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A synthesis of sulfonamide analogs of platensimycin employing a palladium-mediated carbonylation strategy

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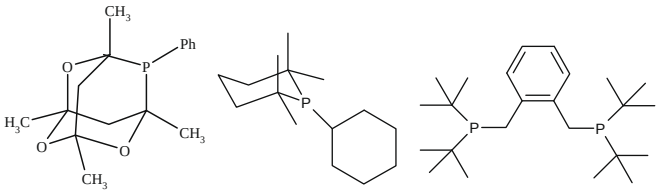
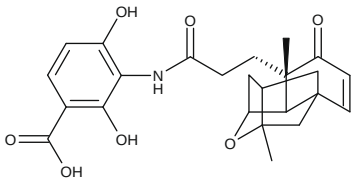
ABSTRACT

The monodentate ligand 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane (PA-Ph) is shown to be highly effective in palladium-catalyzed carbonylative cross-coupling. Aryl and vinyl halides were efficiently converted to carboxylic acids, amides and to primary, secondary, and tertiary esters, respectively. Application of the $Pd(OAc)_2$/PA-Ph (1:1) catalyst system proved critical in the methoxycarbonylation of a functionalized nitroresorcinol halide, allowing convenient access to novel platensimycin sulfonamide analogs.

Organopalladium cross-coupling reactions are among the most selective and reliable methods for carbon–carbon bond formation.[1] Palladium-catalyzed carbonylation is a useful, atom-economical method for the selective introduction of the carbonyl group,[2] making carboxylic acids, esters, and amides readily accessible from aryl, vinyl, and aliphatic halides (or halide equivalents) and olefins. These reactions, originally established in the mid-70s by the pioneering work of Heck and co-workers,[3] have found a number of synthetic applications[4] and have been utilized industrially.[5] Our group has been involved in the development of hindered tertiary phosphines and active catalytic systems for palladium-catalyzed cross-coupling reactions,[6,7] including the use of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane (PA-Ph) **1**,[6a–e] phosphorinanes[6f] such as **2** and more recently the bidentate bis(di-*tert*-butylphosphino)-*o*-xylene (dtbpx) **3**.[6g] Bulky, electron-rich phosphines benefit both oxidative addition and reductive elimination steps in cross-coupling reactions.[8] A catalytic system incorporating $Pd_2(dba)_3{\cdot}CHCl_3$ and PA-Ph was shown to promote Suzuki cross-coupling of aryl iodides, bromides, and chlorides with a variety of aryl boronic acids under mild conditions in solution[6a] and on a solid-phase platform.[6b] In addition, efficient amination, Sonogashira and ketone arylation reactions of aryl halides were demonstrated,[6c,d] while a $Pd(OAc)_2$/PA-Ph **1** catalyst system facilitated Suzuki-type couplings of alkyl halides and tosylates containing β-hydrogens with either boronic acids or alkylboranes.[6e] The activities for the Pd–PA-Ph system rival some of the more common mono- and bidentate phosphine ligands which have been successfully used in palladium-catalyzed formation of C–N, C–O, and C–C bonds.[9] In this Letter, we report on the extension of these studies using the palladium–PA-Ph system to carbonylative cross-coupling and a direct application toward the synthesis of the platensimycin aromatic core.



PA-Ph **1** phosphorinane **2** dtbpx **3**



Platensimycin **4**

In conjunction with our work on the synthesis of bioactive compounds,[10] we became interested in the potent antibiotic platensimycin **4**, recently discovered by researchers at Merck,[11] as a viable candidate for the application of our carbonylation methodology. Platensimycin contains a tetracyclic enone unit attached via amide linkage to an aminoresorcylic acid core. The structure represents a new class of antibiotic isolated from cultures of *Streptomyces platensis* exhibiting potent, broad-spectrum Gram-positive antibacterial activity manifested via selective inhibition of cellular lipid biosynthesis.[11] In view of its mode of action, platensimycin shows no cross-resistance to other key antibiotic-resistant strains, making

