Palladium-catalyzed α,β-dehydrogenation of acyclic ester equivalents promoted by a novel electron deficient phosphinooxazoline ligand

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Abstract

A unique example of Pd-catalyzed decarboxylative dehydrogenation of fully substituted N-acyl allyl enol carbonates is enabled by a new electron deficient phosphinooxazoline (PHOX) ligand. The reaction proceeds from the \(Z\)-enol carbonate to provide dehydrogenation products exclusively in high \(E/Z\) selectivity, while the \(E\)-enol carbonate provides the \(\alpha\)-allylation product with only minor dehydrogenation. The reaction proceeds with a broad scope of \((Z)\)-enol carbonates derived from \(N\)-acyl indoles to furnish acyclic formal \(\alpha,\beta\)-unsaturated ester equivalents.

Graphical Abstract
Keywords
Dehydrogenation; Palladium; PHOX ligand

Introduction

Our lab has recently become interested in developing palladium-catalyzed asymmetric allylic alkylation reactions of acyclic stereodefined fully substituted enol carbonates to generate acyclic quaternary stereogenic centers. In our initial efforts, we reported the application of a highly $E$-selective enolization$^1$ of acyclic $\alpha$-aryl ketones to generate stereodefined fully substituted acyclic ketone enol carbonates which we employed in a highly enantioselective Pd-catalyzed allylic alkylation to generate all carbon quaternary centers.$^2$ More recently, we became intrigued by the possibility of extending this reactivity toward acyclic ester enolate equivalents to generate $\alpha$-quaternary carboxylic acid derivatives. In our initial optimization of this transformation, we investigated new electron deficient phosphinoxazoline (PHOX) ligands with $N$-acyl heterocycle derived enol carbonates as ester enolate equivalents. To our delight, we found that the combination of $N$-acyl indole derived enol carbonate $^1$ and fluorinated ligand $(S)$-$F_{13}$-$t$-BuPHOX afforded allylation product $^2$ in an excellent 94% ee and promising 80% yield (Scheme 1). Further investigation of this reaction revealed that despite excellent conversion of $^1$, allylation product $^2$ was isolated in only 80% yield with a 15% yield of $\alpha$,\,$\beta$-unsaturation product $^3\text{a}$. Surprisingly, when a 79:21 $Z$/E mixture of enol carbonate $^1$ was utilized, $\alpha$,\,$\beta$-unsaturation product $^3\text{a}$ predominated, suggesting a preference for the $Z$-enol carbonate to undergo $\alpha$,\,$\beta$-dehydrogenation rather than a standard $\alpha$-alkylation. Control experiments revealed that the reaction does not proceed in the absence of $(S)$-$F_{13}$-$t$-BuPHOX ligand with either enol carbonate mixture, instead providing >95% recovery of the starting material with unaffected $E$/Z enol carbonate ratios. The high synthetic value of $\alpha$,\,$\beta$-unsaturated carboxylic acids and their derivatives coupled with the limited synthetic methods which enable access to this
motif prompted further investigation of this unusual reactivity with our newly synthesized fluorinated PHOX ligand.

Numerous distinct strategies have been developed to access $\alpha,\beta$-unsaturated moieties from carbonyl and carboxylic acid motifs including selenium, sulfur, hypervalent iodine, and quinone based transformations, as well as palladium catalyzed dehydrogenations. One-step allyl-palladium catalyzed dehydrogenations have recently been developed by Newhouse, with pioneering studies from Tsuji, as an effective method to generate $\alpha,\beta$-unsaturated carbonyls, carboxylic acids, and carboxylic acid derivatives, however, there are limited examples regarding acyclic systems bearing $\alpha$-substitution, especially in high $E/Z$ selectivity. Moreover, to the best of our knowledge, this is the first example of an electron deficient PHOX ligand promoting dehydrogenation reactivity with an allyl-palladium species. This new reactivity complements the available methodology for the generation of $\alpha,\beta$-unsaturated compounds and could serve as a new avenue for methodology development in the $\alpha,\beta$-unsaturation of carbonyl compounds.

