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Metal-Catalyzed Chemoselective Cycloisomerization of *cis*-2,4-Dien-1-als to 3-Cyclopentenones and 4-Alkylidene-3,4-dihydro-2*H*-pyrans

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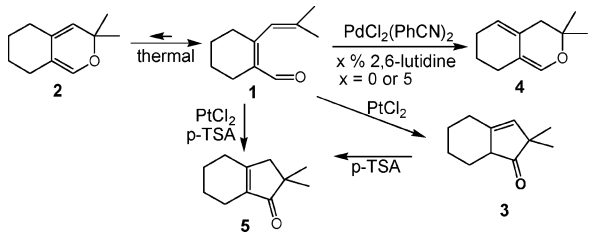
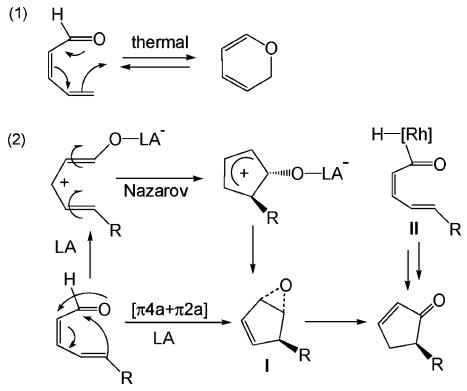
ABSTRACT



$PtCl_2$ (5 mol %) catalyst effected cycloisomerization of *cis*-2,4-dien-1-al (1) to 3-cyclopentenone (3) efficiently in hot toluene. In the presence of p-TSA, this $PtCl_2$ catalysis gave 2-cyclopentenone (5) exclusively because of the secondary isomerization reaction. Although the 1–2 equilibrium state greatly favors aldehyde (1), $PdCl_2(PhCN)_2$ (5 mol %) catalyzed cycloisomerization of aldehyde (1) to 4,6,7,8-tetrahydro-3*H*-isochromene (4) smoothly in hot toluene. A plausible mechanism is proposed on the basis of reaction observation and isotope-labeled experiment.

Metal-catalyzed cycloisomerization of an acyclic molecule to more than one cyclic structure is challenging and useful in organic synthesis. One prominent example is the cycloisomerization of 1,6- and 1,7-enynes with suitable catalysts to produce various carbocyclic and heterocyclic compounds.[1] A *cis*-2,4-dien-1-al functionality is often encountered in organic synthesis, and this species is prone to thermally reversible 6-π-electrocyclization to give 2*H*-pyran as depicted in Scheme 1 (eq 1).[2,3] The state of this equilibrium depends on the nature of its substituents. This thermal cyclization has been employed as a key step to construct complex polycyclic frameworks.[3] Metal-catalyzed cycloisomerization of *cis*-2,4-dien-1-als has been studied extensively;[4,5] such reactions produce 2-cyclopentenones exclusively via two

Scheme 1



(1) (a) Ma, S.-M.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (b) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (d) Mendez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397.

(2) Okamura, W. H.; De Lera, A. R. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 699.

(3) For selected examples, see: (a) Tambar, U. K.; Kano, T.; Stoltz, B. M. *Org. Lett.* **2005**, *7*, 2413. (b) Lumb, J.-P.; Trauner, D. *Org. Lett.* **2005**, *7*, 5865. (c) Shoji, M.; Imai, H.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *J. Org. Chem.* **2004**, *69*, 1548.

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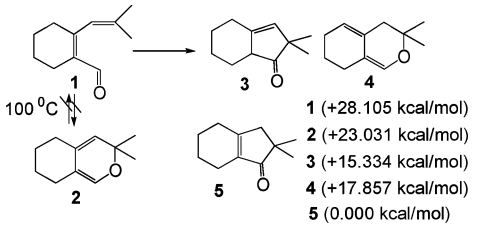
distinct pathways: (1) initial Lewis acid-catalyzed π4a + π2a or Nazarov-type cyclization to give cyclopentadiene epoxide **I** intermediates[4] or (2) initial formation of rhodium-hydride species **II** via oxidative addition.[5] Here, we report new metal-catalyzed chemoselective cyclization of *cis*-2,4-dien-1-als to 3-cyclopentenones and 4-alkylidene-3,4-dihydro-2*H*-pyran**,** respectively, in addition to the expected 3-cyclopentenones.

