New Efficient Nickel- and Palladium-Catalyzed Cross-Coupling Reactions Mediated by Tetrabutylammonium Iodide

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ABSTRACT



The addition of Bu_4NI has been found to accelerate the palladium(0)-catalyzed cross-coupling between benzylic zinc bromides and aryl or alkenyl triflates. Remarkably, it further allows a new nickel(0)-catalyzed cross-coupling between functionalized benzylic zinc reagents and primary alkyl iodides leading to polyfunctional products in good yields under mild reaction conditions (0–20 °C, 4–16 h).

Transition metal-catalyzed cross-coupling reactions beetween C sp² centers have been extensively studied and several efficient Pd-,¹ Ni-,² or Fe-catalyzed³ reactions are now available. Recently, we have investigated cross-coupling between two C sp³ centers⁴ as well as between C sp³ and C sp² centers⁵ and found that Ni(acac)₂-catalyzed cross-coupling

of dialkylzincs or arylzinc derivatives in the presence of *m*or *p*-trifluoromethylstyrene or 4-fluorostyrene (**1**) as promotor proceeds under mild conditions and in satisfactory yields. Attempts to perform cross-coupling reactions between benzylic zinc bromides and alkyl iodides in the presence of the nickel catalytical system failed completely, whereas sluggish reactions were observed between benzylic zinc derivatives and various aryl triflates in the presence of palladium(0). What attracted our attention was the use of ammonium salts for accelerating Sonogashira cross-couplings,⁶ and we have found that these additives allow, for the first time, the Ni-

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Table 1.	Optimization of the Reaction Conditions for the
Cross-Cou	pling between Benzylzinc Bromide and the Aryl
Triflate (3	a)

Additive	Equiv.	Reaction Time (h)	Conversion (%)	
-	-	1	0.5	
Bu ₄ NF	1.0	1	0.7	
Bu ₄ N(ClO ₄)	1.0	1	3.8	
Csl	1.0	1	1.5	
Lil	1.0	1	13	
Bu ₄ NBr	1.0	1	23	
Bu ₄ NI	0.1	1.5	2.4	
Bu ₄ NI	1.0	1	24	
Bu ₄ NI	1.0	1.5	38	
Bu₄NI	3.0	1.5	90	

catalyzed cross-coupling between polyfunctional benzylic zinc reagents and functionalized alkyl iodides. Also, the Pd-

catalyzed cross-coupling between various aryl and alkenyl triflates⁷ and benzylic zinc reagents⁸ was substantially accelerated.

In preliminary experiments, we have investigated the palladium-catalyzed cross-coupling between benzyl zinc bromide (**2a**) and 4-chlorophenyl triflate (**3a**) in the presence of palladium bis(dibenzylideneacetone) (Pd(dba)₂,7 mol %) and diphenylphosphinoferrocene (dppf, 7 mol %) in THF at 60 °C⁹ (Scheme 1). In the absence of additive almost no



reaction occurs after a reaction time of 1 h. In the presence of tetrabutylammonium fluoride or perchlorate as well as CsI little of the cross-coupling product **4a** was observed. Better results are obtained with LiI and both Bu₄NI and Bu₄-NBr give 23-24% yield of **4a** after only 1 h of reaction time. The amount of Bu₄NI added is also of importance for the reaction rate. Thus, a conversion of 2.4% is obtained with 0.1 equiv of Bu₄NI. With 1.0 equiv, 38% of **4a** is formed after a reaction time of 1.5 h, whereas with 3.0 equiv, a conversion of 90% is obtained (Scheme 1 and Table 1).

Entry	Organozinc halide of type 2	Triflate of type 3	Reaction conditions (h, °C)	Product of type 4	Yield (%) ^a
1	BnZnBr 2a	4-RC ₆ H₄OTf 3a : R = Cl	2, 60	Bn	94
2	2a	3b : R = MeO	6, 60	4b : R = MeO	91
3	2a	3c : R = Me	2.5, 60	4 c : R = Me	93
4	2a	3d : R = CO ₂ Et	4, 60	4d : R = CO ₂ Et	84
5	PentZnl 2b	3a	4, 60	Pent — R 4e: R = Cl	92
6	2b	3c	4, 60	4f : R = Me	89
7	PivO(CH ₂₎₄ ZnI 2c	3d	4, 60	PivO(CH ₂) ₄ - CO ₂ Et	92
8	2b	3e OTF	1, 60	4h : R = Pent	76
9	2a	3e	1, 60	4i : R = Bn	84

Table 2. Pd(0)-Catalyzed Cross-Coupling between Benzylic or Alkyl Zinc Halides and Alkenyl or Aryl Triflates in the Presence of Bu_4NI

