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New Multi-Coupling Benzylic Zinc Reagents for the Preparation of Flexible Aromatic Compounds

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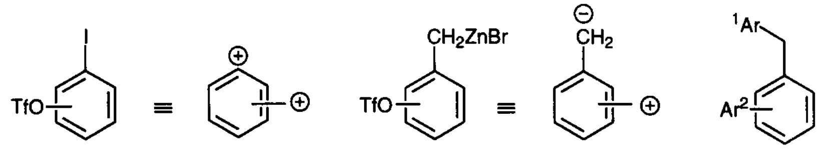
Abstract: The benzylic zinc reagents **3a-c** bearing a triflate group in *o*-, *m*- or *p*-position are new efficient multi-coupling reagents reacting stepwise with an aryl iodide (Ar^1-I) and an arylzinc bromide (Ar^2ZnBr) in the presence of the appropriate palladium catalyst and the suitable phosphine ligand leading to polyfunctional flexible aromatic products of type **5**. This methodology is appropriate for applications in combinatorial chemistry. © 1997 Elsevier Science Ltd. All rights reserved.

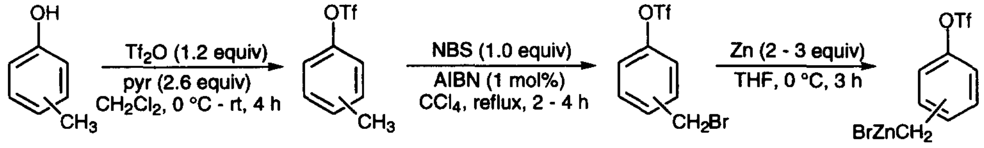
Palladium catalyzed cross-coupling reactions between aromatic halides and organozinc halides (Negishi-reaction)[1] constitute an excellent preparation method for polyfunctional aromatic compounds.[2] The use of aromatic multi-coupling reagents[3] bearing two reactive functional groups participating in cross-coupling reactions is of special interest since it allows the preparation of great diversity of aromatic products of potential biological interest. Recently, we have shown that aromatic *bis*-electrophiles of type **1** bearing an iodide and a triflate function are excellent multi-coupling reagents and are synthetically equivalent to the synthons **2**. They undergo selectively two successive cross-coupling reactions with organozinc leading to a variety of biphenyls and terphenyls.[4]



1 2 3 4 5

Scheme 1

Herein, we wish to report the preparation of new benzylic multi-coupling reagents of type **3** bearing an electrophilic triflate function and a nucleophilic benzylic zinc function. The zinc reagents **3** are synthetically equivalent to the synthon **4** and undergo two successive cross-coupling reactions with a range of aromatic iodides and aromatic zinc reagents leading to various flexible aromatic molecules of type **5** (Scheme 1). The benzylic zinc reagents **3a-c** were prepared from the corresponding cresols **6**. Treatment of **6a-c** with trifluoromethanesulfonic anhydride (1.2 equiv) and pyridine (2.6 equiv) in CH_2Cl_2 (25 °C, 4 h) affords the corresponding triflates **7a-c** in 92-94 % yield.[5] Benzylic bromination of **6a-c** with NBS (1.0 equiv, CCl_4, AIBN, 1 mol %, reflux, 2-4 h) furnishes the expected benzylic bromides **8a-c** in 60-74 % yield.



