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Diversity-Oriented Synthesis of Fused Pyran γ-Lactones via an Efficient Pd−Thiourea-Catalyzed Alkoxycarbonylative Annulation

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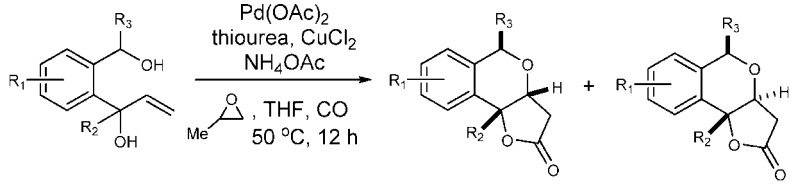
ABSTRACT



We reported herein a diversity-oriented synthesis of a range of fused pyran-γ-lactones that was effected through a versatile Pd−thiourea complex-catalyzed intramolecular alkoxycarbonylative annulation.

Fused pyran-γ-lactones are common structural motifs among many classes of natural products,[1] and some of them possess significant biological activities. For example, crisamicin A (**1**),[2] frenolicin B (**2**),[3] medermycin (**3**),[4] griseusin A (**4**),[5] and BE-54238B (**5**)[6] belong to a family of potent pyranonaphthoquinone antibiotics that feature prominently various stereochemically complex fused pyran-γ-lactone core structures (Figure 1).

Among the several variants for synthesis of fused pyran-γ-lactones,[7] the Pd-mediated tandem carbonylative annulation invented by Semmelhack and co-workers stands out as a valuable synthetic method.[8] The protocol offers an efficient entry to highly functionalized fused pyran-γ-lactones **B** from benzylic alcohols **A** (Figure 2); however, a stoichiometric amount of Pd reagent[8n,o] was employed. In addition, carbonylative annulation mediated by Pd(II) was thought to proceed through an alkoxypalladium(II) intermediate[9] which may undergo oxidation to afford a ketone,[10] thereby interfering with the desired annulation reaction pathway. Since we

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(1) (a) Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Ed.; Pergamon Press: Oxford, 1996; Vol. 2, pp 351. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.
(2) Iwai, Y.; Kora, A.; Takahashi, Y. *J. Antibiot.* **1978**, *31*, 959.
(3) Bergy, M. E. *J. Antibiot.* **1968**, *21*, 454. (b) Hoeksema, H.; Krueger, W. C. *J. Antibiot.* **1976**, *29*, 704.
(4) Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T.; Nakata, M. *J. Antibiot.* **1991**, *44*, 901.
(5) Fang, X.-P.; erson, J. E.; Chang, C.-J.; Fanwick, P. E.; McLaughlin, J. L. *J. Chem. Soc., Perkin Trans 1* **1990**, 1655.
(6) Tsukamoto, M.; Muriika, K.; Hirayama, M.; Hirano, K.; Yoshida, S.; Kojiri, K.; Suda, H. *J. Antibiot.* **2000**, *53*, 26.
(7) (a) Tatsuta, K. *J. Synth. Org. Chem. Jpn.* **1984**, *42*, 497. (b) Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522. (c) Brimble, M. A.; Neville, D.; Duncalf, L. J. *Tetrahedron Lett.* **1998**, *39*, 5647. (d) Brimble, M. A.; Nairn, M. R.; Park, J. *Org. Lett.* **1999**, *1*, 1459. (e) Tatsuta, K.; Hosokawa, S. *Chem. Rev.* **2005**, *105*, 4707.

