ORGANIC LETTERS

2008
Vol. 10, No. 3
437−440

Sequential Rh(I)/Pd-Catalyzed 1,4-Addition/Intramolecular Allylation: Stereocontrolled Construction of γ-Butyrolactones and Cyclopropanes

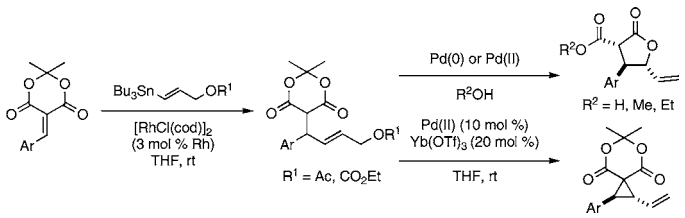
Eric Fillion,* Sébastien Carret, Lauren G. Mercier, and Vincent É. Trépanier

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

efillion@uwaterloo.ca

Received October 26, 2007

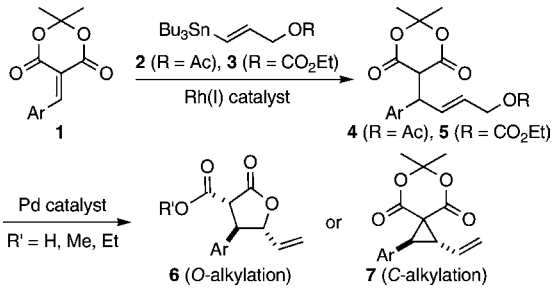
ABSTRACT



The rhodium-catalyzed conjugate addition of functionalized vinyltin reagents to alkylidene Meldrum's acids, followed by Pd-catalyzed intramolecular allylation, is a direct entry into vinyl-substituted γ-lactones via *O*-alkylation and vinylcyclopropanes via *C*-alkylation.

The synthesis of distinct types of polysubstituted cyclic compounds from a single multifunctional reagent based on catalyst selection would be of great synthetic interest.[1] In that regard, introduction of a synthon containing orthogonal nucleophilic and electrophilic moieties could best serve this purpose.[2] Our group has recently reported that 3-(tributylstannyl)-2-propenyl acetates are ambiphilic reagents wherein the vinyl−tin bond acts as a base and the allyl acetate as a Pd-activated electrophile.[3] We reasoned that the latent nucleophilicity of the C−Sn bond could be unveiled by rhodium catalysis to increase the scope of available reactions. In this paper, we report that (*E*/*Z*)-3-(tributylstannyl)allyl acetate (**2**) and ethyl carbonate (**3**) add in a conjugate fashion, under mild reaction conditions, to 5-(phenylmethylene) Meldrum's acids (**1**) in the presence of Rh(I) catalysts (Scheme 1). Polysubstituted γ-butyrolactones **6** and cyclopropanes **7** are then accessed through subsequent Pd-catalyzed transformation of the resulting Meldrum's acids **4** and **5**.

Scheme 1. General Strategy



The [Rh(cod)(MeCN)$_2$]BF$_4$-catalyzed 1,4-addition of alkenyl and arylstannanes to enones and α,β-unsaturated esters is precedented.[4−6] However, the C−C bond-forming reactions required elevated temperatures and harsh conditions and were limited to the introduction of trimethylstannane derivatives. Poor yields were obtained with the analogous but much safer

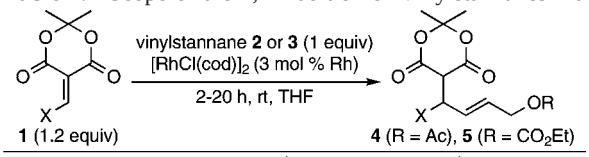
(1) Panne, P.; Fox, J. M. *J. Am. Chem Soc.* **2007**, *129*, 22−23.
(2) Kimura, M.; Mukai, R.; Tamaki, T.; Horino, Y.; Tamaru, Y. *J. Am. Chem. Soc.* **2007**, *129*, 4122−4123.
(3) Trépanier, V. É.; Fillion, E. *Organometallics* **2007**, *26*, 30−32.

10.1021/ol702613f CCC: $40.75
Published on Web 01/10/2008

to use tributylstannanes. Furthermore, functional group compatibility has not been demonstrated.