2 Results and discussion

We began our investigation with an examination of the ligand system (Table 1). To our surprise, when analogous achiral $F_{1,3}$-glyPHOX ligand was employed, no reaction occurred even with elevated reaction temperatures of up to 60 °C (Table 1, entry 1). Though the t-Bu group was required on the ligand scaffold, both enantiomeric series of the $F_{1,3}$-t-BuPHOX provided $\alpha,\beta$-dehydrogenation product 3a in essentially identical yield and $E/Z$ selectivity (entries 2 and 3). These results demonstrate that this unique resolution of the enol carbonate geometries is likely the result of the electron withdrawing nature of the $F_{1,3}$-t-BuPHOX ligand in combination with the preference for dehydrogenation of the Z-enol carbonate. While the E-enol carbonate can be obtained with excellent selectivity (generally $>98:2$) utilizing previously reported selective enolization conditions, selective formation of the Z-enol carbonate is more challenging with modest selectivity of 79:21 Z/E obtained in THF with KHMDS as the base (Scheme 2).

Subsequent optimization of the reaction aimed to identify conditions which favored dehydrogenation for both enol carbonate geometries. Other solvents common for dehydrogenation reactions were examined, but provided no improvement over the 3:1 hexanes/toluene solvent system (Table 2, entries 1–6). With either toluene or MTBE as a solvent full conversion of 1 is observed, albeit with lower selectivity for dehydrogenation product 3a over alkylation product 2 compared with 3:1 hexanes/toluene (entries 2 and 3). In THF, the reaction becomes sluggish and 65% of the enol carbonate mixture is recovered after 24 h with no change in the ratio of enol carbonates (entry 4). Polar, aprotic solvents such as DMF and MeCN utilized in allyl-palladium catalyzed dehydrogenation by Tsuji provide no reaction (entries 5 and 6). Newhouse and co-workers have previously demonstrated the application of zinc salts to disfavor allylation via a postulated transmetalation to afford a less nucleophilic zinc enolate in allyl-palladium catalyzed dehydrogenations. To our disappoint, the incorporation of ZnCl$_2$ in our reaction conditions as a stoichiometric additive stymies both allylation and dehydrogenation pathways (entry 7). Heating the reaction with a 75:25 $Z/E$ mixture of 1 to 60 °C also fails to
promote any measurable level of conversion. Notably, when ZnCl₂ is used with a >98:2 E/Z mixture of enol carbonates, trace conversion to the allylation product is observed after prolonged heating (>24 h) at 60 °C, further exemplifying the importance of enolate geometry in this transformation. In addition, we found N-acyl indole derived enol carbonate 1 was incompatible with Tsuji’s classic decarboxylative dehydrogenation conditions,8a instead providing complex mixtures of decarboxylative allylation and protonation with recovered enol carbonate (Scheme 3).

Bereft of reaction conditions favoring dehydrogenation for both enolate geometries, we examined the reaction scope with pure Z-enol carbonates to simplify reaction analysis and product purification. A variety of N-acyl indoles were enolized using Z-selective conditions (vide supra) and trapped as the corresponding allyl enol carbonates. The geometrically pure Z-enol carbonates were then isolated by preparative chromatography and subjected to our standard reaction conditions (Table 3). Pleasingly, a broad range of alkyl and aryl group substitutions were well tolerated under the reaction conditions and α,β-unsaturated products were obtained in high yield and excellent E-selectivity. With pure Z-enol carbonate 1, product 3a was obtained in >99% yield and in 10:1 E/Z selectivity. Unsubstituted compound 3b was obtained in 84% yield despite elevated potential to undergo intermolecular conjugate addition during the course of the reaction. Longer alkyl chains were well tolerated with n-butyl product 3c isolated in 97% yield and 15:1 E/Z selectivity. Sterically encumbered i-propyl product 3d was also well tolerated with >98:2 E selectivity, albeit in a diminished 77% yield. Product 3e bearing 1,2- diphenyl substitution could be obtained in 75% yield and 6:1 E/Z selectivity. A variety of aryl groups were also compatible with the dehydrogenation reaction. Notably, ortho-substituted product 3f was obtained in an excellent 91% yield and 10:1 E/Z selectivity. Electron rich p-OMe-C₆H₄aryl compound 3g was isolated in an excellent 94% yield and 18:1 E/Z selectivity. Finally, products with electron poor aryl groups p-F-C₆H₄(3h) and p-Cl-C₆H₄(3i) were also obtained in high yields (89% and 79% yield, respectively) and excellent E-selectivity (12:1 and 8:1 E/Z, respectively).

