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Use of Deuterium Labeling Studies to Determine the Stereochemical Outcome of Palladium Migrations during an Asymmetric Intermolecular Heck Reaction

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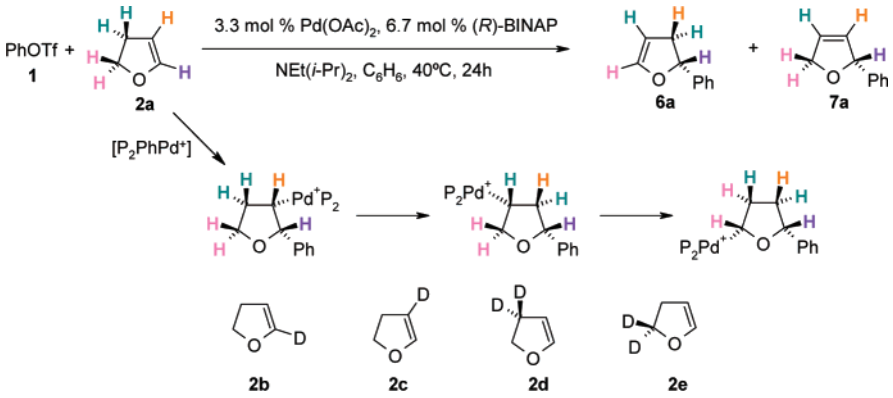

A series of deuterium labeling experiments showed that Pd migrations during an intermolecular asymmetric Heck reaction between phenyl triflate and various deuterated 2,3-dihydrofurans (**2b**, **2c**, **2d**, **2e**) occurs exclusively by either *syn*-1,2-dyotropic shifts or a *syn*-chain-walking mechanism; no evidence was observed to support *anti*-1,2-dyotropic shifts or *anti*-β-H Pd eliminations during the formation of **6** and **7**.

Introduction

In 1997, Brown, Deeth and co-workers[1] reported via low-temperature NMR studies (−60 °C) that **5a** was the first observable intermediate in the asymmetric Heck reaction between phenyl triflate (**1**) and 2,3-dihydrofuran (**2a**, Scheme 1). Subsequent warming of the solution provided **6a** exclusively (<5% **7a**) in 95% ee in accordance with the work of Hayashi and co-workers.[2] While the formation of isomer **7** could be due to a simple *syn* elimination of intermediate **3a**, the formation of isomer **6a** requires some form of isomerization. To rationalize the formation of **5a** as the first intermediate observed by NMR, Brown postulated that intermediate **3a**, formed upon initial P_2-Pd^+−Ph (P_2 = (*R*)-BINAP) addition to the double bond in **2a**, underwent two 1,2-dyotropic rearrangements[3] to afford **4a** and then **5a** successively. Reetz[3a] has proposed that 1,2-dyotropic shifts can proceed via two pathways depending on orbital interactions: namely *syn*-**8** or *anti*-**9**. *Syn* rearrangement via **8** results in retention of stereochemistry at both carbons atoms, while the *anti* rearrangement **9** leads to inversion of configuration of both stationary atoms.

This type of Pd-migration (**3a** → **5a**) has been postulated to occur during metal-catalyzed olefin polymerizations.[4−6] Brookhart

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(4) (a) Shultz, L. H.; Brookhart, M. *Organometallics* **2001**, *20*, 3975−3982. (b) Tempel, D. J.; Johnson, L. K.; Huff, R. L.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **2000**, *122*, 6686−6700. (c) Doherty, M. D.; Trudeau, S.; White, P. S.; Morken, J. P.; Brookhart, M. *Organometallics* **2007**, *26*, 1261−1269.

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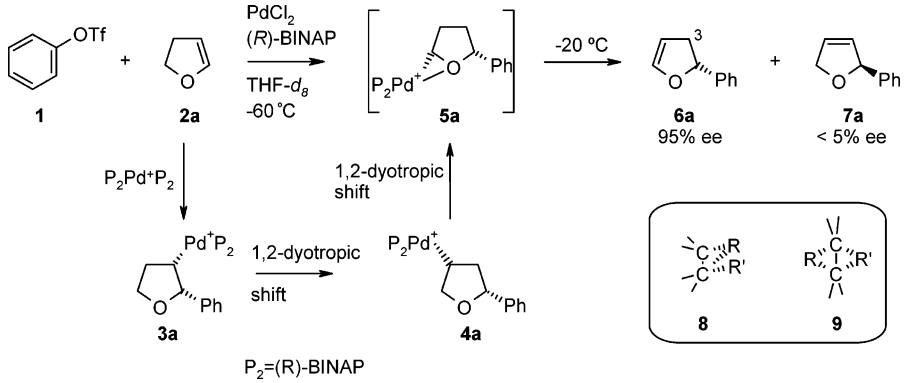
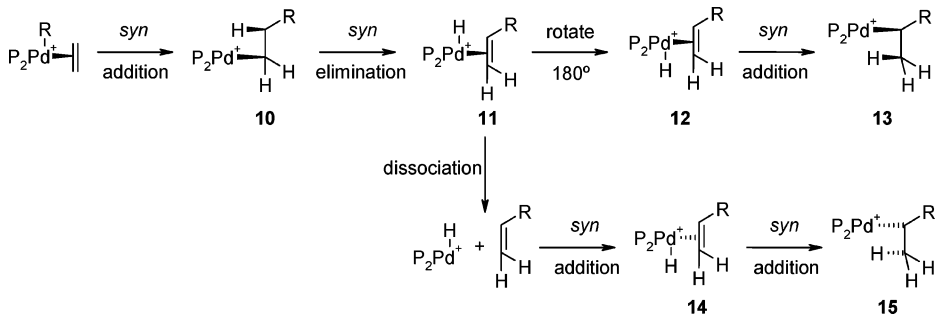
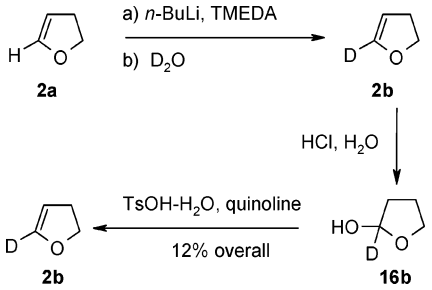
SCHEME 1. Proposed Mechanism of Isomerization of Intermediates in the Heck Reaction



