ORGANIC LETTERS

1999
Vol. 1, No. 9
1323–1326

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

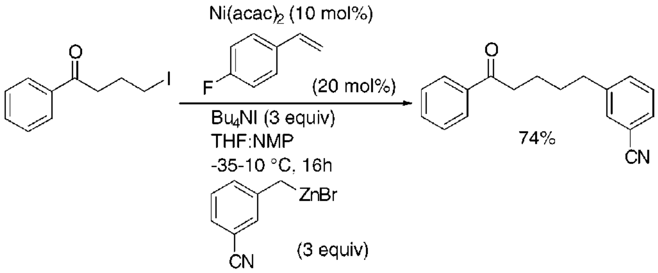
Michael Piber,[†] Anne Eeg Jensen,[†] Mario Rottländer,[‡] and Paul Knochel*,[†]

Institut für Organische Chemie, Ludwig-Maximilians-Universität München,
Butenandtstrasse 5-13, Haus F, 81377 München, Germany, and H. Lundbeck A/S,
Ottiliavej 9, DK-2500 Valby, Denmark

paul.knochel@cup.uni-muenchen.de

Received July 6, 1999

ABSTRACT



The addition of Bu$_4$NI 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 sp^2 centers have been extensively studied and several efficient Pd-,[1] Ni-,[2] or Fe-catalyzed[3] reactions are now available. Recently, we have investigated cross-coupling between two C sp^3 centers[4] as well as between C sp^3 and C sp^2 centers[5] 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-

---

[†] Ludwig-Maximilians-Universität München.

[‡] H. Lundbeck A/S.

[1] *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.

[2] (a) Kumada, M. *Pure Appl. Chem*. **1980**, *52*, 669. (b) Luh, T.-Y. *Acc. Chem. Res*. **1991**, *24*, 257. (c) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem*. **1992**, *57*, 4066. (d) Indolese, A. F. *Tetrahedron Lett*. **1997**, *38*, 3513. (e) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis* **1998**, 1544. (f) Lipshutz, B. H.; Kim, S.-K.; Mollard, P.; Blomgren, P. A.; Stevens, K. L. *Tetrahedron* **1998**, *54*, 6999. (g) Sofia, A.; Karlström, E.; Itami, K.; Bäckvall, J.-E. *J. Org. Chem*. **1999**, *64*, 1745.

[3] (a) Cahiez, G.; Marquais, S. *Pure Appl. Chem*. **1996**, *68*, 53. (b) Cahiez, G. *Synthesis* **1998**, 1199.

[4] (a) Giovanni, R.; Stüdemann, T.; Dussin, G., Knochel, P. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2387. (b) Giovanni, R.; Knochel, P. *J. Org. Chem*. **1999**, *64*, 3544.

[5] Giovanni, R.; Knochel, P. *J. Am. Chem. Soc*. **1998**, *120*, 11186.

[6] (a) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem*. **1994**, *59*, 6095. (b) Nguefack, J.-F.; Bollit, V.; Sinou, D. *Tetrahedron Lett*. **1996**, *33*, 5527. (c) Powell, N. A.; Rychnovsky, S. D. *Tetrahedron Lett*. **1996**, *37*, 7901. (d) Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Synlett*, **1999**, 199. (e) Nakamura, K.; Okubo, H.; Yamaguchi, M. *Synlett* **1999**, 549. (f) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riedermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur*. **1997**, 3, 1357.

10.1021/ol9907872 CCC: $18.00

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

Additive	Equiv.	Reaction Time (h)	Conversion (%)
-	-	1	0.5
Bu_4NF	1.0	1	0.7
$Bu_4N(ClO_4)$	1.0	1	3.8
CsI	1.0	1	1.5
LiI	1.0	1	13
Bu_4NBr	1.0	1	23
Bu_4NI	0.1	1.5	2.4
Bu_4NI	1.0	1	24
Bu_4NI	1.0	1.5	38
Bu_4NI	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 triflates[7] and benzylic zinc reagents[8] 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 °C[9] (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 Bu_4NI and Bu_4NBr give 23−24% yield of **4a** after only 1 h of reaction time. The amount of Bu_4NI added is also of importance for the reaction rate. Thus, a conversion of 2.4% is obtained with 0.1 equiv of Bu_4NI. 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).

