ORGANIC LETTERS
2010
Vol. 12, No. 19
4388−4391

Room Temperature Palladium-Catalyzed Cross Coupling of Aryltrimethylammonium Triflates with Aryl Grignard Reagents

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Received August 10, 2010

ABSTRACT

Aryltrimethylammonium triflates and tetrafluoroborates were found to be highly reactive electrophiles in the Pd-catalyzed cross coupling with aryl Grignard reagents. The coupling reactions proceed at ambient temperature with a nearly stoichiometric quantity of Grignard reagent, and diverse functionality is tolerated. Competition experiments established the reactivity of $PhNMe_3OTf$ relative to PhCl, PhBr, PhI, and PhOTf.

The nickel- or palladium-catalyzed cross coupling of Grignard reagents with aryl and vinyl halides, discovered by Kumada and Corriu in 1972, is among the simplest methods for biaryl synthesis.[1] Numerous alternatives to traditional aryl halide electrophiles have been employed in this reaction, including aryl-oxygen (triflates,[2] tosylates,[3] mesylates,[4] phosphates,[5] alkyl ethers,[6] *O*-carbamates,[2] acetates,[7] diaryl sulfates,[8] phenolic salts[9]) and aryl-sulfur[10] (thiols,[11] sulfides,[11,12] sulfoxides,[13] sulfones,[11,13] *O*-alkyl sulfonates,[14] sulfonamides[15]) derivatives. Electrophiles derived from aryl-nitrogen species, however, have received comparatively little attention. In 1988, Wenkert and coworkers reported the first cross coupling of aryltrimethylammonium iodides with aryl and alkyl Grignard reagents (Scheme 1).[16] This pioneering work demonstrated the

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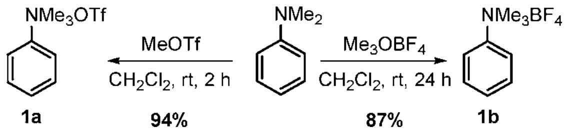
Scheme 1. Wenkert's Ni-Catalyzed Cross Coupling of Ar-NMe_3I and Our Pd-Catalyzed Cross Coupling of Ar-NMe_3OTf

feasibility of oxidative addition of a Ni(0) species into a C−N bond. The low yields obtained, high reaction temperature (benzene reflux), long reaction time (14 h), and functional group intolerance (methoxy and fluoro groups were competitively coupled) left room for improvement, however. In 2003, MacMillan and co-workers reported the $Ni(cod)_2$/IMes-catalyzed Suzuki cross coupling of aryltrimethylammonium triflates.[17] While this procedure gave high yields, the air-sensitive nature of $Ni(cod)_2$ was a concern for large-scale applications. We recently became interested in using aryltrimethylammonium salts in cross-coupling reactions with aryl Grignard reagents. In this communication we report our findings on the dramatic effect of the counterion on reactivity and the subsequent development of conditions which allow for the first time a palladium-catalyzed cross coupling of aryltrimethylammonium triflates with grignard reagents.

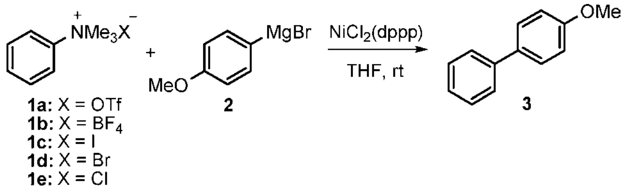
The counterion effect on reactivity was examined first. The reaction of phenyltrimethylammonium salts **1a**−**e** with 4-methoxyphenylmagnesium bromide **2** was chosen as a model reaction. Salts **1a** and **1b** were prepared from *N*,*N*-dimethylaniline in high yields as shown in Scheme 2. Salts **1c**−**e** were purchased from commercial sources.

Scheme 2. Preparation of Triflate and Tetrafluoroborate Salts



Employing Wenkert's catalyst, $NiCl_2(dppp)$[14] (10 mol %), with 1.1 equiv of Grignard **2**, we were gratified to observe a fast reaction at room temperature with salts **1a** and **1b** (Table 1, entries 1 and 2). In contrast, the iodide, bromide, and chloride salts **1c**−**e** reacted much more slowly at room temperature (entries 3−5). The exceptional reactivity of the triflate salt **1a** suggested that the catalyst loading could be lowered; this was indeed possible and the reaction proceeded equally as fast with 1 mol % catalyst (entry 7).