We postulated that the superior electrophilicity of alkylidene Meldrum's acids[7] would allow the efficient addition of alkenyltributylstannane under mild reaction conditions, preferably at room temperature. Gratifyingly, it was found, after some preliminary screening of solvent and catalyst, that $[RhCl(cod)]_2$ (3 mol % of Rh) catalyzed the addition of (*E*)-**2** to **1a** at ambient temperature in just 6 h. As depicted in Table 1, **4a** was isolated in 91% yield. The analogous carbonate

Table 1. Scope of the 1,4-Addition of Vinylstannanes **2** and **3**



1 (1.2 equiv) — **4** (R = Ac), **5** (R = CO_2Et)

X	Bu_3Sn–OAc		Bu_3Sn–OCO_2Et	
	time (h)	yield (%)	time (h)	yield (%)
C_6H_5 (**1a**)	6	91 (**4a**)	8	88 (**5a**)
2-naphthyl (**1b**)	5	71 (**4b**)	5	73 (**5b**)
2-(MeO)C_6H_4 (**1c**)	8	71 (**4c**)	8	80 (**5c**)
3-(MeO)C_6H_4 (**1d**)	3	77 (**4d**)	4	80 (**5d**)
3-ClC_6H_4 (**1e**)	4	86 (**4e**)	5	82 (**5e**)
3,5-$(MeO)_2C_6H_3$ (**1f**)	2	71 (**4f**)[a]	2	66 (**5f**)[a]
4-(MeO)C_6H_4 (**1g**)	20	80 (**4g**)	20	70 (**5g**)
4-ClC_6H_4 (**1h**)	5	75 (**4h**)	5	77 (**5h**)
4-FC_6H_4 (**1i**)	8	88 (**4i**)	8	87 (**5i**)
4-(CN)C_6H_4 (**1j**)	3	81 (**4j**)	3	81 (**5j**)
4-$(NO_2)C_6H_4$ (**1k**)	3	72 (**4k**)[a]	3	70 (**5k**)[a]
4-$(MeO_2C)C_6H_4$ (**1l**)	4	75 (**4l**)	4	78 (**5l**)
Me (**1m**)	3	89 (**4m**)	3	91 (**5m**)

[a] The reaction was carried out at 40 °C.

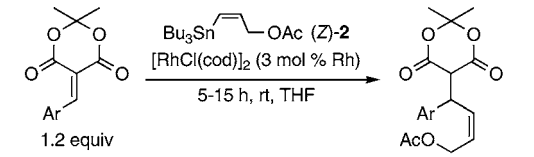
(*E*)-**3** added to **1a** with comparable efficiency.

This result is striking as it represents a large increase in reactivity compared to previously described alkenyl- and arylstannane Rh(I)-catalyzed conjugate additions. This increase is attributed to the electron-withdrawing allylic acetate or carbonate, which seemingly facilitates Rh−Sn transmetalation. This was confirmed by reacting vinyltributyltin with benzylidene Meldrum's acid (**1a**) under $[RhCl(cod)]_2$ (3 mol % Rh) or $[Rh(cod)(MeCN)_2]BF_4$ (3 mol % Rh) catalysis; at rt only 70% conversion was obtained after 18 h.

With these results in hands, the scope of the conjugate addition was defined (Table 1). The nature and electronic character of the group present on the electrophilic carbon atom of the alkylidene did not substantially affect the reactivity, with the exception of derivative **1g**, which required a longer reaction time.[8] As alkylidenes **1f** and **1k** were insoluble in THF at rt, the reactions were carried out at 40 °C. The addition was not limited to benzylidene Meldrum's acids; ethylidene Meldrum's acid **1m** furnished the 1,4-adducts **4m** and **5m** in excellent yields at rt in only 3 h.[9] These results exemplify the mildness and high chemoselectivity of this transformation, as halo, cyano, nitro, and methyl ester substituents were tolerated.

The conjugate addition of the corresponding (*Z*)-stannyl acetate (*Z*)-**2** to alkylidenes **1a** and **1e** was also investigated. Addition products (*Z*)-**4a** and (*Z*)-**4e** were isolated in 82−83% yield at rt with total retention of the double-bond geometry (Scheme 2).

