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Pd-Catalyzed Deoxygenation of Mandelate Esters

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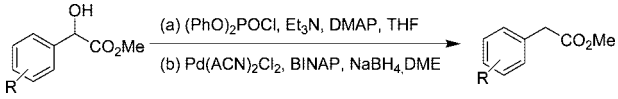
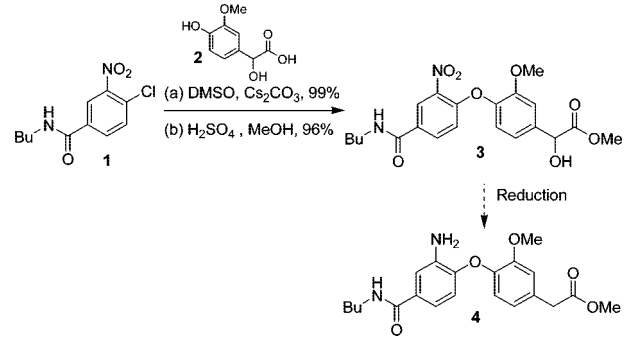


A new approach to the synthesis of phenylacetic acids and esters has been developed via the palladium-catalyzed deoxygenation of mandelate esters.

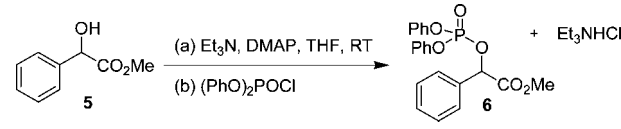
Aryl acetic acids and derivatives are an important class of organic molecules that are prevalent in both pharmaceuticals and natural products. They show a broad range of biological activities[1] including antibacterial, analgesic, and antiviral and are one of the main classes of nonsteroidal anti-inflammatory drugs. During a recent development program, we required an efficient route to the advanced intermediate **4** (Scheme 1).[2]

After reviewing the relevant literature methods[3,4] we became interested in the reduction of mandelic acids as a convenient route to this moiety. Mandelic acids are easily synthesized[5] and a large number of them are commercially available. We envisioned that 4-hydroxy-3-methoxymandelic acid **2** (commonly used for the synthesis of homovanillic acid) could be elaborated to intermediate **3** and reduced to afford **4**. Attempts at a global reduction by metal-catalyzed hydrogenation resulted in exclusive nitro reduction without any evidence of C−O bond cleavage.[6] As a result, we investigated several alternative reduction protocols to effect this transformation. Herein, we report the development and application of a new approach to the synthesis of phenylacetic acids and esters from mandelate esters which involves activation of the α-hydroxy group as the phosphate ester and subsequent palladium-catalyzed deoxygenation.

SCHEME 1. Proposed Synthesis of 4



SCHEME 2. Preparation of the Intermediate Phosphate 6



Our initial investigation utilized methyl mandelate **5** as a model substrate for the deoxygenation reaction. The phosphate **6** was prepared in situ (Scheme 2) and the crude reaction mixture was directly subjected to a screen of metal-catalyzed reduction conditions.[7] A variety of metal catalysts (Pd, Ni, Cu, and Fe) were examined with $NaBH_4$ as the reducing agent and only Pd catalysts afforded significant amounts of product (Table 1, entries 2−6). Various Pd/ligand combinations were examined (entries 10−14). $Pd(ACN)_2Cl_2$/BINAP was identified as a particularly active catalyst system (entry 8) and was shown to be effective at loadings of 0.5% Pd (Table 1, entry 9).

The effects of solvent, temperature, and reducing agent were subsequently examined. It was shown that although the reaction could proceed in THF (Table 2, entry 3), slightly higher yields were obtained in the presence (ca. 35−40%) of a cosolvent (Table 2, entry 1−2). Use of other solvents such as MTBE, PhMe, and DMF for both the phosphate formation and deoxygenation gave lower yields of the desired phenylacetate (Table 2, entries 4−6). At room temperature, the reaction provided 75%

(1) (a) Tuncel, G.; Nergiz, C. *Lett. Appl. Microbiol.* **1993**, *17*, 300–302. (b) Naylor, A.; Judd, D. B.; Brown, D. S. EP 343,900, 1991. (c) Singh, R.; Mall, T. P. *Sci. Cult.* **1979**, *45*, 66–68. (d) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095–4131.

