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Much Improved Conditions for the Negishi Cross-Coupling of Iodoalanine Derived Zinc Reagents with Aryl Halides

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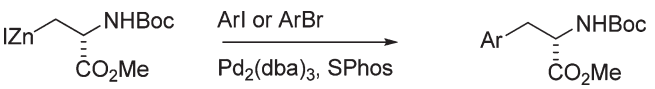
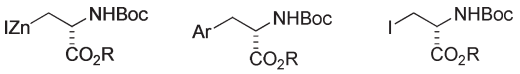
Received October 19, 2009



A combination of $Pd_2(dba)_3$ and SPhos (1:2 molar ratio) is an excellent precatalyst for the Negishi cross-coupling of the serine-derived organozinc reagent **2** with aryl halides, including previously difficult ortho-substituted examples. In the case of meta- and para-substituted aryl halides, Pd-loadings of 0.5 mol % give satisfactory results. Use of 2-iodoaniline as substrate gives the lactam **12** in good yield.

The Negishi cross-coupling of the serine-derived organozinc reagents **1** and **2** with aryl halides under palladium catalysis has proven to be a convenient method for the direct preparation of protected phenylalanine analogues **3** and **4**.[1] Under the original conditions reported (Zn/Cu, ultrasonication, benzene/DMA, $(o\text{-tol}_3P)_2PdCl_2$) yields of the products **3** of cross-coupling with aryl iodides based on iodoalanine **5** were highly variable (10−67%).[2] A substantial increase in yields, especially with ortho-substituted aryl iodides, was achieved in the cross-coupling of zinc reagent **2** with aryl iodides, using a combination of $o\text{-tol}_3P$ and Pd_2dba_3 (in a 4:1 ratio, thus providing a 2:1 ratio of ligand to Pd) as the precatalyst, and using neat DMF as the solvent, together with some modifications to the zinc activation protocol.[3] Under these improved conditions, both yields (40−70%, based on iodoalanine **6**) and reproducibility increased. (An excess of organozinc reagent is often used in Negishi reactions, since the organozinc reagent is generally the less valuable component. In all the work reported here, yields are based on the amount of protected iodoalanine **6**; the yield therefore depends both on the efficiency of formation of the organozinc reagent **2** and the efficiency of the subsequent Negishi reaction.) Use of a combination of $Pd(OAc)_2$ (5 mol %) as palladium source with $o\text{-tol}_3P$ (10 mol %) allowed cross-coupling of aryl bromides in moderate yields, provided the reactions were conducted at 50 °C.[4] However, the yields remain moderate, and moreover the typical palladium loadings required [2.5 mol % of Pd_2dba_3, 5 mol % of $Pd(OAc)_2$] demonstrate that the number of catalytic turnovers prior to organozinc reagent decomposition is modest; furthermore, purification of the protected phenylalanine analogues is complicated by the presence of catalyst residues.

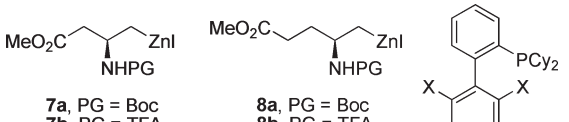


1, R = Bn
2, R = Me

3, R = Bn
4, R = Me

5, R = Bn
6, R = Me

In recent work, the relative reactivity in Negishi cross-coupling reactions of the β-aminoalkyl zinc reagents **7** and **8**, used for the synthesis of protected β- and γ-amino acids, has been studied.[5] The conclusion was that the major factor influencing reactivity is the position of the ester group: the closer the ester function to the carbon−zinc bond, the less reactive the reagent. In accordance with this trend, the pseudo-second order rate constant determined for the reaction of iodobenzene with reagent **2** [with $o\text{-tol}_3P$ and Pd_2dba_3 (4:1 ratio) as precatalyst] was approximately five times less than the corresponding rate constants measured for reagent **7a** under the same conditions;[5,6] reagent **7a** is in turn ten times less reactive than reagent **8a**.[5] It is therefore apparent that the reason for the modest yields of protected phenylalanine analogues **3** and **4** is the low reactivity of the serine-derived reagents **1** and **2**, combined with their tendency to decompose by elimination and protonation. Furthermore, the only way to increase the yields was either by using more catalyst or, in cases where the aryl iodide was the more valuable component, by use of an excess of reagent **1**.[7] Neither of these solutions is ideal, and the need for a more active catalyst is clear.