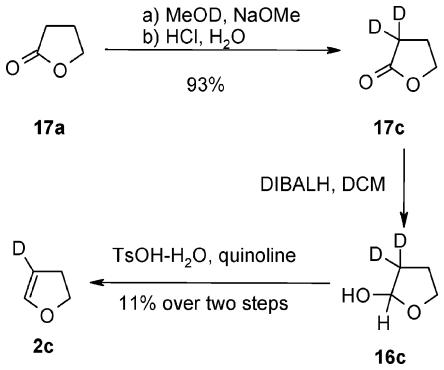
SCHEME 2. *Syn* and *Anti* Palladium-Mediated Isomerization Mechanisms



SCHEME 3. Synthesis of 2b

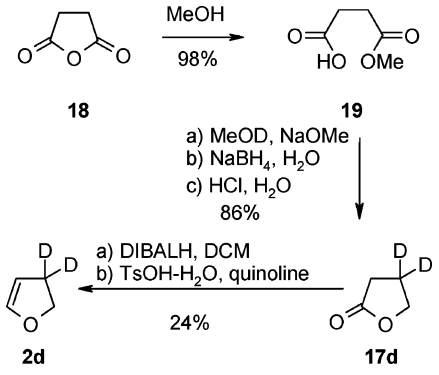


SCHEME 4. Synthesis of 2c

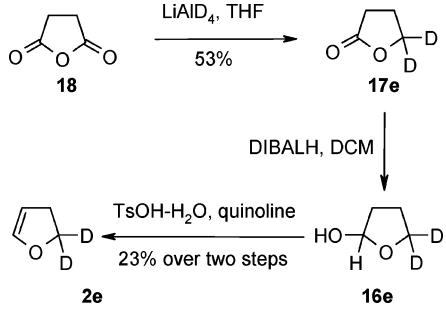


et al.[4] have proposed that the Pd in intermediate **10** undergoes a *syn* metal-hydride elimination to give **11**, followed by a 180° rotation of the π-metal complex leading to **12**, which subsequently does a *syn*-addition of the olefin leading to **13** (Scheme 2). This metal-based mechanism, sometimes referred to as chain-walking, has been supported by DFT calculations performed by Ziegler and co-workers.[5] If the stereochemistry of this process could be followed experimentally, it would be akin to a *syn*-1,2-dyotropic shift. Alternatively, the π-coordinated Pd−H **11**

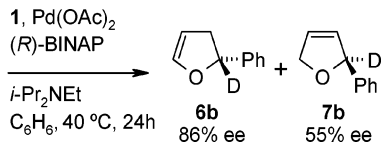
SCHEME 5. Synthesis of 2d



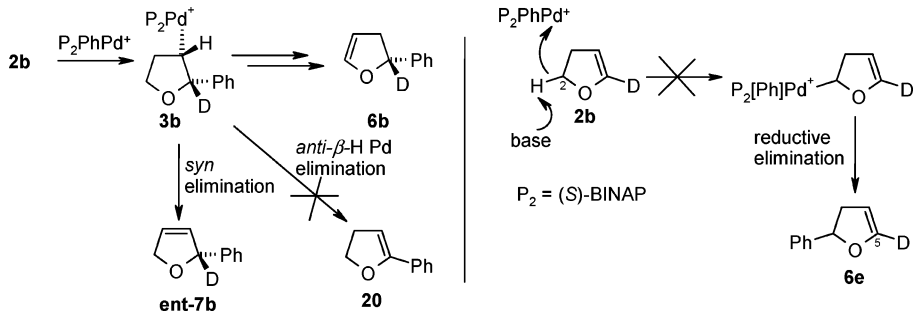
SCHEME 6. Synthesis of 2e



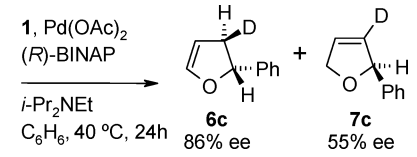
SCHEME 7. Products of the Reaction with 2b



SCHEME 8. Mechanism of Palladium-Mediated Isomerizations in the Heck Reaction with 2b



SCHEME 9. Products of the Reaction with 2c



could dissociate from the olefin and then recoordinate to the opposite face of the olefin providing **14** that ultimately leads to **15**. If this mechanism occurred, the stereochemistry of the process would be similar to that of an *anti*-dyotropic shift. One additional possibility is that an *anti*-β-H Pd elimination could occur. Although rare, these types of Pd eliminations have been reported via an E2 mechanism in the presence of base.[7] We provide evidence herein, via deuterium labeling studies, that the 1,2-migration of Pd (i.e., **3a** → **5a**) proceeds via either two *syn*-1,2-dyotropic shifts or a *syn* chain walking mechanism (**10** → **13**)[4−6] and does not proceed by *anti*-1,2-dyotropic shifts (via **11** → **15**) or by *anti*-β-H Pd eliminations under Hayashi's[2] asymmetric intermolecular Heck reaction conditions, using (*R*)-BINAP.

