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

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The reaction scheme shows the transformation of an alkylated imine into a nitro compound with the assistance of \( \text{Pd}_{2} \text{(dba)}_{3} \) (0.5 mol %) and (S)-\( \text{F}_{3} \text{C} \text{BuPHOX} \) (1.2 mol %) in a 3:1 hexanes/toluene mixture at 25 °C for 16 h. Three examples were reported, achieving up to 99% yield and 20:1 E/Z ratio.

The newly developed electron deficient PHOX ligand is illustrated in the inset.
Palladium-catalyzed $\alpha,\beta$-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.

Dedicated to Professor John F. Hartwig on his receipt of the Tetrahedron Prize.

Keywords: Dehydrogenation; Palladium; PHOX ligand

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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 of acyclic α-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. More recently, we became intrigued by the possibility of extending this reactivity toward acyclic ester enolate equivalents to generate α-quaternary carboxylic acid derivatives. In our initial optimization of this transformation, we investigated new electron deficient phosphinooxazoline (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 α,β-unsaturation product 3a. Surprisingly, when a 79:21 Z/E mixture of enol carbonate 1 was utilized, α,β-unsaturation product 3a predominated, suggesting a preference for the Z-enol carbonate to undergo α,β-dehydrogenation rather than a standard α-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 α,β-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 α,β-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 α,β-unsaturated carboxyls, carboxylic acids, and carboxylic acid derivatives, however, there are limited examples regarding acyclic systems bearing α-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 α,β-unsaturated compounds and could serve as a new avenue for methodology development in the α,β-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$_{13}$-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.

Table 1. Investigation of the ligand.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>E/Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-F$_{13}$-t-BuPHOX</td>
<td>90%</td>
<td>1/2</td>
</tr>
<tr>
<td>2</td>
<td>(S)-F$_{13}$-t-BuPHOX</td>
<td>90%</td>
<td>2/1</td>
</tr>
<tr>
<td>3</td>
<td>(S)-F$_{13}$-t-BuPHOX</td>
<td>90%</td>
<td>3/1</td>
</tr>
</tbody>
</table>

Conditions: 0.2 mmol substrate, 0.5 mol % Pd(dba)$_2$, 1.2 mol % ligand, 2.0 mL solvent, 25 °C. Yields of isolated products. E/Z ratios measured by H NMR integration.

The effectiveness of the F$_{13}$-t-BuPHOX provided α,β-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$_{13}$-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).
Scheme 2. E- and Z-selective enol carbonate formation.

![Scheme 2](image)

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 transformation. In addition, we found trace conversion to the alkylation product is obtained in an excellent 91% yield and 10:1 E/Z selectivity. With pure Z-enol carbonate 1, product 3a was obtained in >99% yield and in 10:1 EIZ 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 EIZ selectivity. Sterically encumbered i-propyl product 3d was also well tolerated with >98:2 E selectivity, albeit in a diminished 77% yield. Products 3e bearing 1,2-diphenyl substitution could be obtained in 75% yield and 6:1 EIZ 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 EIZ selectivity. Electron rich p-OMe-C$_6$H$_4$ aryl compound 3g was also obtained in excellent 94% yield and 18:1 EIZ selectivity. Finally, products with electron poor aryl groups p-F-C$_6$H$_4$ (3h) and p-Cl-C$_6$H$_4$ (3i) were also obtained in high yields (89% and 79% yield, respectively) and excellent E-selectivity (12:1 and 8:1 EIZ, respectively).

While we were pleased with the scope of allylic alkylation, 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 alkylation 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 Pd 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 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$_{13}$-t-BuPHOX 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 experiments
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
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 (\(\delta\) 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 (\(\delta\) 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 optical activity 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 \(\text{Pd} \cdot \text{dba}_{3}\) (1.8 mg/mL) and \((S)\)–\((R)\)-1,2,3-tris(2-naphthyl)propane (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) and 18-crown-6 (0.1 mmol). 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% EtO\(_2\)O in hexanes) to provide a colorless oil (58.9 mg, 0.194 mmol, 75% yield).

\[\text{IR (Neat Film, NaCl)}: 3055, 2926, 1692, 1535, 1496, 1471, 1450, 1378, 1348, 1293, 1205, 1156, 1072, 1016, 931, 880, 752, 696 \text{ cm}^{-1}\]; HRMS (MM: ESI-APCI\(^+\)) m/z calc’d for \(C_{21}H_{18}NO\ [M+H]^+\): 248.1070, found 248.1068.

