Heterogeneous Reductive Isomerization Reaction Using Catalytic Pd/C and H$_2$
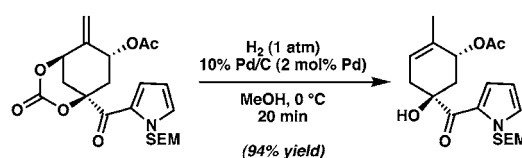
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ABSTRACT

A highly selective catalytic reductive isomerization reaction is described. The extremely mild and neutral reaction conditions (10% Pd/C, H$_2$, and MeOH at 0 °C) tolerate a wide range of functional groups and generally result in excellent yields. Mechanistic studies suggest that this reaction does not proceed via a stepwise reduction/elimination sequence or a π-allylpalladium intermediate.

The power of π-allylpalladium chemistry in organic synthesis has been well documented.[1] Typically, allylic systems functionalized with a leaving group (Scheme 1, **1** or **2**) react

Scheme 1
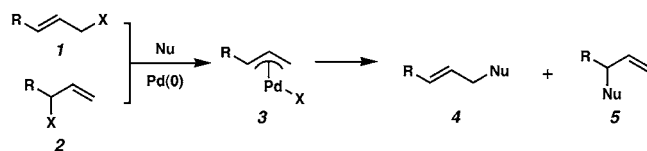
with Pd(0) to form electrophilic π-allylpalladium complexes (**3**). These intermediates can be attacked by assorted nucleophiles to perform a number of bond-forming events. Over-

coming the practical problem of regioselectivity in the nucleophilic addition step (i.e., **3** → **4** or **5**) has been the subject of intense study.[1]

During our explorations of the total synthesis of (+)-dragmacidin F (**8**),[2] we encountered difficulties controlling olefin isomers with a π-allylpalladium hydrogenolysis reaction (Scheme 2, **6** → **7**). Exposure of lactone **9** to an array

Scheme 2
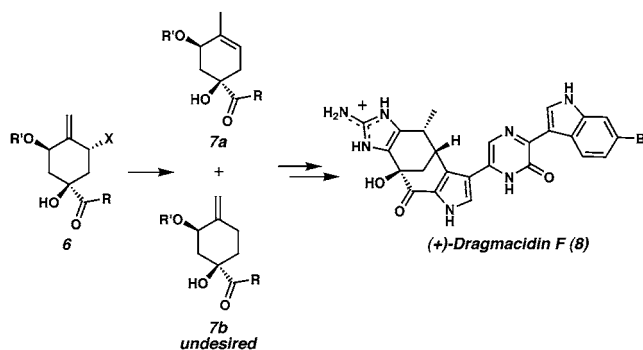
of known literature protocols for homogeneous Pd(0)-

(1) For reviews, see: (a) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (c) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1–14. (d) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959–5989. (e) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195–202. (f) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203–214. (g) Nomura, N.; Tsurugi, K.; Yoshida, N.; Okada, M. *Curr. Org. Synth.* **2005**, *2*, 21–38. (h) Tsuji, J. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 1036–1050. (i) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813–5837. (j) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (k) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol 4, Chapter 3.3.

(2) (a) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552–9553. (b) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5970–5978.

catalyzed π-allyl hydrogenolysis[3] led to complex product mixtures (eq 1). Although reaction of allylic acetate **10** did generate desired cyclohexene **11**, byproducts **12** and **13** were also formed, and **11** could not be isolated by conventional purification techniques (eq 2).
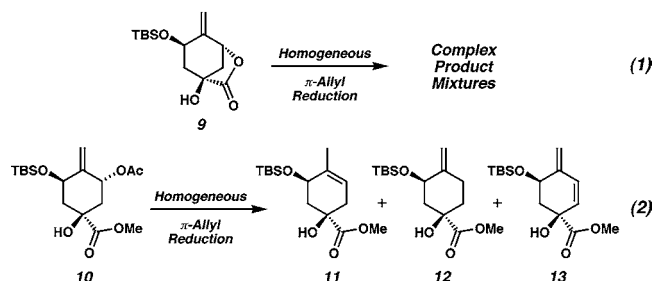
While attempting to solve these problems, we serendipitously discovered a highly selective reductive isomerization reaction that can be executed under extremely mild and neutral conditions. Namely, exposure of lactone **9** to traditional heterogeneous catalytic hydrogenation conditions (Pd/C, 1 atm H$_2$) afforded key fragment **14** en route to (+)-dragmacidin F (**8**) in nearly quantitative yield (eq 3).[4] This
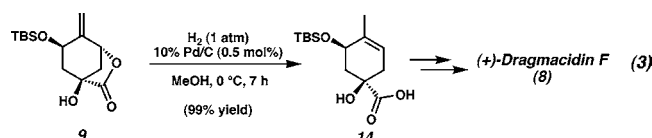
smooth conversion of lactone **9** to carboxylic acid **14** stood in stark contrast to our initial studies using standard π-allylpalladium hydrogenolysis methods to attempt this transformation (**10** → **11** + **12** + **13**). On the basis of these results, we set out to examine the unusual reactivity of the heterogeneous palladium system. Herein, we detail our exploration of the reductive isomerization reaction, an expanded substrate scope, and a mechanistic investigation of its regiochemical fidelity.[5]