Results and Discussion

The synthesis of **2b** has been reported;[8] however, it could not be isolated in pure form due to contamination by residual hexanes from the *n*-BuLi. Therefore, the crude deuterated material was hydrated to give lactol **16b**, from which hexanes could be easily removed under vacuum, and was then dehydrated[9] to give pure **2b** (Scheme 3).

Compound **2c** was prepared from γ-butyrolactone (**17a**) by dideuteration α to the carbonyl.[10] Lactone **17c**[11] was reduced to lactol **16c**[12] (the reduction would only occur in the presence of noncoordinating solvents such as hexanes or dichloromethane) and subsequently dehydrated to give the deuterated dihydrofuran **2c** (Scheme 4).[9,13]

To prepare compound **2d** (Scheme 5), succinic anhydride (**18**) was converted to **19**,[14] which was selectively dideuterated α to the ester.[10] The ester was selectively reduced to the alcohol in the presence of the carboxylic acid with sodium borohydride[15] and cyclized to give lactone **17d**. This lactone was then reduced to the lactol[12] and subsequently dehydrated[9] to give **2d**.

The synthesis of **2e** (Scheme 6) was accomplished by reduction of succinic anhydride (**18**) with $LiAlD_4$ to give 4,4-dideuterio-γ-butyrolactone[11] (**17e**),[16] which was then further reduced to lactol **16e**[12] and dehydrated[9] as previously described.

Each of the deuterated 2,3-dihydrofurans **2b**, **2c**, **2d**, and **2e** was treated with phenyl triflate (**1**) under Hayashi's[2] Heck reaction conditions. As expected when using (*R*)-BINAP, the major isomers formed were (*R*)-2-phenyl-2,3-dihydrofurans (**6b**, **6c**, **6d**, and **6e**), while (*S*)-2-phenyl-2,5-dihydrofurans (**7b**, **7c**, **7d**, and **7e**) were formed in small amounts. The advantage of using 2,3-dihydrofuran (**2a**) in this study was that all of the hydrogen atoms in the products **6a**[17a] and **7a**[18a] have distinct chemical shifts in their respective ^1H and ^2H 400 MHz NMR spectra, which allowed us to determine unequivocally where the deuterium atoms resided in **6b**−**e**[17b−e] and **7b**−**e**.[18b−e]

Products **6b** and **7b** were isolated from the Heck reaction with **2b** (Scheme 7) in a 90:10 ratio (**6b**/**7b**). Although this reaction did not provide any evidence with respect to the stereochemistry of any Pd migrations, the formation of **6b**[17b] and **7b**[18b] did confirm the *syn* addition of the (BINAP)PhPd$^+$ intermediate across the double bond to form intermediate **3b**

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(12) Corey, E. J.; Cheng, H.; Baker, C. H.; Matsuda, S. P. T.; Li, D.; Song, X. *J. Am. Chem. Soc.* **1997**, *119*, 1277−1288.

(13) Due to the ease of proton-deuterium exchange at the α position of γ-butyrolactone (**17**) and at the 4-position of 4-deuterio-2,3-dihydrofuran (**18**), fully-deuterated **18** could not be obtained. By ^2H NMR integration, compound **18** was 95.5% deuterated when used in further Heck reactions.

(14) van Esch, J.; Schoonbeek, F.; de Loos, M.; Kooijman, H.; Spek, A. L.; Kellogg, R. M.; Feringa, B. L. *Chem.—Eur. J.* **1999**, *5*, 937−950.

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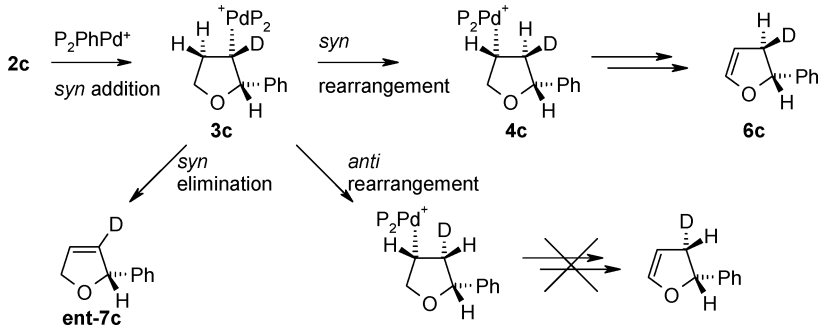
(16) Bloomfield, J. J.; Lee, S. L. *J. Org. Chem.* **1967**, *32*, 3919−3924.

(17) (a) 2-Phenyl-2,3-dihydrofuran (**6a**): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.3 (5H, m, Ph), 6.5 (1H, q, J = 2.39 Hz, H_5), 5.6 (1H, dd, J = 10.76, 8.21 Hz, H_2), 5.0 (1H, q, J = 2.57 Hz, H_4), 3.1 (1H, ddt, J = 14.87, 10.76, 2.31 Hz, $H_{3\beta}$), 2.7 (1H, ddt, J = 15.12, 8.46, 2.31 Hz, $H_{3\alpha}$); The assignment of $H_{3\beta}$ and $H_{3\alpha}$ was done by NOE measurements. Irradiation of H_2 in **6a** resulted in an enhancement of the signal at 3.1 ppm while the signal at 2.7 ppm was unchanged. (b) The signal at 5.6 ppm was missing in the ^1H NMR spectrum of **6b**. (c) The signal at 3.1 ppm was missing in the ^1H NMR spectrum of **6c**. (d) The signals at 5.0 and 2.7 ppm were missing in the ^1H NMR spectrum of **6d**. (e) The signal at 6.5 ppm was missing in the ^1H NMR spectrum of **6e**.

