ORGANIC LETTERS

2009
Vol. 11, No. 23
5514−5517

Palladium-Catalyzed Cross-Coupling Reaction of Secondary Benzylic Bromides with Grignard Reagents

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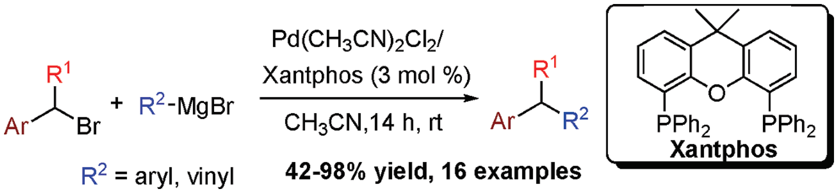
Received October 9, 2009

ABSTRACT



A mild palladium-catalyzed Kumada−Corriu reaction of secondary benzylic bromides with aryl and alkenyl Grignard reagents has been developed. In the presence of the Xantphos ligand, the undesired *β*-elimination pathway is minimized, affording the corresponding cross-coupling products in acceptable to good yields. The reaction proceeds with inversion of the configuration.

Metal-catalyzed cross-coupling reactions are undoubtedly one of the most powerful tools for C−C bond formation[1] and have produced a deep impact in retrosynthesis[2] and industrial synthesis.[3] Although initially focused on aryl and alkenyl electrophiles, the huge progress achieved over the last three decades has allowed the development of very efficient procedures for the cross-coupling reactions between sp-, sp^2-, and sp^3-hybridized carbon atoms, including Csp^3 electrophiles, mainly *primary* alkyl halides and sulfonates.[4] In this context, the *secondary* alkyl halides are more challenging coupling partners due to the extra steric hindrance and electron richness of these substrates. In the last five years great effort has been devoted to this field, and several efficient metal-catalyzed protocols for the coupling of secondary alkyl halides have been reported,[5] especially using nickel, iron, and cobalt catalysts, including a handful of outstanding catalytic asymmetric procedures.[6] On the other hand, efficient protocols for the complementary cross-

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(1) (a) *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: New York, 2005. (b) *Metal-catalyzed Cross-coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (c) Beller, M., Bolm, C., Eds., *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (d) Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1439 (especial issue on metal-catalyzed cross-coupling reactions)

(2) For reviews on applications in natural product synthesis, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(3) Beller, M.; Zapf, A.; Magerlein, W. *Chem. Eng. Technol.* **2001**, *24*, 575.

(4) For recent reviews, see: (a) Liegault, B.; Renaud, J.-L.; Bruneau, C. *Chem. Soc. Rev.* **2008**, *37*, 290. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (c) Fürstner, A.; Martín, R. *Chem. Lett.* **2005**, *34*, 624. (d) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (e) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(5) For a comprehensive recent review on cross-coupling reactions of secondary alkyl electrophiles, see: (a) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656 (and references cited therein). For selected recent examples on metal-catalyzed coupling reactions of secondary alkyl electrophiles with Grignard reagents, see: Ni catalysts. (b) Vechorking, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756. Fe catalysts: (c) Sherry, B. D.; Furstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (d) Cahiez, G.; Duplais, C.; Moyeux, A. *Org. Lett.* **2007**, *9*, 3253. (e) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364. (f) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6521. Co catalysts: (g) Cahiez, G.; Caboche, C.; Duplais, C.; Moyeux, A. *Org. Lett.* **2009**, *11*, 277. (h) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1565. Zn catalysts: (i) Studte, C.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451. Ag catalysts: (j) Someya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* **2009**, *50*, 3270. (k) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 969. V: (l) Yasuda, S.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 287.

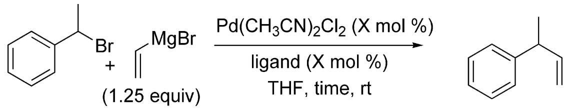
10.1021/ol902335c CCC: $40.75

coupling reaction of secondary alkyl organometallics with Csp^2 electrophiles have also been reported.[7]

