Palladium Catalyzed Preparation of Monoaryl and Diarylphosphinates from Methyl Phosphinate

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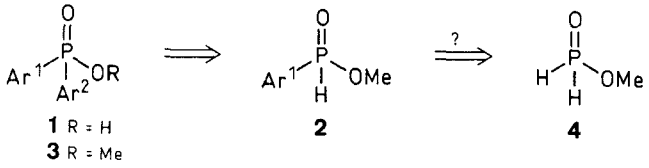
A simple and effective preparation of methyl esters of monoarylphosphinic acids has been developed, which involves palladium catalyzed coupling of aryl iodides with methyl phosphinate in the presence of tertiary amines or propylene oxide (1,2-epoxypropane). This procedure is compatible with various functional groups, and proceeds in reasonable yield despite the thermal and hydrolytic sensitivity of methyl phosphinate. Symmetrically substituted diarylphosphinates may also be prepared using two equivalents of the aryl iodide. Unsymmetrically substituted diarylphosphinates are readily obtained from the monoarylphosphinates by known methods, or by palladium catalyzed reaction of a second aryl iodide without isolation of the intermediate monoarylphosphinate derived from methyl phosphinate.

In connection with our studies on the construction of water soluble cavity-containing materials for use as binding sites, we recently needed to prepare diarylphosphinic acids **1**. Our chosen route involves palladium catalyzed coupling of aryl iodides with methyl esters of monoaryl phosphinic acids **2**.[1] Unfortunately, these phosphinates are not available with useful functionality.

This paper describes our development of a convenient, mild, and general route to the monoarylphosphinic acid methyl esters **2** that we needed as precursors to the diarylphosphinic acids. We also report the synthesis of symmetrical and unsymmetrical methyl diarylphosphinates **3** directly from aryl iodides without isolation of the methyl monoarylphosphinates.



1 R = H
3 R = Me

2 **4**

Scheme

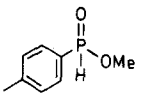
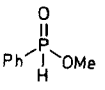
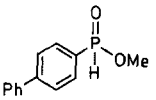
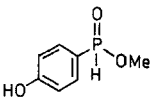
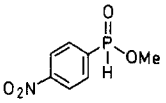
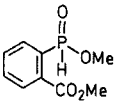
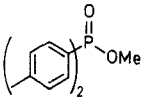
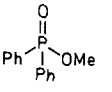
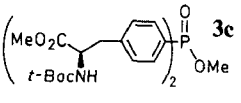
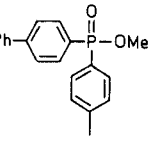
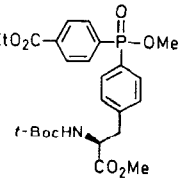
Arylphosphinic acid esters **2** are of interest in themselves as carbonyl isosteres, and have been shown to be useful precursors to phosphonate monoesters,[2] to phosphonate diesters difficult to make by other routes,[3] and to alkyl alkenyl and aryl phosphinates useful as herbicide intermediates.[4]

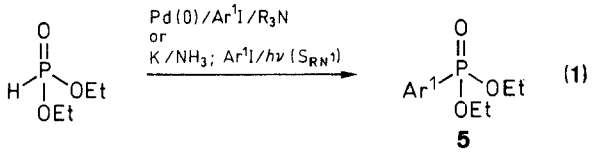
Phosphinic acid esters are generally prepared by esterification of the phosphinic acids with trialkyl phosphite[5] or other reagents,[6] by alcoholysis of an aryl or alkyldichlorophosphine,[5] or by Raney nickel reduction of a phosphonothioate.[7]

An aryl group bound to phosphorus is usually derived ultimately from a Grignard reagent or similar organometallic, or by aluminum chloride catalyzed reaction at high temperature.[8] In addition, alkylphosphinic acids may be derived from phosphinic acid by radical addition to alkenes,[9] or from addition of phosphinic acid to a ketone[10] or imine.[11] These routes are particularly limited by the functional groups compatible with the transformations, so that the phosphinate routes to compounds mentioned above have seen little use because complex phosphinates are unavailable.