(18) (a) 2-Phenyl-2,5-dihydrofuran (**7a**): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.2 (5H, m, Ph), 6.1 (1H, dq, J = 6.0, 2.0 Hz, H_4), 5.9 (1H, dq, J = 6.0, 2.0 Hz, H_3), 5.8 (1H, ddt, J = 5.8, 4.1, 2.1 Hz, H_2), 4.9 (1H, ddt, J = 12.8, 6.0, 2.1 Hz, H_5), 4.8 (1H, ddt, J = 12.8, 4.1, 2.1 Hz, H_5). (b) The signal at 5.8 ppm was missing in the ^1H NMR spectrum of **7b**. (c) The signal at 5.9 ppm was missing in the ^1H NMR spectrum of **7c**. (d) The signals at 5.02 and 6.1 ppm were missing in the ^1H NMR spectrum of **7d**. (e) The signal at 4.9 ppm was missing in the ^1H NMR spectrum of **7e**.

SCHEME 10. Mechanism of Palladium-Mediated Isomerizations in the Heck Reaction with 2c



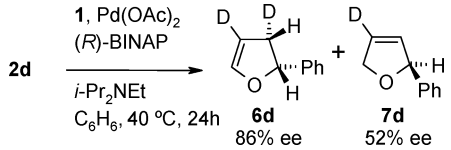
(Scheme 8), transferring the phenyl group to the C-5 position in **2b** via a Heck reaction. This also rules out the formation of **6a** via an alternative mechanism[19] (Scheme 8) involving a possible C−H insertion of (BINAP)PhPd$^+$ at the C-2 position of **2b**. This type of mechanism would have resulted in the formation of **6e** having the deuterium atom at C-5, which was not observed. These results are in agreement with those of Brown et al.,[1a] which were obtained under different Heck reaction conditions. The absence of furan **20** in the product mixture indicates that an *anti*-β-H Pd elimination[7] was not occurring under the reaction conditions in the presence of Hunig's base.

The Heck reaction of **2c** with **1** provided **6c** and **7c** (Scheme 9) in a 90:10 ratio (**6c**/**7c**); examination of the ^{1}H and ^{2}H NMR spectra of **6c** indicated the deuterium atom was only found on C-3 and was exclusively *anti*[17c] to the phenyl group at C-2. This is consistent with a *syn* rearrangement from the first Heck reaction intermediate **3c** to **4c**, either stepwise or concerted, which gives the proper stereochemistry at C-3 in product **6c** (Scheme 10). An *anti* rearrangement of **3c** would result in the opposite stereochemistry at C-3 in the major product of the reaction, and this was not observed. *Syn* elimination of intermediate **3c** leads to product **ent-7c**,[18c] with the deuterium atom on C-3, as expected.

The Heck reaction of **2d** with **1** provided **6d** and **7d** (Scheme 11) in a 90:10 ratio (**6d**/**7d**), and the ^{1}H and ^{2}H NMR spectra of **6d** showed deuterium atoms were found at the C-4 and C-3α[17d] positions with the deuterium atom at C-3 positioned exclusively *syn* to the phenyl group at C-2. Deuterium was not found at the C-3 H$_\beta$ position in **6d**. Based on the evidence of the Heck reaction with **2c**, a *syn* rearrangement following the initial carbon−carbon bond formation should convert **3d** to **4d** (Scheme 12), leading to the observed stereochemistry at C-3 in the product. Another *syn* rearrangement, giving **5d**, leads to product **6d** upon *syn*-elimination. An *anti* rearrangement from intermediate **4d** would lead to a hydrogen atom, instead of a deuterium atom, at C-4 in the major product. As well, **ent-7d**[18d] has a deuterium atom at C-4, which is consistent with a *syn* elimination of intermediate **3d**.

Finally, Heck reaction of **2e** gave **6e**[17e] and **7e**[18e] in a 89:11 ratio (**6e**/**7e**), in which deuterium was only found at the C-5 positions (Scheme 13). These results are consistent with the results from **2b**−**d**, where the carbon−carbon bond formation

SCHEME 11. Products of the Reaction with 2d



gives **3e** (Scheme 14), which either undergoes *syn* elimination to give **ent-7e** or undergoes isomerization to **4e** and then to **5e**, which then undergoes *syn* elimination to give the major product, **6e**.

The results from the Heck reactions with dihydrofurans **2b**−**e** indicate that, after the initial carbon−carbon bond forming Heck reaction, the intermediate species undergoes *syn* rearrangements to form the most stable organometallic palladium species **5b**−**e**, which then undergoes a *syn* elimination to give the major product of the reaction **6b**−**e**. The mechanism of formation of the minor isomers **7b**−**e** can be explained via a *syn* elimination of the initially formed intermediates **3a**−**e**. Products were never observed or isolated in which they would have been formed via *anti*-β-H Pd eliminations or *anti*-dyotropic shifts.