However, a survey of the literature reveals that examples of palladium-catalyzed cross-coupling reactions of secondary alkyl halides are scarce.[8] A pioneering work by Sustmann and co-workers described the Pd(0)-catalyzed Stille coupling reaction of 1-bromoethylbenzene bromide with tetramethyl and tetraethyl tin.[8a] Twenty years later, Glorius and co-workers reported the Sonogashira coupling of secondary alkyl bromides catalyzed by CuI and an N-heterocyclic carbene palladium complex.[8b] Recently, Asensio's group demonstrated that secondary bromo sulfoxides are effective substrates in the Suzuki reaction with aryl boronic acids,[8c] and Lautens' group reported the Catellani intramolecular reaction of secondary alkyl iodides.[8d,e] Interestingly, unlike the Ni-, Fe-, and Co-catalyzed processes, in which there is ample evidence of the participation of radical mechanisms, it has been established that at least some Pd(0)-catalyzed reactions occur by S_N2-type oxidative addition to the alkyl halide.[9] This different mechanistic behavior can have important stereochemical consequences, especially from enantioenriched secondary alkyl halides. Herein, we report our initial results on the Pd-catalyzed Kumada−Corriu cross-coupling reaction of racemic and enantioenriched secondary benzylic bromides with vinyl and aryl Grignard reagents.[10]

We chose as a model reaction the coupling of 1-bromoethylbenzene[11] with vinyl magnesium bromide. Preliminary experiments were performed in THF using 10 mol % of $Pd(CH_3CN)_2Cl_2$ as catalyst and a variety of ligands[12] in an attempt to find a catalytic system capable of minimizing the competitive β-hydride elimination pathway (Table 1). After some experimentation, we found that bidentate ligands with a large bite angle such as dppf (96°) and, especially, Xantphos[13] (111°) turned out to be excellent ligands for the cross-coupling reaction, driving the reaction to complete conversion after 7 h at room temperature, styrene not being detected in the reaction mixture (entries 1 and 2). Interestingly, a similar result was obtained using 3 mol % of the $Pd(CH_3CN)_2Cl_2$/Xantphos catalyst system (entry 3). Nevertheless, no reaction was observed when the catalyst loading was reduced to 1 mol % (entry 4). From a practical point of view, it is interesting to note that both catalyst components are air stable and commercially available.

Table 1. Screening of Ligands for the Kumada−Corriu Cross-Coupling Reaction



entry	X	ligand[a]	time (h)	yield (%)[b]
1	10	dppf	7	86
2	10	Xantphos	7	97
3	3	Xantphos	14	98
4	1	Xantphos	14	--[c]

[a] See Supporting Information for results with other ligands. [b] Isolated yield after column chromatography. [c] No reaction was observed.

Encouraged by these initial findings, we next examined the scope of this protocol with regard to the Grignard reagent (Table 2). Under the standard optimized reaction conditions, the cross-coupling reaction of 1-bromoethylbenzene with phenyl magnesium bromide and a variety of substituted aryl Grignard reagents proceeded in good to excellent yields regardless of the electronic nature of the substituents[14] (entries 1−5). A heteroaryl Grignard reagent, such as 2-thienyl, is also a suitable nucleophile for this reaction (entry 6). However, a lower yield was obtained with 2-naphthyl magnesium bromide (57% yield, entry 7), and no coupling reaction was observed with the bulkier *o*-tolyl Grignard reagent (entry 8) showing that this cross-coupling reaction

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(6) For a review, see: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347. For a very recent example, see: (b) Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 154.

(7) For selected recent references, see: (a) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532. (b) Imao, K.; Glasspoole, B- W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (c) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257. (d) van den Hoogenband, A.; Lange, J. H. M.; Terpstra, J. W.; Koch, M.; Visser, G. M.; Visser, M.; Korstanje, T. J.; Jastrzebski, J. T. B. H. *Tetrahedron Lett.* **2008**, *49*, 4122. (e) Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Shu, L.; Zhang, T.; Lei, A. *Org. Lett.* **2007**, *9*, 4571.

(8) (a) Sustmann, R.; Lau, J.; Zipp, M. *Tetrahedron Lett.* **1986**, *27*, 5207. (b) Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925. (c) Rodríguez, N.; Ramírez de Arellano, C.; Asensio, G.; Medio-Simón, M. *Chem.—Eur. J.* **2007**, *13*, 4223. (d) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485. (e) See also: Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* **2000**, 157. For Pd-catalyzed carbonylation reactions of secondary alkyl electrophiles, see: (f) Urata, H.; Maekawa, H.; Takahashi, S.; Fuchikami, T. *J. Org. Chem.* **1991**, *56*, 4320. (g) Imbeaux, M.; Mestdagh, H.; Moughamir, K.; Roland, C. *J. Chem. Soc., Chem. Commun.* **1992**, 1678. (h) For an isolated example of a Pd-catalyzed cross-coupling with trialkynylindium reagents, see ref 11b.