Intrigued by our initial result (**9** → **14**), we prepared a number of substrates to assess the generality of this reaction (Table 1).[6] As a starting point, a simple variant of lactone **9** bearing an acetate on the secondary allylic alcohol was synthesized (i.e., **15**). We were pleased to see that **15** could be converted to carboxylic acid **16** in good yield (entry 1). The use of allylic acetate **10** as a substrate (entry 2), on the other hand, led to an unexpected result. We anticipated that

(3) For a review, see: Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1−24.

(4) 10% Pd/C was purchased from Aldrich (20,569-9). This has been demonstrated to be a safe and nearly neutral hydrogenation catalyst; see: (a) Sajiki, H.; Ikawa, T.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 7407−7410. (b) Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6189−6195.

(5) Isolated examples of similar reactivity using Pd/C, H$_2$, and a protic solvent have been reported in the literature; see: (a) Paulson, D. R.; Gilliam, L. S.; Terry, V. O.; Farr, S. M.; Parker, E. J.; Tang, F. Y. N.; Ullman, R.; Ribar, G. *J. Org. Chem.* **1978**, *43*, 1783−1787. (b) Dauben, W. G.; Hance, P. D. *J. Am. Chem. Soc.* **1955**, *77*, 2451−2453. (c) Dauben, W. G.; Hayes, W. K.; Schwarz, J. S. P.; McFarland, J. W. *J. Am. Chem. Soc.* **1960**, *82*, 2232−2238.

(6) With the exception of **31** (entry 10), all of the compounds in Table 1 are enantiopure.

Table 1. Reductive Isomerization Reaction[a]

entry	substrate	product		time	yield[b]
1	**15**	**16**		15 min	71%
2[c]	**10**	**17**		1 h	3%[d]
				35 min	10%[e,f]
3[c,e]	**18**	**19**		1.5 h	27%
4	**20**	**17** R = Ac		1 h	81%
5	**21**	**19** R = TBS		8 min	94%
6	**22**	**23** R = Ac		20 min	94%
7	**24**	**25** R = H		15 min	80%
8	**26**	**27**		4 h	90%
9	**28**	**29**		1 h	68%
10[g]	**30**	**31**		1.3 h	91%

[a] Standard conditions: H$_2$ (balloon, 1 atm), 10% Pd/C (2 mol % Pd), MeOH, 0 °C. [b] Isolated yield. [c] Yield based on ^{1}H NMR integration. [d] Performed with 10% Pd/C (0.5 mol % Pd). [e] Performed with 10% Pd/C (1 mol % Pd). [f] Reaction performed at 23 °C. [g] Product formed in 7.2% ee.

methyl ester **11** would be the observed product because acetate is a superior leaving group to silanolate (cf. eq 2). However, the compound obtained (i.e., **17**) resulted from a net loss of the OTBS group.[7] Notably, none of the byproducts formed under homogeneous π-allyl protocols were observed under these heterogeneous conditions (eq 2, **11**–**13**). To probe this result further, a version of **9** with exchanged protecting groups on the secondary alcohols was prepared (**18**, entry 3). In this case, elimination of acetate occurred.[7]

Due to the success of the rigid bicyclic lactone framework in this reaction, we reasoned that the reactivity of **10** and **18** might be improved by restricting them as bicyclic carbonates (**20** and **21**). These carbonate-containing substrates were well tolerated and led to competent production of the correspond-

(7) The major product in this reaction resulted from direct hydrogenation of the olefin moiety and was formed as a mixture of diastereomers.

ing methyl esters (entries 4 and 5). Additionally, carbonates with adjacent heterocyclic moieties such as pyrrole (**22** and **24**) and indole (**26**) could be converted into their reductively isomerized counterparts in excellent yields (entries 6–8). The use of an acetate protecting group on the secondary allylic alcohol (entries 1, 4, and 6), or an unprotected alcohol altogether (entry 7), did not significantly influence the overall reaction efficiency. Interestingly, replacement of the carbonate moiety with a dioxasilyl linkage led solely to diastereoselective hydrogenation of the olefin (entry 9).[8] Somewhat surprisingly, reductive isomerization using a trisubstituted olefin was also quite facile (entry 10).[9]