Conclusions

We have shown that the Pd migrations during the intermolecular Heck reaction between phenyl triflate and 2,3-dihydrofuran proceed via *syn*-rearrangements. Whether these rearrangements occur via *syn*-1,2-dyotropic shifts or by a *syn*-"chain-walking" mechanism is still unknown.

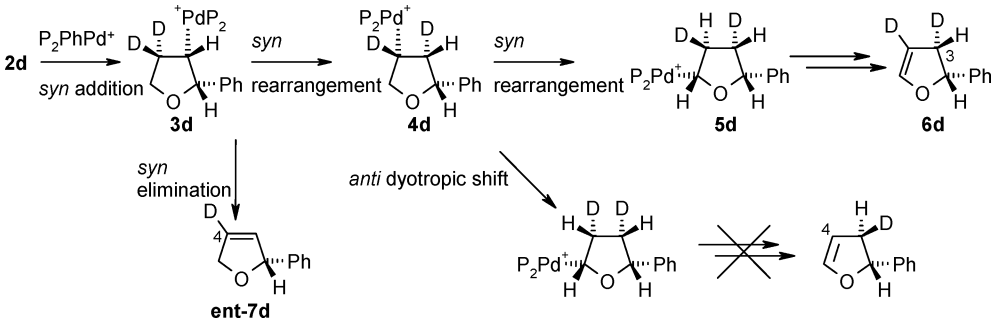
Experimental Section

General Considerations: Heck reactions were performed in scintillation vials with holes in the caps, sealed with Teflon-faced silicone septa, under nitrogen. Unless otherwise specified, all other reactions were performed in oven- or flame-dried glassware that had been cooled under nitrogen. THF was distilled from sodium with benzophenone; benzene, dichloromethane (DCM), and quinoline were distilled from calcium hydride. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer and were referenced to residual $CHCl_3$ in $CDCl_3$, which was stored over potassium carbonate; ^{2}H NMR spectra were obtained on a 300 MHz spectrometer and were referenced to $CHCl_3$. Infrared spectra were recorded on a FT-IR spectrometer. GC analysis was performed on a widebore column (30 m, 0.32 mm, 0.25 μm I.D.) with a solid phase of β-cyclodextrin, using a temperature program of 80 °C for 2 min, followed by a ramp of 1 °C/min, ending at 160 °C. Elemental analyses were not obtained due to the volatility of the compounds. HRMS were not obtained on deuterated compounds, since their protiated compounds are known and have been fully characterized.

Syntheses and NMR Data for Deuterated 2,3-Dihydrofurans 2b, 2c, 2d, 2e. Synthesis of 5-Deuterio-2,3-dihydrofuran (2b).

(19) For examples of C(sp^3)−H functionalizations involving Pd, see: (a) Hitce, J.; Retailleau, P.; Baudoin, O. *Chem.*−*Eur. J.* **2007**, *13*, 792−799. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048−9049. For some recent examples of Pd-catalyzed C(sp^2)−H functionalizations, see: (c) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253−1264 and references therein.

SCHEME 12. Mechanism of Palladium-Mediated Isomerizations in the Heck Reaction with 2d



A solution of **2a** (5.0 mL, 66 mmol) in TMEDA (2 mL) was cooled in an ice−water bath while a solution of *n*-BuLi in hexanes (61.4 mL of 1.25 M, 76.8 mmol) was added slowly. The reaction was stirred at rt for 2 h and was then cooled to −78 °C. D_2O (3 mL) was added dropwise, and the reaction was warmed to rt over 2 h. The product and hexanes were distilled over by short-path distillation ($T \leq 58$ °C). This solution was added dropwise to an aqueous solution of HCl (2 M, 25 mL) that was cooled in ice. The reaction was stirred in ice for 1 h, and then it was extracted with DCM (8 × 19 mL) and the combined extracts were washed with saturated aqueous $NaHCO_3$ solution (25 mL), dried over Na_2SO_4, and concentrated *in vacuo*.

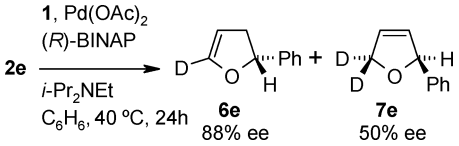
Using general procedure 2: the isolated lactol was treated with a solution of $TsOH{\cdot}H_2O$ (30 mg, 0.16 mmol) in quinoline (3 mL), and the distillate was trapped in a receiving flask containing aqueous NaOH (2 M, 5 mL) to give **2b** (560 mg, 7.88 mmol) in 11.9% yield from 2,3-dihydrofuran. Bp 50 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.96 (1H, t, J = 2.3 Hz), 4.31 (2H, t, J = 9.5 Hz), 2.61 (2H, dt, J = 9.5, 2.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.6 (three lines of equal intensity, J = 28.8 Hz), 99.5 (three lines of equal intensity, J = 2.1 Hz), 69.6, 29.2.

