

Diastereoselective Synthesis of Tetrahydrofurans via Palladium(0)-Catalyzed [3 + 2] Cycloaddition of Vinylcyclopropanes and Aldehydes

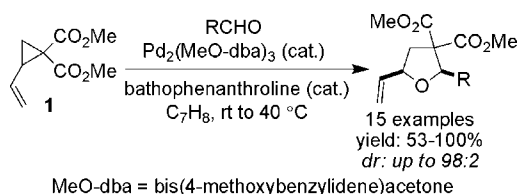
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ABSTRACT



Palladium(0)-catalyzed cycloadditions of malonate-derived vinylcyclopropane **1** and aldehydes to afford 2,5-*cis* disubstituted tetrahydrofuran derivatives are described. Pd loadings as low as 0.5 mol % were effective in catalyzing the transformation with high yields and diastereoselectivities. Electron-poor aldehydes work best, suggesting that a mechanism involving an initial aldol reaction may be operative.

The importance of developing synthetic methods to prepare tetrahydrofurans is evident due to the prevalence of these moieties in structurally and biologically interesting molecules.¹ A common method used to synthesize this scaffold involves the generation of 1,3-dipolar equivalents and subsequent trapping with a dipolarophile. Dipole formation can be achieved by the generation of a carbonyl ylide through thermolysis² or photolysis³ of epoxides, or more commonly by trapping of a metallocarbenoid with a carbonyl.^{4,5} In these

examples, the use of an alkene dipolarophile generates the tetrahydrofuran (THF) product. Alternatively, trapping of a carbonyl with a three-carbon 1,3-dipole equivalent also yields THFs. It has been demonstrated that donor–acceptor (D–A) cyclopropanes, particularly those with heteroatom or other specialized, highly activating donor substituents (e.g., trimethylsilyl methyl), are useful three-carbon building blocks for the Lewis acid-catalyzed cycloaddition of aldehydes⁶ and

(1) Recent examples: (a) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468. (b) Kim, E.-J.; Tian, F.; Woo, M.-H. *J. Nat. Prod.* **2000**, *63*, 1503. (c) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033. (d) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790. (e) Tinsley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818. (f) Mihovilovic, M. D.; Bianchi, D. A.; Rudroff, F. *Chem. Commun.* **2006**, 3214. (g) Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519. (h) Morinaka, B. I.; Skepper, C. K.; Molinski, T. F. *Org. Lett.* **2007**, *9*, 1975. For a review, see: (i) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261.

(2) (a) Huisgen, R. *Angew. Chem. Int. Ed.* **1977**, *16*, 572. (b) Huisgen, R.; de March, P. *J. Am. Chem. Soc.* **1982**, *104*, 4953.

(3) Das, P. K.; Griffin, G. W. *J. Photochem.* **1984**, *27*, 317.

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ketones^{6a,7} to afford THF derivatives. Our group has demonstrated that THF derivatives are accessible from malonate-derived cyclopropanes with a carbon-donor substituent via diastereoselective and enantiospecific Sn(OTf)₂- and SnCl₄-catalyzed cycloadditions with aldehydes.⁸ In this Letter, we describe a new electronically complementary method to synthesize THF derivatives from D–A vinylcyclopropane **1** through a Pd(0)-catalyzed [3 + 2] cycloaddition with aldehydes.

The use of Pd(0) to generate π -allylic species is a well-studied area and is commonly utilized for the allylation of nucleophiles.⁹ π -Allyl chemistry was expanded to cycloadditions nearly three decades ago when Trost introduced palladium-trimethylenemethane (Pd-TMM) as a three-carbon dipole equivalent useful for [3 + 2] cycloadditions (Figure 1, top).¹⁰ More recently, Tsuji generated the three-carbon π -allylpalladium dipole equivalent **2** through ring-opening of **1** by Pd₂(dba)₃•CHCl₃ (Figure 1, bottom). The resulting complex was shown to undergo formal [3 + 2] cycloadditions with potent electrophiles such as aryl isocyanates and various acrylates to yield γ -lactams¹¹ and cyclopentanes,¹² respectively. On the basis of these and other examples of hetero- and carbocycle formation from cyclopropanes,¹³ we envisioned the synthesis of tetrahydrofurans via Pd(0)-catalyzed ring-opening of **1** and subsequent cycloaddition with aldehydes.¹⁴

