Nickel-Catalyzed Cross-Coupling Reactions of Aryltitanium(IV) Alkoxides with Aryl Halides

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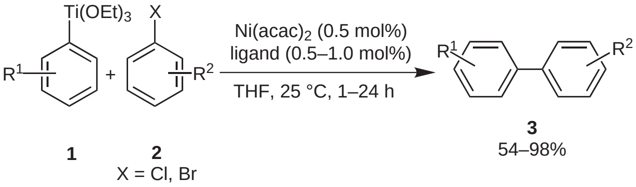
Received 15 May 2007

Abstract: A nickel-catalyzed cross-coupling reaction between aryltitanium(IV) alkoxides and various functionalized aryl halides is described. The reaction requires Ni(acac)$_2$ (0.5 mol%), a phosphine or an N-heterocyclic carbene ligand (NHC ligand; 0.5–1.0 mol%) and proceeds at 25 °C within 1–24 hours.

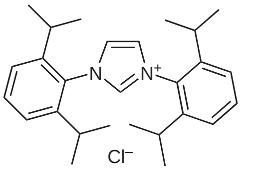
Key words: organotitanium reagents, cross-coupling, nickel

Palladium- or nickel-catalyzed cross-coupling reactions between aryl organometallics and aryl or heteroaryl electrophiles are important methods for the preparation of biaryls in modern organic chemistry.[1] Transition-metal-catalyzed reactions of organomagnesium, -boron, -silicon, -zinc and -tin compounds have been extensively studied.[1] On the other hand, aryltitanium(IV) alkoxides of type **1** have been mainly used for performing addition reactions to carbonyl groups[2] and carbotitanation reactions.[3] Although the required organotitanium compounds can be easily prepared by transmetalation from the corresponding lithium or magnesium organometallics,[4] they have received less attention for the performance of cross-coupling reactions.[5] Herein, we wish to report the cross-coupling between aryltitanium compounds of type **1** and aryl and heteroaryl chlorides or bromides **2**, which proceeds readily at room temperature in THF, using small amounts of Ni(acac)$_2$ (0.5 mol%) (Scheme 1).



Scheme 1 Nickel-catalyzed cross-coupling reaction of aryltitanium alkoxides with aryl halides

The required titanium(IV) reagents of type **1** were obtained by the transmetalation of an aryllithium or arylmagnesium halide with Ti(OEt)$_4$ and provided higher yields and shorter reaction times than a transmetalation with TiCl$_4$, TiF$_4$ or other titanium alkoxides, e.g. Ti(O*i*-Pr)$_4$ (Table 1, entry 8). A broad number of ligands were tested and N-heterocyclic carbene ligand precursor **4**[6] (0.5 mol%; Figure 1) turned out to be the best (Scheme 2). Interestingly, tris(2,4,5-trimethoxyphenyl)phosphine[7] (**5**; 1.0 mol%; Figure 1) gave better results for the cross-coupling reaction with electron-rich aryl halides (Scheme 2). However, for other aryl halides, the phosphine **5** led to slow reactions and poor yields. Other tested N-heterocyclic carbenes, phosphines, diphosphines and phosphites were less effective.[8]



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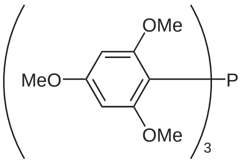

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Figure 1 Ligands for the cross-coupling reaction

The optimized reaction conditions allow performing a broad range of cross-coupling reactions at room temperature within 1–24 hours (Table 1). The used aryltitanium reagents tolerate functionalized aryl halides not compatible with the corresponding lithium or magnesium reagents. Thus phenyltitanium triethoxide (**1a**, 1.5 equiv) obtained from PhMgCl[9] by transmetalation with Ti(OEt)$_4$, reacted with ethyl 4-bromobenzoate (**2a**) in the presence of Ni(acac)$_2$ (0.5 mol%) and ligand **4** (0.5 mol%) at 25 °C, leading to the cross-coupling product **3a** (3 h, 95% yield, entry 1 of Table 1). By using ethyl 4-chlorobenzoate the same cross-coupling reaction required 24 hours and gave **3a** in 73% yield (entry 1). Cross-coupling of the indole derivative **2b** with **1a** provided the product **3b** in 78% yield (entry 2). For most cases, aryl chlorides were suitable electrophiles. Cross-coupling of the protected aldehyde **2d** with *p*-tolyltitanium triethoxide (**1b**) afforded the biphenyl **3d** in 73% yield (25 °C, 17 h, entry 4). Similarly, the reaction of **1b** with the sulfonamide **2e** furnished the desired cross-coupling product **3e** in 75% yield (25 °C, 17 h, entry 5). By using ligand **5**, *p*-tolyltitanium triethoxide (**1b**) reacted with the sterically hindered 2-chloro-1,4-dimethoxybenzene (**2f**) only at 65 °C (3 h), giving the coupling product **3f** in 60% yield (entry 6). Heterocyclic chlorides like 2-chloropyridine (**2h**) reacted with 1-naphthyltitanium triethoxide (**1c**) within six hours at 25 °C, leading to the pyridine **3h** in 98% yield (entry 8). The same reaction with 1-naphthyltitanium triisopropoxide afforded only 35% of **3h** after six hours (entry 8). By using