(9) (a) Hills, I. D.; Netherton, M. R.; Fu, C. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749. (b) For recently reported radical-mediated Kumada cross-couplings with aryl bromides, see: Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 205.

(10) In 1986 the (dppf)Pd(0)-catalyzed cross-coupling reaction of a secondary alkyl iodide with Grignard reagents was reported: (a) Castle, P. L.; Widdowson, D. A. *Tetrahedron Lett.* **1986**, *27*, 6013. Later, these results were re-examined, disclosing that the reaction leads to reduction or β-elimination products rather than the coupling products: (b) Yuan, K.; Scott, W. J. *Tetrahedron Lett.* **1989**, *30*, 4779.

(11) Examples of cross-coupling reaction of secondary benzylic electrophiles are scarce, see: (a) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482. (b) Caeiro, J.; Pérez Sestelo, J.; Sarandeses, L. A. *Chem.—Eur. J.* **2008**, *14*, 74.

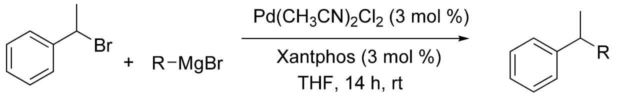
(12) Either no reaction or major formation of styrene was observed in the presence of ligands such as PPh_3, PCy_3, Binap, DTBM-Segphos, or Josiphos (see Supporting Information for ligand screening details).

(13) The great bite angle and flexibility of Xantphos have been invoked as key elements in other Pd-catalyzed processes. For a review, see: (a) Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741. For recent examples, see (b) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102. (c) Dongol, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015.

(14) **Typical procedure for the Kumada−Corriu cross-coupling**: To a solution of the Xantphos ligand (4.6 mg, 0.008 mmol) and $Pd(CH_3CN)_2Cl_2$ (2.0 mg, 0.008 mmol) in THF (1.0 mL), under nitrogen atmosphere, was added 1-bromoethylbenzene (35 mL, 0.26 mmol). The resulting solution was cooled to 0 °C, and the Grignard reagent (1.0 M in THF, 0.33 mL, 0.33 mmol) was added dropwise. The mixture was stirred overnight (10−14 h) at room temperature and filtered through a plug of Celite with the aid of CH_2Cl_2 (5.0 mL). The solvent was removed under reduced pressure, and the residue was purified by silica gel flash chromatography. We also confirmed that the reaction can be performed at a higher scale: in a 500 mg scale reaction (2.6 mmol of the benzylic bromide) the reaction illustrated in entry 2 (Table 2) was accomplished in 93% yield.

is very sensitive to steric effects. Disappointingly, the coupling reaction also did not occur with an alkyl Grignard reagent such as MeMgBr (entry 9).

Table 2. Pd-Catalyzed Kumada–Corriu Reaction of 1-Bromoethylbenzene with Aryl Grignard Reagents[14]



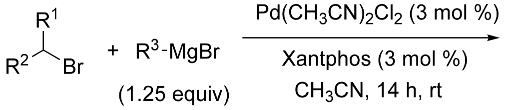
entry	R	yield[b]
1	Ph	96
2	(*p*-F)C_6H_4	95
3	(*p*-OMe)C_6H_4	98
4	(*p*-Ph)C_6H_4	94
5	(*m*-OMe)C_6H_4	70
6	2-thienyl	95
7	2-naphthyl	57[b]
8	(*o*-Me)C_6H_4	0[c]
9	Me	0[c]

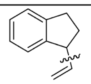
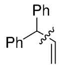
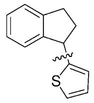
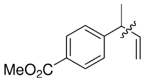
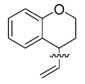
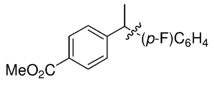
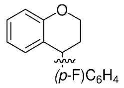
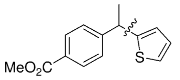
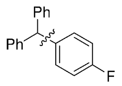
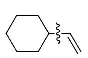
[a] Isolated yield after column chromatography. [b] A 40% yield of styrene was also isolated. [c] A similar outcome was obtained using CH_3CN as solvent.