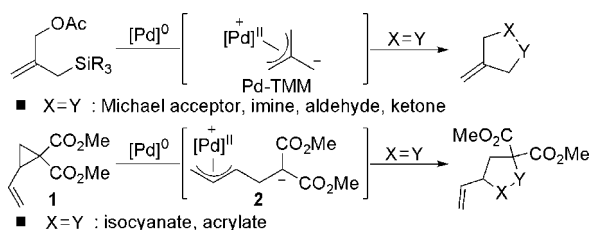


Figure 1. Trost's Pd-TMM reagent (top) and catalytic ring opening/cycloaddition of a malonate-derived vinylcyclopropane via π -allylpalladium formation (bottom).

Preparation of **1** was achieved in one step through a double alkylation of dimethyl malonate with 1,4-dibromo-2-butene

as reported in the literature.^{13d} Due to the need for highly electrophilic substrates in Tsuji's systems, we first examined the use of the electron-deficient 4-trifluoromethylbenzaldehyde. Preliminary results are reported in Figure 2. The reaction was sluggish when commercially available Pd(dba)₂ was used, requiring 28 h to reach completion. Recent reports demonstrating the increased reactivity of Pd(0) with electron-rich dba derivatives prompted us to employ bis(4-methoxybenzylidene)acetone (MeO-dba) ligands on our Pd(0) precatalyst.¹⁵ We noticed a marked improvement in reactivity under the same reaction conditions when Pd₂(MeO-dba)₃ was used (Figure 2). 2,2'-Dipyridyl (bipy) was chosen as the ligand based on initial studies indicating superiority over monodentate amines and phosphines.

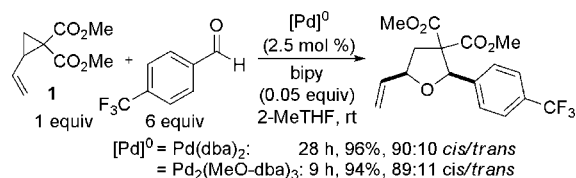


Figure 2. Identity of the Pd⁰ precatalyst has an effect on reaction rate.

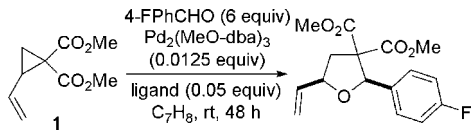
Although 2-MeTHF was found to be a superior solvent for the transformation in Figure 2, it was not found to be generally applicable. Competitive oligomerization of **1** was observed when other aldehydes were employed in 2-MeTHF. A solvent screen revealed that toluene reduced oligomerization substantially and thus was used in subsequent method optimization experiments.

Table 1 summarizes the effect of the supporting ligand on reaction efficiency and diastereoselection. For a uniform comparison, reactions were arbitrarily stopped and analyzed after 48 h. The discrepancy between cyclopropane consumption (% conversion) and tetrahydrofuran yield provides an approximate measure of competitive, nonproductive oligomerization of **1** for a given Pd/ligand complex. By changing the bidentate amine ligand from bipyridine to phenanthroline, we noted an improvement in diastereoselectivity (entry 3). Further improvement in diastereocontrol and reaction efficiency was realized when bathophenanthroline (bphen) was used, although the rate was somewhat slower (entry 5). Both monodentate and bidentate phosphine ligands performed poorly in promoting THF formation (entries 6 and 7).

With both the diastereoselectivity and the product/oligomer

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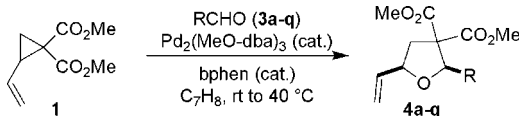
- (13) For selected examples, see: (a) Hiroi, K.; Yamada, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1835. (b) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023–3026. (c) Zuo, G.; Louie, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2277. (d) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573. (e) Liu, L.; Montgomery, J. *Org. Lett.* **2007**, *9*, 3885. (f) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689. (14) For Pd-catalyzed tetrahydrofuran formation from vinyl epoxides and alkenes, see: Shim, J.-G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 3067. (15) (a) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435. (b) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340. (c) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810.