Table 1. Cyclization of *cis*-2,4-Dien-1-al **1** over Various Catalysts[a,b]



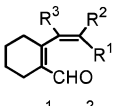
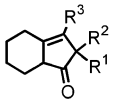
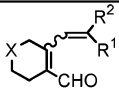
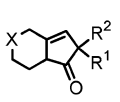
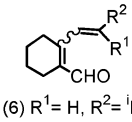
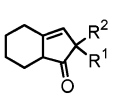
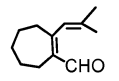
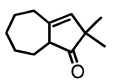
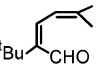
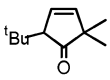
catalysts	solvents	conditions	products
(1) −	toluene	100 °C, 54 h	**1** (81%)
(2) $PtCl_2$	toluene	100 °C, 30 min	**3** (92%)
(3) $PtCl_2$+ p-TSA	toluene	100 °C, 30 min	**5** (88%)
(3) $PdCl_2(PhCN)_2$	toluene	100 °C, 12 h	**4** (87%)
(4) AgOTf	toluene	100 °C, 20 min	**5** (91%)
(5) AuCl	benzene	100 °C, 17 h	**1** (25%), **4** (63%)
(6) $AuClPPh_3$	benzene	100 °C, 11 h	**1** (56%), **4** (32%)
(7) $AuClPPh_3$ + $AgSbF_6$	CH_2Cl_2	23 °C, 20 min	**3** (15%)

[a] 5 mol % catalyst, [substrate] = 0.25 M. [b] Product yields are given after separation from a silica column.

As shown in Table 1, *cis*-2,4-dien-1-al **1** was selected as the studied molecule because similar aldehydes will not form 2*H*-pyran **2** at elevated temperatures.[6] We undertook a theoretic calculation (B3LYP/6-31G**) of the relative energies of its four possible cycloisomerization species **2**−**5**. The ease of formation of 2-cyclopentenone in most catalytic reactions is attributed to its conjugated stabilization energy, ca. 15−28 kcal/mol less than four other species. Heating aldehyde **1** alone in hot toluene (100 °C, 54 h) led to its exclusive recovery although 2*H*-pyran **2** has enthalpy 5 kcal/mol less than aldehyde **1** (entry 1).[6,7] Cyclization of this aldehyde with $PtCl_2$ (5 mol %) catalyst in hot toluene (100 °C, 30 min) gave 3-cyclopentenone **3** efficiently (92%, entry 2), whereas this catalyst produced 2-cyclopentone **5** in the presence of *p*-toluenesulfonic acid (p-TSA, 5 mol %, entry 3). The role of p-TSA is the isomerization of 3-cyclopentenone **3** to its conjugated isomer **5**. Notably, $PdCl_2(PhCN)_2$ (5 mol %) produced 4,6,7,8-tetrahydro-3*H*-isochromene **4** in 87% yield under optimum conditions. Among other π-alkyne activators (entries 4−7), only AgOTf (5 mol %) was catalytically efficient in hot toluene and gave 2-cyclopentenone **5** in 91% yield.

The value of this catalytic cyclization is manifested by formation of not only the expected 2-cyclopentenone **5,** but also the unprecedented 3-cyclopentenone **3** and 4-alkylidene-3,4-dihydro-2*H*-pyran **4**. Table 2 shows additional examples

Table 2. $PtCl_2$-Catalyzed Chemoselective Cycloisomerization of *cis*-2,4-Dien-1-als to 3-Cyclopentenones

cis- 2,4-dien-1-al[a]	product[b] (yields)	*cis*- 2,4-dien-1-al[a]	product[b] (yields)
			