SYNLETT 2007, No. 13, pp 2077–2080
Advanced online publication: 17.07.2007
DOI: 10.1055/s-2007-984906; Art ID: G14607ST

3-chloropyridine (**2i**) the cross-coupling reaction with **1c** required 14 hours and gave the expected product **3i** in 61% yield (entry 9). Electron-poor aryltitanium reagents reacted well only with aryl bromides. Thus, the cross-coupling of ethyl 4-bromobenzoate (**2a**) with the titanium reagent **1d**, bearing a trifluoromethyl group, provided biphenyl **3j** in 70% yield (25 °C, 16 h, entry 10). The reaction of **1b** with the less reactive aryl chloride afforded the product **3j** in only 49% yield after 28 hours of reaction time (entry 10). Reaction of 2-chloroquinoline (**2j**) with the aryltitanium triethoxide **1e** afforded dubamin (**3l**), a haplophyllum alkaloid,[10] in 90% yield (25 °C, 18 h, entry 12). The coupling of titanated heterocycles requires elevated temperatures. Thus, 2-chloroquinoline (**2j**) reacted with 2-titanated *N*-methylpyrrole (**1f**), obtained from the corresponding lithium compound,[11] within 24 hours at 65 °C, leading to the quinoline **3m** in 98% yield (entry 13). In the case of titanated benzofurane **1g**, prepared by transmetalation from the lithium reagent,[12] the cross-coupling with 2-chloroquinoline (**2j**) afforded the heterocycle **3n** in 73% yield after 24 hours at 65 °C (entry 14). Aryl bromides may bear a keto function, but require lower temperatures. Thus, 4-bromovalerophenone (**2c**) reacted with phenyltitanium triethoxide (**1a**) within six hours at –10 °C leading selectively to the desired cross-coupling product **3c** (60% yield, entry 3). Similarly, the reaction of **1e** with 4-bromovalerophenone (**2c**) afforded within six hours at –10 °C the biphenyl **3k** in 57% yield (entry 11). The cross-coupling reaction of 4-bromoacetophenone (**2g**) with **1b** required lower temperatures of –20 °C in order to avoid an addition on the keto function and furnished the expected product **3g** in 54% yield (entry 7).

Finally we have compared the reactivity of organotitanium compounds with the corresponding arylzinc halides, which are widely used in Negishi cross-couplings.[13] The reaction of PhTi(OEt)$_3$ (**1a**) with *N*,*N*-dimethyl-4-bromoaniline (**2k**) afforded the biphenyl **3o** in 92% yield after 16 hours at 25 °C (Scheme 2). The same reaction with the arylzinc halide **6**, gave only 17% of **3o** at 25 °C after 24 hours in the presence of a polar co-solvent like NMP.[14] The same behavior was observed with 4-bromoanisole (**2l**) as electrophile.

Table 1 Cross-Coupling Reactions of Aryltitanium Reagents with Functionalized Aryl Halides

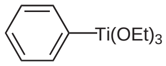
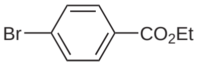
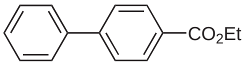
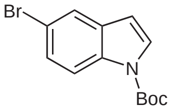
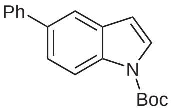
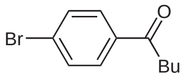
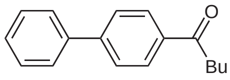
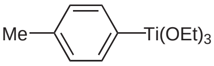
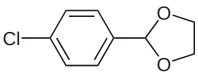
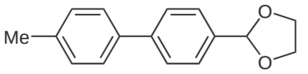
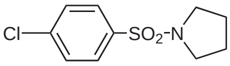
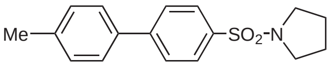
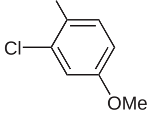
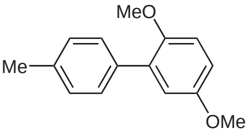
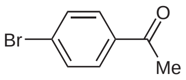
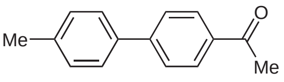
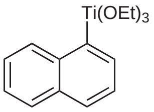
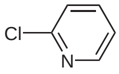
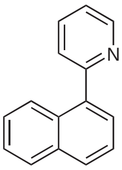
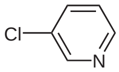
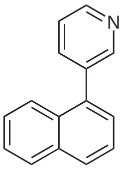
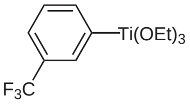
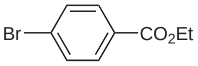
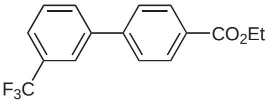
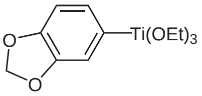
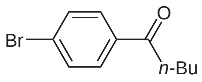
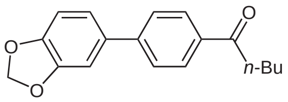
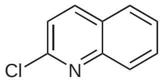
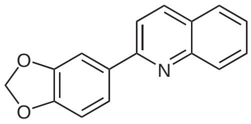
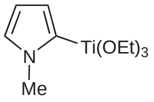
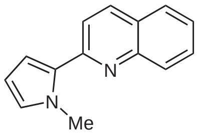
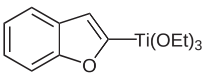
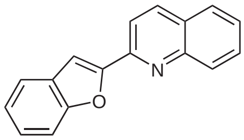
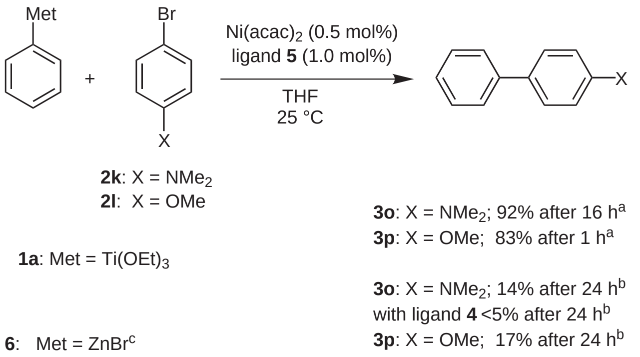
Entry	Aryltitanium **1**	Aryl halide **2**	Product **3**	Ligand	Reaction time (h)[a]	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**[15]	**4**	3	95 (73)[c]
2	**1a**	 **2b**	 **3b**	**4**	18	78
3	**1a**	 **2c**	 **3c**	**4**	6[d]	60
4	 **1b**	 **2d**	 **3d**	**4**	17	73
5	**1b**	 **2e**	 **3e**	**4**	17	75
6	**1b**	 **2f**	 **3f**	**5**	3[e]	60