7a, PG = Boc
7b, PG = TFA

8a, PG = Boc
8b, PG = TFA

9, X = OMe
10, X = OPr^i
11, X = NMe_2

Evidence has been building that the most reactive type of Pd catalyst in cross-coupling reactions is in fact monoligated

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DOI: 10.1021/jo902238n Published on Web 11/25/2009

Pd, rather than bisligated Pd.[8−10] This has led to the design and widespread applications of biarylphosphine ligands,[11−14] which have been applied to great effect in Suzuki−Miyaura cross-coupling reactions,[15] as well as aryl amination reactions.[16,17] The most useful generally applicable ligand is SPhos **9** and the closely related analogue RuPhos **10**, which each have the capacity to stabilize a monoligated Pd(0) center by interaction between the *ipso*-carbon of the lower ring and Pd, and also to stabilize a Pd(II) center by coordination of the alkoxy group to Pd. This combination results in highly reactive catalysts that are also rather stable. In the initial report,[13] ligand to Pd ratios of 1:1 [with $Pd(OAc)_2$ as the Pd source] were shown to be most effective for Suzuki−Miyaura reactions with aryl chlorides at room temperature. In the subsequent full paper, ligand to Pd ratios of 2:1 were generally used for reactions conducted at elevated temperatures.[14] The use of very low loadings of RuPhos and SPhos, in combination with Pd, for the Negishi reaction to form biaryls was reported by Buchwald in 2004;[18] the active catalysts were prepared by combining $Pd_2(dba)_3$ with 4 equiv of the biarylphosphine ligand (resulting in a ligand to Pd ratio of 2:1). Following this report, Bach reported the use of RuPhos in combination with $Pd_2(dba)_3$ for the cross-coupling of a range of functionalized alkylzinc halides to β-bromo-α,β-unsaturated lactams.[19] In a series of papers, Knochel has shown that SPhos (and RuPhos), in combination with $Pd(OAc)_2$, is a highly effective catalyst for the Negishi cross-coupling of a wide range of organozinc reagents with a number of substrates, including those containing acidic protons.[20−23] It is interesting that Knochel's procedures also employ a ligand to Pd ratio of 2:1, although the use of a Pd(II) precursor does leave open the possibility that 1 equiv of ligand might be consumed reducing Pd(II) to Pd(0), rather than the reduction being effected either by zinc or the alkylzinc halide. Very recently, Buchwald has introduced a new ligand, CPhos **11**, which, in combination with $Pd(OAc)_2$, is highly effective for the Negishi cross-coupling of secondary organozinc reagents.[24] Once more a ligand to Pd ratio of 2:1 was employed. We now report our results on the application of biarylphosphine ligands to the Negishi cross-coupling of serine-derived organozinc reagent **2** with aromatic halides.

TABLE 1. Influence of Catalyst[a] on the Yield of Protected Phenylalanine 4a

entry	Pd precursor	mol %	ligand	mol %	yield (%)[b]
1	$Pd(OAc)_2$	5	RuPhos	10	70
2	Pd_2dba_3	2.5	RuPhos	10	85
3	Pd_2dba_3	2.5	SPhos	10	80
4	$Pd(OAc)_2$	1	RuPhos	2	25
5	$Pd(OAc)_2$	1	SPhos	2	63
6	Pd_2dba_3	0.5	RuPhos	2	24
7	Pd_2dba_3	0.5	SPhos	2	73
8	Pd_2dba_3	0.25	SPhos	1	72
9	Pd_2dba_3	0.15	SPhos	0.6	59
10	Pd_2dba_3	0.125	SPhos	0.5	51
11	Pd_2dba_3	0.05	SPhos	0.2	48

[a]In all cases, the Pd:L ratio is 2:1. [b]Yields determined by ^{1}H NMR.

TABLE 2. Influence of L:Pd Ratio on the Yield of 4a, Using Pd_2dba_3

entry	Pd_2dba_3(mol. %)	ligand	mol %	L:Pd	yield (%)[a]
1	0.5	SPhos	2	2:1	73
2	0.5	SPhos	1	1:1	77
3	0.5	SPhos	0.5	0.5:1	75
4	0.25	SPhos	1	2:1	72
5	0.25	SPhos	0.5	1:1	80[b]
6	0.25	SPhos	0.5	1:1	73[c]
7	0.5	RuPhos	2	2:1	24
8	0.5	RuPhos	1	1:1	61
9	0.5	RuPhos	0.5	0.5:1	47
10	0.5		none	0:1	17

[a]Yields determined by ^{1}H NMR. [b]Pd_2dba_3 and SPhos added as separate solutions. [c]A solution of Pd_2dba_3 and SPhos used.