While we were pleased with the scope of α,β-unsaturated N-acyl indoles afforded by the Pd-catalyzed decarboxylative dehydrogenation, we ultimately desired to extend this methodology toward a general manifold of carbonyl compounds. In these initial efforts, we determined this reaction was unsuccessful with other substrates commonly utilized in Pd-catalyzed asymmetric decarboxylative allylic alkylation in our laboratory (Figure 1). Cyclic allyl enol carbonate 4 and β-ketoesters 5–7 failed to convert to either allylation or dehydrogenation products with these reaction conditions. Even with the analogous acyclic phenyl ketone derived allyl enol carbonate 8 (75:25 Z/E) no conversion was observed. Future efforts will be directed toward investigation of the dehydrogenation reaction with substrate classes unsuccessful in this unique system toward a more general transformation and understanding the nature of the ligand promoted dehydrogenation.

We posit a plausible catalytic cycle for this transformation can proceed as shown in Figure 2 where the allyl group of the enol carbonate ultimately serves as a hydride acceptor. A ligated Pd⁰ species can undergo oxidative addition to allyl enol carbonate 1, generating palladium carboxylate 9. Subsequent decarboxylation produces allyl palladium complex 10 and enolate 11 which can form carbon-bound palladium enolate 12. At this stage, β-hydride elimination
can occur to furnish product 3a and palladium hydride 13. Finally, reductive elimination of 13 regenerates the Pd$^0$ species and generates propene as a by-product.

3 Conclusion and outlook

In summary, we have developed the first example of an allyl-palladium catalyzed decarboxylative dehydrogenation reaction of fully substituted N-acyl indole derived allyl enol carbonates promoted by a newly developed electron deficient PHOX ligand. The reaction was quite general with respect to N-acyl indole derived allyl enol carbonates and occurs only with $F_{1-tBu}$PHOX ligand. Other substrate classes typically utilized in decarboxylative allylic alkylation in our laboratory proved unreactive. Future efforts will aim to probe the nature of this unusual resolution of enolate geometries and expand this methodology into a more general transformation for α,β-dehydrogenation. Ultimately, this methodology provides new precedent for ligand controlled selectivity of dehydrogenation over allylic alkylation with allyl-palladium catalysis.

4 Selected experimentals

4.1 General

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, p-anisaldehyde, or KMnO$_4$ staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. The Z-enol carbonates were purified by preparative LC on a Teledyne Isco ACCQPrep HP125; column: C–18, 100 Å, 5 μm, ID 20 mm. $^1$H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual CHCl$_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to CHCl$_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm$^{-1}$). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Reagents were purchased from commercial sources and used as received unless otherwise stated.
4.2 General procedure for dehydrogenation

A representative procedure for the decarboxylative dehydrogenation of N-acyl indole derived enol carbonates:

In a nitrogen-filled glovebox, a solution of Pd$_2$(dba)$_3$ (1.8 mg/mL) and (S)-F$_{13}$-t-BuPHOX (2.8 mg/mL) in toluene was stirred for 30 min at 25 °C, then 0.5 mL of the resulting catalyst solution was added to a one dram vial containing the allyl enol carbonate substrate (0.2 mmol) dissolved in hexanes (1.5 mL). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 25 °C for 16 h unless noted otherwise. The crude reaction mixture was concentrated then purified by silica gel flash chromatography to provide the desired dehydrogenation product.