(2) Medina, J. C.; Liu, J.; Fu, Z.; Schmitt, M.; Wang, Y.; Derek, M. C.; Tang, H. L.; Sullivan, T.; Tonn, G.; Collins, T. Discovery of AMG 009: A CRTH2 and DP dual antagonist. *Abstracts of Papers*; 234th National Meeting of the ACS, Boston, MA, Aug 19−23, 2007; American Chemical Society: Washington, DC, 2007; No. 883609.

(3) Recent syntheses of phenylacetic acids and esters: Pd-catalyzed α-arylation: Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002. Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1549–1552. Rh-catalyzed carbonylation: Giroux, A.; Nadeau, C.; Han, Y. *Tetrahedron Lett.* **2000**, *41*, 7601–7604. One carbon elongation of aldehydes: Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925–9932. Zhou, G.-B.; Zhang, P.-F.; Pan, Y.-J. *Tetrahedron,* **2005**, *61*, 5671–5677. Pd-catalyzed carbonylation: Kohlpaintner, C. W.; Beller, M. *J. Mol. Catal. A: Chem.* **1997**, *116*, 259–267. Willerodt-Kindler: Alam, M. M.; Adapa, S. R. *Synth. Commun.* **2003**, *33*, 59–63. Reduction of mesylates: Inokuchi, T.; Sugimoto, T.; Kusumoto, M.; Torii, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3200–3202. Nakamura, K.; Yasui, S.; Ohno, A.; Oka, S. *Tetrahedron Lett.* **1983**, *24*, 2001–2004.

(4) Reduction of Mandelic acids: Mitchell, A.; Bailey, T. Br. Patent 2 078 718, 1982. Spielmann, W.; Schaeffer, G. DE 3 001 511, 1980. . Vallejos, J.-C.; Christidis, Y. EP 0 221 815, 1986. PhilipN. E. Br. Patent 1 576 333, 1976. Vallejos, J.-C.; Legrand, O.; Christidis, Y. *Bull. Soc. Chim. Fr.* **1997**, *134*, 101–104. Ronchin, L.; Toniolo, L.; Cavinato, G. *Appl. Catal., A* **1997**, *165*, 133–145.

(5) Synthesis of mandelic acids: (a) Corson, B. B.; Dodge, R. A.; Harris, S. A.; Yeaw, J. S. *Org. Synth.* **1926**, *6*, 58–62. (b) Bjorsvik, H.-R.; Liguori, L.; Minisci, F. *Org. Process Res. Dev.* **2000**, *4*, 534–543. (c) Weist, S.; Kittel, C.; Bischoff, D.; Bister, B.; Pfeifer, V.; Nicholson, G. J.; Wohlleben, W.; Sussmuth, R. D. *J. Am. Chem. Soc.* **2004**, *126*, 5942–5943. (d) Gathergood, N.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517–12522.

(6) The aromatic amino group may suppress C−O bond cleavage: Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465–3468.

(7) The use of triflates, sulfonates, and carbonates was also investigated. Formation of the triflate of methyl mandelate was unsuccessful possibly due to instablity at RT: Feenstra, R. W.; Stokkingreef, E. H. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron* **1988**, *44*, 5583–5595. The mesylate, tosylate, and ethyl carbonate did not give high yields of desired product **7**, when subjected to the Pd-catalyzed deoxygenation.

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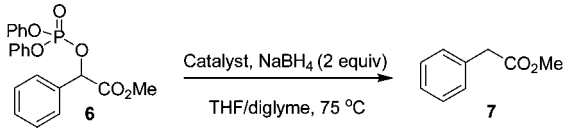
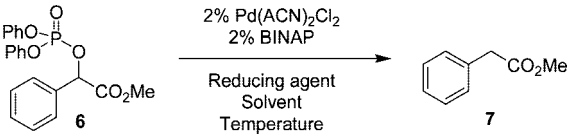
TABLE 1. Deoxygenation of Methyl Mandelate Catalyst Optimization



	catalyst	yield (%)[b]
1	none	0
2	20 mol % $Ni(acac)_2$	16
3	20 mol % $Ni(dppf)Cl_2$	14
4	10 mol % CuI/1,10-phenanthroline	8
5	20 mol % $Fe(acac)_3$	0
6	2 mol % $Pd(dippf)Cl_2$	95
7	2 mol % $Pd(ACN)_2Cl_2$ /no ligand	27
8	**2 mol % $Pd(ACN)_2Cl_2$/BINAP**	**100**
9	0.5 mol % $Pd(ACN)_2Cl_2$/BINAP	94
10	2 mol % $Pd(OAc)_2$/BINAP	87
11	2 mol % $Pd(OAc)_2$/Cy-JohnPhos	88
12	2 mol % $Pd(OAc)_2$ /XantPhos	49
13	2 mol % $Pd(OAc)_2$/*t*-Bu_3P	29
14	2 mol % $Pd(OAc)_2$/*n*-Bu_3P	28