Table 1. Counterion Screening with $NiCl_2(dppp)$[a]



entry	salt	mol % catalyst	time [h][b]	yield [%][c]
1	**1a**	10	2	58
2	**1b**	10	2	56
3	**1c**	10	48[d]	19
4	**1d**	10	48[d]	12
5	**1e**	10	48[d]	5
6	**1a**	2.5	2	60
7	**1a**	1.0	4	61

[a] Reaction conditions: $PhNMe_3X$ **1** (1.0 mmol), THF (1 mL), $NiCl_2(dppp)$, 4-MeO(C_6H_4)MgBr **2** (2.2 mL, 0.5 M in THF, 1.1 equiv), rt. [b] Time for complete conversion of **1** by HPLC analysis. [c] HPLC assay yield. [d] Complete conversion of **1** not achieved after 48 h.

Having established the greater reactivity of triflate **1a** over halide salts, we next explored alternative catalysts in an effort to further increase the yield of **3**. The results are summarized in Table 2.

Table 2. Catalyst Screening Results[a]

entry	catalyst	time [h][b]	yield [%][c]
1	none	24[d]	3
2	$NiCl_2$	24	34
3	$NiCl_2(dppp)$	4	61
4	$NiCl_2(dppe)$	2	65
5	$NiCl_2(dppf)$	2	65
6	$NiCl_2(PPh_3)_2$	1	69
7	$NiCl_2(PCy_3)_2$	5	60
8	$PdCl_2$	24	12
9	$Pd(OAc)_2$	24	14
10	$PdCl_2(dppf)$	1	81
11	$PdCl_2(PPh_3)_2$	1	93
12	$PdCl_2[P(o\text{-tolyl})_3]_2$	5	65
13	$Pd(PPh_3)_4$	30	88
14	$PdCl_2(PCy_3)_2$	24[d]	5
15	$CoCl_2 + 2PPh_3$	2	30

[a] Reaction conditions: $PhNMe_3OTf$ **1a** (1.0 mmol), THF (1 mL), catalyst (1.0 mol %), 4-MeO(C_6H_4)MgBr **2** (2.2 mL, 0.5 M in THF, 1.1 equiv), rt. [b] Time for complete conversion of **1a** by HPLC analysis unless noted otherwise. [c] HPLC assay yield. [d] Complete conversion of **1a** not achieved after 24 h.

With no catalyst (entry 1), little background reaction was observed. By using ligand free $NiCl_2$ (entry 2), a low yield

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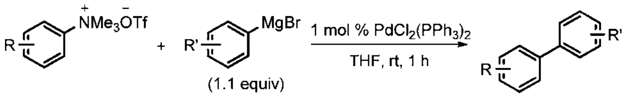
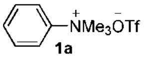
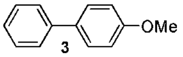
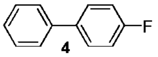
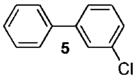
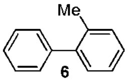
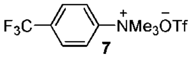
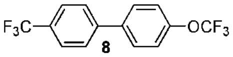
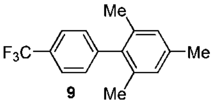
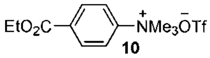
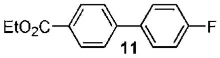
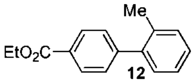
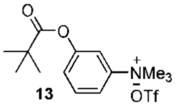
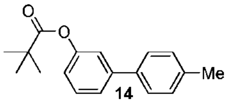
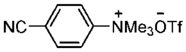
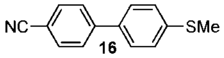
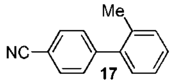
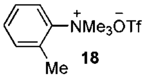
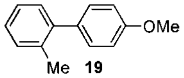
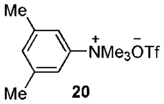
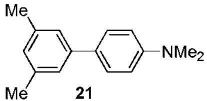
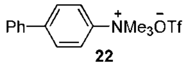
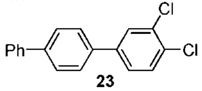
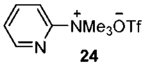
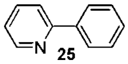
Table 3. Pd-Catalyzed Coupling of Aryltrimethylammonium Triflates with Aryl Grignard Reagents[a]