The related arylphosphonic acid diesters **5** may be prepared from aryl iodides and diethyl phosphonates by an

Table. Arylphosphinates Prepared From Aryl Iodides and Methyl Phosphinate

Product		Method	Yield (%)	J_{PH} (Hz) of POMe group
	**2a**	A	80	12.0
	**2b**	A	63	12.0
	**2c**	A	69	11.9
	**2d**	A	42	12.1
	**2e**	A	23 (NMR yield)	12.0
	**2f**	A	44	12.3
	**3a**	B	55	11.1
	**3b**	B	49	11.1
	**3c**	B	59	11.2
	**3d**	C	51	11.2
	**3e**	C	44	11.2

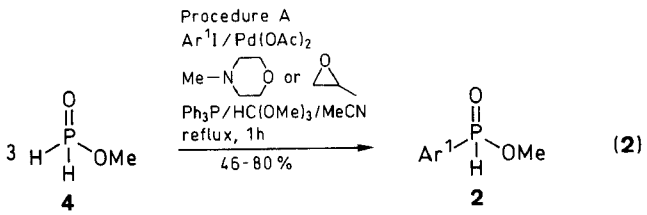


(1)

$S_{RN}1$ process[12] or by a palladium catalyzed route from the same precursors.[13] This latter route has been shown to be compatible with functional groups present in peptides, and to not cause their epimerization.[14] A variety of similar palladium catalyzed reactions are known, wherein a halide or triflate is formally displaced by a nucleophile.[15–18] Phosphorus nucleophiles compatible with the process include: esters of alkyl[4,19] and phenyl[1] phosphinic acids, alkyl phenyl phosphine oxides,[20,21] triphenylphosphine,[22] as well as the aforementioned phosphonate esters.[13,14,23,24] Stereochemistry at the phosphorus is retained in these displacements.[25–27] Intramolecular variants are known.[28,29]

A palladium catalyzed cross coupling of methyl phosphinate **4** (the methyl ester of hypophosphorous acid) with an aryl iodide could, in principle, provide the desired methyl monoarylphosphinates. However, there were several reasons this might not work. Phosphinic acid, a more powerful reducing agent than phosphonic acid, is known to reduce active aryl halides to arenes.[30] Phosphinate salts, in the presence of transition metal catalysts, are known to reduce ketones, nitriles and nitro groups with antipodal selectivity depending on the catalyst.[31] Even diethyl phosphonate, known to couple with vinyl bromides under palladium catalysis,[13] readily reduces vinylidene bromides to monobromides.[32] The major problem, however, is that methyl phosphinate rapidly decomposes at the temperatures used for palladium catalyzed coupling reactions.

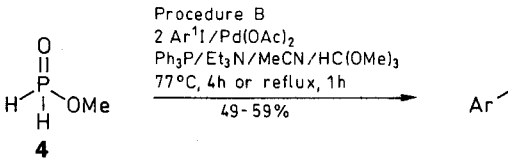
Methyl phosphinate **4** may be readily prepared[33] by treatment of anhydrous phosphinic (hypophosphorus) acid with trimethyl orthoformate, though phosphinate esters of more complex alcohols have been successfully prepared only recently.[34] In contrast to the stability of phosphonate esters, neat methyl phosphinate has been reported to thermally decompose even at 0 °C.[33] We find, however, that trimethyl orthoformate solutions are relatively stable at room temperature for days.[35] The extreme hydrolytic sensitivity of this material dictates that carefully dried reagents must be used, along with the exclusion of air.



(2)

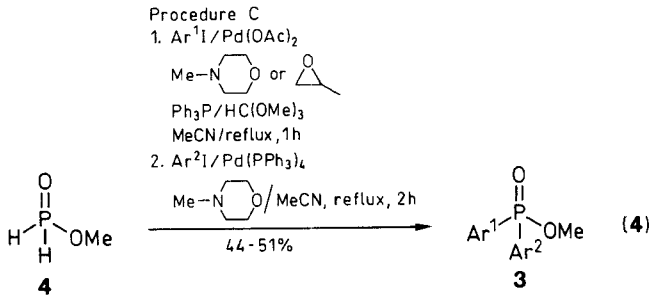
We have found that even though methyl phosphinate rapidly decomposes, methyl arylphosphinates may be prepared under certain conditions. Our procedure A conveniently converts aryl iodides to methyl monoarylphosphinates: A solution of 3 equivalents methyl phosphinate in trimethyl orthoformate is added to a mixture of the aryl iodide, acid scavenger (usually tertiary amine, propylene oxide was used in some of the later reactions, see below), and palladium catalyst (2–5% Pd based on aryl iodide) in acetonitrile. The reaction generally takes 1 hour at reflux. Longer reaction times are useless as methyl phosphinate is completely decomposed at this temperature, even in the absence of other components.

If symmetrical diarylphosphinates are desired, procedure B most conveniently will provide these.