Scheme 1

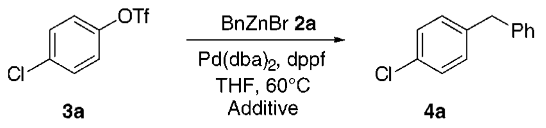
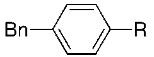
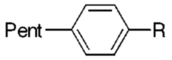
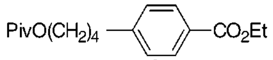
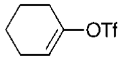
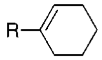
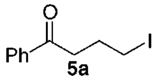
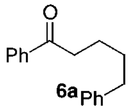
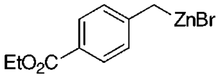
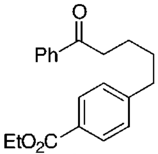
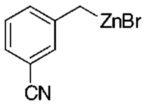
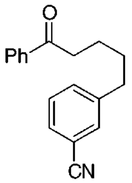


Table 2. Pd(0)-Catalyzed Cross-Coupling between Benzylic or Alkyl Zinc Halides and Alkenyl or Aryl Triflates in the Presence of Bu_4NI

Entry	Organozinc halide of type **2**	Triflate of type **3**	Reaction conditions (h, °C)	Product of type **4**	Yield (%)[a]
1	BnZnBr **2a**	$4\text{-}RC_6H_4OTf$ **3a**: R = Cl	2, 60	 **4a**: R = Cl	94
2	**2a**	**3b**: R = MeO	6, 60	**4b**: R = MeO	91
3	**2a**	**3c**: R = Me	2.5, 60	**4c**: R = Me	93
4	**2a**	**3d**: R = CO_2Et	4, 60	**4d**: R = CO_2Et	84
5	PentZnI **2b**	**3a**	4, 60	 **4e**: R = Cl	92
6	**2b**	**3c**	4, 60	**4f**: R = Me	89
7	$PivO(CH_2)_4ZnI$ **2c**	**3d**	4, 60	 **4g**	92
8	**2b**	 **3e**	1, 60	 **4h**: R = Pent	76
9	**2a**	**3e**	1, 60	**4i**: R = Bn	84

[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

Entry	Benzylic zinc reagent of type **2**	Alkyl iodide of type **5**	Reaction conditions (h, °C)	Product of type **6**	Yield (%)[a]
1	BnZnBr **2a**	 **5a**	16, 10	 **6a**	67
2	**2a**	Oct-I **5b**	4, 0	Oct-Bn **6b**	77
3	**2a**	$I(CH_2)_4OPiv$ **5c**	4, 0	$Bn(CH_2)_4OPiv$ **6c**	81
4	**2a**	$I(CH_2)_3SPh$ **5d**	16, rt	$Bn(CH_2)_3SPh$ **6d**	63
5	 **2d**	**5a**	16, rt	 **6e**	71
6	 **2e**	**5a**	16, 10	 **6f**	74

[a] Isolated yield of analytically pure products

Thus, in the presence of 3 equiv of Bu_4NI, efficient cross-coupling 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_4NI 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

---

(7) Ritter, K. *Synthesis* **1993**, 735.

(8) Berk, S. C.; Yeh, M. C. P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053.

(9) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.

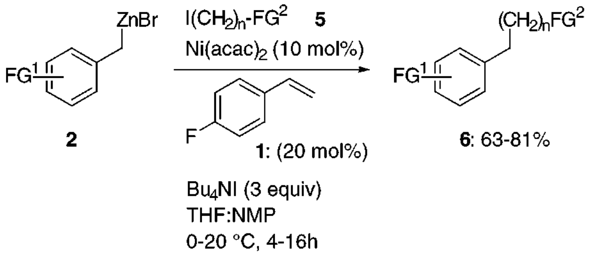
(10) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955.

(11) By using nonaflates (ArONf) even faster reactions were observed; this observation is consistent with earlier results: Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203.

(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 Bu_4NI (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. (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 Bu_4NI (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 × 70 mL). The combined organic phases were dried ($MgSO_4$) 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 sp^3−C sp^3 cross-coupling products of type **6** in good yields (Scheme 2 and Table 3).

Scheme 2



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 cross-coupling between benzylic zinc bromides and alkenyl or aryl triflates. It allows a new and efficient Ni(0)-catalyzed cross-coupling between alkyl iodides and benzylic zinc reagents. Further application of the dramatic effect of Bu_4NI in cross-coupling reactions as well as some mechanistic aspects of this acceleration are currently investigated in our laboratories.[12]

Acknowledgment. We thank the Leibniz program and the BMBF (03D00562), BASF AG for financial support A.E.J. thanks L'Oréal (Paris, France) for a fellowship.

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.

OL9907872