(1) $R^1 = R^2 = R^3$ = H (**6**)	**21** (81%)	(9) $R^1 = R^2$ = Me X = CH(^{t}Bu) (**14**)	**29** (91%)
(2) $R^1 = R^2$ = H, R^3 = Me (**7**)	**22** (83%)	(10) $R^1 = {}^n$Pr, R^2=H X = CH(^{t}Bu) (E/Z=2.25, **15**)	**30** (dr = 1.40, 92%)
(3) R^3 = H, R^1, R^2 = -$(CH_2)_4$- (**8**)	**23** (92%)	(11) $R^1 = R^2$ = Me X = O (**16**)	**31** (88%)
(4) R^3 = H, R^1, R^2 = -$(CH_2)_5$- (**9**)	**24** (92%)	(12) $R^1 = {}^n$Pr, R^2=H X = O (E/Z=1.2,**17**)	**32** (dr = 1.35, 82%)
(5) $R^1 = R^3$ =H, $R^2 = {}^n$Bu (**10**)	**25** (dr =1.10, 92%)	(13) R^1, R^2 = -$(CH_2)_4$- X = O (**18**)	**33** (72%), **51** (18%)
			
(6) R^1= H, R^2= ^{i}Pr, (E/Z = 2.34, **11**)	**26** (dr = 2.45, 89%)	(14) **19**	**34** (81%)
(7) R^1= Me, R^2=Et, (E/Z = 1.39, **12**)	**27** (dr = 1.17, 91%)		
(8) R^1= Me, R^2=^{n}Pr, (E/Z =1.10, **13**)	**28** (dr = 1.70, 90%)	(15) **20**	**35** (81%)

[a] 5% $PdCl_2(PhCN)_2$, toluene, [substrate] = 0.25 M, 100 °C, 12 h for entries 6 and 8, 14 h for entry 10, 16 h for entry 5, 18 h for entries, 1, 3−4, and 11, and 24 h for entries 2, 7, and 9. [b] Yields of products are given after separation from a silica column.

to generalize the catalytic cycloisomerization of various *cis*-2,4-dien-1-als **6**−**20** to corresponding 3-cyclopentenones **21**−**35** with $PtCl_2$ catalyst (5 mol %); the resulting yields were as high as 81−92% except for **18**, which gave desired **33** (72%) in addition to 4-alkylidene-3,4-dihydro-2*H*-pyran **51** (see Table 3) in 17% yield.[8] These catalytic reactions were completed in hot toluene (100 °C) within 30−50 min, except for entry 15, which requires a longer period (6 h). 3-Cyclopentenone **25** was obtained in two isomeric forms (dr = 1.10) from aldehyde **10** bearing a *trans*-hexene substituent (entry 5). In entry 14, aldehyde **19** equilibrates with its thermally 6-π-cyclized 2*H*-pyran species (aldehyde:

(4) To the best of our knowledge, there is only one example for catalytic cycloisomerization of *cis*-2,4-dien-1-als to 2-cyclopentenones with use of Lewis acids, see: Miller, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919 and reference therein.

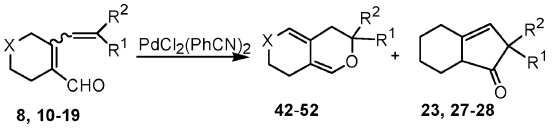
(5) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042.

(6) Tekevac, T. N.; Louie, J. *Org. Lett.* **2005**, *7*, 4037.

(7) The absence of 2*H*-pyran **2** in this thermal equlibrium is attributed to the negative entropy change because acyclic 2,4-dien-1-al **1** is more conformationally flexible.

(8) Formation of 2*H*-pyran **51** is attributed the acidity of the O−CH_2 of *cis*-2,4-dien-1-al **18**. This hypothesis is verified by treatment of alcohol **18** with $PtCl_2$ (5 mol %) and 2,6-lutidine (5 mol %) in hot toluene (100 °C, 14 h), which increased the yield of 2*H*-pyran **51** to 85%.