Synthesis of 4-Deuterio-2,3-dihydrofuran (2c). Sodium metal (740 mg, 32.2 mmol) was dissolved in MeOD (60 mL). Once all sodium was consumed, **17a** (4.4 mL, 58 mmol) was added, followed by MeOD (64 mL). The solution was heated to reflux for 19 h. It was then cooled in ice and CD_3CO_2D (1.9 mL, 32 mmol) was added, followed by two drops of concentrated HCl. The solvent was then removed by short-path distillation, and the residue was filtered and the solid was washed with DCM (50 mL). The filtrate was concentrated *in vacuo* and was then dissolved in water (34.6 mL). Concentrated HCl (3.2 mL) was added, and the solution was heated to 110 °C for 1 h. It was then cooled to rt, saturated with NaCl, and extracted with DCM (4 × 100 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled several times to give **17c** as a clear colorless liquid (4.25 g, 48.2 mmol) in 83.3% yield, with 95% deuterium incorporation. Bp 55 °C (aspirator) (lit.[11] 76−78 °C, 5 Torr); IR (film) ν_{max} 2990 (w, C−H), 2913 (w, C−H), 1765 (s, C=O), 1172 (s), 1024 (s, C−O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.3 (2H, t, J = 7.2 Hz), 2.2 (2H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.0, 68.7, 27.3 (5 lines with relative intensities of 1:2:3:2:1, J = 20.8 Hz), 22.0; ^{2}H NMR ($CHCl_3$, 300 MHz): δ 2.55 (br s); MS: *m*/*z* 88 (15%, molecular ion), 58 (19%, loss of HC_2=O), 44 (100%, CO_2 or $C_3H_4D_2$); HRMS calcd for $C_4H_4O_2D_2$, 88.049 33; found, 88.049 01.

Using general procedure 1: lactone **17c** (3.91 g, 44.4 mmol) in DCM (17.3 mL) was cooled for 90 min and then treated with a solution of DIBALH in DCM (1.0 M, 52.0 mL, 52.0 mmol); the reaction was quenched with MeOD (3.5 mL) and saturated aqueous Rochelle salt solution in D_2O (3.5 mL), and the crude lactol was isolated and used immediately.

Using general procedure 2: the isolated lactol was treated with a solution of $TsOH{\cdot}H_2O$ (16 mg, 0.085 mmol) in quinoline (1.9 mL), and the distillate was trapped in a receiving flask containing aqueous NaOH (2 M, 3 mL) to give **2c** (363 mg, 5.04 mmol) in 11.3% yield over two steps, with 78% deuterium incorporation. Bp 54 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.3 (1H, t, J = 2.1 Hz), 4.3 (2H, t, J = 9.5 Hz), 2.6 (2H, dt, J = 9.5, 2.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.8, 99.5 (three lines of equal intensity, J = 26.7 Hz), 69.6, 29.1.

SCHEME 13. Products of the Reaction with 2e



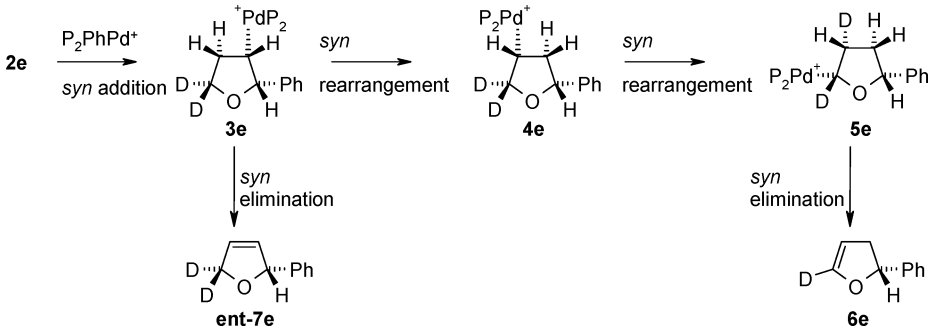
Synthesis of 3,3-Dideuterio-2,3-dihydrofuran (2d). Succinic anhydride (**18**, 15.0 g, 150 mmol) was suspended in MeOH (115 mL) and was refluxed for 2 h. The reaction was then concentrated *in vacuo* to give a white solid (19.4 g, 146 mmol) in 97.7% yield that was used without further purification.

Sodium metal (1.19 g, 51.8 mmol) was dissolved in MeOD (60 mL). Once all sodium was consumed, the ester (4.44 g, 33.6 mmol) was added, followed by MeOD (68 mL). The solution was heated to reflux for 24 h. It was then cooled in ice, and CD_3CO_2D (1.0 mL, 18 mmol) was added. The solution was stirred for 20 min, and the solvent was then removed *in vacuo*. The white solid was dissolved in water (50 mL) and cooled in a water bath while $NaBH_4$ (10.9 g, 288 mmol) was added slowly, followed by more water (15 mL). The reaction was stirred at rt for 12.5 h and was then cooled in ice. Concentrated HCl (29 mL) was added to acidify the solution. Then additional concentrated HCl (5.9 mL) was added, and the solution was heated to 110 °C for 1 h. It was then cooled to rt, saturated with NaCl, and extracted with DCM (4 × 150 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give **17d** as a clear colorless liquid (2.30 g, 26.1 mmol) in 77.7% yield. Bp 50 °C (aspirator); IR (film) ν_{max} 2984 (w, C−H), 2916 (w, C−H), 1773 (s, C=O), 1375 (s), 1175 (s), 1017 (s, C−O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.29 (2H, br s), 2.43 (2H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.1, 68.6, 27.7, 21.6 (5 lines with relative intensities of 1:2:3:2:1, J = 20.5 Hz); ^{2}H NMR ($CHCl_3$, 300 MHz) δ 2.35 (br s); MS: *m*/*z* 88 (16%, molecular ion), 58 (19%, loss of HC_2=O), 44 (100%, CO_2 or $C_3H_4D_2$); HRMS calcd for $C_4H_4O_2D_2$, 88.04933; found, 88.04906.