[a] All phosphates prepared in THF. [b] hplc assay yield. [c] dippf = 1,1′-bis(di-isopropylphosphino)ferrocene; Cy-JohnPhos = 2-(dicyclohexylphosphino)biphenyl.

TABLE 2. Deoxygenation of Methyl Mandelate Reaction Optimization[a]



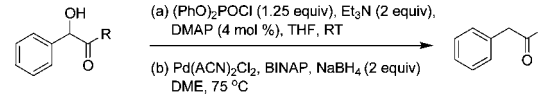
	reductant	solvent	*T* (°C)	yield (%)[b]
1	$NaBH_4$	THF/diglyme	75	100
2	$NaBH_4$	THF/DME	75	95
3	$NaBH_4$	THF	75	88
4	$NaBH_4$	PhMe	75	55
5	$NaBH_4$	MTBE	75	76
6	$NaBH_4$	DMF	75	20
7	$NaBH_4$	THF/DME	40	97
8	$NaBH_4$	THF/DME	rt	75
9	Et_3N/HCO_2H	THF/DME	75	95
10	HCO_2NH_4	THF/DME	75	95

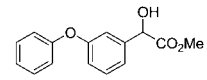
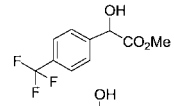
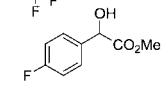
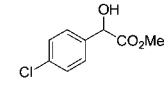
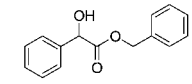
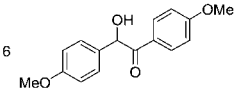
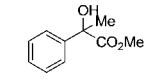
[a] All phosphates prepared in THF except entries 4, 5, and 6. In these cases phosphate was prepared in solvent stated in table [b] hplc assay yield.

yield of the desired product **7**. However, an increase in the reaction temperature to just 40 °C improved the conversion to afford **7** in 97% yield (Table 2, entries 7 and 8). Interestingly, the reaction is not limited to the use of $NaBH_4$, which can be replaced by either Et_3N/formic acid or ammonium formate as the reducing agent (Table 2, entries 9 and 10). In addition, it is worth noting that while all reaction optimization was performed under an inert atmosphere, 94% of **7** could be obtained by using 2% Pd without the exclusion of air.

With the optimal conditions in hand, we next examined the scope of the method. A range of mandelate esters were subjected to the deoxygenation procedure and the phenylacetic acid/ester products were obtained in yields ranging from 73% to 99%. As shown in Table 3, examples include substrates with both electron-rich and -poor substituents on the aromatic ring. It is noteworthy that the deoxygenation of methyl 2-(4-chlorophenyl)-2-hydroxyacetate (entry 4) proceeds without concomitant cleavage of the C−Cl bond. In addition, the benzyl group remained intact when benzyl

TABLE 3. Substrate Scope



	Mandelate Ester	Pd %	Yield[a]
1		5	85
2		2	86[b]
3		2	73[b]
4		2	93[b]
5		2	99
6		2	56
7		5	85[b,c]

[a] Yields on 5 mmol scale. [b] Isolated after hydrolysis to the acid. [c] Phosphate prepared at 45 °C, using 1 equiv of DMAP.

2-hydroxy-2-phenylacetate was subjected to our deoxygenation protocol despite the lability of these groups under other Pd-catalyzed reduction conditions[8] (entry 5). Furthermore, this method tolerates steric hindrance at the α-position and can be applied to the synthesis of phenyl propanoic acids (entry 7). Despite the additional steric bulk, C−O cleavage to the desired product was achieved in 85% yield. The success of this tertiary alcohol example is noteworthy since the olefin side product from the possible competing β-hydride elimination pathway was not observed. Employing similar benzylic phosphates containing β-hydrogens in Pd-catalyzed cross-coupling reactions has shown β-hydride elimination to dominate.[9,10]

To gain further insight, we examined the deoxygenation of (*S*)-methyl 2-hydroxy-2-phenylpropanoate (100% ee). The phosphate was prepared without loss of chiral purity. However, since the deoxygenation step presumably proceeds via a Pd enolate, partial racemization was observed, regardless of whether *rac*- or (*S*)-BINAP was employed (Scheme 3).

