ORGANIC LETTERS

2009
Vol. 11, No. 12
2663−2666

# Synthesis of 5,5-Disubstituted Butenolides Based on a Pd-Catalyzed $\gamma$-Arylation Strategy

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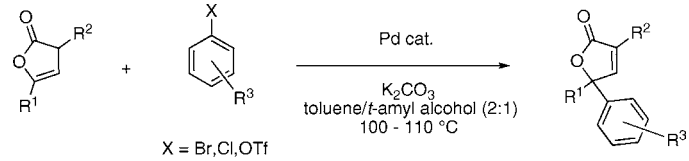
**Received April 3, 2009**

## ABSTRACT




**Methods for the construction of quaternary carbon centers are of great interest to synthetic chemists due to their presence in natural products. Development of the Pd-catalyzed arylation of butenolides with high selectivity for the $\gamma$-position allows for a facile construction of quaternary centers. The preparation of a wide variety of $\gamma$-aryl butenolides containing a number of functional groups is outlined. An application of this chemistry for a one-pot synthesis of a tricyclic tetrahydroisoquinolinone is demonstrated.**

The functionalization of pre-existing heterocyclic scaffolds through carbon−carbon bond formation represents a key route to new structures. This allows the rapid synthesis of a family of compounds sharing a common structural motif—an attractive strategy for medicinal chemists and others exploring structure−activity relationships. This approach has been applied extensively through the use of cross-coupling methods, in which the heterocyclic component can act either as a nucleophile or an electrophile.[1]

Butenolides, unsaturated $\gamma$-butyrolactones, are often substructures of natural products and other biologically active compounds.[2] Given their prevalence in nature, many methods have been developed for their de novo preparation from simpler precursors.[3] Of equal importance is the derivatization of preformed butenolides, often involving C−C bond formation with an appropriate electrophile at the $\gamma$-carbon. Such reactions include alkylations,[4a−c] vinylogous Mukaiyama aldol condensations,[4d−f] vinylogous Mukaiyama−Michael reactions,[4g−i] and vinylogous Mukaiyama−Mannich reactions.[4j,k] It has been found that butenolide dienolates are more nucleophilic at the $\gamma$-position, and very good selectivities are usually observed for this position.

We envisioned preparing $\gamma$-aryl butenolides from $\alpha,\beta$- or $\beta,\gamma$-unsaturated butyrolactones through a Pd-catalyzed cross-coupling process (Scheme 1). The cross-coupling of ester enolates with aryl and vinyl halides has emerged as an

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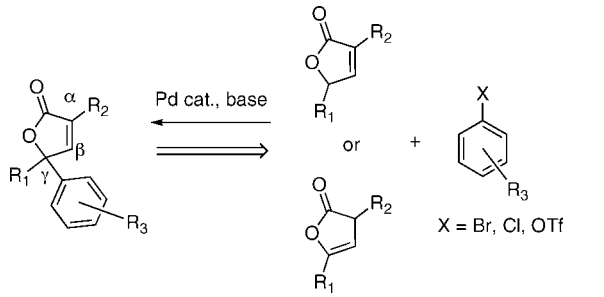
(3) For general reviews, see: (a) Avetisyan, A. A.; Dangyan, M. T. *Russ. Chem. Rev.* **1977**, *46*, 643. (b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. For an approach based on ring-closing metathesis: (c) Bassetti, M.; D'Annibale, A.; Fanfoni, A.; Minissi, F. *Org. Lett.* **2005**, *7*, 1805. For approaches based on Lewis- or Brønsted-acid-initiated cyclization: (d) Browne, D. M.; Niyomura, O.; Wirth, T. *Org. Lett.* **2007**, *9*, 3169. (e) Goldsmith, D.; Liotta, D.; Lee, C.; Zima, G. *Tetrahedron Lett.* **1979**, *20*, 4801. For methods which rely on the oxidation of furans: (f) Pelter, A.; Rowlands, M. *Tetrahedron Lett.* **1987**, *28*, 1203. (g) Kuwajima, I.; Urabe, H. *Tetrahedron Lett.* **1981**, *22*, 5191. (h) Machado-Araujo, F. W.; Gore, J. *Tetrahedron Lett.* **1981**, *22*, 1969. For a metal-mediated carbonylative ring closure: (i) Yoneda, E.; Kaneko, T.; Zhang, S.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441.