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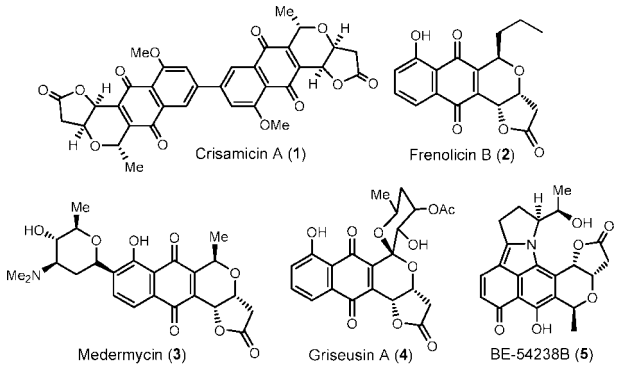


Figure 1. Bioactive pyranonaphthoquinone antibiotics.

were interested in diversity-oriented synthesis of pyranonaphthoquinone antibiotics, further study of this powerful reaction in a catalytic manner and profile of the reaction scope is an essential step toward this goal. Herein we describe that TMTU-Pd(OAc)$_2$ is an efficient catalyst system promoting carbonylative annulation for the formation of structurally diverse fused pyran-γ-lactones.

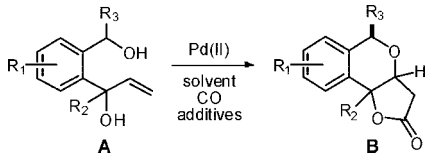
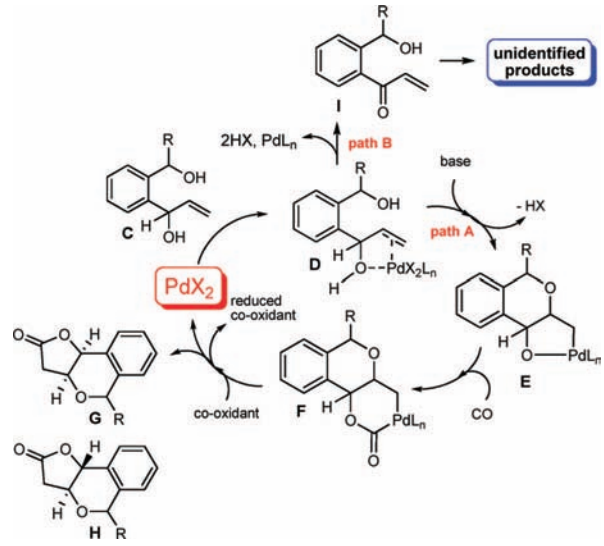


Figure 2. Pd(II)-mediated carbonylative annulation.

Our study employed compound **6** as a model substrate to test its annulation with both stoichiometric and catalytic amounts of palladium according to the published procedures;[8j,n,o] however, we found that in most of the cases starting material either yielded complex mixture or underwent decomposition, presumably because of its oxidative degradation.

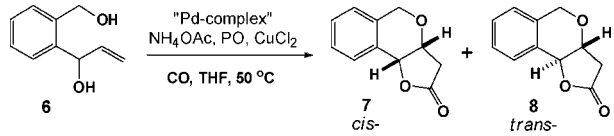
Scheme 1. Possible Mechanistic Pathways Involved in Pd/TMTU-Catalyzed Alkoxycarbonylative Annulation



We recently identified that TMTU (tetramethyl thiourea) was an efficient ligand in $Co_2(CO)_8$ and $PdCl_2$ catalyzed Pauson−Khand reactions[11] and $AuCl_3$-catalyzed cycloalkylation of aryl epoxides.[12] The stability of TMTU-ligated transition-metal complexes toward air and moisture,[13] together with its cheap price and commercial availability, inspired us to explore Pd−TMTU complex in this Pd-catalyzed carbonylative annulation.