Encouraged by the scope of our method we returned our focus to the synthesis of **4**. Fortunately, subjection of phosphate **10** to our Pd-catalyzed reduction conditions concomitantly reduced both the C−O and nitro groups[11] to directly provide the target

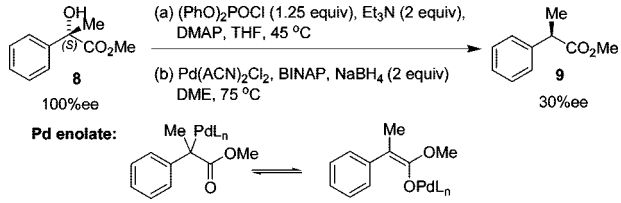
(8) Benzyl removal: Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194–4196.

(9) Coupling of benzylic phosphates: McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875–4878.

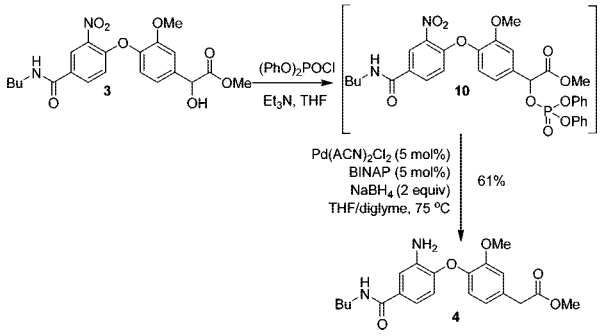
(10) The product of β-elimination methyl 2-phenylacrylate is not observed in the reaction mixture. It is unlikely that this is a major intermediate in the reaction pathway. When subjected to the Pd-catalyzed deoxygenation conditions described in this paper, a number of products are formed.

(11) Pd-catalyzed nitro reductions: Petrini, M.; Ballini, R.; Rosini, G. *Synthesis* **1987**, *71*, 3–714. Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Synthesis* **2006**, *331*, 6–3340.

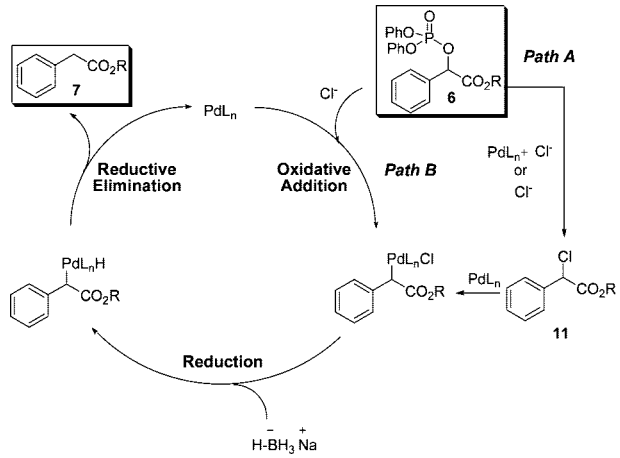
SCHEME 3



SCHEME 4



SCHEME 5



4 (Scheme 4). Interestingly, in this case, diglyme cosolvent was necessary to obtain a moderate yield (61%). Reactions conducted solely in THF gave 66% conversion of phosphate **10**, affording only 2% of the desired product **4**. The main product in this case was the nitro methyl ester, a result of selective C−O cleavage of the phosphate. At lower temperatures and catalyst loadings inferior yields were obtained.