As a model reaction, we selected the Negishi cross-coupling of organozinc reagent **2** with iodobenzene at room temperature. Initial studies employed a ligand to Pd ratio of 2:1, and the results from screening combinations of Pd precursor and biarylphosphine ligand at varying concentrations are included in Table 1. At high Pd loadings (5 mol %) use of either RuPhos or SPhos provided excellent yields of the product **4a**. It was striking that at reduced Pd loadings (1 mol %) SPhos was clearly superior (entries 5 and 7 compared with entries 4 and 6). In all cases, use of Pd_2dba_3 gave improved results to those obtained with $Pd(OAc)_2$. Even with substantially lower catalyst loadings (down to 0.1 mol % Pd), respectable yields of product **4a** were obtained, although use of less than 0.5 mol % Pd (i.e., less than 0.25 mol % Pd_2dba_3, entries 9−11) did result in a significant reduction in yield. These very encouraging results testify to the suitability of SPhos as a ligand for Negishi coupling reactions of unreactive organozinc reagents.

The next stage of the optimization process focused on determining the influence of the ligand to Pd ratio. As is evident from Table 2, the optimum results arise from a ligand to Pd ratio of 1:1, which appears to be entirely consistent with the proposals by Buchwald on the identity of the active catalytic species.[12,14] The optimum catalytic system is a 1:1 ratio of SPhos to Pd (entries 5 and 6), at a Pd loading of 0.5 mol %. It is striking that an excess of RuPhos is actually worse than a substoichiometric amount (entries 7 and 9), which implies that the formation of L_2Pd complexes results in a smaller concentration of the catalytically active species. The control experiment (entry 10) established that the

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SCHEME 1. Improved Synthesis of Phenylalanine Derivatives 4a−t

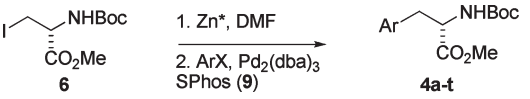

TABLE 3. Synthesis of Phenylalanine Derivatives 4a−t

		ArI		ArBr
Ar	product	method A[a] yield (%)[d]	method B[b] yield (%)[d]	method C[c] yield (%)[d]
C_6H_5	**4a**	80	79	77
1-naphthyl	**4b**	29	84	
2-naphthyl	**4c**			79
9-anthracenyl	**4d**			40
2-MeC_6H_4	**4e**	23	66	67
2-HOC_6H_4	**4f**	50	75	
2-$MeOC_6H_4$	**4g**	8	66	58
2-FC_6H_4	**4h**	21	70	65
2-ClC_6H_4	**4i**	29	76	
2-$O_2NC_6H_4$	**4j**	49	66	
3-HOC_6H_4	**4k**	70	88	
3-$MeOC_6H_4$	**4l**	67	71	
3-$O_2NC_6H_4$	**4m**	34	53	
4-MeC_6H_4	**4n**	53	83	80
4-HOC_6H_4	**4o**	77	82	51
4-$MeOC_6H_4$	**4p**	65	76	69
4-FC_6H_4	**4q**	77	80	75
4-ClC_6H_4	**4r**	58	69	
4-$H_2NC_6H_4$	**4s**	49	79	
4-$O_2NC_6H_4$	**4t**	38	51	59

[a]Method A: 0.25 mol % of Pd_2dba_3, 0.5 mol % of SPhos, room temperature, overnight. [b]Method B: 2.5 mol % of Pd_2dba_3, 5 mol % of SPhos, room temperature, overnight. [c]Method C: 2.5 mol % of Pd_2dba_3, 5 mol % of SPhos, 50 °C, 3 h. [d]Isolated yields.

presence of phosphine ligand is helpful but not essential for cross-coupling.