The feasibility of Pd−TMTU as a unique catalyst has been demonstrated in the construction of a fused pyran-γ-lactone, a key intermediate in our total synthesis of crisamicin A.[9] To further study catalyst precursors and solvent effect on the outcome of this carbonylative annulation, we had screened several catalyst precursors including Pd(OAc)$_2$,

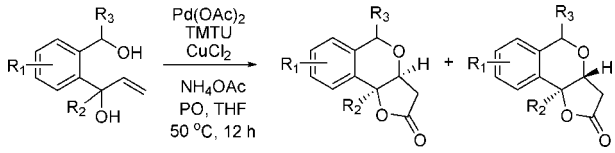
Table 1. Pd/TMTU-Catalyzed Annulation[a]

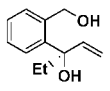
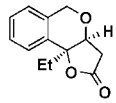
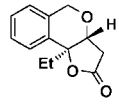
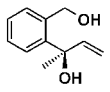
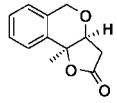
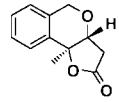
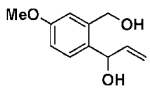
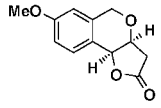
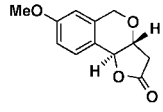
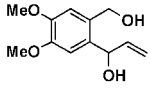
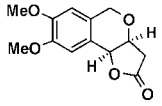
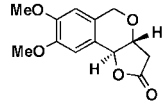
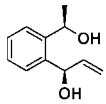
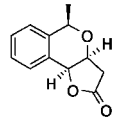
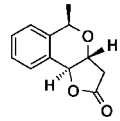
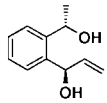
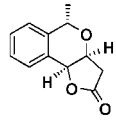
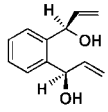
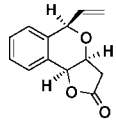
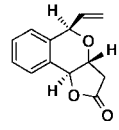
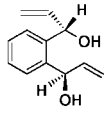
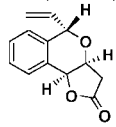
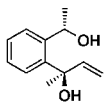
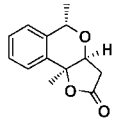
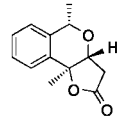
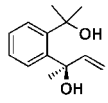
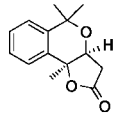
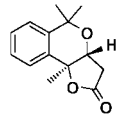


					yield[b] (%)			
entry	catalyst system	Pd(OAc)$_2$ (equiv)	thiourea (equiv)	time (h)	**7**	**8**	total	dr
1	Pd(OAc)$_2$ + TMTU	0.1	0.1	12	83	11	94	7.5
2	$PdCl_2$ + TMTU	0.1	0.1	12	58 (70)[c]	10 (12)[c]	68 (82)[c]	5.8
3	PdI_2 + TMTU	0.1	0.1	12	23 (59)[c]	4 (10)[c]	27 (69)[c]	5.9
4	[PdCl(C$_3$H$_5$)]$_2$ + TMTU	0.05	0.1	12	43 (66)[c]	8 (12)[c]	51 (78)[c]	5.4
5	$PdCl_2(PPh_3)_2$ + TMTU	0.1	0.1	12	trace			

[a] Reaction conditions: substrate **6**, PdLn (0.1 equiv), thiourea, and $CuCl_2$ (2.5 equiv) were combined in THF, and the mixture was allowed to react under a balloon pressure of CO at the indicated time. [b] Isolated yield. [c] Based on recovery of SM.

Table 2. Pd/Thiourea-Catalyzed Annulation[a]



entry	substrate	product		yield (%)[b]
1	 **9**	 **9a** (*cis* 70%)	 **9b** (*trans* 23%)	93%
2	 **10**	 **10a** (*cis* 69%)	 **10b** (*trans* 21%)	90%
3	 **11**	 **11a** (*cis* 75%)	 **11b** (*trans* 16%)	91%
4	 **12**	 **12a** (*cis* 73%)	 **12b** (*trans* 18%)	91%
5	 **13**	 **13a** (*cis* 62%)	 **13b** (*trans* 9%)	71%
6	 **14**	 **14a** (*cis* 53%)		53%
7	 **15**	 **15a** (*cis* 30%)	 **15b** (*trans* 16%)	46%
8	 **16**	 **16a** (*cis* 44%)		44%
9	 **17**	 **17a** (*cis* 68%)	 **17b** (*trans* 25%)	93%
10	 **18**	 **18a** (*cis* 48%)	 **18b** (*trans* 34%)	82%

[a] Reaction conditions: substrate (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), TMTU (0.05 mmol), $CuCl_2$ (2.5 mmol), and NH_4OAc (1.0 mmol) in THF at 50 °C for 12 h. [b] Isolated yield.