10.1021/ol9007102 CCC: $40.75 
**Published on Web 05/18/2009**

**Scheme 1.** General Reaction for the Preparation of 5,5-Disubstituted Butenolides




important and convenient route for the production of either α-aryl- or α-vinyl-substituted esters.[5] We and others have developed procedures for the γ-arylation of α,β- or β,γ-unsaturated ketones,[6] but to date, no analogous method to our knowledge has been reported for the direct arylation of an unsaturated ester.[7]

One potential issue is that butenolides are prone to dimerize in the presence of base through Michael reactions.[4g] Therefore, we began our studies by reacting silyl dienol ether **1** with bromobenzene in the presence of $Pd_2dba_3$, MePhos (**2**, Figure 1), and a fluoride source (Table 1). We found that

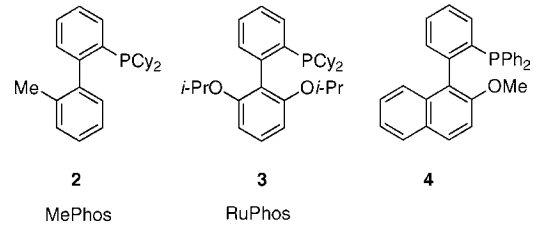
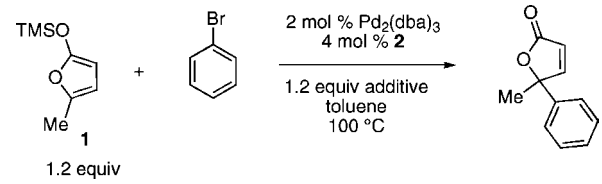



**Figure 1.** Ligands used in these studies.

**Table 1.** Arylation of Silyl Dienol Ether **1**




| additive | % yield[a] |
|---|---|
| CsF | 0 |
| KF | 0 |
| $ZnF_2$ | 0 |
| $CuF_2$ | 0 |
| TBAF | 0 |
| TBAT | 7 |
| $Bu_3SnF$ | 83 |

[a] GC yield (calibrated).

this approach worked quite well, but unfortunately $Bu_3SnF$ was the only fluoride source that efficiently promoted the reaction. The difficulty in separating the stoichiometric tin byproducts from the product coupled with the extra step to prepare the substrate prompted us to find conditions to arylate butenolides directly.

We next attempted the arylation of commercially available α-angelicalactone (**5**) with bromobenzene under a variety of conditions in the presence of a Pd catalyst and a base as shown in Table 2. It should be pointed out that the β,γ-unsaturated isomer is the more stable form of this lactone. This is fortunate because we previously showed that β,γ-unsaturated ketones are arylated more efficiently than their α,β-unsaturated counterparts.[6a] We immediately found that the nature of the solvent was critical to the success of this reaction—in most cases, only decomposition products were observed. Although the use of either toluene or *tert*-amyl alcohol alone gave poor yields (3% and 11%, respectively), remarkably, use of a 2:1 mixture of toluene/*tert*-amyl alcohol gave the product in 75% yield. One explanation for the role of the *tert*-amyl alcohol cosolvent is that it stabilizes the dienolate, preventing decomposing. DMA also works well as a solvent (77% yield), but we chose to adopt the toluene/*tert*-amyl alcohol system because its use proved more general

(4) (a) Jefford, C. W.; Sledeski, A. W.; Boukouvalas, J. *Chem. Commun.* **1988**, 364. (b) Ma, S.; Lu, L.; Lu, P. *J. Org. Chem.* **2005**, *70*, 1063. (c) Jiang, Y.; Shi, Y.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202. (d) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 8. (e) Asaoka, M.; Yanagida, N.; Ishibashi, K.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 4269. (f) Kong, K.; Romo, D. *Org. Lett.* **2006**, *8*, 2909. (g) Kraus, G. A.; Roth, B. *Tetrahedron Lett.* **1977**, *18*, 3129. (h) Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun.* **2004**, 1414. (i) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (j) de Oliveira, M. C. F.; Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6995. (k) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319.