4.2.1 (E)-1-(1H-indol-1-yl)-2-phenylbut-2-en-1-one (3a)—Purified by column chromatography (5% Et$_2$O in hexanes) to provide a colorless oil (52.1 mg, 0.199 mmol, >99% yield, 10:1 E/Z); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.47 (dq, J = 8.3, 0.9 Hz, 1H), 7.54 (dq, J = 7.6, 0.8 Hz, 1H), 7.43–7.27 (m, 8H), 6.50 (dd, J = 3.8, 0.7 Hz, 1H), 6.46 (q, J = 7.2 Hz, 1H), 1.99 (d, J = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.2, 138.0, 136.0, 134.9, 134.6, 130.8, 129.1, 128.8, 127.2, 125.6, 125.0, 123.9, 120.9, 116.7, 108.5, 15.3; IR (Neat Film, NaCl) 3054, 2918, 2854, 1682, 1585, 1535, 1495, 1472, 1451, 1385, 1359, 1331, 1240, 1158, 1144, 1079, 1016, 946, 881, 815, 752, 703 cm$^{-1}$; HRMS (MM:ESI-APCI+) m/z calc’d for C$_{18}$H$_{16}$NO [M+H]$^+$: 262.1226, found 262.1222.

4.2.2 1-(1H-indol-1-yl)-2-phenylprop-2-en-1-one (3b)—Purified by column chromatography (5% Et$_2$O in hexanes) to provide a colorless oil (41.4 mg, 0.167 mmol, 84% yield); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.57–8.54 (m, 1H), 7.57 (dt, J = 7.7, 1.0 Hz, 1H), 7.51–7.45 (m, 2H), 7.43–7.28 (m, 6H), 6.54 (d, J = 3.7 Hz, 1H), 6.08 (s, 1H), 5.70 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.7, 144.5, 135.7, 135.4, 131.0, 129.2, 129.2, 127.1, 126.2, 125.3, 124.3, 121.0, 116.8, 109.3; IR (Neat Film, NaCl) 3055, 2926, 1692, 1535, 1496, 1471, 1450, 1378, 1348, 1293, 1205, 1156, 1072, 1016, 931, 880, 752, 696 cm$^{-1}$; HRMS (MM:ESI-APCI+) m/z calc’d for C$_{17}$H$_{14}$NO [M+H]$^+$: 248.1070, found 248.1063.

4.2.3 (E)-1-(1H-indol-1-yl)-2-phenylhept-2-en-1-one (3c)—Purified by column chromatography (3% Et$_2$O in hexanes) to provide a colorless oil (58.9 mg, 0.194 mmol, 97% yield, 14:1 E/Z); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.47 (d, J = 8.3 Hz, 1H), 7.42 – 7.26 (m, 7H), 6.57–6.48 (m, 2H), 6.33 (t, J = 7.5 Hz, 1H), 2.36 (q, J = 7.5 Hz, 2H), 1.50 (tt, J = 8.2, 6.9 Hz, 2H), 1.37 (dq, J = 14.4, 7.2 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.2, 140.2, 136.8, 136.0, 135.2, 130.8, 129.0, 128.8, 127.2, 125.0, 123.9, 120.9, 116.7, 108.5, 31.5, 28.9, 14.0; IR (Neat Film, NaCl) 3053, 2957, 2928, 2858, 1688, 1636, 1600, 1585, 1534, 1494, 1472, 1450, 1379, 1333, 1205, 1157, 1143, 1113, 1078, 1016, 938, 882, 816, 769, 752, 702 cm$^{-1}$; HRMS (MM:ESI-APCI+) m/z calc’d for C$_{21}$H$_{22}$NO [M+H]$^+$: 304.1696, found 304.1688.