Using general procedure 1: lactone **17d** (3.13 g, 35.6 mmol) in DCM (13.9 mL) was cooled for 120 min and then treated with a solution of DIBALH in DCM (1.0 M, 41.7 mL, 41.7 mmol); the reaction was quenched with MeOH (2.8 mL) and saturated aqueous Rochelle salt solution (2.8 mL), and the crude lactol was isolated.

Using general procedure 2: the isolated lactol was treated with a solution of $TsOH{\cdot}H_2O$ (15 mg, 0.080 mmol) in quinoline (1.8 mL), and the distillate was trapped in a receiving flask containing aqueous NaOH (2 M, 3 mL) to give **2d** (616 mg, 8.54 mmol) in 24.0% yield over two steps. Bp 54 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.33 (1H, d, J = 2.6 Hz), 4.95 (1H, d, J = 2.6 Hz), 4.30 (2H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.9, 99.4, 69.4, 28.5 (five lines with relative intensities of 1:2:3:2:1, J = 20.3 Hz).

SCHEME 14. Mechanism of Palladium-Mediated Isomerizations in the Heck Reaction with 2e



Synthesis of 2,2-Dideuterio-2,3-dihydrofuran (2e). $LiAlD_4$ (300 mg, 7.15 mmol) was suspended in THF (25 mL) and refluxed for 30 min. It was then cooled to −55 °C, and a solution of **18** (1.24 g, 12,4 mmol) in THF (20 mL) was added dropwise over 15 min. The solution was then warmed to rt over 90 min and then cooled to 0 °C for 10 min and then finally to −15 °C. A solution of HCl in water (6 M, 5 mL) was added slowly, and the reaction was then warmed to rt and stirred for 20 min. It was then saturated with NaCl, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give **17e** as a clear colorless liquid (548 mg, 6.22 mmol) in 50.2% yield. Bp 65 °C (aspirator) (lit.[11] 75−76 °C, 5 Torr); IR (film) ν_{max} 2960 (w, C−H), 1771 (s, C═O), 1250 (s), 1185 (s), 978 (s, C−O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.4 (2H, t, J = 8.1 Hz), 2.1 (2H, t, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.1, 71.1 (5 lines with relative intensities of 1:2:3:2:1, J = 23.2 Hz), 30.8, 25.0; ^2H NMR ($CHCl_3$, 300 MHz) δ 4.38 (br s); MS: *m*/*z* 88 (16%, molecular ion), 56 (20%, loss of DC_2═O), 44 (100%, CO_2 or $C_3H_4D_2$); HRMS calcd for $C_4H_4O_2D_2$, 88.049 33; found, 88.049 03.

Using general procedure 1: lactone **17e** (3.91 g, 44.4 mmol) in DCM (17.3 mL) was cooled for 75 min and then treated with a solution of DIBALH in DCM (1.0 M, 52.0 mL, 52.0 mmol); the reaction was quenched with MeOH (3.5 mL) and saturated aqueous Rochelle salt solution (3.5 mL), and the crude lactol was isolated and used immediately.

Using general procedure 2: the isolated lactol **16e** was treated with a solution of $TsOH·H_2O$ (15 mg, 0.080 mmol) in quinoline (1.8 mL), and the distillate was trapped in a receiving flask containing aqueous NaOH (2 M, 3 mL) to give **2e** (740 mg, 10.3 mmol) in 23.1% yield over two steps. Bp 54 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.3 (1H, q, J = 2.6 Hz), 5.0 (1H, q, J = 2.6 Hz), 2.60 (2H, pentet, J = 2.57 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.8, 99.6, 68.9 (five lines with relative intensities of 1:2:3:2:1, J = 22.4 Hz), 29.0.

NMR Data for 2-Phenyl-2,3-dihydrofuran (6a): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.3 (5H, m), 6.5 (1H, q, J = 2.4 Hz), 5.6 (1H, dd, J = 10.8, 8.2 Hz), 5.0 (1H, q, J = 2.4 Hz), 3.1 (1H, ddt, J = 14.9, 10.8, 2.3 Hz), 2.67 (1H, ddt, J = 14.9, 8.2, 2.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.5, 143.3, 128.7, 127.8, 125.8, 99.2, 82.5, 38.1. MS: *m*/*z* 146 (34%, M^+), 117 (100%,[3,3]-sigmatropic rearrangement then loss of CHO), 77 (12%, Ph^+).

NMR Data for 2-Phenyl-2,5-dihydrofuran (7a): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.2 (5H, m), 6.1 (1H, dq, J = 6.0, 2.0 Hz), 5.9 (1H, dq, J = 6.0, 2.0 Hz), 5.8 (1H, ddt, J = 5.8, 4.1, 2.1 Hz), 4.9 (1H, ddt, J = 12.8, 6.0, 2.1 Hz), 4.8 (1H, ddt, J = 12.8, 4.1, 2.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.2, 130.1, 128.6, 127.9, 126.8, 126.5, 88.0, 76.0. MS: *m*/*z* 146 (42%, M^+), 105 (100%, Ph−C≡O^+), 77 (43%, Ph^+).