Table 1 Cross-Coupling Reactions of Aryltitanium Reagents with Functionalized Aryl Halides (continued)

Entry	Aryltitanium **1**	Aryl halide **2**	Product **3**	Ligand	Reaction time (h)[a]	Yield (%)[b]
7	**1b**	 **2g**	 **3g**	**4**	6[f]	54
8	 **1c**	 **2h**	 **3h**	**4**	6	98 (35)[g]
9	**1c**	 **2i**	 **3i**	**4**	14	61
10	 **1d**	 **2a**	 **3j**	**4**	16	70 (49)[c]
11	 **1e**	 **2c**	 **3k**	**4**	6[d]	57
12	**1e**	 **2j**	 **3l**	**4**	18	90
13	 **1f**	**2j**	 **3m**	**4**	24[e]	98
14	 **1g**	**2j**	 **3n**	**4**	24[e]	73

[a] Reaction time at 25 °C.
[b] Yield of analytically pure product.
[c] Yield of analytically pure product obtained with the corresponding aryl chloride.
[d] Reaction performed at –10 °C.
[e] Reaction performed at 65 °C.
[f] Reaction performed at –20 °C.
[g] GC yield determined with *n*-teradecane as internal standard by using $Ti(Oi\text{-}Pr)_4$ for transmetalation.



Scheme 2 Comparison of aryltitanium and -zinc reagents. ^{a} Yield of analytically pure product. ^{b} Yield determined by GC analysis with *n*-tetradecane as an internal standard. ^{c} Solvent: THF–NMP (8:1).

In summary, we have developed an efficient Ni-catalyzed cross-coupling reaction of aryltitanium reagents with aryl chlorides and bromides. The reaction scope is broad and most of the cross-couplings proceed at room temperature or even at lower temperatures.

Acknowledgment

We thank the Fonds der Chemischen Industrie and the DFG for financial support and Saltigo (Leverkusen), Degussa (Hanau), Chemetall (Frankfurt) and BASF (Ludwigshafen) for the generous gift of chemicals.

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(8) Polar solvents such as NMP, NEP (*N*-ethyl-2-pyrrolidinone), DMPU or DME were not effective as co-solvents, as it is known in other cross-coupling reactions. See also: Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2005**, *7*, 4871.

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(14) Not using NMP leads to heterogeneous reactions and lower yields.

(15) **Typical Procedure for the Cross-Coupling Reaction; Preparation of Biphenyl-4-carboxylic Acid Ethyl Ester (3a)**: A flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with a Ti(OEt)$_4$ solution (1.0 mL, 1.5 M in THF). First phenylmagnesium chloride (0.84 mL, 1.79 M in THF) was added dropwise at 0 °C, then Ni(acac)$_2$ (1.3 mg, 0.005 mmol), ligand **4** (2.1 mg, 0.005 mmol) and 4-bromobenzoic acid ethyl ester (**2a**; 229 mg, 1.00 mmol) were added. The reaction mixture was stirred for 3 h at r.t. Then the mixture was quenched with a sat. NH$_4$Cl solution and extracted with Et$_2$O. Column chromatography (pentane–Et$_2$O, 9:1) of the crude residue yielded **3a** as colorless solid (215 mg, 95%).