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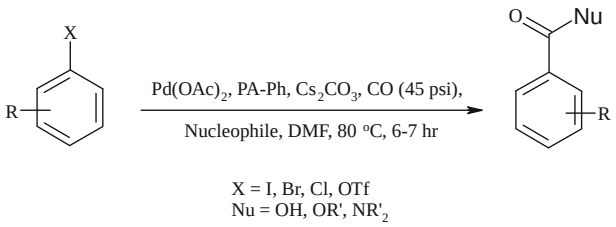
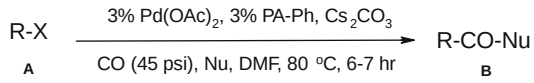


Scheme 1. Carbonylation with $Pd(OAc)_2$/PA-Ph catalyst system.

it a highly privileged lead for drug design and biological evaluation.[12] Herein we detail our findings that palladium complexes of **1** are useful general catalysts for the hydroxy-, alkoxy-, and aminocarbonylation of aryl and vinyl halides. In addition, we describe a novel approach toward the synthesis of the aromatic core of platensimycin **4**. This route installs the carboxylic group using $Pd(OAc)_2$/PA-Ph-catalyzed methoxycarbonylation of a nitroresorcinol halide, leading to functionalized sulfonamide analogs.

The general reaction for carbonylation with the $Pd(OAc)_2$/PA-Ph catalyst system is outlined in Scheme 1. An efficient catalyst system comprising 3% $Pd(OAc)_2$, 3% PA-Ph, 1.5 equiv Cs_2CO_3, 2 equiv methanol, CO (45 psi), and DMF (at 80 °C) was readily identified using 4-iodotoluene as substrate. This initial screen provided butyl (4-methyl)benzoate in 97% isolated yield, after only 6–7 h. With these standard conditions in hand, the scope of the reaction was then rapidly expanded to include a selected series of aryl and vinyl substrates in reaction with a range of nucleophiles (Table 1). With methanol as nucleophile, aryl iodides and bromides, *para*-substituted with either electron-releasing or electron-withdrawing groups gave the corresponding methyl esters in excellent yields (Table 1, entries 1, 2, 5 and 6). Aryl chlorides and triflates suffered from poor conversion to the ester products (Table 1, entries 3 and 4). We and others have made similar observations for these substrates.[6g,7f,13] However, some success has been achieved with carbonylation of aryl chlorides using palladium complexes of 1, 4-bis(diphenylphosphino)- butane(dppb), 1,4-bis(diphenylphosphino)ferrocene (dppf), and 1,4-bis(dicyclohexylphosphino)ferrocene (dcpf),[14] as well as employing more electrophilically activated substrates (such as 4-chloroacetophenone) in conjunction with alcohols of low nucleophilicity, such as 2,2,2-trifluoroethanol.[13] As far as *ortho*-steric effects are concerned, these were