Table 3. $PtCl_2$-Catalyzed Chemoselective Cycloisomerization of *cis*-2,4-Dien-1-als to 3-Cyclopentenones



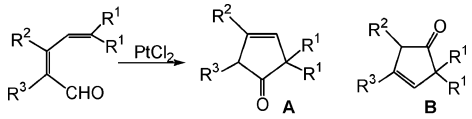
cis−2,4-dien-1-al[a]	additive	product (yields)[b]
(1) R^1 = H, R^2 = ^{n}Bu X = CH_2 (*E*-isomer, **10**)	−	**42** (77%)
(2) R^1 = H, R^2 = ^{i}Pr X = CH_2 (*E*/*Z* = 2.34, **11**)	−	**43** (75%)
(3) R^1 = Me, R^2 = Et	−	**44** (21%), **27** (58%)
X = CH_2, (*E*/*Z* = 1.39, **12**)	5% 2,6-lutidine	**44** (78%)
(4) R^1 = Me, R^2 = ^{n}Pr	-	**45** (11%), **28** (69%)
X = CH_2 (*E*/*Z* = 1.10, **13**)	5% 2,6-lutidine	**45** (75%)
(5) R^1, R^2 = −$(CH_2)_4$−	-	**46** (13%), **23** (72%)
X = CH_2, (**8**)	5% 2,6-lutidine	**46** (75%)
(6) R^1, R^2 = Me X = CH(^{t}Bu) (**14**)	−	**47** (82%)
(7) R^1 = H, R^2 = ^{n}Pr X = CH(^{t}Bu) (*E*/Z = 2.25, **15**)	−	**48** (75%)
(8) R^1, R^2 = Me X = O (**16**)	−	**49** (85%)
(9) R^1 = Me, R^2 = ^{n}Pr X = O (*E*/*Z* = 1.20, **17**)	−	**50** (83%)
(10) R^1, R^2 = −$(CH_2)_4$− X = O (**18**)	−	**51** (83%)
(11) R^1, R^2 = Me X = −$(CH_2)_2$− (**19**)	5% 2,6-lutidine	**52** (61%)

[a] 5% $PdCl_2(PhCN)_2$, toluene, [substrate] = 0.25 M, 100 °C, 12 h for entries 6 and 8, 14 h for entry 10, 16 h for entry 5, 18 h for entries 1, 3−4, and 11, and 24 h for entries 2, 7, and 9. [b] Yields of products are given after separation from a silica column.

2*H*-pyran = 12:88), and such an equilibrium mixture can be transformed into 3-cyclopentenone **34** (81%) efficiently with $PtCl_2$. This catalytic reaction is further compatible with an acyclic 2,4-dien-al **20** and gave the expected 3-enone **35** in 81% yield.

The $PtCl_2$-catalyzed synthesis of 3-cyclopentenones involves unusual skeletal rearrangement for special *cis*-2,4-dien-1-als **36**−**38** bearing a bulky *tert*-butyl and phenyl group at the C(2)-carbon. As shown in Scheme 2, treatment of

Scheme 2



cis-2,4-dien-1-als[a]	3-en-1-ones[b]
(1) R^1 = R^2 = H R^3 = ^{t}Bu (**36**)	**39** (82%, A:B=1:2)
(2) R^1 = H, R^2 = Me R^3 = Ph (**37**)	**40** (90%, A:B=1:1.7)
(3) R^1 = R^2 = Me R^3 = Ph (**38**)	**41** (91%, A:B=2:1)

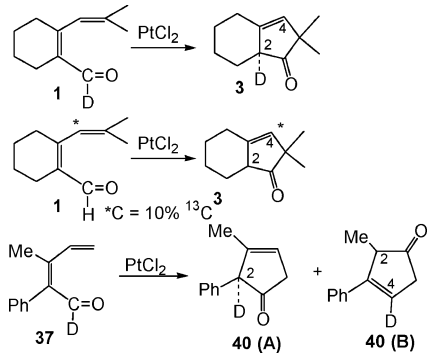
[a] 5% $PtCl_2$, [substrate] = 0.25 M, toluene, 100 °C, 10 h for entries 1 and 2 h for entries 2 and 3. [b]Yields of products are given after separation from a silica column.

aldehydes **36**−**38** with $PtCl_2$ (5 mol %) in hot toluene (100 °C) for 2 h gave two isomeric products **39**−**41**(**A**) and **39**−**41**(**B**) which were not separable from silica column. 3-Cyclopententones **39**−**41**(**A**) are related to their isomeric forms **39**−**41**(**B**) by a 1,3-migration of the oxygen atom.