A model to rationalize some of these anomalous differences in reactivity is presented in Figure 1. An examination of the three-dimensional structures of the starting materials in Table 1 reveals that the leaving group is positioned preferentially in an axial orientation with respect to the six-membered ring.[10] Furthermore, structurally rigid bicyclic lactones and carbonates with locked axial leaving groups (e.g., **9** and **32**) exhibited enhanced yields relative to their more flexible monocyclic counterparts (**10** and **18**). The difference in yield between substrates **10** and **18** can be attributed to leaving group ability (i.e., AcO^- > $Me_2(t\text{-}Bu)SiO^-$). This leaving group effect was also observed when the carbonate functionality was replaced with a dioxasilyl moiety (entry 9), in which case only direct olefin hydrogenation occurred.
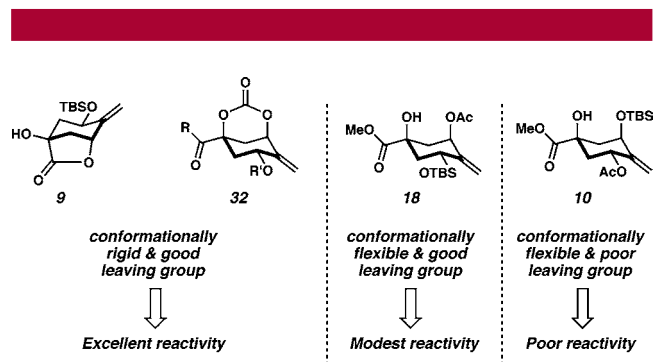

Figure 1. Model for reactivity differences.

We began a more detailed study of this reductive isomerization by examining the origin of the hydrogen atom in the newly formed C–H bond. Experiments employing D_2 indicate that the deuterium delivered at the allylic positions of **33** and **34** originates from D_2, whereas no C–D incorporation was observed by using CD_3OD (Scheme 3). Furthermore, deuterium incorporation occurs with complete stereo-
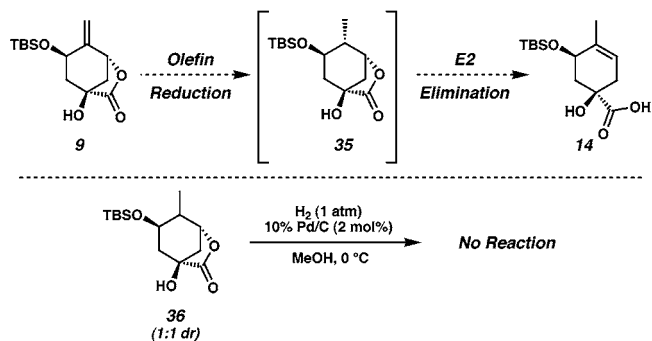

Scheme 3
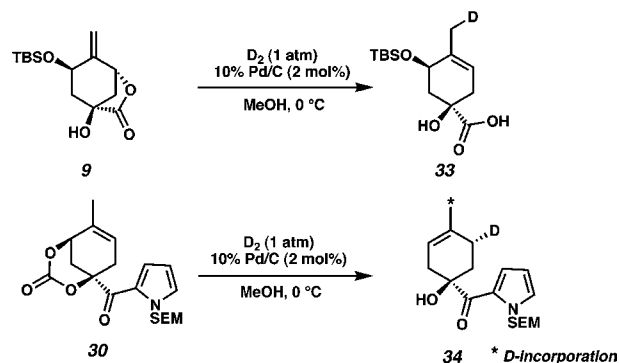
selectivity (**30** → **34**), with additional incorporation at the exocyclic methyl group.[11]

In terms of mechanism, we considered the simple possibility that our transformation could be proceeding in a tandem fashion via hydrogenation of the olefin followed by E2 elimination (e.g., **9** → **35** → **14**, Scheme 4). However,

Scheme 4

subjection of an independently prepared sample of saturated lactone **36** (1:1 dr) to identical reaction conditions (10% Pd/C, H₂, MeOH, 0 °C) led to no reaction, allowing us to dismiss its potential as a viable intermediate.[12]

A π-allyl mechanism could be probed by using carbonate-bearing trisubstituted olefin **30** (entry 10). Under π-allyl hydrogenolysis conditions, racemic **31** was obtained (Scheme 5A).[13] Interestingly, analysis by chiral HPLC revealed that, under our reductive isomerization conditions at 0 °C, cyclohexene **31** was produced in 7.2% ee (Scheme 5B). In fact, by lowering the reaction temperature, up to 23.1% ee could be achieved.[13] Although complete optical purity was not maintained in the product, this result suggests a reaction pathway that does not solely involve a *meso*-π-allylpalladium complex (e.g., **37**).