(3)

Simply by reducing the amount of methyl phosphinate to close to a stoichiometric amount, (0.5–0.7 equivalents) allows further substitution of the first formed monoarylphosphinic acid derivative. Dissimilar aryl substituents are most easily installed by procedure C, a sequential process without isolation of the monoaryl derivative. In procedure C, procedure A is followed to install the first aryl substituent, the excess methyl phosphinate is removed by filtration through silica gel or aqueous extraction, and the crude material is allowed to react with the second aryl iodide.



(4)

These procedures are compatible with quite a variety of functional groups, as can be seen in the Table. In addition, nitriles, alcohols, and formate esters are apparently compatible, as acetonitrile is the usual solvent, and methanol and methyl formate, coproducts of methylphosphinate formation, do not affect the reaction. Lower yields of methyl monoarylphosphinates isolated in the more polar cases are a consequence of the lability of these esters on silica gel. Two dimensional TLC confirms that these esters decompose to slowly migrating species (the acids) on standing on silica gel. The methyl diarylphosphinates are quite stable. The poor yield of the *p*-iodonitrobenzene reactions may be due to partial reduction of the nitro group competing with the desired reaction,[31] though we have not attempted to isolate side products.

Ketones may not be compatible with our reaction conditions as they readily react, both with methyl phosphinate[36] and with product methyl arylphosphinates. In fact, the ^{1}H NMR spectrum of crude product from subjection

of a 1 : 1 iodotoluene/acetone mixture to procedure A (propylene oxide version) appeared equivalent to that of reactions run in the absence of acetone. This aspect was not pursued further.

We have fixed upon a convenient standard set of conditions for these reactions, but our experience in the delineation of this set encourages us to mention which are the critical variables. First, the hydrolytic sensitivity of methyl phosphinates requires scrupulously anhydrous conditions and exclusion of air. One reason this is important is that hypophosphorous acid, the hydrolysis product of methyl phosphinate, appears to modify the reaction such that aryl iodide is consumed without formation of P–C bonds. We have isolated deiodinated protected phenylalanine from a reaction that gave a low yield of **3c**. We also note that Pd(0) catalyzed reaction of *o*-dibromobenzene with diethyl phosphonate has been similarly reported to give diethyl phenylphosphonate.[13] Addition of one equivalent (based on iodide) of water to our reaction mixture decreased the yield of methyl (4-methylphenyl)phosphinate **(2a)** from 80% to 13% even though a twofold excess of methyl phosphinate remained for reaction. Most of the reactions reported in this paper were carried out using 4-methylmorpholine or triethylamine as bases to neutralize the hydrogen iodide (HI) formed, and presumably to deprotonate the phosphinate to increase its reactivity. All previously reported cross-coupling reactions of PH bonded substances with aryl halides use amine bases. We have recently noted that propylene oxide may be substituted for the amine in the preparation of either the monoaryl or the diarylphosphinates with good result. The HI is scavenged sufficiently that *t*-Boc protecting groups are not cleaved, and base is seen not to be required for the reaction. The major operational advantage of this modification is that the need for anhydrous conditions is lessened because in the absence of base, any free phosphinic acid formed by hydrolysis is reconverted to methyl phosphinate in situ. The superiority of the use of propylene oxide as acid scavenger may be appreciated when the result of addition of three equivalents of water, enough to completely prevent product formation in the amine-mediated reaction, is considered: **2a** is isolated in 77% yield.

Large excesses of methyl phosphinate (10x) are deleterious, perhaps because of catalyst inactivation by phosphinate decomposition products. In any case, large excesses are not required to produce the monoarylphosphinates in preference to the diarylphosphinates; three equivalents are sufficient. The first addition must, therefore, be significantly more rapid than the second.

Attempts to use trimethylsilyl and tributylstannyl esters of hypophosphorous acid led to only trace quantities of the desired phosphinates. Water scavengers such as bis(trimethylsilyl)acetamide or molecular sieves also failed to improve the yields in reactions of the methyl phosphinate.

Solvent appeared not to be a critical variable: toluene, tetrahydrofuran (THF), acetonitrile, and dimethylformamide (DMF) at temperatures from 23 °C to 110 °C all form phosphinate products in 10–20% yield. Removal of the methanol and methyl formate (formed on reaction of trimethyl orthoformate and phosphinic acid) was irrelevant. The concentration, on the other hand, proved critical. At concentrations below 200 mM yields below 20% were always obtained.

