Fe(III)-Catalyzed Cross-Coupling Between Functionalized Arylmagnesium Compounds and Alkenyl Halides

Wolfgang Dohle,^a Felix Kopp,^a Gerard Cahiez,^{*b} Paul Knochel^{*a}

- ^a Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13, 81377 München, Germany Fax +49(89)21807680; E-mail: Paul.Knochel@cup.uni-muenchen.de
- ^b Département de Chimie (associé au CNRS), Ecole Supérieure de Chimie Organique et Minérale, 13, Boulevard de l'Hautil, 95092 Cergy-Pontoise, France

Received 17 July 2001

Abstract: Functionalized arylmagnesium reagents bearing an ester, cyano, nonaflate or trialkylsilyloxy group undergo fast cross-coupling reactions with alkenyl iodides or bromides in the presence of catalytic amounts of Fe(acac)₃ (5 mol%) at -20 °C within 1 hour resulting in the formation of the desired cross-coupling products in satisfactory yields. Excellent yields can be achieved by performing the cross-coupling reaction on solid phase by generating the Grignard reagent on the resin.

Key words: magnesium, iodine-magnesium exchange, iron(III)catalysis, cross-coupling reaction

Transition metal catalyzed cross-coupling reactions are amongst the most useful methods for forming new carbon-carbon bonds between two Csp²-centres.¹ Although in most of these reactions Pd(0)-catalysis² is used, other transition metals such as $Cu(I)^3$ or $Ni(0)^4$ have been used. Following the pioneering work of Kochi,⁵ one of us has recently shown the synthetic utility of $Fe(acac)_3$ as a catalyst in cross-coupling reactions between alkylmagnesium reagents and various alkenyl halides.⁶ Herein, we wish to report that iron(III) catalysis also allows cross-coupling reactions between functionalized arylmagnesium reagents and alkenyl iodides or bromides to take place under very mild reaction conditions. This is especially important if arylmagnesium derivatives bearing sensitive functional groups like an ester or cyano are used, since these organometallics are only stable up to 0 °C for a few hours.⁷ Thus, various aryl iodides of type **1** bearing functional groups such as an ester, cyano, trialkylsilyloxy group or nonaflate $(OSO_2(CF_2)_3CF_3 = ONf)^8$ are smoothly converted into the corresponding arylmagnesium reagents of type **2** by the reaction with *i*-PrMgBr (1.1 equiv) in THF at -20 °C for 1–4 hours. The resulting functionalized organomagnesium reagent **2** is treated with an alkenyl iodide or bromide **3** (0.7 equiv) at -20 °C in the presence of Fe(acac)₃ (5 mol%) for 15–30 min. A fast cross-coupling reaction occurs affording the desired polyfunctionalized products of type **4** in 50–73% yield (Scheme 1 and Table). The reaction proceeds with retention of the configuration of the double bond, affording only *E*-products.

Thus, *p*-carbethoxyphenylmagnesium bromide 2a reacts with (E)-1-iodohexene **3a** providing the cross-coupling product $4a^{11a}$ in 60% yield (entry 1 of the Table). Similarly, sulfonylamido-alkenyl iodide $3b^9$ reacts with 2a producing the (E)-styrene derivative 4b in 69% yield (entry 2). Both reactions give as side products the cross-coupling product (10-15%) of the alkenyl halide **3** and the excess of *i*-PrMgBr and reductive coupling of the functionalized arylmagnesium species 2 affording the corresponding homo-coupling biaryl derivatives (10–15%) as shown by GC and GC/MS analysis. Interestingly, cross-coupling reactions between functionalized aryl iodides 1 and phenylmagnesium bromide **2b** to the corresponding biaryls do not occur under various reaction conditions. In order to establish, if the carbethoxy group influences the yield of the reaction, we carried out a calibration experiment with phenylmagnesium bromide and **3b**, but the desired crosscoupling product 4c was obtained in a similar yield (65%; entry 3). The cyano- or nonaflate-substituted arylmagnesium species 2c and 2d undergo a cross-coupling reaction



 $FG = CO_2Et$, CN, OTIPS, ONf

Scheme 1

Synlett 2001, No. 12, 30 11 2001. Article Identifier: 1437-2096,E;2001,0,12,1901,1904,ftx,en;G14701ST.pdf. © Georg Thieme Verlag Stuttgart · New York ISSN 0936-5214