4.2.4 (E)-1-(1H-indol-1-yl)-4-methyl-2-phenylpent-2-en-1-one (3d)—Purified by column chromatography (3% Et$_2$O in hexanes) to provide a colorless oil (44.3 mg, 0.153 mmol, 77% yield, >20:1 E/Z); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.46 (dd, J = 8.3, 1.0 Hz, 1H),
7.55 (ddd, J = 7.7, 1.3, 0.7 Hz, 1H), 7.42–7.27 (m, 8H), 6.54 (d, J = 3.8 Hz, 1H), 6.10 (d, J = 10.5 Hz, 1H), 2.80 (dhept, J = 10.5, 6.6 Hz, 1H), 1.11 (d, J = 6.6 Hz, 6H); 13C NMR (100 MHz, CDCl3) δ 169.2, 146.6, 136.0, 135.3, 130.9, 128.9, 128.8, 128.8, 127.2, 125.0, 123.9, 116.7, 108.5, 28.3, 22.7; IR (Neat Film, NaCl) 3054, 2926, 2868, 1687, 1534, 1494, 1450, 1377, 1334, 1238, 1201, 1112, 1078, 1017, 882, 795, 769, 752, 694 cm⁻¹; HRMS (MM:ESI-APCI+) m/z calc’d for C20H20NO [M+H]^+: 290.1539, found 290.1528.

4.2.5 (E)-1-(1H-indol-1-yl)-2,3-diphenylprop-2-en-1-one (3e)—Purified by column chromatography (5% EtO in hexanes) to provide a colorless oil (48.3 mg, 0.149 mmol, 75% yield, 6:1 E/Z); 1H NMR (400 MHz, CDCl3) δ 8.67 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 11.3, 7.5 Hz, 2H), 7.65 (d, J = 3.8 Hz, 1H), 7.59–7.44 (m, 7H), 7.44–7.30 (m, 5H), 6.71 (d, J = 3.8 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 169.2, 136.4, 136.1, 134.6, 130.9, 130.0, 129.3, 129.2, 128.9, 128.7, 127.1, 126.0, 125.1, 124.1, 121.0, 116.8, 108.9; IR (Neat Film, NaCl) 3053, 3026, 2923, 1684, 1535, 1492, 1472, 1450, 1381, 1333, 1235, 1206, 1155, 1141, 1112, 1077, 1016, 908, 882, 862, 753, 721, 694 cm⁻¹; HRMS (MM:ESI-APCI+) m/z calc’d for C23H18NO [M+H]^+: 324.1383, found 324.1380.

4.2.6 (E)-1-(1H-indol-1-yl)-2-(α-tolyl)but-2-en-1-one (3f)—Purified by column chromatography (3% EtO in hexanes) to provide a colorless oil (50.1 mg, 0.182 mmol, 91% yield, 12:1 E/Z); 1H NMR (400 MHz, CDCl3) δ 8.40 (d, J = 8.2 Hz, 1H), 7.46 (dd, J = 7.7, 1.1 Hz, 1H), 7.31–7.26 (m, 1H), 7.25 (d, J = 3.8 Hz, 1H), 7.22–7.16 (m, 3H), 7.12 (d, J = 7.9 Hz, 2H), 6.42 (d, J = 3.8 Hz, 1H), 6.35 (q, J = 7.2 Hz, 1H), 2.28 (s, 3H), 1.91 (d, J = 7.2 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 169.4, 138.0, 137.9, 135.9, 134.0, 131.9, 130.8, 129.7, 128.9, 127.2, 125.5, 124.9, 123.9, 120.8, 116.7, 21.4, 15.3; IR (Neat Film, NaCl) 3027, 2919, 2856, 1688, 1533, 1513, 1472, 1450, 1384, 1329, 1239, 1206, 1157, 1143, 1113, 1080, 1017, 946, 882, 828, 770, 753, 723 cm⁻¹; HRMS (MM:ESI-APCI+) m/z calc’d for C19H18NO [M+H]^+: 276.1383, found 276.1375.