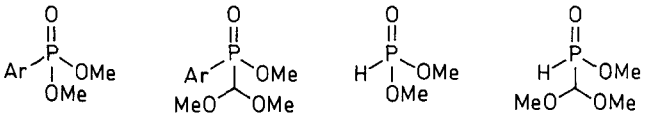
A temperature dependence study of iodotoluene reaction, carried out in deuterated acetonitrile and followed by NMR, showed that at low temperatures, while the methyl phosphinate decomposition is slow, the desired reaction with iodotoluene is slower still. At 70–82 °C, the desired reaction proceeds rapidly, and high yields of monoarylphosphinate product may be obtained, even though the decomposition of methyl phosphinate itself is quite rapid at these temperatures. The rapidity of the coupling reaction of methyl phosphinate, necessary for reasonable yields, is significantly greater than that of dimethyl phosphonate (dimethyl phosphite) and other PH compounds. Dimethyl phosphonate may be observed by NMR as a byproduct of methyl phosphinate decomposition, but under normal circumstances does not couple with aryl iodide. Addition of more protected (iodophenyl)alanine to a reaction mixture after coupling, and prolonged heating, led to formation of the arylphosphonate product, demonstrating that the dimethyl phosphonate is capable of reaction, but does not effectively compete with phosphinate.

A 4 : 1 ratio of triphenylphosphine: palladium(II) acetate [$Pd(OAc)_2$] appears to have the same catalytic behavior as preformed tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] in the same amount (and to be more effective than a 1 : 1, 2 : 1, or 6 : 1 ratio of phosphine to palladium). A series of other phosphines was also screened, and none were significantly more reactive than triphenylphosphine, though 1,3-bis(diphenylphosphino)propane appeared slightly more active at room temperature. Enhanced reactivity with this phosphine would be expected if oxidative addition of palladium to aryl iodide were rate determining.[37,38] There is also a scale effect: better yields are obtained at larger scale. Possibly this is another manifestation of the water sensitivity of the intermediates. We have found the preformed complex bis(triphenylphosphine)dichloropalladium(II) [$(Ph_3P)_2PdCl_2$] to be effective as well. With this catalyst we do not need extra phosphine.

Aryl bromides and triflates react similarly to, though more slowly than, iodides in most of the palladium catalyzed processes referred to above. We have been unable, however, to obtain arylphosphinate products from the reaction of methyl phosphinate with aryl bromides or triflates. Presumably that is because the competitive decomposition of the methyl phosphinate does not allow product formation, and not because of a fundamental difference in mechanism. Curran has recently demonstrated that palladium(0) functions as a radical initiator in reactions of α-iodoketones.[39] Aryl radicals are involved in cross-couplings of certain vinyl stannanes and aryl iodides,[40] a transformation which can also be catalyzed by palladium(0).[18,41] Phosphonyl radicals are also capable of addition to aromatic rings.[42] In order to rule out similar processes involving aryl or phosphinyl radicals in

the formation of aryl phosphinates, we allowed *p*-iodotoluene and methyl phosphinate to react, replacing the palladium acetate and phosphine with 0.01 equivalents of (phenylazo)triphenylmethane, an initiator known to produce aryl radicals at 80 °C.[43] Under conditions otherwise identical to procedure A, we found no production of aryl phosphinate, but complete destruction of the methyl phosphinate, leaving unreacted iodotoluene. Our very *mildly basic* conditions are in this way quite different from the $S_{RN}1$ conditions of Bunnett.[12]

In cases where reaction has not proceeded rapidly, prolonged reflux has led to other compounds: side products are formed whose ^{1}H NMR spectra are consistent with dimethyl arylphosphonates **6** and methyl (dimethoxymethyl)arylphosphinates **7**. These are presumably derived from dimethyl phosphonate (dimethyl phosphite) **8** and methyl (dimethoxymethyl)phosphinate **9**, respectively. Compound **8** is a thermal decomposition product of methyl phosphinate, and compound **9** is a side product in its preparation.[35] Compounds **8** and **9** must form and cross-couple with aryl iodides more slowly than does methyl phosphinate because these side products are not usually observed.



6 **7** **8** **9**

Identification of phosphinate products is simplified by their characteristic ^{1}H NMR spectral signals. Methyl arylphosphinates **2** may be recognized by their P-H signals at $\delta = 7.4-7.1$ ($J_{PH} = 550-633$ Hz). In addition, we have noted that the hydrogens of the methoxy bound to phosphorus demonstrate a 12 Hz coupling constant (to P) in **2**, the monoaryl cases, in contrast to the 11 Hz coupling constant we observe in the diaryl cases **3**.

In conclusion, we have developed a convenient route to a wide variety of phosphinates. Our route is compatible with functionality not stable to other procedures. Application of this method to the synthesis of candidate binding sites is in progress.