Entry	Grignard reagent 2	Alkenyl halide 3	Product of type 4	Yield (%) ^a
1	EtO ₂ C MgBr	I Bu 3a	EtO ₂ C Bu	60
	2a		4a	
2	2a	N Ph SO ₂ CF ₃	EtO ₂ C	69
		3b	Ph Noo or	
			4b	
3	MgBr	3b	Ph	65
	2b		Ph_N_SO ₂ CF ₃	
			4c	
4	NC	3a	NC	60
	MgBr		4d	
5	NfO	3a	NfO	73
	MgBr 2d		4e	
6	NfOMgBr	3a	NfO	50
	2e		4f	
7	2e	Br	NfOPh	62
		3c		
			4g	
8	TIPSO	3c	TIPSO	62
	2f		4h	

TableCross-Coupling Products 4 Obtained by the Reaction of Functionalized AryImagnesium Bromides 2 with Alkenyl Bromides or Iodides3 in the Presence of Catalytic Amounts of $Fe(acac)_3$ in THF

^a Yield of analytically pure product.

with (*E*)-1-iodohexene in 60% and 73% yield respectively (entries 4–5). A reactive alkenyl bromide, such as [(E)-2-bromoethenyl]benzene (**3c**), reacts smoothly with the Grignard reagent **2e** leading to the *E*-stilbene derivative **4g** in 62% yield (entry 7). Similarly, the electron-rich

arylmagnesium compound **2f** reacts with **3c** providing the desired product **4h** in 62% yield (entry 8).

These cross-coupling reactions can be easily performed on solid phase by generating the arylmagnesium species on the resin.¹⁰ Thus, the resin-attached m- and p-iodoben-



Scheme 2 ^aHPLC puritity measured at 254 nm. Isolated yields are >85%.

zoate **5a** and **5b** were treated with an excess of *i*-PrMgBr (5 equiv) in THF (–20 °C; 1 h), producing the corresponding arylmagnesium species. Its reaction with an excess of alkenyl halide (**3a** or **3c**; 15 equiv) in the presence of Fe(acac)₃ (5 mol%) at –20 °C for 30 min produces, after cleavage from the resin (TFA/CH₂Cl₂/H₂O 9:1:1; 15 min at r.t.), the corresponding benzoic acid derivatives **6a–d**^{11b} with excellent HPLC purities and usually in more than 85% isolated yield (Scheme 2).

In summary, we have shown that alkenyl iodides or bromides react under mild conditions (-20 °C, less than 1 h) with functionalized arylmagnesium bromides in the presence of Fe(acac)₃ (5 mol%). This method is of special interest when functionalized arylmagnesium reagents are used since with a Ni(0) or Pd(0) catalysis the cross-coupling reaction occurs only at temperatures above 20 °C resulting in a destruction of the sensitive functions (ester, cyano) present in the magnesium reagent or in the crosscoupling product.

Acknowledgement

We thank the DFG (Leibniz program) for financial support. W. D. thanks BASF AG (Ludwigsafen) for a fellowship. We thank BASF AG and Degussa (Hanau) for generous gifts of chemicals.

References

- (a) Metal-catalyzed Cross-Coupling Reactions; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**.
 (b) Nicolaou, K. C.; Sorensen, E. J. Classics in Total Synthesis; VCH: Weinheim, **1996**, 565. (c) Tsuji, J. Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis; Wiley: New York, **1995**. (d) Erdik, E. Tetrahedron **1992**, 48, 9577.
- (2) Tsuji, J. Palladium Reagents and Catalysts: Innovations in Organic Synthesis; Wiley: Chichester, 1995, .
- (3) For an excellent review, see: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