We next extended the scope of this reaction to other secondary benzyl-type electrophiles[15] (Table 3). The reaction of 1-bromoindene with vinyl magnesium bromide under the standard conditions afforded the coupling product in low yield (entry 1). Pleasingly, a very efficient coupling reaction occurred when acetonitrile was used as solvent instead of THF[16] (entry 1 vs 2). 4-Bromochromene was also a suitable substrate, albeit the isolated yields in the coupling products were moderate due to the competitive *β*-elimination pathway (entries 4 and 5). The coupling reaction proceeded in nearly quantitative yield from bromodiphenylmethane, allowing the straightforward construction of triarylmethanes (entry 6). Interestingly, this procedure tolerates the presence of an ester moiety at the electrophile (entries 8–10). Unfortunately, neither the cyclohexyl bromide nor the cyclohexyl iodide coupled with vinyl magnesium bromide (entry 11).

Finally, we studied the stereochemical course of the reaction from a nonracemic secondary bromide (Scheme 1). The Pd-catalyzed reactions of (*S*)-1-bromoethylbenzene (85–86% ee)[17] with *p*-methoxy and *p*-fluorophenyl magnesium bromide provided the coupling products with nearly full inversion of the configuration[18,19] (84%–85% ee). This stereochemical outcome is in full agreement with the previously reported Pd-catalyzed Suzuki-type,[8c,20b] Catellani-type,[8d] and Heck-type reactions[20a] of enantiopure secondary halides.

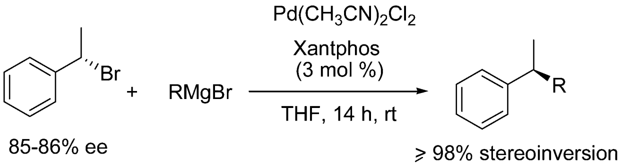
Table 3. Pd-Catalyzed Kumada–Corriu Reaction of Secondary Benzylic Bromides



entry	product	yield(%)[a]	entry	product	yield(%)[a]
1		27[b]	7		50
2		94			
3		93	8		61[c]
4		42[c]	9		94
5		53[c]	10		72[c]
6		98	11		0

[a] Isolated yield after column chromatography. [b] THF was used as solvent. [c] The *β*-elimination product was also isolated as a minor product (see Supporting Information for details).

Scheme 1



R	product	yield
(*p*-MeO)C_6H_4	**1**	97%
(*p*-F)C_6H_4	**2**	94%

In summary, we have developed a procedure for the Pd-catalyzed cross-coupling reaction of secondary benzylic bromides with aryl and vinyl Grignard reagents. This protocol strongly relies on the use of the Xantphos ligand to minimize

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(15) The primary benzyl bromides are also suitable substrates for this Kumada–Corriu coupling reaction (see Supporting Information for details).

(16) Low yields were also obtained in other solvents, such as DMA, DMF, NMP, or toluene.

(17) (*S*)-1-Bromoethylbenzene was prepared in 85–86% ee by bromination of (*R*)-1-phenyl-1-ethanol (94% ee) with $POBr_3$ using DMAP as base. See also: Dauben, H. J.; McCoy, L. L. *J. Am. Chem. Soc.* **1959**, *81*, 5404.

(18) Compound (*R*)-**1** had been previously described, which allowed us to confirm the inversion of configuration: Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331.

(19) In contrast, it has been reported that the Fe-catalyzed reaction of enantiopure secondary halides with Grignard reagents leads to racemic coupling products: Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. For the Zn-catalyzed enantiospecific reaction of α-hydroxy ester triflates, see ref 5i.

(20) (a) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340. (b) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910.

the β-hydride elimination pathway. In addition, we have shown that the reaction proceeds with inversion of the configuration. Further investigations into this and related methods, as well as mechanistic studies, are ongoing.

Acknowledgment. This work was supported by the Spanish Ministerio de Ciencia e Innovación (grants CTQ2006-01121 and CTQ2009-07791) and UAM-Consejería de Educación de la Comunidad Autónoma de Madrid (project CCG08-UAM/PPQ-4454). A.L. thanks the Comunidad Autónoma de Madrid for a predoctoral fellowship.

Supporting Information Available: Experimental procedures and characterization data for new compounds and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902335C