^{1}H NMR spectra were obtained at 300 MHz on a Nicolet NT-300 or a Varian VXR-300, and ^{13}C NMR spectra at 75 MHz on the same instruments; chemical shifts are reported relative to TMS, coupling constants (J) in Hz. ^{13}C NMR spectra are ^{1}H decoupled; the coupling constants reported are for doublets due to ^{31}P. High resolution EI mass spectra were obtained on a Kratos MS 50, CI mass spectra on a Finnegan 4000. In some cases a significant M-H peak was observed, in which cases it was used for calculation of the molecular mass because of isotopic interference with the M peak. In those cases, low resolution CI MS (NH_3) always gave the correct M + H and M + NH_4 peaks. Flash chromatography was carried out as described.[44] MeCN used for reactions (not chromatography) was freshly distilled from P_4O_{10}. 4-methylmorpholine and Et_3N were distilled from CaH_2. Other materials were used as received for Aldrich, except for drying in vacuo. (Iodophenyl)alanine was obtained from Serva, and protected by standard procedures.[45] Glassware was predried at > 80 °C and allowed to cool unter N_2 flow or vacuum. Elemental analyses were performed by Galbraith Labs.

Procedure A. Methyl 4-Methylphenylphosphinate (2a); Typical Procedure:

A solution of methyl phosphinate in $HC(OMe_3)$ was prepared by the method of Fitch.[33] Anhydrous crystalline phosphinic acid, prepared by rotary evaporation of 50% aq H_3PO_2[33] (52 mg, 7.9×10^{-4} mol), was allowed to react with $HC(OMe)_3$ (490 mg, 4.6×10^{-3} mol), in a pressure equalizing funnel at 23 °C under N_2 for 1 h. This methyl phosphinate solution was added to a solution of *p*-iodotoluene (65.2 mg, 2.99×10^{-4} mol), 4-methylmorpholine (30 mg, 3.0×10^{-4} mol), $Pd(OAc)_2$ (3.4 mg, 1.5×10^{-5} mol), and Ph_3P (15.7 mg, 6.0×10^{-5} mol) in MeCN (1.5 mL). This yellow solution was refluxed under N_2 for 1 h, cooled to r. t., and the solvent removed at reduced pressure. The dark brown residue was triturated with EtOAc, the EtOAc filtered, and the solvent removed at reduced pressure. The resulting yellow oil was purified by flash chromatography (MeCN) to yield 40.8 mg (80%) **2a** as a colorless oil. This compound has been reported, but not spectroscopically characterized.[46]

^{1}H NMR ($CDCl_3$): $\delta = 7.54$ (d, $J = 564.1$, 1 H), 7.67 (dd, $J = 8.0$, 13.6, 2 H), 7.33 (dd, $J = 3.1$, 7.9, 2 H), 3.78 (d, $J = 12.0$, 3 H), 2.43 (s, 3 H).

^{13}C NMR ($CDCl_3$): $\delta = 143.89$, 130.95 ($J = 12.0$), 129.49 ($J = 14.2$), 126.06 ($J = 13.40$), 51.48 ($J = 7.1$), 21.75.

IR (neat): $\nu = 2341$, 1603, 1234, 959, 791 cm^{-1}.

HRMS: m/z, $C_8H_{11}O_2P$, calc.: 170.04967 (M^+), found: 170.04935.

Methyl Phenylphosphinate (**2b**):

Procedure A was followed, starting with iodobenzene (61 mg, 2.99×10^{-4} mol). Flash chromatography (MeCN) yielded 29.3 mg (63%) **2b** as a colorless oil. This material was identical by TLC, IR and ^{1}H NMR to an authentic sample prepared by treatment of $PhPCl_2$ with MeOH.[5]

^{1}H NMR ($CDCl_3$): $\delta = 7.56$ (d, $J = 565.5$, 1 H), 7.79 (dd, $J = 13.8$, 10.4, 2 H), 7.63–7.52 (m, 3 H, 6 distinguishable peaks all match authentic spectrum), 3.80 (d, $J = 12.0$, 3 H).

IR (neat): $\nu = 2351$, 1593, 1231, 1042, 997, 798 cm^{-1}.

Methyl 4-Phenylphenylphosphinate (**2c**):

The propylene oxide modification of procedure was followed; starting with 4-iodobiphenyl (1.48 g, 5.28×10^{-3} mol) and propylene oxide (3.70 mL, 5.3×10^{-3} mol) instead of 4-methylmorpholine. Flash chromatography (EtOAc) and recrystallization from EtOAc/hexane gave **2c** (840 mg, 69%). mp 55–56 °C.