Table 1. Ligand Effect on Reaction Efficiency and Diastereoselection^a


entry	ligand	% conversion ^b	% yield ^b	dr ^c (cis/trans)
1	2,2'-bipyridyl	83	48	79:21
2	4,4'-dimethyl-2,2'-dipyridyl	45	32	87:13
3	phenanthroline	78	47	87:13
4	bathocuproine	61	14	77:23
5	bathophenanthroline	65	48	89:11
6	PPh ₃	12	9	64:36
7	<i>rac</i> -binap	85	16	57:43

^a Conditions: 1.0 equiv of **1**, 6.0 equiv of aldehyde, 0.0125 equiv of Pd₂(MeO-dba)₃, 0.05 equiv of ligand, 0.30 mL of C₇H₈ ([**1**]₀ = 1.09 M), 48 h, rt under N₂. ^b Determined by ¹H NMR analysis using a mesitylene internal standard (average of at least two trials). ^c Determined by ¹H NMR spectroscopy.

ratio maximized using the bathophenanthroline/Pd₂(MeO-dba)₃-derived complex, we examined a variety of electronically diverse aromatic aldehydes with this catalyst system (Table 2). This method works best for electron-poor aldehydes,

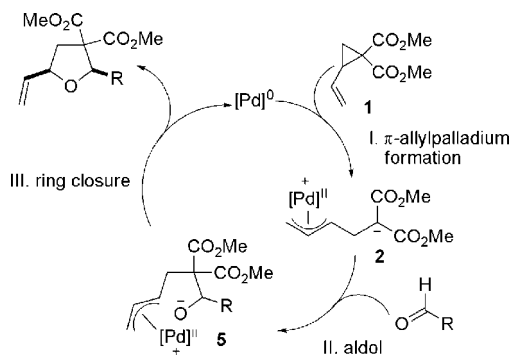
Table 2. Cycloaddition of **1** with Aldehydes **3a–q**^a


entry	R	equiv [Pd] ₂ ^b	temp (°C)	time (h)	% yield ^c	dr ^d (cis/trans)
1	C ₆ H ₅ (3a)	0.0075	40	25	53	89:11
2	4-MeC ₆ H ₄ (3b)	0.025	rt	96	71	92:8
3	4-MeOC ₆ H ₄ (3c)	0.025	40	24	<5	nd
4 ^e	4-BrC ₆ H ₄ (3d)	0.0125	rt	24	80	92:8
5	4-ClC ₆ H ₄ (3e)	0.005	40	12	91	89:11
6	4-FC ₆ H ₄ (3f)	0.0125	rt	96	64	87:13
7 ^e	4-MeO ₂ CC ₆ H ₄ (3g)	0.005	40	27	80	83:17
8 ^e	4-NCC ₆ H ₄ (3h)	0.005	rt	5.5	93	83:17
9	4-F ₃ CC ₆ H ₄ (3i)	0.0125	rt	4	98	91:9
10 ^e	4-O ₂ NC ₆ H ₄ (3j)	0.0025	rt	5	96	80:20
11	3-ClC ₆ H ₄ (3k)	0.0125	40	21	95	89:11
12 ^e	3-O ₂ NC ₆ H ₄ (3l)	0.005	rt	2	99	82:18
13	2-ClC ₆ H ₄ (3m)	0.025	40	3.5	92	98:2
14	2-FC ₆ H ₄ (3n)	0.005	40	20	98	95:5
15 ^e	2-O ₂ NC ₆ H ₄ (3o)	0.0125	rt	3	100	87:13
16	ⁿ C ₅ H ₁₁ (3p)	0.0125	40	22	89	69:31
17	^c C ₆ H ₁₁ (3q)	0.0125	40	24	<5	nd

^a Conditions: 1 equiv of **1**, 6 equiv of RCHO, 4 equiv of bphen relative to equiv Pd₂(MeO-dba)₃, 0.30 mL of C₇H₈ ([**1**]₀ = 1.09 M), under N₂. ^b [Pd]₂ = Pd₂(MeO-dba)₃. ^c Isolated yield after column chromatography (average of at least two trials). ^d Determined by ¹H NMR analysis of the unpurified product. ^e Three equivalents of aldehyde were used.

hydes, providing high yields and short reaction times (entries 8–10, 12, 15). Electron-rich aldehydes are problematic, with only trace product obtained with *p*-anisaldehyde, despite complete consumption of cyclopropane (entry 3). The linear, unbranched aliphatic hexanal was also a successful substrate, although the dr was poor (entry 16). An aliphatic aldehyde containing α-branching was unreactive (entry 17). Although the reaction rate can often be increased by boosting the catalyst loading, nonproductive oligomerization increases as well. Catalyst loading and reaction temperature were variables found to be in a delicate balance that required some fine-tuning for each substrate; therefore, the reaction conditions in Table 2 vary slightly as the aldehyde partner changes.