Table 1
PA-Ph-mediated carbonylative cross-coupling



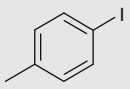
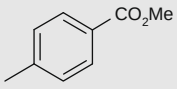
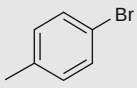
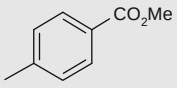
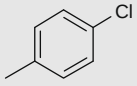
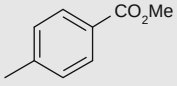
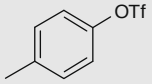
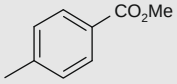
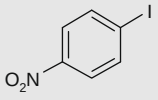
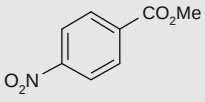
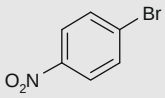
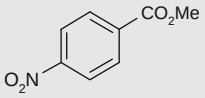
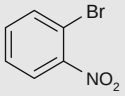
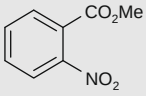
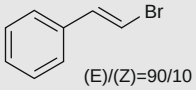
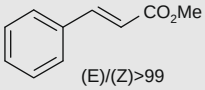
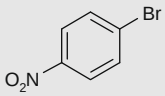
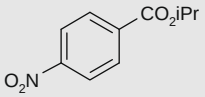
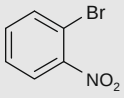
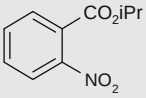
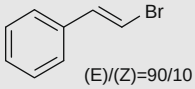
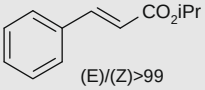
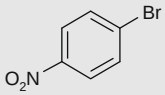
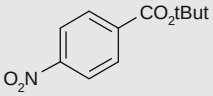
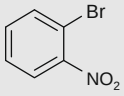
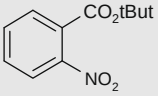
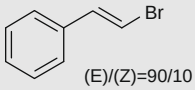
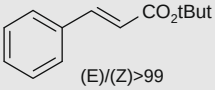
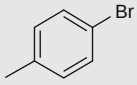
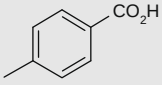
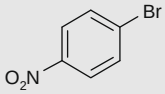
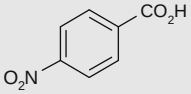
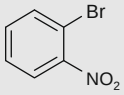
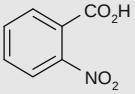
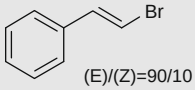
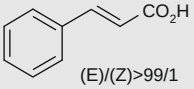
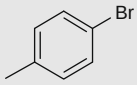
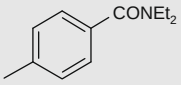
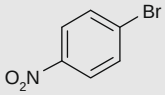
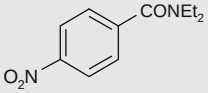
Entry	R–X	Nu	Product B	Isolated yield of B (%)
1		MeOH		97
2		MeOH		85
3		MeOH		30
4		MeOH		22
5		MeOH		98
6		MeOH		94
7		MeOH		81
8	 (E)/(Z)=90/10	MeOH	 (E)/(Z)>99	83
9		*i*-PrOH		70

Table 1 (*continued*)

Entry	R–X	Nu	Product B	Isolated yield of B (%)
10		*i*-PrOH		66
11		*i*-PrOH		67
12		*t*-BuOH		40
13		*t*-BuOH		38
14		*t*-BuOH		35
15		H_2O		74
16		H_2O		86
17		H_2O		77
18		H_2O		75
19		$NHEt_2$		83
20		$NHEt_2$		84

seen to be minimal (Table 1, entry 7), while vinyl substrates (e.g., β-bromostyrene) were converted to the corresponding α,β-unsaturated ester (Table 1, entry 8) with complete (*E*)-geometry in 83% isolated yield. A pronounced steric effect of the nucleophile was observed in going from methanol to *i*-PrOH to *t*-BuOH which caused a decrease in yield as the bulk of the alcohol increased (e.g., compare Table 1, entries 6, 9, and 12). Hydroxycarbonylation was easily facilitated with both aryl and vinyl halides giving carboxylic acids in 74–86% isolated yield. Electronic and steric effects again appear to be minimal (entries 15–18). The use of a secondary amine as incoming nucleophile was also demonstrated in the conversion of aryl bromide substrates to the corresponding diethylamides (Table 1, entries 19 and 20).