Several mechanistic scenarios can be envisioned for the described transformation. Our optimized protocol involved using solutions of phosphate that were prepared in situ and directly subjected to the reduction conditions. To our surprise, when the phosphate **6** was isolated by aqueous workup and subjected to the reaction conditions only 15% of the desired product was observed. Interestingly, when repeated with the addition of 2 equiv of LiCl or Et_3NHCl (a byproduct from the phosphate formation), 68% and 99% yield of the phenylacetate **7** was obtained, respectively. To explain this observation we envisioned that the reaction could proceed via two plausible pathways as depicted in Scheme 5. Path A involves intermediacy of the chloro compound **11**, which could form by substitution of the phosphate group with a chloride. In support of this theory, it was shown that when ethyl α-chlorophenylacetate was treated under the deoxygenation conditions, ethyl phenylacetate was obtained in 70% yield. However, **11** was not readily formed under the reaction conditions.[12] Therefore, we suggest that the most likely rationale is described by path B. In this case, the role of the chloride is to replace the phosphate as a ligand on Pd, forming the Pd(II)Cl complex, which is capable of undergoing transmetalation/reduction. There is much precedent that the presence of chloride ion has a positive effect on the Pd-catalyzed couplings of aryl and vinyl triflates.[13] Similarly, LiCl has been employed to facilitate the cross-coupling reactions of phosphates.[13d]

In summary, we have demonstrated a new procedure for the synthesis of phenylacetic acids and esters from methyl mandelates. This approach required activation of the α-hydroxyl by the preparation of an intermediate phosphate, which was reduced with sodium borohydride by using a Pd catalyst. The ready availability of mandelate esters should make this an attractive method. The generality and functional group compatibility of this deoxygenation was demonstrated by using a variety of substrates.

Experimental Section

Methyl 2-(4-(2-Amino-4-(butylcarbamoyl)phenoxy)-3-methoxyphenyl)acetate (4). Methyl 2-(4-(4-(butylcarbamoyl)-2-nitrophenoxy)-3-methoxyphenyl)-2-hydroxyacetate (1 g, 2.3 mmol, 1 equiv) and DMAP (11 mg, 0.09 mmol, 4%) were dissolved in THF (10 mL) in a vial sealed with a rubber septum. Triethylamine (0.64 mL, 6.4 mmol, 2 equiv) was added dropwise followed by diphenyl phosphoryl chloride (0.60 mL, 2.88 mmol, 1.25 equiv). The reaction was stirred at rt until 100% complete (checked by hplc).

$Pd(ACN)_2Cl_2$ (30 mg, 5 mol %) and BINAP (72 mg, 5 mol %) were weighed into a glass vial and sealed with a rubber septum. The vial was evacuated and filled with N_2 three times. The phosphate reaction mixture was transferred by syringe with THF (2 mL) wash. $NaBH_4$ (9.2 mL, 0.5 M solution in diglyme, 2 equiv) was added dropwise with a syringe. The reaction was heated to 75 °C until complete (checked by hplc). The resulting crude reaction was filtered, concentrated, and purified by column chromatography (silica, eluent heptane:EtOAc 20:1 to 1:1) to yield solid methyl 2-(4-(2-amino-4-(butylcarbamoyl)phenoxy)-3-methoxyphenyl)acetate (0.546 g, 1.4 mmol, 61%); mp 108.3−109.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.13 (t, J = 5.5 Hz, 1H), 7.24 (s, 1H), 7.07 (s, 1H), 6.93 (dd, J = 8.1, 2.0 Hz, 1H), 6.85 (m, 2H), 6.44 (d, J = 8.5 Hz, 1H), 5.04 (s, 2H), 3.76 (s, 3H), 3.68 (s, 2H), 3.63 (s, 3H), 3.20 (q, J = 6.5 Hz, 2H), 1.47 (m, 2H), 1.30 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 171.6, 166.3, 150.5, 146.0, 143.1, 138.4, 131.0, 130.0, 121.8, 120.0, 115.1, 114.5, 114.4, 55.7, 51.7, 38.7, 31.3, 19.6, 13.7; IR (neat) 3443, 3364, 3293, 1737, 1631; HRMS calcd for $C_{21}H_{27}N_2O_5$ [M + H]$^+$ 387.1914, found 387.1904

Acknowledgment. The authors wish to thank Jenny Chen for her help in chiral hplc analysis. Mr. Jim Yang is acknowledged for early experiments.

Supporting Information Available: Experimental procedures, compound characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) When the crude solution of phosphate was heated to 75 °C in either the presence or absence of catalyst conversions to the chloro compound were 39% and 9%, respectively

(13) Role of LiCl: (a) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486. (b) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630–4632. (c) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040. (d) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gartner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467–5468.