4.2.7 (E)-1-(1H-indol-1-yl)-2-(4-methoxyphenyl)but-2-en-1-one (3g)—Purified by column chromatography (8% EtO in hexanes) to provide a colorless oil (50.0 mg, 0.189 mmol, 94% yield, 19:1 E/Z); 1H NMR (400 MHz, CDCl3) δ 8.48 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.41–7.24 (m, 5H), 6.96–6.87 (m, 2H), 6.50 (d, J = 3.8 Hz, 1H), 6.40 (q, J = 7.1 Hz, 1H), 3.81 (s, 3H), 1.99 (d, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 169.6, 159.4, 137.6, 135.9, 133.6, 130.8, 130.3, 127.2, 124.9, 123.9, 120.8, 116.7, 114.2, 108.4, 15.3; IR (Neat Film, NaCl) 2934, 2361, 1684, 1607, 1511, 1450, 1328, 1292, 1250, 1202, 1178, 1110, 1079, 1032, 948, 881, 838, 815, 770, 753 cm⁻¹; HRMS (MM:ESI-APCI+) m/z calc’d for C19H18NO2 [M+H]^+: 292.1332, found 292.1340.

4.2.8 (E)-2-(4-fluorophenyl)-1-(1H-indol-1-yl)but-2-en-1-one (3h)—Purified by column chromatography (5% EtO in hexanes) to provide a colorless oil (49.8 mg, 0.178 mmol, 89% yield, 13:1 E/Z); 1H NMR (400 MHz, CDCl3) δ 8.45 (d, J = 8.2 Hz, 1H), 7.55 (dt, J = 7.7, 0.9 Hz, 1H), 7.40–7.32 (m, 4H), 7.32–7.26 (m, 1H), 7.13–7.06 (m, 2H), 6.53 (d, J = 3.8 Hz, 1H), 6.45 (q, J = 7.1 Hz, 1H), 1.96 (d, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 169.0, 162.45 (d, J_C-F = 248.2 Hz), 135.9, 134.9, 130.9, 130.8, 127.0, 125.1, 124.0, 116.6, 116.0, 115.7, 108.7, 15.2; 19F NMR (282 MHz, CDCl3) δ –113.18 (dtq, J =
10.8, 5.3, 2.3 Hz). IR (Neat Film, NaCl) 3051, 2917, 1685, 1602, 1534, 1509, 1472, 1385, 1331, 1224, 1202, 1160, 1101, 1016, 948, 881, 842, 786, 770, 754 cm$^{-1}$; HRMS (MM:ESI-APCI$^+$) m/z calc’d for C$_{18}$H$_{15}$FNO [M+H]$^+$: 280.1132, found 280.1137.

### 4.2.9 (E)-2-(4-chlorophenyl)-1-(1H-indol-1-yl)but-2-en-1-one (3i)—Purified by column chromatography (5% Et$_2$O in hexanes) to provide a colorless oil (46.7 mg, 0.158 mmol, 79% yield, 8:1 E/Z);

1$^H$ NMR (400 MHz, CDCl$_3$) $\delta$ 8.45 (d, $J = 8.1$ Hz, 1H), 7.59–7.51 (m, 1H), 7.40–7.26 (m, 7H), 6.53 (d, $J = 3.7$ Hz, 1H), 6.46 (q, $J = 7.2$ Hz, 1H), 1.97 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.7, 136.9, 135.9, 135.3, 134.2, 133.2, 130.4, 129.2, 129.0, 127.0, 125.1, 124.1, 116.6, 108.8, 15.3; IR (Neat Film, NaCl) 3051, 2916, 1688, 1534, 1491, 1472, 1451, 1384, 1330, 1204, 1143, 1089, 1016, 947, 881, 838, 802, 770, 754 cm$^{-1}$; HRMS (MM:ESI-APCI$^+$) m/z calc’d for C$_{18}$H$_{15}$ClNO [M+H]$^+$: 296.0837, found 296.0835.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Unsuccessful substrates for the Pd-catalyzed decarboxylative dehydrogenation.
Figure 2.
Plausible catalytic cycle.
Scheme 1.
Initial reaction discovery.
Scheme 2.
*E*- and *Z*-selective enol carbonate formation.
Scheme 3.
Investigation of Tsuji’s classic dehydrogenation.
## Table 1.