^{1}H NMR ($CDCl_3$): $\delta = 7.61$, (d, $J = 566.5$, 1 H), 7.89–7.40 (m, 9 H), 3.83 (d, $J = 11.9$, 3 H).

^{13}C NMR ($CDCl_3$): $\delta = 146.08$, 139,73, 131.52 ($J = 12.6$), 128.98, 128,35, 127.85 ($J = 133.0$), 127.49 ($J = 14.1$), 127.31, 52.12 ($J = 6.6$).

IR (neat): $\nu = 2359$, 1242, 1038, 962, 797 cm^{-1}.

HRMS: *m/z*, $C_{13}H_{13}O_2$, calc.: 232.06532 (M^+), found: 232.06543.

Methyl 4-Hydroxyphenylphosphinate (**2d**):

Procedure A was followed, starting with *p*-iodophenol (82.3 mg, 3.74×10^{-4} mol). Flash chromatography (MeCN) gave 29.3 mg (46%) **2d** as a colorless oil. This material was ca. 95% pure. Repeated chromatography gave less pure material as the desired product decomposed, but was not well separated from an impurity.

^{1}H NMR ($CDCl_3$): $\delta = 9.50$ (s, 1 H), 7.54 (d, $J = 569.7$, 1 H), 7.61 (dd, $J = 8.5$, 13.5, 2 H), 7.04 (dd, $J = 2.8$, 8.5, 2 H), 3.78 (d, $J = 12.1$, 3 H).

^{13}C NMR ($CDCl_3$): $\delta = 162.41$ ($J = 3.0$), 133.15 ($J = 13.6$), 116.41 ($J = 15.2$), 52.7 ($J = 6.6$).

IR (neat): $\nu = 3123$, 2380, 1603, 1290, 1200, 1076, 962 cm^{-1}.

MS CI (NH_3): $m/z = (M + H, M + NH_4)$ 173, 190.

HRMS: *m/z*, $C_7H_8O_3P$, calc.: 171.02111 ($M - H^+$), found: 171.02093.

Methyl 2-(Methoxycarbonyl)phenylphosphinate (**2f**):

Procedure A was followed starting with methyl *o*-iodobenzoate (92.4 mg, 3.53×10^{-4} mol). Crude product was purified by flash chromatography (4 : 1 $MeCN/CH_2Cl_2$) to yield 37.2 mg **2f** as a colorless oil (46%).

^{1}H NMR ($CDCl_3$): δ = 8.27–7.64 (m, 4H), 8.04, (d, J = 616.8, 1H), 3.97 (s, 3H), 3.84 (d, J = 12.3, 3H).

^{13}C ($CDCl_3$): δ = 166.63, 133.76 (J = 7.6), 132.70 (J = 2.6), 132,53 (J = 12.1), 130.90 (J = 9.1), 130.58 (J = 14.6), 53.11 (J = 6.0), 52.73.

IR (neat): ν = 2407, 1726, 1223, 1038, 1007, 797 cm^{-1}.

MS CI (NH_3): m/z = (M + H, M + NH_4) 215, 232.

HRMS: m/z, $C_9H_{10}O_4P$, calc.: 213.03167 (M-H$^+$), found: 213.03167.

Procedure B. Methyl Bis{4-[2-(*tert*-butoxycarbonylamino)-2-(methoxycarbonyl)ethyl]phenyl}phosphinate (3c); Typical Procedure:

Phosphinic acid (9.1 mg, 1.38×10^{-4} mol) and $HC(OMe)_3$ (73 mg, 6.88×10^{-4} mol) were allowed to stand under N_2 for 1 h to form methyl phosphinate as described for procedure A.

(*S*)-*N*-*t*-Boc-*p*-iodophenylalanine methyl ester (79.7 mg, 1.9×10^{-4} mol), Ph_3P (4.0 mg, 1.52×10^{-5} mol), Pd(OAc) (9 mg, 3.8×10^{-6} mol), Et_3N (20 mg, 2.0×10^{-4} mol) were placed and sealed under N_2 in a 3 mL vial containing MeCN (450 μL) freshly distilled from P_4O_{10}. Methyl phosphinate solution was added by syringe. The yellow mixture was then heated in an oil bath at 77°C for 4 h. Solvent was removed from the dark brown solution at reduced pressure, and the residue was purified by flash chromatography (EtOAc) to yield 35.6 mg **3c** (59%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ = 7.73 (dd, J = 8.1, 12.0, 4H), 7.24 (dd, J = 22.7, 8.1, 4H), 5.02–5.00 (m, 2H), 4.61–4.59 (m, 2H), 3.74 (d, J = 11.1, 3H), 3.71 (s, 6H), 3.22–3.00 (m, 4H), 1.40 (s, 18H).

