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Negishi Cross-Couplings Compatible with Unprotected Amide Functions

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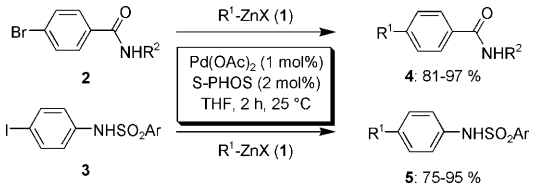
The Pd-catalyzed cross-coupling of unsaturated halides with organometallic reagents is one of the best methods for making C_{sp2}–C_{sp2} bonds.[1] Among many organometallic reagents used in these cross-couplings, organozinc reagents (Negishi reaction) have proven to react under very mild conditions.[2,3] Furthermore, organozinc compounds are compatible with many functionalities and allow therefore the elaboration of polyfunctional molecules without the need for protecting groups.[4] Recently, we have demonstrated, that acidic hydrogens of amines, alcohols, and phenols are compatible with the Negishi cross-coupling conditions and do not require the use of protecting groups.[5] Herein, we report reaction conditions that are compatible with the amide function (Scheme 1). This functional group is ubiquitous in pharmaceutically active compounds and its tolerance in cross-coupling reactions is therefore especially important.[6] Only boronic esters or acids have so far been reported to undergo in general couplings with organic halides bearing amide functions.[7]



Scheme 1. Cross-coupling of zinc reagents with unprotected amides and sulfonamides. R^1 = alkyl, aryl, heteroaryl, benzylic, R^2 = H, alkyl, aryl, benzyl. S-PHOS = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

Preliminary kinetic experiments revealed large differences in the reactivity between different types of orgoanozinc reagents. Thus, a 0.4 M solution of OctZnBr is completely protonated within 25 min at 25 °C when treated with one equivalent of benzamide (Figure 1). From the reaction time required for 50 % conversion of the zinc reagent (< 1 min for PhZnI, 2.5 min for OctZnBr, and 20 min for BnZnCl), one can derive approximate structure–reactivity relationships. For secondary amides, the protonation rate is somewhat lower, but 50 % of the zinc reagent is protonated within 30 min (for PhZnI), 60 min (for OctZnBr), and 2.5 h (for BnZnCl, Figure 2). These results indicate, that the reactivity towards NH acids increases from benzyl < alkyl < aryl and that a very active cross-coupling catalyst will be required to avoid competitive protonation. Recently, Buchwald reported the high activity of S-PHOS[8] for various cross-couplings.

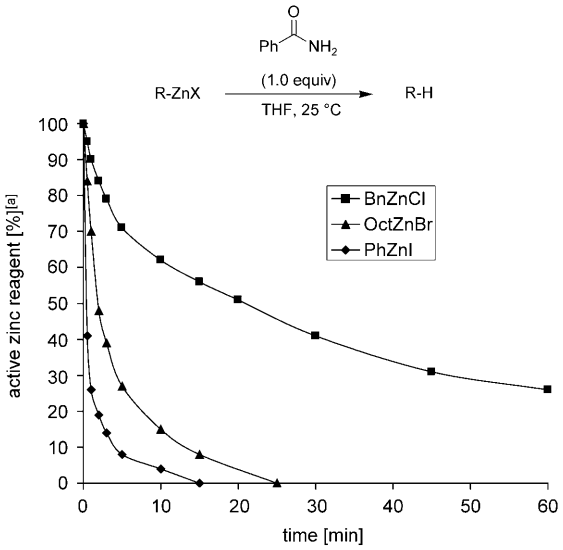


Figure 1. Stability of organozinc reagents towards benzamide. [a] Yields are determined by quenching with CuCN/allyl bromide in THF followed by GC analysis with tetradecane as internal standard.

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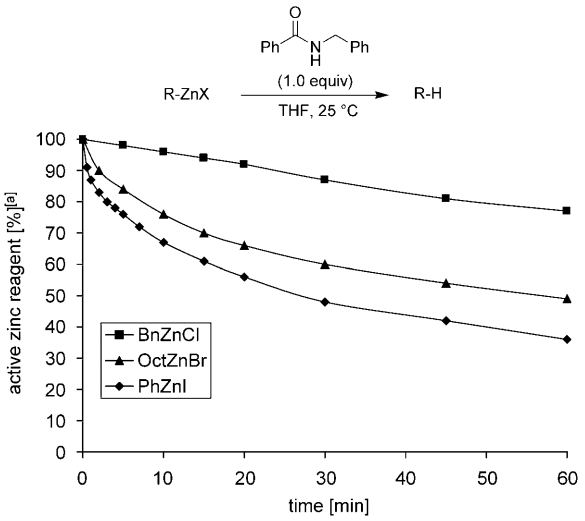


Figure 2. Reactivity of organozinc reagents with *N*-benzylbenzamide. [a] Yields are determined by quenching with CuCN/allyl bromide in THF followed by GC analysis with tetradecane as internal standard.