Investigation of the ligand.\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>result\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F\textsubscript{13}glyPHOX</td>
<td>95% recovery of 1 (75:25 Z/E)</td>
</tr>
<tr>
<td>2</td>
<td>(S)-t-Bu-F\textsubscript{13}PHOX</td>
<td>80% yield 3a (10:1 E/Z), 18% yield 2</td>
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<tr>
<td>3</td>
<td>(R)-t-Bu-F\textsubscript{13}PHOX</td>
<td>79% yield 3a (10:1 E/Z), 17% yield 2</td>
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</table>

Conditions:

\textsuperscript{a} 0.2 mmol substrate, 0.5 mol % Pd\textsubscript{2}(dba)\textsubscript{3}, 1.2 mol % ligand, 2.0 mL solvent, 25 °C.

\textsuperscript{b} Yields of isolated products. E/Z ratios measured by \textsuperscript{1}H NMR integration.
### Table 2.
Optimization of the Pd-catalyzed dehydrogenation.

<table>
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<th>entry</th>
<th>solvent</th>
<th>additive</th>
<th>result&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>3:1 hexanes/toluene</td>
<td>none</td>
<td>80% yield 3a (10:1 E/Z), 18% yield 2</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>none</td>
<td>70% yield 3a (10:1 E/Z), 26% yield 2</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>MTBE</td>
<td>none</td>
<td>71% yield 3a (10:1 E/Z), 28% yield 2</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>none</td>
<td>65% recovery of 1 (75:25 Z/E)</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>none</td>
<td>94% recovery of 1 (75:25 Z/E)</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>none</td>
<td>92% recovery of 1 (75:25 Z/E)</td>
</tr>
<tr>
<td>7</td>
<td>3:1 hexanes/toluene</td>
<td>ZnCl&lt;sub&gt;2&lt;/sub&gt; (6.0 equiv)</td>
<td>92% recovery of 1 (75:25 Z/E)</td>
</tr>
<tr>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3:1 hexanes/toluene</td>
<td>ZnCl&lt;sub&gt;2&lt;/sub&gt; (6.0 equiv)</td>
<td>94% recovery of 1 (75:25 Z/E)</td>
</tr>
</tbody>
</table>

**Conditions:**

<sup>a</sup>0.2 mmol substrate, 0.5 mol % Pd<sub>2</sub>(dba)<sub>3</sub>, 1.2 mol % ligand, 2.0 mL solvent, 25 °C, 24 h reaction time.

<sup>b</sup>Yields of isolated products. E/Z ratios measured by <sup>1</sup>H NMR integration.

<sup>c</sup>Incomplete conversion.

<sup>d</sup>Reaction performed at 40 °C.

<sup>e</sup>Reaction performed at 60 °C.
Table 3.

Substrate scope of the Pd-catalyzed decarboxylative dehydrogenation.\(^a\)

<table>
<thead>
<tr>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
<th>E/Z Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>&gt;99% yield, 10:1 E/Z</td>
<td>99% yield</td>
<td>&gt;98:2 E/Z</td>
</tr>
<tr>
<td>3b</td>
<td>84% yield</td>
<td>97% yield, 15:1 E/Z</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>77% yield, 20:1 E/Z</td>
<td>91% yield, 10:1 E/Z</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>75% yield, 6:1 E/Z</td>
<td>91% yield, 10:1 E/Z</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>94% yield, 19:1 E/Z</td>
<td>89% yield, 12:1 E/Z</td>
<td></td>
</tr>
<tr>
<td>3f</td>
<td>79% yield, 8:1 E/Z</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Conditions: 0.2 mmol substrate, 0.5 mol % Pd(dba)\(_3\), 1.2 mol % ligand, 2.0 mL solvent, 25 °C, 16 h reaction time. Yields of isolated product. Product E/Z ratios were measured by \(^1\)H NMR integration.