entry	ArNMe$_3$OTf	product	yield [%][b]
1	 **1a**	 **3**	91
2	**1a**	 **4**	94
3	**1a**	 **5**	93
4	**1a**	 **6**	92
5	 **7**	 **8**	94
6	**7**	 **9**	87[c]
7	 **10**	 **11**	88
8	**10**	 **12**	84
9	 **13**	 **14**	90
10	 **15**	 **16**	81
11	**15**	 **17**	79
12	 **18**	 **19**	88
13	 **20**	 **21**	92
14	 **22**	 **23**	89
15	 **24**	 **25**	91

[a] See the Supporting Information for procedures for preparation of ArNMe$_3$OTf and for all cross-coupling reactions. [b] Isolated yield after chromatography on SiO$_2$. [c] Reaction run at 60 °C for 2 h.

of **3** was obtained. Bidentate (entries 3−5) and monodentate (entries 6−7) ligands on nickel gave similar yields, with NiCl$_2$(PPh$_3$)$_2$ being optimal (69% assay yield of **3**). Interestingly, NiCl$_2$(PCy$_3$)$_2$, which has been shown to be a powerful catalyst for many difficult cross-coupling reactions, was significantly slower (5 h) than the other arylphosphine-based catalysts. Next, palladium catalysis was investigated. Nonligated Pd gave slow reactions and low yields (entries 8 and 9). Using PdCl$_2$(dppf), however, gave complete reaction in <1 h and an excellent yield (81%). The best result (93% assay yield) was obtained with PdCl$_2$(PPh$_3$)$_2$ (entry 11). Variation to a more bulky (entry 12) or more electron-rich (entry 14) phosphine gave lower yields. Interestingly, Pd(PPh$_3$)$_4$ also gave an excellent assay yield of 88%, but proceeded much more slowly, requiring 30 h for complete conversion of **1a** (entry 13). Catalysis by cobalt proceeded in low yield (entry 15).

The scope of the cross-coupling reaction was explored with use of the optimized reaction conditions (Table 3). Para-, meta-, and ortho-substituted aryl Grignard reagents all coupled with salt **1a** in excellent yields (entries 1−4). Notably, the presence of chloro groups was well tolerated under the reaction conditions (entries 3 and 14). The sterically hindered 2-mesitylmagnesium bromide coupled only slowly at rt, but on heating to 60 °C for 2 h, an excellent yield of biaryl **9** was obtained (entry 6). The functional group compatibility of the reaction extended to alkyl esters (entries 7 and 8), an aryl ester (entry 9), and nitriles (entries 10 and 11). In addition, a methyl thioether was tolerated (entry 10). A terphenyl could be produced by employing the 4-biphenyl salt **22** (entry 14). Finally, the 2-pyridyl salt **24** also coupled smoothly (entry 15).

Given the nearly quantitative nature of the methylation reaction of *N*,*N*-dimethylanilines with methyl triflate, we suspected the methylation and cross-coupling reactions could be telescoped into a one-pot process. Thus, treatment of *N*,*N*-dimethylaniline with a slight excess of methyl triflate in CH$_2$Cl$_2$ gave the salt **1a**. Subsequent addition of THF, PdCl$_2$(PPh$_3$)$_2$, and finally 4-fluorophenylmagnesium bromide gave biaryl **4** in 88% isolated yield (Scheme 3). The reaction time was longer for this one-pot protocol (5 h vs 1 h for the direct reaction of **1a**), but the yield was nonetheless comparable.