Table 3 shows the generalization of the $PdCl_2$-catalyzed synthesis of 4-alkylidene-3,4-dihydro-2*H*-pyran derivatives **42**−**52** with use of the same *cis*-2,4-dien-1-als **8** and **10**−**19**. Synthesis of such 2*H*-pyrans is extendable to aldehydes **10**−**11**, and gave desired products **42** and **43** in 77% and 75% yields, respectively. In entries 3−5, cyclization of aldehydes **12**−**13** and **8** by using $PdCl_2(PhCN)_2$ catalyst (5 mol %) produced preferably 3-cyclopentenones **27**−**28** and **23**, rather than the desired 2*H*-pyrans **44**−**46**. This chemoselectivity problem was circumvented by using 2,6-lutidine (5%), and in such cases 2*H*-pyrans **44**−**46** were produced exclusively (75−78%). For the remaining aldehydes **14**−**18**, $PdCl_2$ maintains high cyclization efficiencies toward formation of 2*H*-pyrans **47**−**51** with 75−83% yields in the absence of 2,6-lutidine additives. Cyclization of aldehyde **19** requires 2,6-lutidine (5%) and $PdCl_2(PhCN)_2$ to furnish 2*H*-pyran **52** in 61% yield.

We also prepared ^{2}H- and ^{13}C-labeled samples **1** and **37** to elucidate the mechanism of formation of 3-cyclopentenones. As shown in Scheme 3, species **1** bearing a deuterated

Scheme 3



aldehyde produced 3-enone **3** with a 1,2-deuterium migration. In contrast, we did not observe an oxygen migration for 3-enone **3** produced from species **1** bearing a 10% ^{13}C-enriched alkenyl C(1) carbon. Cyclization of *cis*-2,4-dien-al **37** bearing a deuterated aldehyde gave two 3-enones **40(A)** and **40(B)** bearing a deuterium at their C(2)Ph and =C(4) carbons, respectively, and no loss of deuterium occurred.

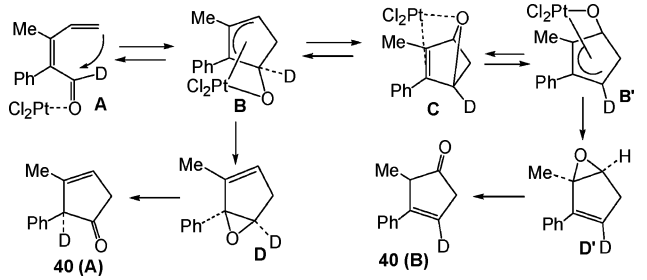
The 1,3-oxygen migration shown by 3-cyclopentenones **39**−**41**(**B**) (Scheme 2) excludes a conventional Lewis-catalyzed c4a + c2a cyclization mechanism.[4,9] Nazarov-type cyclization[4,10,11] is also unlikely to occur because *cis*-2,4-dien-1-al **10** bearing a *trans*-hexenyl substituent gave two

(9) (a) Ireland, C.; Faulkner, D. J.; Solheim, B. A.; Clardy, J. *J. Am. Chem. Soc.* **1972**, *94*, 6767. (b) George, M. V.; Mitra, A.; Sukumaran, K. B. *Angew. Chem., Int. Ed.* **1980**, *19*, 973.

(10) Habermas, K. L.; Denmark, S. E.; Jones, K. T. *Org. React.* **1994**, *45*, 1.

isomers of 3-cyclopentenone **25** in equal population (see Table 2, entry 5), inconsistent with the expected trans isomer according to Nazarov cyclization. Scheme 4 shows a