We believe that electron-rich aldehydes are not electrophilic enough to undergo nucleophilic attack by π-allylpalladium complex **2**. As a result, the majority of the starting material oligomerizes prior to cycloaddition. It is interesting that in the absence of aldehyde, only 15% conversion of the cyclopropane to oligomer occurs.^{16a} To examine the effect of the aldehyde on oligomerization, we carried out an experiment using the standard reaction conditions with 0.50 equivalents of *p*-anisaldehyde. Analysis by ¹H NMR spectroscopy revealed 91% consumption of **1** but only 22% of the aldehyde.^{16b} The reaction was accompanied by significant oligomer formation, suggesting that *p*-anisaldehyde plays some role in copromoting the oligomerization.

**Figure 3.** Proposed catalytic cycle.

Data from the aldehyde screen provided mechanistic insight into this reaction. Electron-poor aldehydes react at a much faster rate and require a lower catalyst loading, supporting an aldol-type mechanism in which π-allylpalladium complex **2** attacks the electrophilic aldehyde to form alkoxide **5** (Figure 3).¹⁷ Ring closure and displacement of the Pd(0) catalyst yields the THF product to complete the catalytic cycle. The inability of *p*-anisaldehyde to participate productively in the reaction is consistent with this hypothesis.

(16) Conditions: (a) One equivalent of **1** (0.326 mmol), 0.025 equiv of Pd₂(MeO-dba)₃ (0.0082 mmol), 0.10 equiv of bphen (0.0164 mmol), 0.30 mL C₇H₈ ([**1**]₀ = 1.09 M), 40 °C, 17.5 h. (b) One equivalent of **1** (0.326 mmol), 0.50 equiv of *p*-anisaldehyde (0.163 mmol), 0.025 equiv of Pd₂(MeO-dba)₃ (0.0082 mmol), 0.10 equiv of bphen (0.0164 mmol), 0.30 mL of C₇H₈ ([**1**]₀ = 1.09 M), 40 °C, 18 h under N₂. ¹H NMR analysis was carried out using a mesitylene internal standard.

(17) (bphen)PdCl₂ does not catalyze the cycloaddition, suggesting that a mechanism involving a Pd(II) Lewis acid is unlikely.

Recent work in our laboratory showed that the rearrangement of enantioenriched vinylcyclopropanes via a π -allylnickel complex affords dihydrofurans without loss of stereochemical fidelity.^{13c} On the basis of these results, we were interested in examining the stereochemical outcome of the Pd(0)-catalyzed [3 + 2] cycloaddition when enantioenriched (**S**)-**1** (er: 99:1) was used. Under the standard reaction conditions (Figure 4), we observed

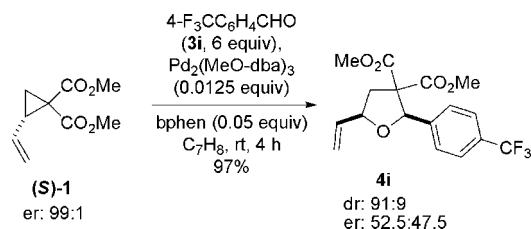


Figure 4. Use of enantioenriched starting material results in nearly racemic product.

nearly complete degradation of enantioenrichment in the product (er: 52.5:47.5), suggesting the generation of an

achiral intermediate and/or racemization of the starting material.

In conclusion, we have developed an efficient, diastereoselective method to synthesize tetrahydrofuran derivatives via a Pd(0)-catalyzed [3 + 2] cycloaddition of vinylcyclopropanes and aldehydes. This reaction works well for electron-poor aldehydes, which is complementary to the Lewis acid-catalyzed cycloaddition developed in our laboratory. Research to develop an asymmetric variant of this reaction is currently underway.

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

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