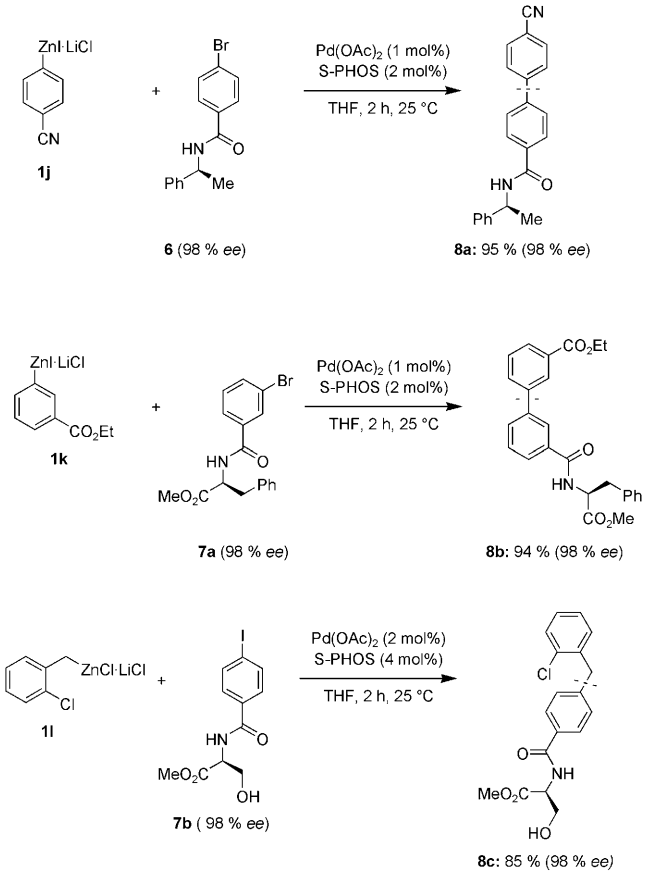
This ligand has already been successfully applied for Negishi cross-couplings in the presence of free alcohols and amines.[5]

As shown in Table 1, we have found that by using $Pd(OAc)_2$ (1 mol%) and S-PHOS (2 mol%) and adding the zinc reagent within 90 min to the aryl bromide at 25°C, it was possible to perform efficient cross-couplings between various aryl bromides bearing amide groups (1.0 equiv) and functionalized zinc reagents (1.2 equiv, Scheme 1 and Table 1). This procedure has a remarkably broad scope and affords high yields (75–96%). Importantly *no large excess of the zinc reagent* is needed and *no extra base was added* to deprotonate the amide function prior to the cross-coupling. As shown in Table 1, the cross-coupling proceeds well with arylzinc reagents, prepared by the direct zinc insertion in the presence of LiCl (such as **1a** and **1b**; entries 1 and 2).[9] Zinc reagents derived from electron-poor heteroarenes, such as 3-pyridylzinc iodide (**1c**) and electron-rich heterocycles, such as 2-thienylzinc chloride (**1d**)[10] or the uracil-derived zinc reagent **1e**,[11] react smoothly, providing the cross-coupling products **4c**–**4f** in 81–89% yield (entries 3–6). Ester- and nitrile-substituted alkylzinc reagents **1f** and **1g**, respectively, react at the same rate. After addition of the zinc reagent and stirring for 30 min at 25°C, the cross-coupling of the primary or secondary amides are complete, furnishing the polyfunctional molecules **3g**–**3i** in 83–96% yield (entries 7–9).[12] Finally, the polyfunctional benzylic zinc reagents **1h** and **1i** lead to the cross-coupling products **4j** and **4k** in 90–91% yield (entries 10 and 11). Interestingly, also iodosulfonamides such as **3a** and **3b** are excellent substrates, requiring no protection of the acidic N–H and cross-coupling with the alkylzinc reagents **1f** and **1g**, and the benzylic zinc chloride **1h** affords the desired polyfunctional sulfonamides (**5a**–**5c**) in 75–95% yield (entries 12–14).

The cross-coupling conditions are mild enough that chiral amides such as bromobenzamide **6** or amino acid derivatives such as **7a** and **7b** undergo Negishi cross-coupling with aryl and benzylic zinc regents **1j**–**1l**, leading to the products **8a**–**8c** in 85–94% yield (Scheme 2).