Scheme 2. Conjugate Addition of (*Z*)-Stannyl Acetate



1a (Ar = C_6H_5)
1e (Ar = 3-ClC_6H_4)

(*Z*)-**4a**; 82%, 15 h
(*Z*)-**4e**; 83%, 5 h

1,4-Addition products **4** and **5** feature an enolizable Meldrum's acid moiety with, respectively, an appending allyl acetate and carbonate that can be activated by introduction of catalytic palladium. Further synthetic elaboration was envisaged in which Meldrum's acid, an ambident nucleophile, could trap the π-allylpalladium complex to lead directly and selectively to a vinyl γ-butyrolactone by *O*-alkylation or a vinylcyclopropane by *C*-alkylation.[10,11]

Conditions previously described for intramolecular allylic *C*-alkylation of malonate derivatives and cyclopropane formation ($Pd(PPh_3)_4$ (7 mol %), Et_3N (4 equiv) in THF at reflux for 16 h), when applied to **4a**, afforded exclusively the product of *O*-alkylation, lactone **8**, in 28% yield rather than vinylcyclopropane **7a** (Scheme 3).[12] A similar low yield

(4) (a) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91−97. (b) Oi, S.; Moro, M.; Ono, S.; Inoue, Y. *Chem. Lett.* **1998**, 83−84.

(5) (a) Venkatraman, S.; Meng, Y.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 4459−4462. (b) For an intramolecular version, see: Dziedzic, M.; Maleka, M.; Furman, B. *Org. Lett.* **2005**, *7*, 1725−1727. (c) For a review on Rh(I)-catalyzed conjugate additions, see: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844.

(6) To date, a single asymmetric example has been reported, see: Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508−11509.

(7) Asymmetric synthesis of all-carbon quaternary centers from alkylidene Meldrum's acids via Cu-catalyzed conjugate addition of dialkylzinc reagents, see: Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774−2775.

(8) The conversion was >99% in all cases.

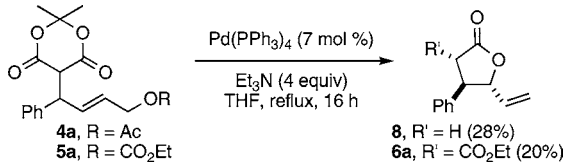
(9) Similar results were obtained with $[Rh(cod)(MeCN)_2]BF_4$. An 86% yield of **4m** was obtained with 6 mol % of Rh at rt for 15 h.

(10) Intermolecular *C*-allylation of Meldrum's acids with π-allylpalladium complexes: (a) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2007**, *9*, 3961−3964. (b) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3687−3696. (c) Ross, J.; Chen, W.; Xu, L.; Xiao, J. *Organometallics* **2001**, *20*, 138−142.

(11) Meldrum's acid *C*- and *O*-dialkylation: Snyder, C. A.; Selegue, J. P.; Dosunmu, E.; Tice, N. C.; Parkin, S. *J. Org. Chem.* **2003**, *68*, 7455−7459.

(12) The Pd-catalyzed synthesis of vinylcyclopropanes via intramolecular *C*-allylation of malonate derivatives with π-allylpalladium complexes has been reported; see: (a) Bäckvall, J. E.; Vågberg, J. O.; Zercher, C.; Genêt, J.-P.; Denis, A. *J. Org. Chem.* **1987**, *52*, 5430−5435. (b) Trost, B. M.; Tometzki, G. B.; Hung, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 2176−2177. (c) Hashimoto, S.; Shinoda, T.; Ikegami, S. *Tetrahedron Lett.* **1986**, *27*, 2885−2888. (d) Genêt, J.-P.; Balabane, M.; Charbonnier, F. *Tetrahedron Lett.* **1982**, *23*, 5027−5030.

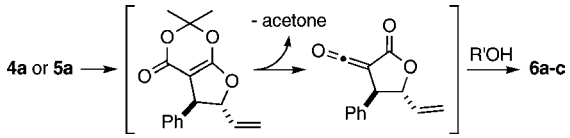
Scheme 3. Initial Cyclization Attempts



(20%) but equal *O*- vs *C*-alkylation selectivity was observed with allyl carbonate **5a**, which led to lactone ester **6a** (Scheme 3).

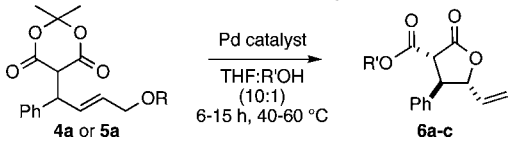
Formation of **6a** pointed to the intermediacy of an acylketene formed by cycloreversion of the dioxinone resulting from *O*-alkylation,[13] trapping with ethoxide accounts for **6a**, while rapid decomposition of the acylketene explains the low yields (Scheme 4).[14]

Scheme 4. Lactone Formation Mechanism



Therefore, performing the reactions with alcohol or water as cosolvent allowed efficient interception of the acylketene, and lactones **6a**−**c** were formed from **5a** in 73−87% yield, with excellent diastereoselectivity (Table 2, entries 1−3).[15]