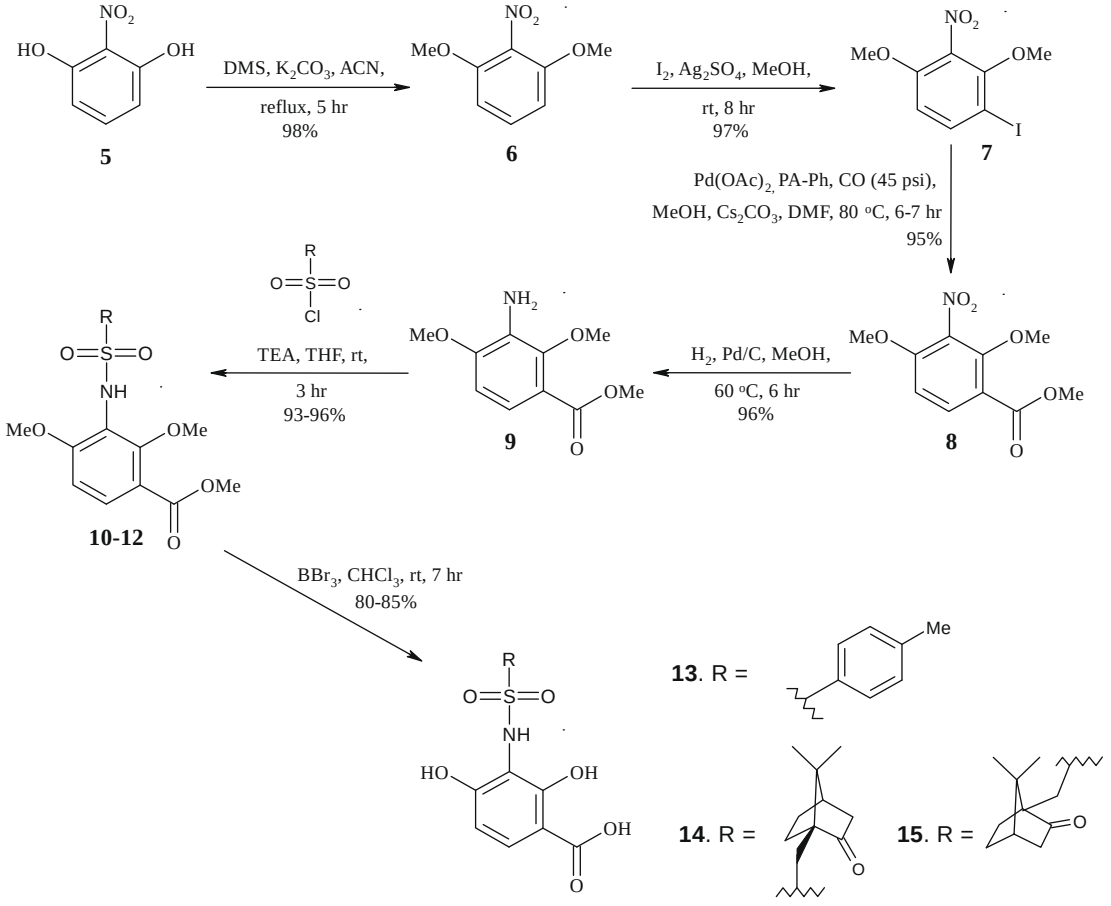
Returning to platensimycin **4**, we were interested in the synthesis of structural mimics incorporating the natural aromatic core but replacing the bulky tetracyclic enone residue with a lipophilic

sulfonamide moiety. Sulfonamides represent a classic component of antibiotics,[15] and related FAB inhibitors incorporating aryl sulfonamide residues have also been recently reported.[15b] This functional group provides hydrolytic stability under both chemical and biological conditions. Our overall approach to the synthesis of these derivatives is outlined in Scheme 2.

The base-catalyzed double methylation of commercially available 2-nitroresorcinol **5** with dimethylsulfate (DMS) gave nitrodimethylether **6** in near quantitative yield. This was smoothly iodinated at room temperature with I_2/Ag_2SO_4 (1:1) in methanol to nitroaryl iodide **7** (97% yield) (Scheme 2). With this intermediate in hand, $Pd(OAc)_2$/PA-Ph catalyzed methoxycarbonylation was successfully carried out under the conditions outlined in Table 1, affording the desired nitroester **8** in 95% isolated yield. [17] We note that the use of several other mono- and bidentate ligands were attempted in this specific alkoxycarbonylation including triphenylphosphine, tri-*tert*-butylphosphine, tricyclohexylphosphine, phosphorinane **2**, dtbpx **3**, dppb, dppf and dcpf. All of these led only to poor conversions to ester product (**7** to **8**). Furthermore, the bromide corresponding to **7** was unreactive under a variety of conditions utilizing the ligands described above, and provided up to ~50% conversion to **8** using the $Pd(OAc)_2$/PA-Ph system. Thus the critical alkoxycarbonylation of **7** to **8** required both the use of the aryl iodide derivative **7** as well as the reactive Pd–PA-Ph catalyst system for efficient turnover. Catalytic reduction of **8** proceeded without event to give amino ester **9** which was subsequently converted to the corresponding sulfonamide ester **10–12**, respectively, in 93–96% yield. Demethylation of both methyl ethers and the methyl ester was achieved in one pot using boron tribromide (3.5 equiv) in chloroform, furnishing the respective sulfonamide acids **13–15** in good overall yields.