6a: *o*-Me
6b: *m*-Me
6c: *p*-Me

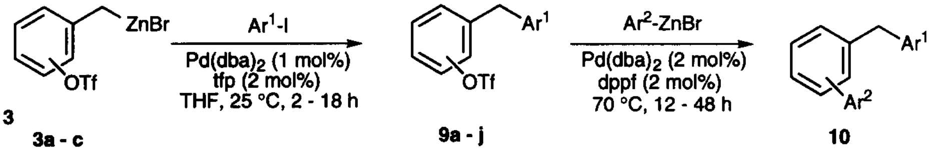
7a: *o*-Me
7b: *m*-Me
7c: *p*-Me

8a: *o*-Me
8b: *m*-Me
8c: *p*-Me

overall yields: **3a**: *o*- ; 44%
3b: *m*- ; 53%
3c: *p*- ; 54%

Scheme 2

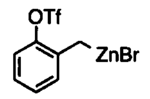
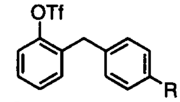
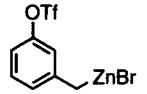
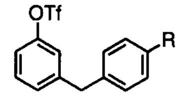
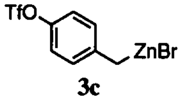
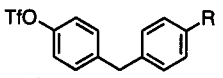
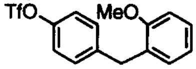
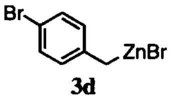
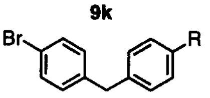
The conversion of the benzylic bromides **8a-c** to the corresponding benzylic zinc reagents[6] is best performed with cut zinc foil (2-3 equiv) which has been activated with 1,2-dibromoethane (2 mol %).[7] The zinc insertion is complete in THF within 3 h at 0 °C and provides clear solutions of the benzylic zinc **3a-c** containing less than 10-15 % of Wurtz-homocoupling product (Scheme 2). The zinc derivatives **3a-c** undergo a smooth cross-coupling reaction with various functionalized aryl iodides in the presence of palladium *bis*(dibenzylideneacetone)[8] (Pd(dba)$_2$; 1 mol %) and tri-*o*-furylphosphine [9] (tfp, 2 mol %) in THF (25 °C, 2-18 h) leading to polyfunctional triflate substituted diarylmethane derivatives of type **9** in 74 % - 93 % yield (Scheme 3 and Table 1).



Scheme 3

Remarkably, the triflate group does not react under these mild reaction conditions. It was also possible to prepare a benzylic zinc bromide bearing a bromide substituent for the second cross-coupling reaction. Thus *p*-bromobenzylzinc bromide **3d** undergoes a cross-coupling reaction with unactivated aryl iodides like *p*-methoxyiodobenzene and *p*-chloroiodobenzene leading to the expected products **9l** and **9m** respectively in

Table 1. Functionalized aryl triflates **9a-m** obtained by the Pd(0) catalyzed cross-coupling between aryl iodides Ar^1-I and the benzylic zinc bromides **3a-d**.

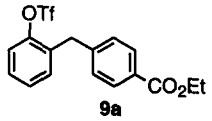
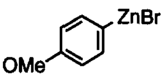
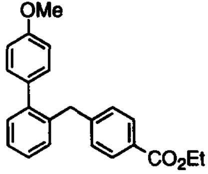
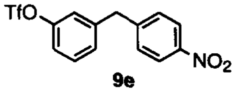
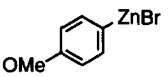
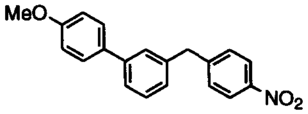
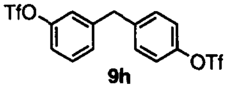
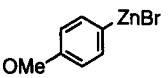
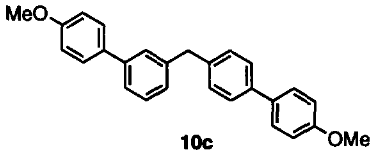
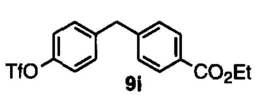
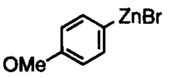
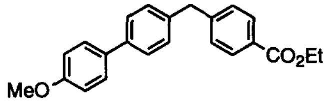
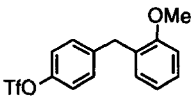
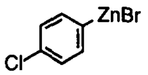
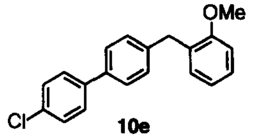
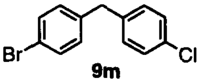
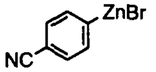
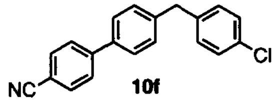
entry	benzylic zinc reagent **3**	Ar^1-I	product of type **9**	yield (%)[a]
				
1	**3a**	*p*-EtO$_2$C-C$_6$H$_4$I	**9a**: R = CO$_2$Et	93[b]
2	**3a**	*p*-Cl-C$_6$H$_4$I	**9b**: R = Cl	88[b]
3	**3a**	*p*-O$_2$N-C$_6$H$_4$I	**9c**: R = NO$_2$	90[b]
4	**3a**	*p*-AcO-C$_6$H$_4$I	**9d**: R = OAc	82
				
5	**3b**	*p*-O$_2$N-C$_6$H$_4$I	**9e**: R = NO$_2$	85
6	**3b**	*p*-Cl-C$_6$H$_4$I	**9f**: R = Cl	85[b]
7	**3b**	*p*-EtO$_2$C-C$_6$H$_4$I	**9g**: R = CO$_2$Et	79
8	**3b**	*p*-TfO-C$_6$H$_4$I	**9h**: R = OTf	74
				
9	**3c**	*p*-EtO$_2$C-C$_6$H$_4$I	**9i**: R = CO$_2$Et	92
10	**3c**	*p*-O$_2$N-C$_6$H$_4$I	**9j**: R = NO$_2$	90
11	**3c**	*o*-MeO-C$_6$H$_4$I	 **9k**	84
				
12	**3d**	*p*-MeO-C$_6$H$_4$	**9l**: R = OMe	79
13	**3d**	*p*-Cl-C$_6$H$_4$I	**9m**: R = Cl	82

[a] Isolated yield of analytically pure products. [b] The reaction was performed at 65 °C.