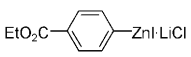
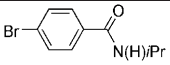
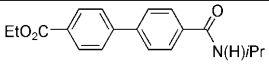
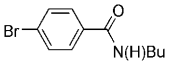
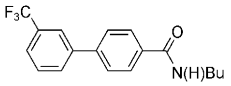
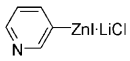
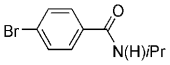
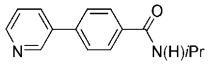
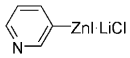
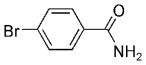
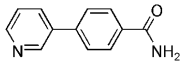
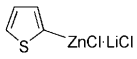
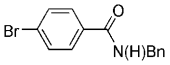
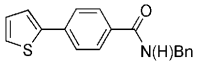
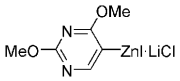
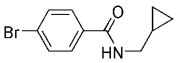
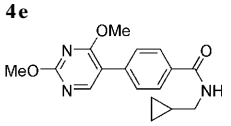
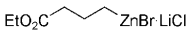
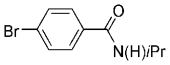
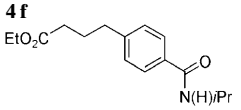
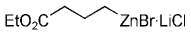
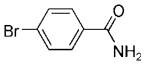
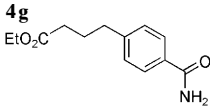
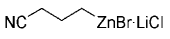
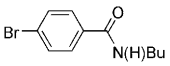
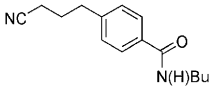
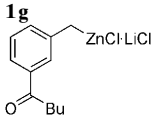
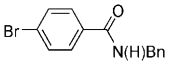
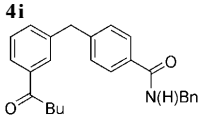
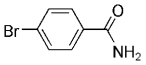
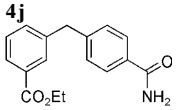
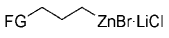
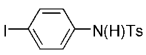
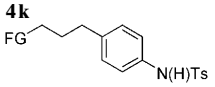
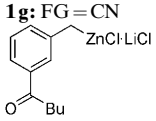
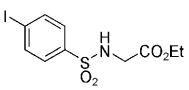
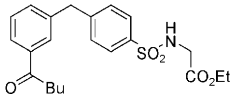
As mentioned above, numerous pharmaceuticals bear an amide function with an acidic proton. To demonstrate the broad applicability of our method, we have prepared several biologically active compounds. Thus, the antiarrythmic agents **10a** and **10b** (Bristol–Myers Squibb)[13] were prepared in 92–97% yield by the direct cross-coupling of the zinc reagents **1m**[14] and **1e** under the standard conditions from the bromoamide **9** (Scheme 3). The reaction of the heterocyclic zinc reagent **1n**, prepared by direct zinc insertion,[9,13] with the secondary amides **11** and **2e** led to the kinase inhibitors **12a** and **12b** (GlaxoSmithKine)[15] in 91–96% yield (Scheme 3). Finally, the sodium channel blockers **15a**–**15c** (Merck)[16] were synthesized from the primary amide **14** and the zinc reagents **1o**–**1q**[14,17] in 94–97% yield (Scheme 3).

In summary, we have reported reaction conditions, using Buchwald's S-PHOS, which allow a general Pd-catalyzed Negishi cross-coupling of functionalized alkyl, aryl, heteroaryl, and benzylic zinc reagents with aryl halides bearing amide or sulfonamide functions with acidic hydrogens. The mild reaction conditions considerably increase the applica-



Scheme 2. Cross-coupling of optically active aryl halides.

Table 1. Products of type **4** and **5** obtained by the cross-coupling between functionalized zinc reagents **1** and amides **2** or sulfonamides **3**.