While the examples in Table 3 demonstrated the present reaction conditions are tolerant of several functional groups which have been shown to be competent electrophiles in various Ni- and Pd-catalyzed cross-coupling reactions (F,[18] Cl,[19] OMe,[6] OCF$_3$,[20] OPiv,[21] SMe,[9,10] CN[22]), we sought to establish reactivity trends relative to the most common electrophiles. A set of competition experiments, outlined in Table 4, was conducted. Thus, an equimolar mixture of salt **1a** and PhX (X = Cl, Br, I, or OTf) and 1 mol % PdCl$_2$(PPh$_3$)$_2$ in THF at rt was treated with 1 equiv of 4-fluorophenylmagnesium bromide. The reactions were

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(18) Bohm, V. P. W.; Gstottmayer, C. W. K.; Weskamp, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3387.

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Scheme 3. One-Pot Methylation/Cross Coupling of *N*,*N*-Dimethylaniline

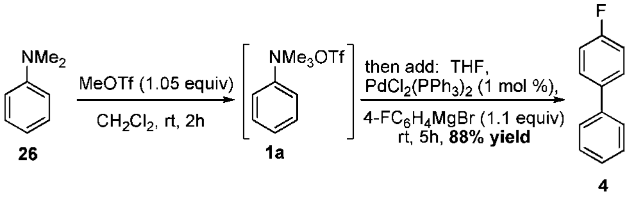
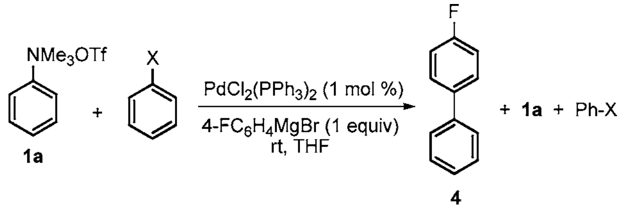


Table 4. Competition Experiments in the Coupling of **1a** and Phenyl Electrophiles with 4-Fluorophenylmagnesium Bromide[a]



entry	PhX	yield of **4**[b] [%]	recovery of **1a**[b] [%]	recovery of PhX[b] [%]
1	PhCl	94	0	97
2	PhBr	94	4	92
3	PhI	93	53	41
4	PhOTf	91	22	80

[a] Reaction conditions: $PhNMe_3OTf$ **1a** (1.0 mmol), PhX (1.0 mmol), THF (2 mL), $PdCl_2(PPh_3)_2$ (1.0 mol %), $4\text{-}F(C_6H_4)MgBr$ (1.0 mL, 1.0 M in THF, 1.0 equiv), rt. [b] HPLC assay yield.

monitored by HPLC for complete consumption of 4-fluorophenylmagnesium bromide. Upon completion, the reactions were quenched with MeOH and HPLC assay yields of product **4**, residual **1a** and residual PhX were obtained. The salt **1a** reacted much faster than PhCl or PhBr, as nearly complete consumption of **1a** was observed in both cases, along with nearly complete recovery of PhCl and PhBr (entries 1 and 2). The experiment with PhI, however, showed a slight preference in reactivity of PhI over **1a** (53% of **1a** recovered vs 41% of PhI recovered; entry 3). Finally, the experiment employing PhOTf showed a preferential reaction of **1a** (22% of **1a** recovered vs 80% of PhOTf recovered; entry 4). From these experiments the relative reactivities, under the present reaction conditions, can be ascribed as follows: PhI is slightly more reactive than $PhNMe_3OTf$, which is in turn slightly more reactive than PhOTf, and much more reactive than either PhBr or PhCl.

In conclusion, we have demonstrated that aryltrimethylammonium triflates and tetrafluoroborates are highly reactive electrophiles for Pd-catalyzed cross coupling with aryl Grignard reagents. Palladium was found to be more efficient than nickel for catalysis of this process. The reaction proceeds under mild reaction conditions (rt) and with only a slight excess of Grignard reagent, and therefore is tolerant of a wide range of functional groups. The methylation of *N*, *N*-dimethylaniline and subsequent cross coupling may be combined into a one-pot operation while maintaining a high yield of biaryl product. Finally, the reactivity of $PhNMe_3OTf$ relative to the most common cross-coupling electrophiles was established through competition experiments.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all products and unknown substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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