Having established that the optimum catalyst composition for the coupling of serine-derived organozinc reagent **2** with iodobenzene is Pd_2dba_3 (0.25 mol %) in combination with SPhos (0.5 mol %), the scope of this catalytic system (method A) for the preparation of a range of phenylalanine derivatives containing substituents in ortho-, meta-, and para-positions was explored (Scheme 1, Table 3). While the use of a Pd loading of 0.5 mol % proved entirely satisfactory for most of the meta- and para-substituted iodobenzene derivatives investigated, the yields with all of the ortho-substituted iodobenzene derivatives were poor (with the exception of 2-iodoaniline, see below). Very substantial increases in yield could be obtained by increasing the catalyst loading by a factor of 10 (method B); these conditions provide good to excellent yields in most cases. The excellent yields obtained with coupling to all three iodophenols (with the yields based on protected iodoalanine **6**) are striking, showing an improvement on our previous results,[25] and confirming clearly the benefit of the highly reactive catalysts derived from SPhos for Negishi couplings with substrates containing acidic protons.[20,21] The only substrates where moderate yields were obtained were 1-iodo-3-nitrobenzene and 1-iodo-4-nitrobenzene, for which use of the original catalytic system employing *o*-tol_3P as ligand is superior.[3] For all the substrates containing a nitro group, the organozinc reagent was transferred from excess zinc (in order to avoid reduction of the nitro group) prior to the cross-coupling, and this will contribute to the lower yields obtained. Simple modification of the reaction conditions by conducting the reaction for 3 h at 50 °C (method C), rather than room temperature, allowed good yields to be obtained in the coupling reaction with aromatic bromides, a very substantial improvement on our previous efforts.[4] It is striking that the yields of product derived from ortho-substituted iodo- and bromobenzene derivatives are very substantially improved over all our previous results.[3,4] This outcome appears entirely consistent with the presence of a sterically unencumbered monoligated-Pd catalytic species, compared with the presumed Pd(*o*-$tol_3P)_2$ that was employed previously.

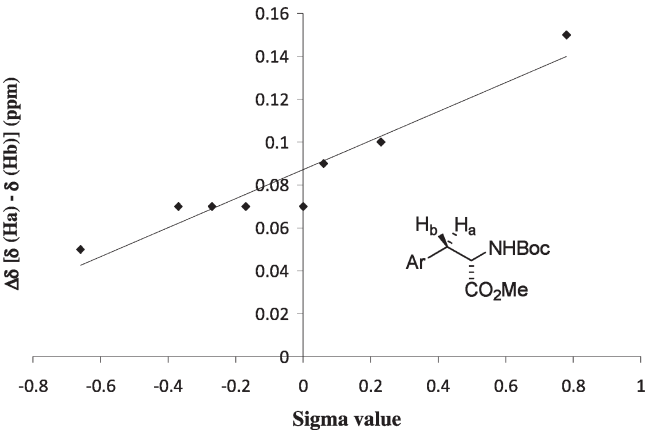

FIGURE 1. Correlation between the chemical shift difference of the two diastereotopic benzylic methylene protons and the Hammett σ-parameter of protected phenylalanines **4a** and **4n−t**.

The availability of such a variety of identically protected phenylalanine derivatives **4a−t** allowed the recording of specific rotations of the compounds under identical conditions. The data are included in the Supporting Information. Furthermore, a systematic study of the dependence of NMR spectroscopic parameters on the substituent, in particular the anisochrony of the two diastereotopic benzylic methylene protons,[26] was possible. In the series of 4-substituted phenylalanines **4n−t**, including phenylalanine itself, **4a**, a reasonable correlation between the chemical shift difference of the two diastereotopic benzylic methylene protons and the Hammett σ-parameter was noted (Figure 1). The correlation is entirely consistent with an early proposal that the magnetic anisotropy of a phenyl group strongly influences such nonequivalence.[27]

Use of 2-iodoaniline as a substrate in the cross-coupling reaction with organozinc reagent **2** led to the formation of the lactam **12** in excellent yield, rather than the expected 2-aminophenylalanine derivative. The low yield of 2-aminophenylalanine derivatives that had previously been obtained[3] suggests that the lactam **12** may also have been formed, but was not isolated. Lactam **12** has been used as a building block for the synthesis of glycogen phosphorylase inhibitors, and has been prepared previously by multistep sequences