To date, four different approaches toward the synthesis of the aminoresorcylic acid core of platensimycin have been published.[12a,16] Nicolaou et al.[12a] utilized a directed *ortho*-metalation (DOM) strategy on the bis-MOM-Boc-protected aminoresorcinol followed by quenching with methyl cyanoformate to install the carboxylate group (in 45% yield over the last two steps in a five-step sequence). In the second procedure,[16a] direct nitration of commercial methyl 2,4-dihydroxybenzoate afforded a (1:1) mixture of 3- and 5-nitro-2,4-dihydroxybenzoates (in 68% isolated yield) which were separated by fractional crystallization and elaborated further to the bis-MOM functionalized aniline. In the third approach,[16b] a Kolbe–Schmitt electrophilic aromatic carboxylation placed the carboxyl group *ortho* to the phenol in several 2-amidoresorcinol substrates, in 15–52% yield. In the most recent approach, the carboxyl group was efficiently introduced (78% yield) to a bis-MOM-protected 2-nitroresorcinol iodide via metal-halogen exchange with PhMgBr and subsequent quenching with methyl cyanoformate.[16c] It is clear from these reports that the palladium-catalyzed carbonylation described herein offers a more concise and efficient route to the aminoresorcylic acid core of platensimycin.

In summary, we have shown that palladium complexes of PA-Ph **1** are highly effective catalysts in the carbonylation of aryl as well as vinyl halide substrates, with the scope of the reaction being limited by aryl chlorides. Application of the $Pd(OAc)_2$/PA-Ph catalyst system to the carbonylation of a functionalized nitroresorcinol iodide allowed for the regioselective introduction of the carboxyl group, leading to the platensimycin aminoresorcylic acid core which was elaborated further to novel sulfonamide analogs. Biological evaluation of these and other targets of interest are presently being actively pursued.



Scheme 2. Methoxycarbonylation as key-step in synthesis of platensimycin sulfonamide analogues.

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17. *Synthesis of methyl (2,4-dimethoxy-3-nitro)benzoate* **8**. 2,4-Dimethoxy-3-nitro-1-iodobenzene **7** (0.300 g, 0.971 mmol), palladium(II) acetate (6.5 mg, 0.0291 mmol), and PA-Ph (8.5 mg, 0.0291 mmol) were added consecutively to a steel reactor in a glove box under nitrogen, followed by 2 ml dry DMF (2 ml/mmol), methanol (80 μl, 1.94 mmol), and Cs_2CO_3 (0.474 g, 1.46 mmol). The reactor was sealed and connected via Swage line to a cylinder of CO. After three purges, the reactor was pressurised to 45 psi, submerged in an oil bath set at 80 °C and stirred via an internal magnet. After ~7 h, TLC (30% EtOAc/Hex) indicated the reaction to be complete. The mixture was diluted with saturated NH_4Cl, extracted with ethyl acetate (3 × 5 ml), the combined organic fractions dried (Na_2SO_4), filtered, and concentrated to an amorphous residue which was chromatographed (30% EtOAc/Hex) on silica to give methyl (2,4-dimethoxy-3-nitro)benzoate **8** (95%). ^1H NMR ($CDCl_3$, 200 MHz); δ (ppm): 8.02 (1H, d, J = 9.0 Hz), 6.81 (1H, d, J = 9.0 Hz), 3.96 (3H, s), 3.94 (3H, s), 3.91 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz); δ (ppm): 164.8, 157.3, 154.9, 134.6, 117.3, 107.4, 106.9, 64.5, 56.9, 52.6.