^a Isolated yield of analytically pure products

Table 3. Ni(0)-Catalyzed Cross-Coupling between Benzylic Zinc Bromides and Primary Alkyl Iodides in the Presence of 1c and Bu_4NI



Thus, in the presence of 3 equiv of Bu_4NI , efficient crosscoupling reactions could be realized with a range of aryl and alkenyl triflates (Table 2). Remarkably the reaction can be extended to functionalized alkylzinc iodides^{1,10} without the extensive formation of homocoupling side products. In all cases, the reaction was complete within 6 h at 60 °C.¹¹ Comparative experiments performed in the absence of Bu_4 -

(12) Typical Procedure. (a) Palladium-Catalyzed Cross-Coupling. Preparation of 4-(4-Ethyloxycarbonylphenyl)butyl Pivalate (4g). The aryl triflate 3d (299 mg, 1.00 mmol), Pd(dba)₂ (40 mg, 0.07 mmol), dppf (38 mg, 0.07 mg), and Bu₄NI (1.11 g, 3.00 mmol) were dissolved in THF/ NMP (1.5 mL, 1:1). To this mixture was added organozinc halide 2c (1.45 mL, 1.60 mmol, 1.1 M in THF). The reaction mixture was stirred at 60 °C for 4 h. The mixture was cooled to room temperature and quenched as usual. The crude product was purified by flash chromatography (silica gel, pentane/ethyl acetate 95:5) to give 282 mg (0.92 mmol, 92%) of the desired product as a clear, colorless oil. (b) Nickel Catalyzed Cross-Coupling. NI led to reaction times between 20 and 30 h. Further trials with Bu_4NBr showed that the initial reaction rate slows down faster than in the case of Bu_4NI , leading to slighty longer reaction times. As indicated above, benzylic zinc reagents were found to be unreactive in nickel-catalyzed cross-coupling with primary alkyl iodides of type **5**. We found that in the presence of Bu_4NI (3 equiv) and **1** as promotor

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⁽i) Preparation of Benzylic Zinc Bromide (2e). A 25-mL flask charged with cut zinc foil (1.5 g, 22.5 mmol) and a stirring bar was flame-dried and flushed with argon. THF (1 mL) and 1,2-dibromoethane (400 mg, 2.3 mmol) were added, and the zinc was activated by heating to reflux, then allowing to cool. This procedure was repeated until foam no longer occurred as a result of heating. The mixture was cooled to 0 °C before adding 3-cyanobenzyl bromide (1.8 g, 7.5 mmol) in THF (5 mL) dropwise (0.1 drop/s). The mixture was keept at 0 °C until the reaction had completed as checked by GC (~2 h). The solution was concentrated in vacuo to 2.5 M before use. (ii) Preparation of 5-[3-Cyanophenyl]pentyl Phenyl Ketone (6f). A dried 10-mL two-neck flask was charged with Ni(acac)₂ (77 mg, 0.3 mmol). Dry THF (2 mL), NMP (1 mL), 4-iodobutyl phenyl ketone 5a (820 mg, 3 mmol), 4-fluorostyrene (1) (74 mg, 0.6 mmol), and Bu₄NI (3.3 g, 9 mmol) were successively added at room temperature. The mixture was cooled to -35 °C before slowly adding a solution of 3-cyanobenzyl zinc bromide (2.5 M, 7.5 mmol). The reaction mixture was then allowed to warm to 0 °C and after 1 h to 10 °C. The reaction was complete after 16 h as checked by GC. The reaction mixture was worked up as usual and extracted with diethyl ether (4 \times 70 mL). The combined organic phases were dried (MgSO₄) before evaporating the solvents in vacuo. Flash chromatography on silica gel (pentane/diethyl ether 20:1) furnished the cross-coupling product 6f as pale yellow crystals (582 mg, 74%).

(0.2 equiv) efficient cross-coupling reactions were now obtained leading to the desired C sp³-C sp³ cross-coupling products of type **6** in good yields (Scheme 2 and Table 3).



The reaction is complete within a few hours at 0-20 °C and importantly tolerates a range of functional groups

(ketone, ester, nitrile, thioether) both in the benzylic zinc reagent and in the alkyl iodide. In summary, the addition of Bu_4NI significantly accelerates the Pd(0)-catalyzed crosscoupling between benzylic zinc bromides and alkenyl or aryl triflates. It allows a new and efficient Ni(0)-catalyzed crosscoupling between alkyl iodides and benzylic zinc reagents. Further application of the dramatic effect of Bu_4NI in crosscoupling reactions as well as some mechanistic aspects of this acceleration are currently investigated in our laboratories.¹²

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Supporting Information Available: Experimental procedures and full characterization for compounds 4a-i and 6a-f. This information is available free of charge via the Internet at http://pubs.asc.org.

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