$PdCl_2$, PdI_2, $PdCl_2(PPh_3)_2$, and $PdCl_2$(dppf) in various solvents, such as THF, benzene, DMF, and CH_3CN.

The catalytic activities of these Pd complexes were examined by generating the Pd complex in situ from the reaction of a catalyst precursor with TMTU. As indicated in Table 1, $Pd(OAc)_2$ was proved to be the best catalyst precursor for the formation of TMTU−$Pd(OAc)_2$ complex in the presence of NH_4OAc and propylene oxide (PO)[9] in THF, and lactones **7** and **8** were obtained in high yield (94%) with a cis/trans ratio of 7.5 (entry 1).

With the optimized conditions in hand, we started to profile the substrates' substitutent effect (Figure 2) on the outcome of annulation and suspected that the hydrogen at the allylic position might play a critical role in the entire carbonylative annulation process. We envisioned that the allylic alcohol-derived enyl Pd complex **D** (Scheme 1) could undergo an intramolecular nucleophilic addition across the double bond to give intermediate **E** (path A). A sequential CO insertion−reductive elimination events on the alkyl-Pd species **E** then would deliver the fused pyran γ-lactones **G** and **H**.

On the other hand, intermediate **D** could either undergo a Pd-mediated oxidation[9] to yield the ketone **I** and various byproducts decomposed thereafter (path B)[14] or be subject to a double-bond migration to form certain types of intermediates which might lead to decomposition.[15] Based on this analysis, we believed that the relative rate between paths A and B could be critical in the proposed carbonylative annulation and the substitutent of R group should play a pivotal role to control the speed for the formation of intermediate **E**. To support our analysis, two groups of compounds **11**−**14** (entries 1−4 in Table 2) and **15**−**18** (entries 5−8) were selected as suitable precursors to probe the steric effect of R groups on the annulation, and their annulated results were summarized in Table 2. In general, the primary benzylic alcohol-derived substrates (entires 1−4) appeared to give products in higher yields than those secondary alcohol-derived substrates (entries 5−8). It was worthy of noting that the substitution on the benzylic position seemed to have a marked influence not only on the yields but also on the reaction diastereoselectivities (entries 5−8). A substitution at the benzylic position generally favored the *cis*-lactones, and when chirality at this position was matched with that at the allylic position, the corresponding *cis*-lactone was exclusively formed (entries 6 and 8). It should be added here that both *cis*- and *trans*-lactones were readily separated; thus, this protocol offered a stereochemically flexible solution to construct diverse pyran-fused lactones.[16]

To further confirm that the lability of intermediate **D** accounts for the failure for the desired reaction, we then synthesized substrates **17** and **18** by replacing the allylic hydrogen with a methyl group, which would prevent the proposed oxidative degradation. As expected, the desired products were obtained in high yields, indicating the allylic hydrogen indeed plays a pivotal role in the Pd-catalyzed carbonylative annulation.

It appeared to be reasonable that in a substrate structure an increase of steric size of its benzylic R_3 group could retard the formation of the bicyclic intermediate **E**, and the presence

of allylic hydrogen could promote the oxidation pathway B; therefore, both factors under otherwise similar molecular settings should pose a detrimental effect on reaction yield.

In summary, we have established Pd/TMTU to be an efficient and general catalytic system in promoting alkoxycarbonylative annulation to generate interesting fused pyran γ-lactones in high yields. This simple catalyst was readily accessible and applicable to a wide range of substrates bearing useful stereochemical information, thus advancing this important methodology. We believe that this enabling methodology should find utility in diversity- and target-oriented synthesis of biologically significant pyran γ-lactone-derived molecules.