4.2.4 (E)-1-(1H-indol-1-yl)-4-methyl-2-phenylpent-2-en-1-one (3d)

Purified by column chromatography (3% EtO\(_2\)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\(_3\)) \(\delta\) 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, 3H); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 169.2, 146.6, 133.5, 130.3, 128.9, 128.8, 128.7, 127.2, 125.0, 124.9, 123.9, 120.9, 116.7, 108.5, 28.3, 22.7; IR (Neat Film, NaCl) 3053, 2927, 2928, 2958, 2926, 2868, 1687, 1535, 1496, 1471, 1450, 1378, 1348, 1293, 1205, 1156, 1072, 1016, 931, 880, 752, 702 \text{ cm}^{-1}; HRMS (MM: ESI-APCI\(^+\)) m/z calc’d for \(C_{21}H_{18}NO\ [M+H]^+\): 304.1696, found 304.1688.
4.2.7 (1H-indol-1-yl)-2-(o-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, 5:1 E/Z); 1H NMR (400 MHz, CDCl3) δ 8.40 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.7 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, 129.5, 128.9, 127.2, 125.5, 124.9, 123.9, 120.8, 116.7, 108.4, 21.4, 15.3; IR (Neat Film, NaCl) 3029, 2919, 2856, 1688, 1533, 1513, 1472, 1450, 1384, 1329, 1239, 1206, 1187, 1143, 1113, 1080, 947, 882, 828, 770, 753, 727 cm⁻¹; HRMS (MM:ESI-APCI⁺) m/z calc’d for C20H16NO [M+H⁺]: 296.1383, found 296.1375.

4.2.8 (E)-2-(4-fluorophenyl)-1H-indol-1-yl)-2-but-3-en-1-one (3h)

Purified by column chromatography (3% EtO in hexanes) to provide a colorless oil (46.7 mg, 0.158 mmol, 79% yield, 9:1 E/Z); 1H NMR (400 MHz, CDCl3) δ 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). 13C NMR (100 MHz, CDCl3) δ 168.7, 136.9, 135.9, 135.3, 134.2, 133.2, 130.4, 129.2, 129.0, 127.0, 125.1, 124.1, 120.9, 116.6, 108.8, 15.3; IR (Neat Film, NaCl) 3051, 2917, 1685, 1602, 1534, 1509, 1472, 1450, 1385, 1331, 1224, 1202, 1160, 1101, 1080, 1016, 948, 881, 842, 786, 770, 754 cm⁻¹; HRMS (MM:ESI-APCI⁺) m/z calc’d for C18H15FNO [M+H⁺]: 280.1132, found 280.1137.

4.2.9 (E)-2-(4-chlorophenyl)-1H-indol-1-yl)-2-but-3-en-1-one (3i)

Purified by column chromatography (5% EtO in hexanes) to provide a colorless oil (46.7 mg, 0.158 mmol, 79% yield, 9:1 E/Z); 1H NMR (400 MHz, CDCl3) δ 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). 13C NMR (100 MHz, CDCl3) δ 167.8, 136.9, 135.9, 135.3, 134.2, 133.2, 130.4, 129.2, 129.0, 127.0, 125.1, 124.1, 120.9, 116.6, 108.8, 15.3; IR (Neat Film, NaCl) 3051, 2917, 1685, 1533, 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 C18H15ClNO [M+H⁺]: 296.0837, found 296.0835.

Supplementary data

NMR spectra for compounds 3a–3i, as well as experimental and characterization data for substrate and ligand synthesis.

Acknowledgments

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