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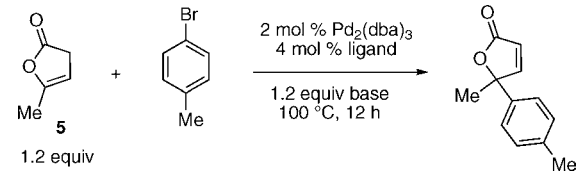
(6) (a) Hyde, A. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 177. (b) Yamamoto, Y.; Hatsuya, S.; Yamada, J. *Chem. Commun.* **1988**, 86. (c) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203. (d) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2345. (e) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967. (f) Wang, T.; Cook, J. *Org. Lett.* **2000**, *2*, 2057. (g) Varseev, G. N.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3881.

(7) For the Pd-catalyzed γ-arylation of an *O*-silyl furan with aryl antimonates, see: (a) Kang, S.; Ryu, H.; Hong, Y. *Perkin Trans. 1* **2000**, 3350. (b) For the Pd-catalyzed γ-arylation of an *O*-silyl furan with hypervalent iodonium salts, see: Kang, S.; Yamaguchi, T.; Ho, P.; Kim, W.; Yoon, S. *Tetrahedron Lett.* **1997**, *38*, 1947. (c) For one example of a γ-arylated butenolide generated as a side product from the α-arylation of a butyrolactone, see: Malcolm, S. C.; Ribe, S.; Wang, F.; Hewitt, M. C.; Bhongle, N.; Bakale, R. P.; Shao, L. *Tetrahedron Lett.* **2005**, *46*, 6871. (d) For the Pd-catalyzed arylation of γ-stannyl α,β-unsaturated esters, see: Yamamoto, Y.; Hatsuya, S.; Yamada, J. *Chem. Commun.* **1988**, 86.

(8) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23.

**Table 2.** Optimization of Conditions for the Arylation of α-Angelicalactone (**5**)




| entry | ligand | base | solvent | % yield[a] |
|---|---|---|---|---|
| 1 | **2** | $K_2CO_3$ | dioxane | 3 |
| 2 | **2** | $K_2CO_3$ | DME | 0 |
| 3 | **2** | $K_2CO_3$ | ethyl propionate | 39 |
| 4 | **2** | $K_2CO_3$ | *t*-amyl alcohol | 11 |
| 5 | **2** | $K_2CO_3$ | toluene | 3 |
| 6 | **2** | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 75 |
| 7 | **2** | $K_2CO_3$ | DMA | 77 |
| 8 | **2** | $Cs_2CO_3$ | tol/*t*-amylOH (2:1) | 50 |
| 9 | **2** | $Na_2CO_3$ | tol/*t*-amylOH (2:1) | 0 |
| 10 | **2** | $K_3PO_4$ | tol/*t*-amylOH (2:1) | 28 |
| 11 | **2** | NaO*t*-Bu | tol/*t*-amylOH (2:1) | 14 |
| 12 | **2** | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 84[b] |
| 13 | XPhos | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 7 |
| 14 | SPhos | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 67 |
| 15 | IMes[c] | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 0 |
| 16 | JohnPhos | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 0 |
| 17 | DavePhos | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 61 |
| 18 | $PPh_3$ | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 0 |
| 19 | P(*t*-Bu)$_3$[d] | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 10 |
| 20 | Xantphos | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 26 |
| 21 | dppf | $K_2CO_3$ | tol/*t*-amylOH (2:1) | 0 |

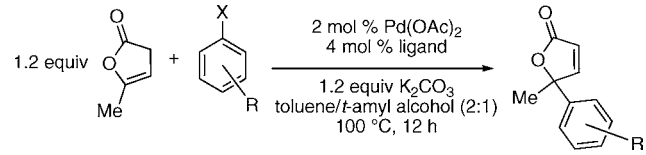
[a] GC yield (calibrated). [b] 2 mol % of $Pd(OAc)_2$ used in place of $Pd_2(dba)_3$. [c] $[(IMes)Pd(NQ)]_2$ complex used; IMes = 1,3-bis(mesityl)imidazole-2-ylidene, NQ = naphthoquinone. [d] $HBF_4$ salt used.