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Supporting Information Available: Experimental procedure and ^{1}H NMR and ^{13}C NMR spectra This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034. (b) Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*, 3171. (c) Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 3207. (d) Tamaru, Y.; Higashimura, H.; Naka, K.; Hojo, M.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1045. (e) Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 4479. (f) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731. (g) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035. (h) Gracza, T.; Jäger, V. *Synthesis* **1992**, 191. (i) Gracza, T.; Jäger, V. *Synthesis* **1992**, 191. (j) Kraus, G. A.; Li, J. *J. Am. Chem. Soc.* **1993**, *115*, 5859. (k) Kraus, G. A.; Li, J.; Gordon, M. S.; Jensen, J. H. *J. Org. Chem.* **1995**, *60*, 2254. (l) Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *63*, 916. (m) McCormick, M.; Monahanm, R., III; Soria, J.; Goldsmith, D.; Liotta, D. *J. Org. Chem.* **1999**, *54*, 4485. (n) Semmelhack, M. F.; Shanmugam, P. *Tetrahedron Lett.* **2000**, *41*, 3567. (o) Boukouvalas, J.; Pouliot, M.; Robichaud, J. I.; MacNeil, S.; Snieckus, V. *Org. Lett.* **2006**, *8*, 3597. For a recent review regarding this type of reaction, see: (p) Muzart, J. *Tetrahedron* **2005**, *61*, 5955.

(9) Li, Z.; Gao, Y.; Tang, Y.; Dai, M.; Wang, G.; Wang, Z.; Yang, Z. *Org. Lett.* **2008**, *10*, 3017.

(10) (a) Berzelius, J. J. *Ann.* **1828**, *13*, 435. (b) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. For a recent review regarding this type of reaction, see: (c) Muzart, J. *Tetrahedron* **2003**, *59*, 5789.

(11) (a) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 593. (b) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 1657.

(12) Liu, Y.; Li, X.; Lin, G.; Xiang, Z.; Xiang, J.; Zhao, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2008**, *73*, 4625.

(13) (a) Dai, M.; Wang, C.; Dong, G.; Xiang, J.; Luo, T.; Liang, B.; Chen, J.; Yang, Z. *Eur. J. Org. Chem.* **2003**, 4346. (b) Dai, M.; Liang, B.; Wang, C.; You, Z.; Xiang, J.; Dong, G.; Chen, J.; Yang, Z. *Adv. Synth. Catal.* **2004**, *346*, 1669.

(14) Ganchegui, B.; Bouquillon, S.; Hénin, F.; Muzart, J. *J. Mol. Catal. A: Chem.* **2004**, *214*, 65.

(15) (a) Riahi, A.; Muzart, J. *J. Organomet. Chem.* **1999**, *585*, 256. (b) Chevin, C.; Le Bras, J.; Muzart, J. *Synthesis* **2005**, 2615. (c) Thiery, E.; Chevrin, C.; Le Bras, J.; Harakat, D.; Muzart, J. *J. Org. Chem.* **2007**, *72*, 1859. (d) Thiery, E.; Harakat, D.; Le Bras, J.; Muzart, J. *Organometallics* **2008**, *27*, 3996.

(16) For recent examples, see: (a) Ford, P. W.; Gadepalli, M.; Davidson, B. S. *J. Nat. Prod.* **1998**, *61*, 1232. (b) Léo, P.-M.; Morin, C.; Philouze, C *Org. Lett.* **2002**, *4*, 2711. (c) Léo, P.-M.; Morin, C.; Philouze, C. *Org. Lett.* **2002**, *4*, 2711. (d) Williamson, R. T.; McDonald, L. A.; Barbieri, L. R.; Garter, G. T. *Org. Lett.* **2002**, *4*, 4659.