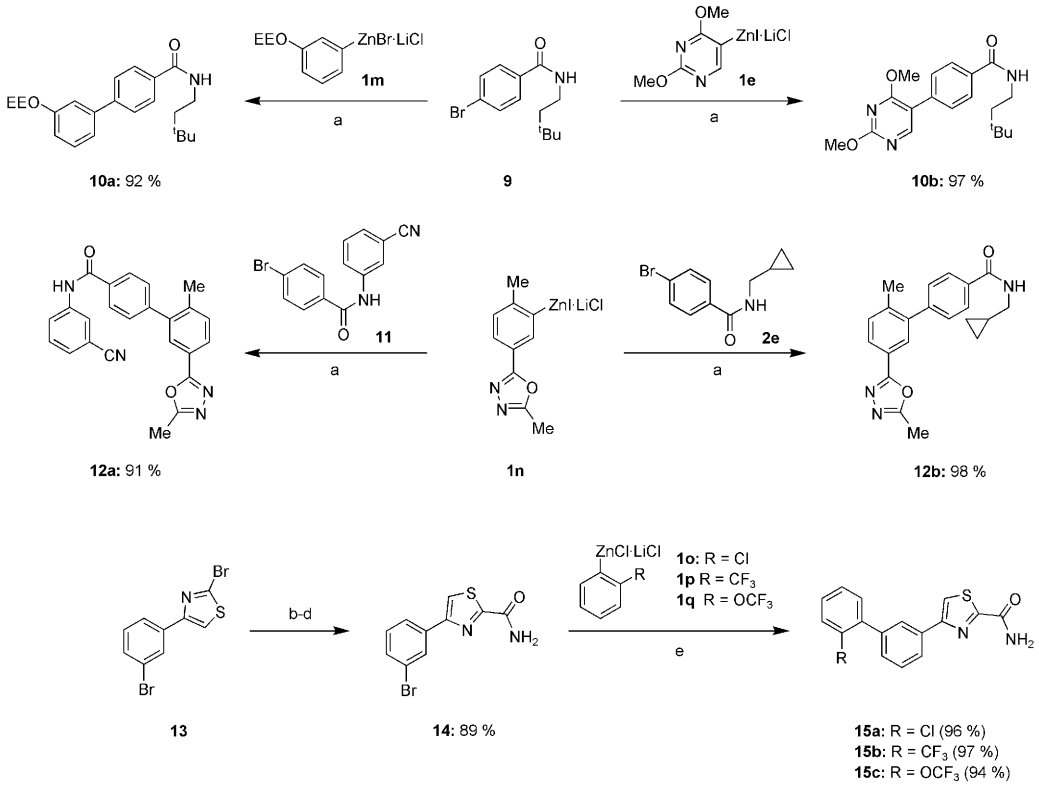
Entry	Zinc Reagent[a]	Electrophile	Product	Yield [%][b]
				
1	**1a** 	**2a** 	**4a** 	96
2	**1b** 	**2b** 	**4b** 	92
3	**1c** 	**2a** 	**4c** 	89
4	**1c** 	**2c** 	**4d** 	81
5	**1d** 	**2d** 	**4e** 	86
6	**1e** 	**2e** 	**4f** 	87
7	**1f** 	**2a** 	**4g** 	90
8	**1f** 	**2c** 	**4h** 	83
9	**1g** 	**2b** 	**4i** 	96
10	**1h** 	**2d** 	**4j** 	96
11	**1i** 	**2c** 	**4k** 	91
12	**1f:** FG = CO_2Et	**3a**	**5a:** FG = CO_2Et	75
13	**1g:** FG = CN 	**3a** 	**5b:** FG = CN 	95
14	**1h**	**3b**	**5c**	85

[a] The zinc reagent (1.2 equiv) was slowly added over 90 min via syringe pump. [b] Isolated yield of analytically pure product.

bility of the Negishi cross-coupling in the synthesis of complex molecules and natural products.

Experimental Section

Typical procedure: preparation of *N*-benzyl-4-(3-pentanoyl-benzyl)-benzamide (4j): A dry and argon flushed 10 mL Schlenk-tube was charged with *N*-benzyl-4-bromobenzamide (**2d**, 580 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-PHOS (16.4 mg, 0.04 mmol), and THF (2 mL).



Scheme 3. Preparation of biologically active biphenylamides: a) $Pd(OAc)_2$ (1 mol%), S-PHOS (2 mol%), slow addition of the zinc reagent over 90 min, THF 25°C; b) *i*PrMgCl·LiCl, THF, −30°C, 45 min, then $ZnCl_2$, −30°C to 25°C; c) $Cl_3C(O)NCO$, −40°C to 25°C; d) K_2CO_3, MeOH, 25°C, 16 h; e) $Pd(OAc)_2$ (2 mol%), S-PHOS (4 mol%); EE = 1-ethoxyethyl.

After the mixture had been stirred for 5 min, 3-pentanoyl-benzylzinc chloride (**1h**, 1.8 mL, 1.34 M in THF, 2.4 mmol, prepared by the direct zinc insertion into the benzylic chloride)[17] was added slowly over 90 min with a syringe pump. The reaction mixture was stirred for 1 h at 25°C. Then the reaction mixture was quenched with a saturated NH_4Cl solution and extracted with diethyl ether. The combined organic phases were washed with an aqueous thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 4:1) gave *N*-benzyl-4-(3-pentanoyl-benzyl)-benzamide (**4j**) as a colorless solid (755 mg, 96%).

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