^{13}C NMR ($CDCl_3$): δ = 171.85, 154.91, 140.85, 131.83 (J = 8.2), 129.58 (J = 13.5), 129.55 (J = 137.51), 80.08, 54.14, 52.35, 51.52 (J = 6.8), 38.39, 28.26.

IR (neat): ν = 3369, 1745, 1713, 1221, 1020 cm^{-1}.

HRMS: m/z, $C_{31}H_{43}N_2O_{10}P$, calc.: 634.26554 (M$^+$), found: 634.26649.

Methyl Bis(4-methylphenyl)phosphinate (**3a**):

A modified procedure B was followed, starting with phosphinic acid (5.2 mg, 8.97×10^{-4} mol), *p*-iodotoluene (391.2 mg, 1.79×10^{-3} mol), Ph_3P (16.9 mg, 6.44×10^{-5} mol), $Pd(OAc)_2$ (3.6 mg, 1.61×10^{-5} mol) and Et_3N (163 mg, 1.61×10^{-3} mol) using the glassware described in procedure A. After 1 h of reflux, the solvent was removed at reduced pressure. The residue was dissolved in EtOAc, washed with sat. NaCl, and dried ($MgSO_4$). After removal of solvent at reduced pressure, crude product was purified by flash chromatography (EtOAc/hexane 85 : 5) to yield 25.8 mg **3a** (55%).

^{1}H NMR and IR spectra match literature values,[47] but are reported here to greater precision, along with ^{13}C NMR data.

^{1}H NMR ($CDCl_3$): δ = 7.69 (dd, J = 8.1, 12.3, 4H), 7.25 (dd, J = 3.6, 8.1, 4H), 3.73 (d, J = 11.1, 3H), 2.37 (s, 6H).

^{13}C NMR ($CDCl_3$): δ = 142.55 (J = 2.5), 131.57 (J = 10.6), 129.20 (J = 13.7), 127.93 (J = 139.5), 51.30 (J = 6.0), 21.54 (J = 1.1).

IR (neat): ν = 1605, 1231, 1036, 928, 810.

Methyl Diphenylphosphinate (**3b**):

Procedure B was followed, starting with iodobenzene (204 mg, 1.00×10^{-3} mol). Product was purified by flash chromatography (EtOAc/hexane, 4 : 1) to yield 56.8 mg (49%) **3b** as a white crystalline material, mp 56°C (Lit.[47] 57°C), identical by TLC, ^{1}H NMR, and IR to an authentic sample prepared from diphenylphosphinyl chloride and MeOH.[47]

^{1}H NMR ($CDCl_3$): δ = 7.83–7.45 (m, 10H), 3.77 (d, J = 11.1, 3H).

^{13}C NMR ($CDCl_3$): δ = 132.13, 131.58 (J = 10.0), 130.95 (J = 138.2), 128.46 (J = 13.2), 51.48 (J = 6.5).

IR (neat): ν = 1591, 1437, 1229, 1024, 797 cm^{-1}.

Procedure C. Methyl (4-Methylphenyl)-(4-phenylphenyl)phosphinate (3d); Typical Procedure:

Procedure A was followed, using *p*-iodobiphenyl (84 mg, 3.0×10^{-4} mol), except that the monoaryl phosphinate was not isolated. The reaction mixture was filtered through silica gel to remove methyl phosphinate and its decomposition products, and volatile material removed at reduced pressure. This crude product was treated with $Pd(PPh_3)_4$ (10.4 mg, 9×10^{-6} mol), *p*-iodotoluene (65.4 mg, 3×10^{-4} mol) and 4-methylmorpholine (30 μl, 3×10^{-4} mol) in freshly distilled MeCN (2 mL). The resulting solution was refluxed for 2 h under N_2. The yellow mixture was evaporated and purified by flash chromatography (EtOAc/hexane 8 : 3) to yield 49.3 mg of **3d** (51%). This material was identical to that prepared by the reverse order of reaction (first iodotoluene, then iodobiphenyl) with isolation of the intermediate monoarylphosphinate. Yield over those two steps: 50%.

^{1}H NMR ($CDCl_3$): δ = 7.90–7.27 (m, 13H), 3.78, (d, J = 11.2, 3H), 2.39 (s, 3H).