(8) No reductive isomerization product could be isolated from this reaction.

(9) The absolute stereochemistry of **31** (entry 10) depicted is shown by analogy to the other products in Table 1.

(10) The three-dimensional conformations of **10** and **18** were ascertained by ¹H NMR homonuclear decoupling and NOESY-1D experiments.

(11) Control experiments demonstrate that the deuterium incorporation at the exocyclic methyl group can happen after the reductive isomerization has occurred. The stereochemistry of the deuterium in **34** was elucidated by ¹H NMR homonuclear decoupling and NOESY-1D experiments.

(12) Conducting this experiment in the presence of **9** did not lead to consumption of **36**.

(13) See Supporting Information for details.

Scheme 5

Scheme 5

%ee 31	temperature
4.8	23 °C
7.2	0 °C
16.5	-25 °C → -15 °C
23.1	-78 °C → -15 °C
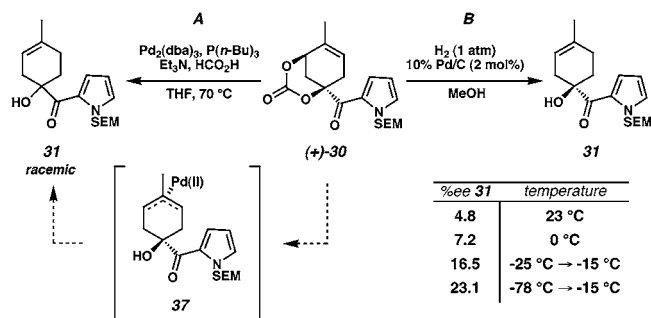
Recently, both Sajiki and Hara have invoked a single-electron transfer (SET) mechanism for other transformations involving the use of 10% Pd/C and MeOH.[14] In accordance with this hypothesis, exposing either lactone **9** or carbonate **30** to our standard conditions in the presence of tetracyano-ethylene (TCNE) as a SET inhibitor completely halts all reactivity, even at 23 °C (Scheme 6).[15]
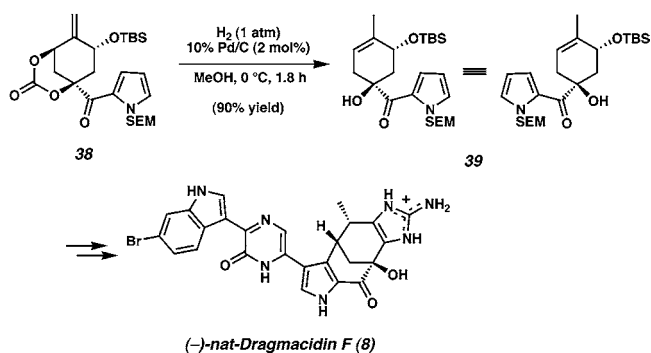
Scheme 6

Scheme 6
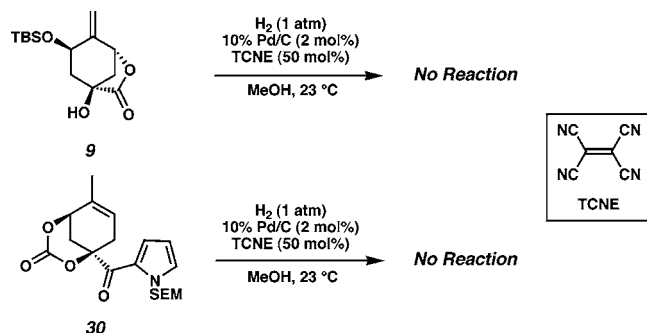
To highlight the utility of the reductive isomerization reaction, we constructed carbonate **38** and carried out the

Scheme 7

Scheme 7

synthesis of the (−)-enantiomer of dragmacidin F (**8**) utilizing **39** as a synthetic intermediate (Scheme 7).[2b]

In conclusion, we have discovered an extremely selective catalytic reductive isomerization reaction that is carried out using Pd/C, H₂, and MeOH at 0 °C. The mild and neutral reaction conditions tolerate a wide range of functional groups and generally proceed in excellent yield. Optimal substrates for this transformation possess a good leaving group that is restricted to an axial orientation. Evidence suggests that neither a stepwise addition/elimination sequence nor a π-al-lylpalladium species are operative. Further experiments to elucidate the mechanism of this reductive isomerization process are currently underway.

Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* **2002**, *43*, 7247−7250. (b) Ishizaki, M.; Yamada, M.; Watanabe, S.-i.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. *Tetrahedron* **2004**, *60*, 7973−7981.

(15) Simple control experiments suggest that the presence of TCNE does not prevent the direct reduction of olefins from occurring.