Table 2. Lactone Formation via O-Alkylation



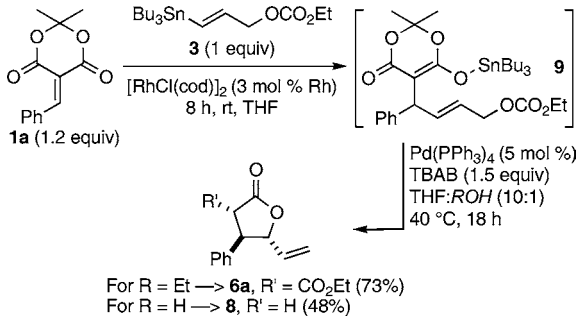
entry	R	R′	time (h)	*T* (°C)	yield (%)
1	CO_2Et (**5a**)	Et (**6a**)	6	60	80[a]
2	CO_2Et (**5a**)	Me (**6b**)	6	60	73[a]
3	CO_2Et (**5a**)	H (**6c**)	15	40	87[a]
4	Ac (**4a**)	Et (**6a**)	8	50	69,[b] 73[c]
5	Ac (**4a**)	Me (**6b**)	8	50	60,[b] 56[c]

[a] Method A: $Pd(PPh_3)_4$ (7 mol %). [b] Method B: $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol %), $[(p\text{-}MeO)C_6H_4]_3P$ (18 mol %), Et_3N (1.2 equiv). [c] Method C: $PdCl_2(MeCN)_2$ (5 mol %) in R′OH at 60 °C.

In the case of the acetate derivative **4a**, the conditions were modified to obtain lactones **6a** and **6b**, as a more electron-rich phosphine and Et_3N were required. Cyclization of **4a** could also be achieved under Pd(II) catalysis with similar results (Table 2, entries 4 and 5).[16] Two mechanisms can be considered for the formation of the lactones. The first one involves η^3-allyl species for Pd(0) catalysts.[17] Alternatively, for Pd(II) catalysts, the new C−O bond would be formed by hydroxypalladation of the alkene, followed by elimination of the acetate.[18]

A one-pot lactone synthesis was also developed (Scheme 5). Starting with **1a** and **3**, Rh(I)-catalyzed 1,4-addition was

Scheme 5. One-Pot γ-Butyrolactone Synthesis



carried out using the optimal conditions leading to tin enolate intermediate **9**.[19] Addition of $Pd(PPh_3)_4$ and tetrabutylammonium bromide (TBAB) in THF/EtOH provided lactone **6a** in 73% yield, also with excellent stereoselectivity.[20−22] Of note, lactone **6c** was not formed from **9** when water was used as cosolvent; rather, lactone **8** was isolated in 48% yield (Scheme 5).[23]

3,4-Disubstituted lactone **8** could alternatively be obtained by decarboxylation of lactone ester **6a** in 89% yield (Scheme 6).[24]

The selective synthesis of cyclopropanes[25,26] through intramolecular *C*-alkylation was then studied. As Pd(0) and Pd(II) only afforded *O*-alkylation, in the absence and

(13) Sato, T.; Ban, H.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38*, 6689−6692.

(14) The formation of **8** from **4a** in the absence of excess alcohol may be attributed to the interception of the acylketene by the actetate formed in the course of the reaction. The resulting anhydride is then hydrolyzed in the workup with concommitent decarboxylation.

(15) Selectivities of 18:1 up to >20:1 anti/syn for the β- and γ-substituents were determined by analysis of the ^{1}H NMR spectra of the crude reaction mixtures.

(16) Attempts to generate the π-allylrhodium complex by modifying the catalyst in situ by the addition of $P(OEt)_3$ failed; see: (a) Evans, P. A.; Robinson, J. E.; Moffett, K. K. *Org. Lett.* **2001**, *3*, 3269−3271. (b) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581−5582.

(17) Hayashi, T.; Yamane, M.; Ohno, A. *J. Org. Chem.* **1997**, *62*, 204−207.

(18) Tenaglia, A.; Kammerer, F. *Synlett* **1996**, 576−578.

(19) The formation of tin enolate **9** was confirmed by analysis of the ^{1}H NMR spectra of the crude mixture.

(20) *C*-Allylation of stannyl ketone enolates with Pd(II) π-allyl complexes was reported; see: (a) Trost, B. M.; Schroeder, G. M. *Chem. Eur. J.* **2005**, *11*, 174−184. (b) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759−6760.