79 % and 82 % yield (entries 12 and 13 of Table 1). In some cases heating to 65 °C for a few hours is required prohibiting the general use of bromo-substituted benzylic zinc reagents. The resulting aromatic triflates **9a-m** can be further coupled with a different functionalized aryl iodide in the presence of a more activating phosphine ligand 1,1'-*bis*(diphenylphosphino)ferrocene[10] (dppf, 2 mol %) and Pd(dba)$_2$ (2 mol %) resulting in the formation of flexible polyfunctional aromatic compounds of type **10** in good yields (70 % - 93 %; Scheme 4 and Table 2).

In all cases, the reaction mixtures have to be heated to 70 °C for 12 h to 48 h in order to obtain a complete conversion. The reaction proceeds equally well with *o*-, *m*- and *p*-substituted aryl triflates. A double cross-coupling reaction with the *bis*-triflate **9h** (entry 3 of Table 2) furnishes the *bis*-arylated product **10c** in 70 % yield. Finally the aromatic bromide **9m** reacts with *p*-C_6H_4ZnBr[11] affording the desired product **10f** in 90 % yield (entry 6).

Table 2. Polyfunctional aromatic cross-coupling products **10a-f** obtained by the reaction of the aryl triflates of type **9** with arylzinc derivatives in the presence of Pd(dba)$_2$ (2 mol %) and dppf (2 mol %).

entry	aryl triflate **9**	Ar2ZnBr	product of type **10**	yield (%)[a]
1	 **9a**		 **10a**	86
2	 **9e**		 **10b**	82
3	 **9h**		 **10c**	70
4	 **9i**		 **10d**	90
5	 **9k**		 **10e**	93
6	 **9m**		 **10f**	90

[a] Isolated yield of analytically pure products.

In summary,[12] we have shown that the benzylic zinc reagents **3a-c** constitute excellent multi-coupling reagents allowing a short and efficient entry to various flexible polyfunctional aromatics of type **10**.

Efforts to adapt this methodology for solid-phase synthesis with applications in combinatorial chemistry are currently underway.

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12. **Typical procedures.** (a) *Preparation of the zinc reagent 3c* . A three-necked flask equipped with argon inlet, glass stopper, rubber septum was charged with cut zinc foil (1.05 g, 16 mmol, 2 equiv), THF (1.5 mL) and 1,2-dibromoethane (60 mg) and the mixture was heated twice to reflux with a hot air gun. After 5 minutes, the mixture was cooled with an ice bath to 0 °C. The glass stopper and the rubber septum were replaced by a thermometer and a dropping funnel charged with *p*-benzyl bromide **8c** (2.55 g, 8 mmol) in THF (4 mL). The solution of **8c** was added dropwise to the suspension of zinc foil in THF within 45 minutes keeping the temperature below 3 °C. After stirring for 1 h, the reaction was complete as judged by GC analysis of hydrolyzed and iodolyzed reaction aliquots, and the yield of **3c** (94 %) was determined using an internal standard. The solution of **3c** was directly used in the cross-coupling reaction.

    (b) *Preparation of the triflate 9i* (Table 1). A two-necked flask with argon inlet, rubber septum was charged with Pd(dba)$_2$ (63 mg, 0.11 mmol, 2 mol %), tfp (51 mg, 0.22 mmol, 4 mol %), and THF (6 mL). The solution was stirred for 5 min at room temperature whereas the initial red color turned to yellow. After cooling to 0 °C, ethyl 4-iodobenzoate (1.47 g, 5.33 mmol) was added followed by the solution of **3c**. The mixture was warmed up to rt and was stirred for 12 h. The reaction mixture was then poured into sat. aq. NH_4Cl and was extracted twice with AcOEt. The organic layer was washed with water and brine and after reextraction the combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (2-10 % ethyl acetate in hexanes) yielding **9i** (1.90 g, 4.90 mmol, 92 %) as colorless oil.

    (c) *Preparation of the triaryl 10d* (Table 2). A two necked flask equipped with argon inlet and rubber septum was charged with Pd(dba)$_2$ (35 mg, 0.06 mmol, 2 mol %), dppf (33 mg, 0.06 mmol, 2 mol %), and THF (3 mL). After stirring for 10 min, the triflate **9i** (1.17 g, 3.0 mmol) was added at 0 °C followed by a solution of *p*-methoxyphenylzinc bromide (6.0 mL, c = 0.83 M in THF/hexane, 1.67 equiv). The reaction mixture was heated to 65 °C for 2 h. After usual workup as described above, the crude product was purified by filtration over silicagel and recrystallisation from 20 % ethyl acetate in hexanes yielding **10d** (0.94 g, 2.7 mmol, 90 %) as white solid (mp = 102-103 °C).

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