic Iodides

entry	R ¹	product	time (h)	isolated yield of 3a (%)	ratio 3a:4a
1	Ph	3aa	8	100	100:0
2	4-MeC ₆ H ₄	3ab	8	87	100:0
3	4-MeOC ₆ H ₄	3ac	8	89	100:0
4	4-MeO ₂ CC ₆ H ₄	3ad	8	58	99:1
5	4-AcC ₆ H ₄	3ae	2	100	97:3
6	4-BrC ₆ H ₄	3af	8	80	99:1
7	1-naphthyl	3ag	8	77	100:0
8	1-(<i>E</i>)-hexenyl	3ah	7	81	100:0
9	2-thienyl	3ai	2	84	99:1

electron-deficient (entries 4 and 5, Table 3), Br-substituted (entry 6, Table 3) phenyl halides, and naphthyl (entry 7, Table 3), hexenyl (entry 8, Table 3), and thienyl (entry 9, Table 3) iodides all afforded the corresponding 4,5-dihydrofurans with high selectivity.

Different 2-(2',3'-allenyl)acetylacetates can also be used in this reaction (Table 4).

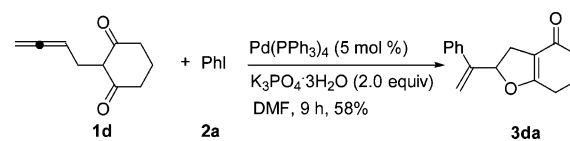
Table 4. Steric Effect in the Reaction of 2-(2',3'-Allenyl)acetylacetates with Phenyl Iodide

1	temp (°C)	product	isolated yield (%)	ratio 3:4^a
1b (R = <i>n</i> -Pr)	85	3ba	91	4ba 99:1
1c (R = <i>i</i> -Pr)	85	3ca	81	4ca 98:2
1c	60	3ca	40	4ca 97:3
1c	100	3ca	40	4ca 97:3

^a Determined by NMR analysis.

The reaction of 2-(2',3'-butadienyl)cyclohexane-1,3-dione afforded the bicyclic product **3da**, providing an opportunity for the construction of a bicyclic skeleton (Scheme 2).

Scheme 2. Reaction of 2-(Buta-2',3'-dienyl)cyclohex-1,3-dione and Phenyl Iodide



In conclusion, we have developed an efficient method for the synthesis of substituted 4,5-dihydrofurans with different substitution patterns in high chemo- and regioselectivity. The study of new chemo-, regio-, and stereoselective reactions for differently substituted 2-(2',3'-allenyl)acetylacetates are currently being carried out in our laboratory.

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Supporting Information Available: Analytical data for all products not listed in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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