- (4) (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) Sophia, A.; Karlström, E.; Itami, K.; Bäckvall, J.-E. J. Org. Chem. 1999, 64, 1745. (g) Tang, X. Q.; Montgomery, J. J. Am. Chem. Soc. 2000, 122, 6950. (h) Montgomery, J. Acc. Chem. Res. 2000, 33, 467. (i) Giovannini, R.; Knochel, P. J. Am. Chem. Soc. 1998, 120, 11186. (j) Lipshutz, B. H. Adv. Synth. Catal. 2001, 343, 313. (k) Lipshutz, B. H.; Bulow, G.; Fernandez-Lazaro, F.; Kim, S.-K.; Lowe, R.; Mollard, P.; Stevens, K. L. J. Am. Chem. Soc. 1999, 121, 11664.
- (5) (a) Tamura, M.; Kochi, J. K. J. Am. Chem. Soc. 1971, 93, 1487. (b) Tamura, M.; Kochi, J. K. Synthesis 1971, 93, 303. (c) Tamura, M.; Kochi, J. K. J. Organomet. Chem. 1971, 31, 289. (d) Tamura, M.; Kochi, J. K. Bull. Chem. Soc. Jpn. 1971, 44, 3063. (e) Tamura, M.; Kochi, J. K. Synthesis 1971, 303. (f) Kochi, J. K. Acc. Chem. Res. 1974, 7, 351. (g) Neumann, S.; Kochi, J. K. J. Org. Chem. 1975, 40, 599. (h) Smith, R. S.; Kochi, J. K. J. Org. Chem. 1976, 41, 502. (i) See also: Molander, G.; Rahn, B.; Shubert, D. C.; Bonde, S. E. Tetrahedron Lett. 1983, 24, 5449.
- (6) (a) Cahiez, G.; Marquais, S. Pure Appl. Chem. 1996, 68, 669. (b) Cahiez, G.; Marquais, S. Tetrahedron Lett. 1996, 37, 1773. (c) Cahiez, G.; Avedissian, H. Synthesis 1998, 1199.
- (7) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* 2001, 477; and references cited therein.
- (8) Rottländer, M.; Knochel, P. J. Org. Chem. 1998, 63, 203.
- (9) Preparation of the iodosulfonamide **3b**: *N*-Benzyl-1,1,1trifluoromethanesulfonamide¹² (3.70 g; 15.5 mmol) was dissolved in acetone (8 mL) and potassium carbonate (4.28 g; 31.0 mmol) was added. The suspension was stirred overnight at r.t. Then (*E*)-1,5-diiodopent-1-ene¹³ (5.00 g; 15.5 mmol) was added and the reaction mixture was stirred overnight at r.t. until completion (GC analysis). The reaction mixture was then quenched with saturated NH₄Cl solution and extracted with ether. The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography using pentane as eluent to give **3b** (4.50 g; 10.4 mmol; 67%) as a colourless oil.

- (10) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. Angew. Chem. Int. Ed. **1998**, 37, 1701.
- (11) Typical Procedures: (a) Reaction in solution. Preparation of Ethyl 4-[(1E)-hex-1-enyl]benzoate 4a (entry 1 of the table): Ethyl 4-iodobenzoate (384 mg; 1.4 mmol)was placed in a dry argon flushed 50 mL Schlenk-flask equipped with a rubber septum and magnetic stirring bar. Dry THF (3.0 mL) was added and the solution was cooled to -20 °C. Then isopropylmagnesium bromide (6.0 mL; 0.55 M in THF; 3.3 mmol) was added slowly and the reaction mixture was stirred at this temperature until the exchange reaction was complete (checked by TLC). The resulting suspension was then transferred dropwise via cannula into another dry argon flushed Schlenk-flask containing a solution of iron (III) acetylacetonate (18 mg; 5.1 µmol)and 1-iodohex-1-ene (212 mg; 1.0 mmol) in dry THF (2.0 mL) stirring at -20 °C. After the reaction was complete (checked by TLC and GC) methanol (3 mL) and water (30 mL) were added and the reaction mixture was extracted with ethyl acetate (3×30) mL). The combined organic phases were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography using 98:2 pentane/ethyl acetate as eluent giving the product 4a (140 mg; 0.60 mmol; 60%) as a colourless oil. (b) Reaction on solid phase. Preparation of 4[(1E)-Hex-1-enyl]benzoic

Acid 6c: Wang resin loaded with 4-iodobenzoic acid (150 mg; 0.63 mmol/g; 0.095 mmol) was placed in a dry argon flushed 10 mL Schlenk tube equipped with a rubber septum and a magnetic stirring bar and allowed to swell in dry THF (0.5 mL) for 5 min at -20 °C. Then iso-propylmagnesium bromide (0.87 mL; 0.55 M in THF; 0.48 mmol) was added slowly and the resin was stirred for 1 h. Then a solution of iron (III) acetylacetonate (1.7 mg; 4.8 µmmol) and 1iodohex-1-ene (303 mg; 1.44 mmol) in THF was added at -20 °C and the reaction mixture was stirred for 30 min at this temperature. After completion of the reaction (checked by analytical HPLC) the resin was filtered and sequentially washed three times with THF (2 mL), DMF (2 mL) and methanol (2 mL). Finally it was washed three times with CH₂Cl₂ (2 mL). The product resin (100 mg) was placed in a 2 mL-syringe equipped with a polyethylene filter plate and treated with TFA/ CH_2Cl_2/H_2O 9:1:1 (1 mL) for 15 min at r.t. After removing the volatiles in vacuo 6c (11.2 mg; 54.9 $\mu mol;\,87\%$ yield; 94% HPLC purity) was obtained as a white solid (mp: 238-245 °C dec.).

- (12) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. *Tetrahedron* **1975**, *31*, 2517.
- (13) Jabri, N.; Alexakis, A.; Normant, J. F. Bull. Soc. Chim. Fr. 1983, 2, 321.