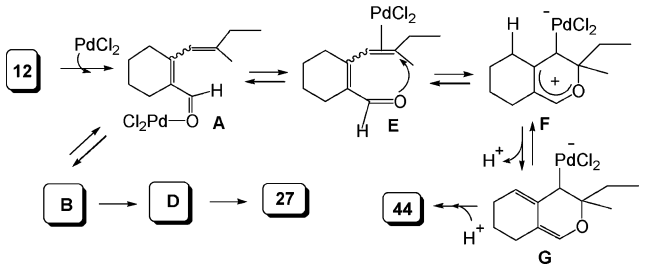
Scheme 4



plausible pathway to rationalize the oxygen migration and isotopic labeling experiments. The formation of 3-cyclopentenone is initiated with an intramolecular ene-aldehyde condensation[12] to form an OPt(IV)-allyl species **B**. This species preferably generates cyclopentadiene epoxide **D** via reductive elimination, leading to 3-cyclopentenone **40A** with a 1,2-deuterium migration.[13] In the case of a bulky R^1 group, species **B** likely undergoes reductive elimination to form oxabicyclic alkene species **C** reversibly. The reversible nature of this transformation allows the formation of a second OPt-(IV)-allyl intermediate **B′**, and ultimately gave the isomeric 3-cyclopentenone **40B** via intermediate **D**. Most *cis*-2,4-dien-1-als with a moderate size R^1 substituent are expected to give 3-cyclopentenone such as species **40A** without oxygen migration.[14] The feasibility of the interconversion between intermediates **B** and **C**, as well as **C** and **B**, was recently proposed in a ruthenium-based catalysis.[15]

For *cis*-2,4-dien-1-al **12,** the use of 2,6-lutidine (5%) to alter the cyclization chemoselectivity in the $PdCl_2$-based catalysis (Table 3, entries 3) is informative about the relation of the two new cyclizations. This observation indicates that an equilibrium exists between **A** and **E** as depicted in Scheme 5. With $PdCl_2$ catalyst, most *cis*-2,4-dien-als follow the **A**

Scheme 5



→ **E** → **F** → **G** pathway except for alcohol such as **12**, which gave 3-cyclopentenone **27** as major products unless 2,6-lutidine is present. We envision that this pyridine base accelerates the deprotonation reaction of intermediate **F** and preferably gives 2*H*-pyrans **44** with alternation of chemoselectivity.

In summary, we have achieved chemoselective cycloisomerization of *cis*-2,4-dien-1-als to 3-cyclopentenones and 4-alkylidene-3,4-dihydro-2*H*-pyrans using $PtCl_2$ and $PdCl_2(PhCN)_2$, respectively. In the presence of p-TSA catalyst, $PtCl_2$ also led to formation of conjugated 2-cyclopentenones. These new metal-catalyzed reactions highlight the synthetic utility of *cis*-2,4-dien-1-als with the availability of various carbocyclic and oxygen heterocyclic compounds. The use of *cis*-2,4-dien-1-al as a building block to construct a complex molecular framework will be more attractive than before.

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Supporting Information Available: Experimental procedures, spectral data, and NMR spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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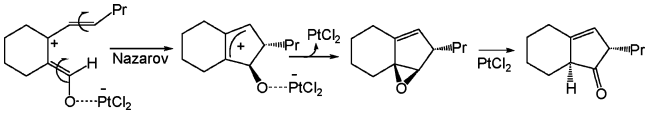
(11) In the Nazarov-type cyclization, the cyclization follows the conrotatory mode to give epoxide opposite to the *n*-propyl substituent. $PtCl_2$-catalyzed rearrangement of this vinyl epoxide is expected to give *trans*-3-cyclopentenone via a 1,2-hydrogen shift.



(12) Review: Snider, B. In *The Prins Reaction and Carbonyl Ene Reactions*; Trost B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561.

(13) For metal-catalyzed transformation of vinyl epoxides into 3-en-1-ones, see: (a) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 63. (b) Rosenberger, M.; Jackson, W.; Saucy, G. *Helv. Chim. Acta* **1980**, *63*, 1665.

(14) The *gem*-dialkyl group of the alkenyl substituent of 2,4-dien-1-al is expected to block this oxygen transfer process, and this hypothesis is supported by a high A/B ratio (A/B = 2.0) of species **38** compared to that (A/B = 0.58) of its vinyl analogue **37**.

(15) Villeneuve, K.; Tam, W. *J. Am. Chem. Soc.* **2006**, *128*, 3514.