^{13}C NMR ($CDCl_3$): δ = 144.85 (d, J = 3.1), 142.81 (J = 3.9), 139.95, 132.09 (J = 10.1), 131.72 (J = 10.6), 129.94 (J = 139.0), 129.36 (J = 13.7), 128.90, 128.10, 127.76 (J = 140), 127.24, 127.21 (J = 13.1), 51.48 (J = 6.1), 21.63 (J = 1.0).

IR (neat): ν = 1601, 1229, 1032, 791 cm^{-1}.

HRMS: m/z, $C_{20}H_{19}O_2P$, calc.: 322.11227 (M$^+$), found: 322.11163.

$C_{20}H_{19}O_2P$	calc.	C 74.51	H 5.90
(322.3)	found	74.69	5.99

Methyl {4-[2(tert-Butoxycarbonylamino)-2-(methoxycarbonyl)-ethyl]phenyl}[4-(ethoxycarbonyl)phenyl]phosphinate (**3e**):

Procedure C was followed starting with (*S*)-*N*-*t*-Boc-*p*-iodophenylalanine methyl ester (125.3 mg, 2.99×10^{-4} mol) with a 2 h reflux in step-one. The crude monoarylphosphinate in MeCN (2 mL) was treated with ethyl 4-iodobenzoate (82.8 mg, 3×10^{-4} mol), and other reagents as described. Flash chromatography (EtOAc) gave 66.3 mg **3e** (44%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ = 8.11 (dd, J = 3.3, 8.3, 2H), 7.88 (dd, J = 8.2, 11.8, 2H), 7.74 (dd, J = 8.0, 12.1, 2H), 7.26 (dd, J = 5.2, 11.9, 2H), 5.07–5.04 (m, 2H), 4.61–4.58 (m, 1H), 4.39 (q, J = 7.1, 2H), 3.78 (d, J = 11.2, 3H), 3.71 (s, 3H), 3.17–3.06 (m, 2H), 1.39 (t, J = 7.0, 3H), 1.38 (s, 9H).

^{13}C NMR ($CDCl_3$): δ = 171.89, 165.71, 154.95, 141.30, (J = 2.0), 135.73 (J = 134.9), 133.78 (J = 2.5), 131.88 (J = 10.1), 131.67 (J = 10.1), 129.86 (J = 138.0), 129.78 (J = 13.6), 129.52 (J = 13.1), 80.13, 61.46, 54.14, 52.40, 51.74 (J = 6.0), 38.44, 28.24, 14.28.

IR (neat): ν = 3267, 2980, 1720 (b), 1605, 1223, 1034, 798 cm^{-1}.

HRMS: m/z, $C_{25}H_{32}NO_8P$, calc.: 505.18656 (M$^+$), found: 505.18654.

Methyl Bis(4-nitrophenyl)phosphinate (**3f**):

Procedure A was followed in an attempt to prepare methyl 4-nitrophenylphosphinate (**2e**) starting with *p*-iodonitrobenzene (93.1 mg, 3.74×10^{-4} mol). Product was formed in 23% yield, calculated on the basis of NMR integration (internal standard: 1,3,5-trimethoxybenzene). **2e** decomposed on silica gel and was not isolated in pure form.

^{1}H NMR ($CDCl_3$): δ = 8.38 (dd, J = 2.4, 8.7, 2H), 8.01 (dd, J = 8.7, 12.8, 2H), 7.65 (d, J = 577.5, 1H), 3.87 (d, J = 12.0, 3H).

IR (neat): ν = 2381, 1601, 1524, 1350, 1231, 1030, 995, 856, 797.

Procedure B was followed, starting with *p*-nitroiodobenzene (335 mg, 1.35×10^{-3} mol). The product was purified by flash chromatography (EtOAc/hexanes, 4 : 1), yielding 11.4 mg **3f** as colorless oil (5%).

^{1}H NMR ($CDCl_3$): δ = 8.34 (dd, J = 2.7, 9.0, 4H), 8.03 (dd, J = 9.0, 11.4, 4H), 3.88 (d, J = 11.1, 3H).

^{13}C NMR ($CDCl_3$): δ = 145.13, 137.01 (J = 136.0), 133.06 (J = 11.1), 123.88 (J = 13.6), 52.46 (J = 6.0).

IR (neat): ν = 1524, 1350, 1236, 1034, 850, 800 cm^{-1}.

HRMS: m/z, $C_{13}H_{11}N_2O_6P$, calc.: 322.0355 (M$^+$), found: 322.0348.

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