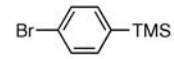
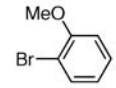
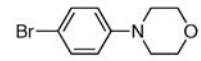
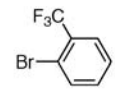
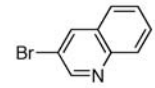
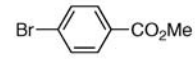
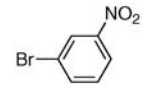
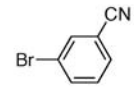
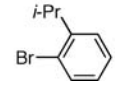
and did not require an aqueous workup. Further, we found $K_2CO_3$ to be the optimal base, while stronger bases (e.g., NaO*t*-Bu) promoted rapid decomposition of **5**. Changing the Pd source to $Pd(OAc)_2$ also increased the yield slightly (entry 12).

With the base and solvent chosen, we conducted a broad screen examining the use of a diverse range of ligand architectures which revealed that moderately hindered biaryl monophosphines were uniquely effective for this transformation, with MePhos (**1**) giving the highest yields.[8] The use of more hindered monophosphines (XPhos, entry 13), *N*-heterocyclic carbenes (IMes, entry 15), smaller phosphines ($PPh_3$, entry 18; P(*t*-Bu)$_3$, entry 19), and bidentate ligands (Xantphos, entry 20; dppf, entry 21) resulted in the formation of the product in very low yields. In contrast to our method published for the γ-arylation of ketones,[6a] the identity of the ligand did not have any effect on the regioselectivity of the process. In all cases, excellent selectivity favoring arylation at the γ-position was observed (>98:2).

As shown in Table 3, electron-neutral and slightly electron-rich aryl bromides (entries 1, 4, and 5) are efficiently coupled using MePhos. An aryl chloride was also successfully coupled when the more hindered ligand RuPhos (**3**) was used (entry 2). Further, aryl triflates may be efficiently coupled

**Table 3.** γ-Arylation of α-Angelicalactone



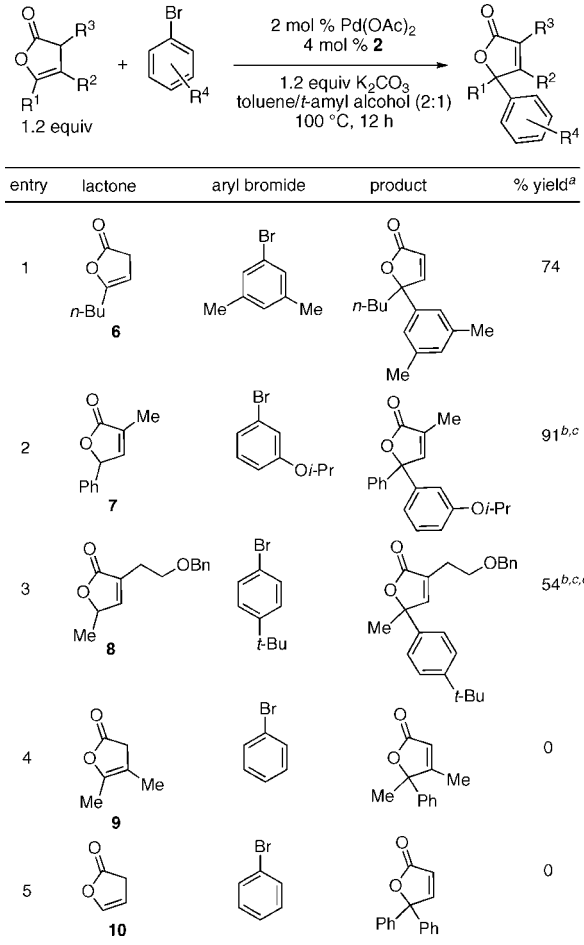

| entry | aryl electrophile | ligand | % yield[a] |
|---|---|---|---|
| 1 | X = Br | **2** | 85 |
| 2 | X = Cl  | **3** | 68[b,c] |
| 3 | X = OTf | **2** | 76[d] |
| 4 |  | **2** | 74 |
| 5 |  | **2** | 80 |
| 6 |  | **3** | 68 |
| 7 |  | **4** | 81 |
| 8 |  | **4** | 78 |
| 9 |  | **4** | 79 |
| 10 |  | **4** | 65 |
| 11 |  | **4** | 81 |
| 12 |  | **4** | 74[c,e] |

[a] Isolated yields (average of two runs). [b] Reaction run with 4 mol % of Pd and 8 mol % of ligand. [c] Reaction run at 110 °C. [d] DMA used as the solvent. [e] Reaction run for 18 h.