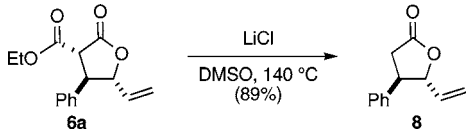
(21) Activation of stannyl ketone enolates with TBAB: Yasuda, M.; Chiba, K.; Ohigashi, N.; Katoh, Y.; Baba, A. *J. Am. Chem. Soc.* **2003**, *125*, 7291−7300.

(22) Unfortunately, the addition of both catalysts at the beginning of the domino reaction failed.

(23) It is postulated that decarboxylation to **8** is promoted by tributyltin species in combination with TBAB.

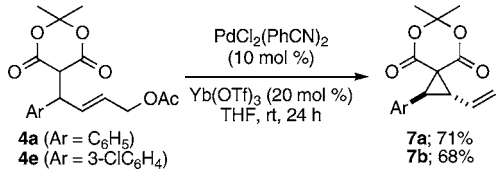
(24) (a) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, J. E. G. E.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138−147. (b) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, *12*, 957−960.

Scheme 6. Decarboxylation of Lactone **6a**



presence of base, the intramolecular allylic alkylation was attempted under Lewis acidic conditions. After screening a wide range of Lewis acids in the presence of various sources of Pd(II),[27] it was found that $PdCl_2(PhCN)_2$ (10 mol %) and $Yb(OTf)_3$ (20 mol %) in THF at rt gave the best selectivity between *C*- and *O*-allylic alkylation (Scheme 7). Under these

Scheme 7. Cyclopropane Synthesis



conditions, an 8:1 mixture of cyclopropane **7a** to lactone **6c** was formed from Meldrum's acid **4a**.[14,28] The cyclopropanation proceeded with excellent stereoselectivity, and **7a** was isolated in 71% yield as a single diastereomer. The relative stereochemistry was confirmed by X-ray analysis. Similar results were obtained with **4e**, demonstrating the efficiency of this methodology to access trans-vinylcyclopropanes.

In summary, we have shown that distinct types of polysubstituted cyclic compounds can be accessed from a single multifunctional reagent based on catalyst and reaction conditions selection. Bisfunctionalized 3-(tributylstannyl)-2-propenyl acetate and ethyl carbonate reagents add in a conjugate fashion to various alkylidene Meldrum's acids at room temperature under mild reaction conditions. The ease of Rh−Sn transmetalation in 3-(tributylstannyl)-2-propenyl acetate and ethyl carbonate reagents is noteworthy and deserving of further study. Treatment of the 1,4-addition products with Pd catalyst, in a sequential or one-pot fashion, led to the highly stereocontrolled synthesis of vinyl-γ-butyrolactones and vinylcyclopropanes.

Acknowledgment. This work was supported by AstraZeneca Canada, Inc., Boehringer Ingelheim (Canada) Ltd., the Merck Frosst Centre for Therapeutic Research, the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canadian Foundation for Innovation, the Ontario Innovation Trust, and the University of Waterloo. V.É.T. is indebted to NSERC for a PGS-D scholarship. We thank Aaron M. Dumas, University of Waterloo, for helpful suggestions and proofreading the manuscript and the late Dr. N. J. Taylor, University of Waterloo, for X-ray structure determination.

Supporting Information Available: Experimental procedures, NMR spectra, and X-ray data for **7a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL702613F

(25) (a) Melancon, B. J.; Perl, N. R.; Taylor, R. E. *Org. Lett.* **2007**, *9*, 1425−1428. (b) For a review on the stereoselective synthesis of cyclopropanes, see: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977−1050.

(26) (a) Müller, P.; Allenbach, Y.; Robert, E. *Tetrahedron: Asymmetry* **2003**, *14*, 779−785. (b) Chen, Y.; Ding, W.; Cao, W.; Lu, C. *Synth. Commun.* **2002**, *32*, 1953−1960. (c) Sato, M.; Hisamichi, H.; Kaneko, C. *Tetrahedron Lett.* **1989**, *30*, 5281−5284. (d) Livinghouse, T.; Stevens, R. V. *J. Chem. Soc. Chem. Commun.* **1978**, 754−756.

(27) Yang, D.; Li, J.-H.; Gao, Q.; Yan, Y.-L. *Org. Lett.* **2003**, *5*, 2869−2871.

(28) As proposed in footnote 14, the acylketene intermediate en route to **6c** is likely intercepted by the acetate leaving group to furnish an anhydride. However, no data are available to rationalize the divergence in reaction pathways and the absence of decarboxylation in the presence of $Yb(OTf)_3$ to form byproduct **6c**.