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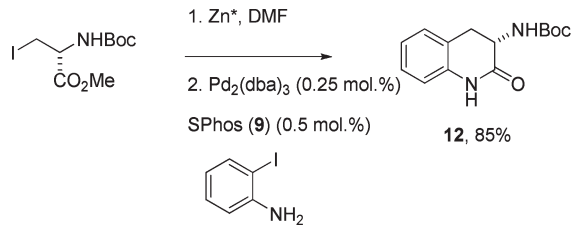
SCHEME 2. Preparation of Lactam 12



involving either a resolution,[28] or employing phenylalanine as a chiral pool starting material.[29] The one-step synthesis reported in Scheme 2 represents a convenient alternative. The isolation of such a good yield from an ortho-substituted aryl iodide with only 0.5 mol % Pd was somewhat unexpected given the results obtained with the other ortho-substituted substrates, and suggests a rate enhancement due to the *o*-amino group. It is tempting to suggest that an interaction of the amino group with the coordinatively unsaturated SPhos·Pd complex prior to oxidative addition may be responsible. It is possible that a similar effect is responsible for the much higher yield obtained when using only 0.5 mol % Pd in the reaction of organozinc reagent **2** with 2-iodophenol (**4f**), compared with 2-iodoanisole (**4g**), although in this case it is not possible to exclude a steric argument.

In conclusion, it has been established that the combination of Pd_2dba_3 and SPhos in a 1:2 molar ratio (giving a Pd:SPhos ratio of 1:1) is the most efficient precatalyst so far employed for the Negishi coupling of serine-derived organozinc reagents **2** with aryl halides to give protected phenylalanine derivatives **4**. In the case of meta- and para-substituted aryl iodides, Pd loadings of 0.5 mol % give satisfactory results, but higher yields are obtained with aryl bromides and ortho-substituted aryl iodides provided Pd loadings of 5 mol % (2.5 mol % Pd_2dba_3) are used; these conditions are therefore recommended as a starting point for the synthesis of protected phenylalanine derivatives from organozinc reagent **2**.

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Experimental Section

Preparation of Organozinc Reagent 2. Zinc dust (190 mg, 3 mmol) was added to a flame-dried, nitrogen-purged side arm round-bottomed flask. Dry DMF (1 mL) was added via syringe, followed by a catalytic amount of iodine (40 mg, 0.15 mmol). A color change of the DMF was observed from colorless to yellow and back again. Protected iodoalanine **6** (329 mg, 1 mmol) was added immediately, followed by a catalytic amount of iodine (40 mg, 0.15 mmol). The solution was stirred at room temperature; successful zinc insertion is accompanied by a noticeable exotherm. The solution of organozinc reagent **2** was allowed to cool to room temperature before use.

General Cross-Coupling: Method A. Solutions of Pd_2dba_3 (11 mg, 0.0125 mmol) in dry DMF (0.5 mL) and SPhos **9** (11 mg, 0.025 mmol) were prepared in dry flasks under nitrogen. Aliquots of the Pd_2dba_3 solution (100 μL, 0.0025 mmol) and SPhos solution (100 μL, 0.005 mmol) were added via syringe to the solution of organozinc reagent **2**, followed by the aryl iodide (1.3 mmol). The reaction mixture was stirred at room temperature overnight under positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column to afford the purified cross-coupled product.

General Cross-Coupling: Method B. Pd_2dba_3 (22 mg, 0.025 mmol), SPhos (21 mg, 0.05 mmol), and the aryl iodide (1.3 mmol) were added to the solution of organozinc reagent **2** and the mixture was stirred at room temperature overnight, under a positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column to afford the purified cross-coupled product.

General Cross-Coupling: Method C. Pd_2dba_3 (22 mg, 0.025 mmol), SPhos (21 mg, 0.05 mmol), and the aryl bromide (1.3 mmol) were added to the solution of organozinc reagent **2** and the mixture was heated at 50 °C for 3 h, under a positive pressure of nitrogen. The reaction mixture was allowed to cool to room temperature and applied directly to a silica gel column to afford the purified cross-coupled product.

Acknowledgment. We thank Dr. Craig S. Harris (AstraZeneca, Reims) for helpful suggestions and discussion, and the Department of Chemistry, The University of Sheffield, for the award of an EPSRC DTA studentship (A.R.).

Supporting Information Available: Comparison of NMR chemical shift for the diastereotopic protons of substituted phenylalanine derivatives (Table 4), tabulated specific rotations for all phenylalanine derivatives in $CHCl_3$ (Table 5), characterization data for all compounds, and ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.