in good yield if DMA is used as solvent. The electron-rich aryl bromide 4-morpholinobromobenzene was not a good substrate using MePhos but could be coupled in reasonably good yield (68% yield) with RuPhos (entry 6). Electron-deficient and hindered aryl bromides also did not react efficiently, prompting us to re-evaluate the general conditions which led us to discover that ligand **4** was much more effective in these cases than MePhos or RuPhos. The use of this ligand allowed the efficient coupling of electron-deficient (entries 7 and 9−11), heterocyclic (entry 8), and even very hindered aryl bromides (entry 12). Although **4** closely resembles Hayashi's MOP ligand,[9] its use gives slightly improved yields over MOP and is straightforward to prepare (see Supporting Information).

We next evaluated the reaction of butenolides with other substitution patterns to further probe the scope of the reaction (Table 4). A larger substituent at the $\gamma$-position was tolerated

**Table 4.** Arylation of Substituted Butenolides

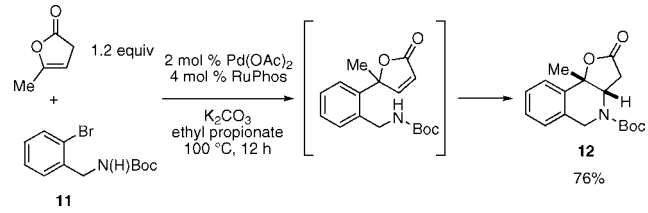



[a] Isolated yield (average of two runs). [b] Reaction run with 4 mol % of Pd and 8 mol % of ligand. [c] Reaction run for 18 h. [d] Reaction run at 110 °C.

in this reaction as was demonstrated in the case of *n*-butyl-substituted lactone **6**, which coupled to 3,5-dimethylbromobenzene in 74% yield (entry 1). $\gamma$-Aryl, $\alpha$-alkyl-disubstituted lactone **7** may be reacted with 3-isopropoxy bromobenzene in 91% yield (entry 2). The reaction of lactone **8** gave the $\gamma$-arylated product in a modest yield of 54% (entry 3). It is likely that this lower yield can be attributed to the use of an $\alpha,\beta$-unsaturated lactone without an acidifying group (e.g., lactone **7**). Another problematic group of substrates are $\beta$-substituted butenolides with an enolizable group (e.g., methyl) at this position such as **9** (entry 4). Furthermore, the lack of substitution at the $\gamma$-position, as demonstrated with **10**, also failed to provide any desired arylation products (entry 5). We believe that in both cases unhindered dienolates are formed which rapidly decompose.

To demonstrate the utility of this method further, we reacted Boc-protected 2-bromobenzylamine **11** with $\alpha$-angelicalactone using slightly modified conditions that afforded tricyclic compound **12** in 78% yield (Scheme 2). Similar to

**Scheme 2.** Synthesis of Tricyclic Tetrahydroisoquinolinone **12**




what we have seen for analogous reaction of ketone enolates,[6a] we believe that the reaction proceeds via C—C bond formation, followed by conjugate addition to form the tricyclic structure. Attempts to perform this reaction with alternative protecting groups or with unprotected benzylamines failed to give the desired product.

In summary, we have described an efficient preparation of quaternary $\gamma$-aryl butenolides with a Pd-catalyzed cross-coupling method. Careful optimization of the conditions was required to suppress decomposition of the butenolide starting material. We have shown that this reaction is quite general with respect to the aryl halide. The butenolide component must be substituted at the $\gamma$-position, and $\alpha$-substitution is tolerated. Further, we have applied this reaction to a one-pot synthesis of a novel tricyclic tetrahydroisoquinolinone. We are currently studying the mechanism of the reaction with the purpose of explaining the observed regioselectivity.

**Acknowledgment.** We are grateful to the National Institutes of Health (GM46059) as well as Merck, Amgen, and Boehringer Ingelheim for support of this research. We are indebted to BASF for providing a generous gift of $Pd(OAc)_2$ and Rhodia for providing ligand **2**. AMH would like to thank Sigma-Aldrich for a Graduate Student Innovation Award and MIT for a Nicholas A. Milas Fellowship supporting this research. The Varian NMR instruments used for these studies were purchased with funds from the NSF (CHE 9808061 and DBI 9729592).

**Supporting Information Available:** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9007102

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