General procedure 3 using **2b** gave **6b** and **7b** upon column chromatography. NMR data for **6b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.3 (m), 6.5 (1H, q, J = 2.6 Hz), 5.0 (1H, q, J = 2.6 Hz), 3.1 (1H, br d, J = 15.4 Hz), 2.7 (1H, br d, J = 15.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.5, 143.2, 128.7, 127.8, 125.8, 99.2, 77.3 (three lines equal intensity, J = 22.8 Hz), 37.9; ^2H NMR ($CHCl_3$, 300 MHz) δ 5.51 (br s); MS: *m*/*z* 147 (97%, M^+), 118 (100%,[3,3]-sigmatropic rearrangement then loss of CHO), 77 (11%, Ph^+). NMR data for **7b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.3 (5H, m), 6.1 (1H, dt, J = 6.2, 1.5 Hz), 5.9 (1H, dt, J = 6.2, 1.5 Hz), 4.9 (1H, br d, J = 12.3 Hz), 4.79 (1H, br d, J = 12.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.1, 130.0, 128.6, 128.0, 126.8, 126.5, 87.6 (three lines equal intensity, J = 22.7 Hz), 76.0; ^2H NMR ($CHCl_3$, 300 MHz) δ 5.86 (br s, D_2). MS: *m*/*z* 147 (100%, M^+), 105 (92%, Ph−C≡O^+), 77 (29%, Ph^+).

General procedure 3 using **2c** gave **6c**, with 76% deuterium incorporation, and **7c**, with 77% deuterium incorporation, upon column chromatography. NMR data for **6c**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.3 (5H, m), 6.5 (1H, t, J = 2.3 Hz), 5.6 (1H, d, J = 7.7 Hz), 5.0 (1H, t, J = 2.6 Hz), 2.7 (1H, dt, J = 7.7, 2.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.6, 143.3, 128.7, 127.8, 125.8, 99.1, 82.5, 37.7 (three lines equal intensity, J = 20.6 Hz); ^2H NMR ($CHCl_3$, 300 MHz) δ 3.1 (br s); MS: *m*/*z* 147 (75%, M^+), 118 (100%,[3,3]-sigmatropic rearrangement then loss of CHO), 77 (13%, Ph^+). NMR data for **7c**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.3 (5H, m), 6.1 (1H, br s), 5.8 (1H, m), 4.9 (1H, dd, J = 12.8, 6.2 Hz), 4.79 (1H, dd, J = 12.8, 4.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.2, 130.1 (three lines equal intensity, J = 26.1 Hz), 128.7, 128.0, 126.6, 126.5, 88.0, 76.0; ^2H NMR ($CHCl_3$, 300 MHz) δ 6.0 (br s). MS: *m*/*z* 147 (61%, M^+), 105 (100%, Ph−C≡O^+), 77 (30%, Ph^+).

General procedure 3 using **2d** gave **6d**, with 96% and 86% deuterium incorporation at the 3- and 4-positions, respectively, and **7d**, with 84% deuterium incorporation, upon column chromatography. NMR data for **6d**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.3 (5H, m), 6.5 (1H, d, J = 2.0 Hz), 5.6 (1H, d, J = 10.8 Hz), 3.1 (1H, dq, J = 10.8, 2.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.5, 143.2, 128.7, 127.8, 125.8, 98.9 (three lines equal intensity, J = 26.7 Hz), 82.5, 37.6 (three lines equal intensity, J = 20.3 Hz); ^2H NMR ($CHCl_3$, 300 MHz) δ 4.9 (1D, br s), 2.54 (1D, br s). MS: *m*/*z* 148 (45%, M^+), 119 (100%,[3,3]-sigmatropic rearrangement then loss of CHO), 77 (8.3%, Ph^+). NMR data for **7d**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.2 (5H, m), 5.9 (1H, br s), 5.8 (1H, t, J = 4.9 Hz), 4.9 (1H, ddd, J = 12.7, 6.0, 2.5 Hz), 4.8 (1H, ddd, J = 12.7, 4.9, 2.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.2, 130.0, 128.6, 127.9, 126.5, 88.1, 75.9, one signal was lost in the baseline of the NMR; ^2H NMR ($CHCl_3$, 300 MHz) δ 6.0 (1D, br s). MS: *m*/*z* 147 (73%, M^+), 105 (100%, Ph−C≡O^+), 77 (31%, Ph^+).

General procedure 3 using **2e** gave **6e** and **7e** upon column chromatography. NMR data for **6e**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.3 (5H, m), 5.6 (1H, dd, J = 10.8, 8.2 Hz), 5.0 (1H, t, J = 2.3 Hz), 3.1 (1H, ddd, J = 15.1, 10.8, 2.3 Hz), 2.6 (1H, ddd, J = 15.1, 8.2, 2.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.3 (three lines equal intensity, J = 29.1 Hz), 143.2, 128.7, 127.8, 125.7, 99.0 (three lines equal intensity, J = 1.8 Hz), 82.5, 38.0; ^2H NMR ($CHCl_3$, 300 MHz) δ 6.5 (1D, br s). MS: *m*/*z* 147 (63%, M^+), 117 (100%,[3,3]-sigmatropic rearrangement then loss of CDO), 77 (12%, Ph^+). NMR data for **7e**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.2 (5H, m), 6.0

(1H, dd, $J = 6.2$, 2.0 Hz), 5.9 (1H, dd, $J = 6.2$, 1.5 Hz), 5.8 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.2, 130.2, 128.6, 127.9, 126.6, 126.5, 88.0, one signal was lost in the baseline of the NMR; ^{2}H NMR ($CHCl_3$, 300 MHz) δ 4.8 (1D, br s), 4.7 (1D, br s). MS: *m*/*z* 148 (75%, M^+), 105 (100%, Ph—C≡O^+), 77 (32%, Ph^+).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **2b**−**e**, **6a**−**e**, **7a**−**e**, and **17c**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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