ORGANIC LETTERS

2012
Vol. 14, No. 13
3316–3319

Nickel-Catalyzed Monosubstitution of Polyfluoroarenes with Organozinc Reagents Using Alkoxydiphosphine Ligand

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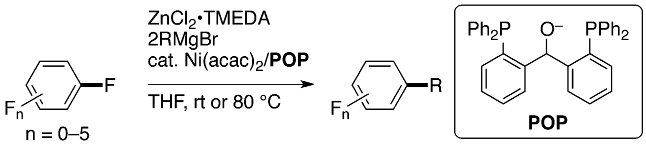
Received May 10, 2012

ABSTRACT



A new diphosphine (POP) ligand bearing an alkoxide group allows us to synthesize partially fluorinated arenes. A nickel-catalyzed cross-coupling between a polyfluoroarene and an organozinc reagent in the presence of POP selectively produces a monosubstitution product. Aryl and alkylzinc reagents smoothly take part in the reaction. It is speculated that monosubstitution is the result of accelerated product expulsion from the product/catalyst complex.

Partially fluorinated arenes have received much attention in drug discovery and materials science.[1] However, they are synthetically difficult to access because neither selective partial fluorination of aromatic compounds[2] nor partial C–F bond activation of polyfluoroaromatics[3] is easy to achieve. The conventional nickel- or palladium-catalyzed cross-coupling reactions via C–F bond activation[4,5] of polyfluoroarenes displace more than one C–F bond[6] or they are limited in substrate scope,[7,8] respectively. The difficulty arises from (1) robustness of the C–F bond to undergo oxidative addition,[9] (2) slow reductive elimination with highly electron-deficient substrates,[10] and (3) "ring walking" in the product/catalyst complex caused by strong back-donation from a transition metal that inhibits smooth catalyst turnover, making it difficult to activate only one C–F bond in a polyfluoroarene (particularly problematic in nickel catalysis).[11] To achieve the difficult monosubstitution of a C–F bond

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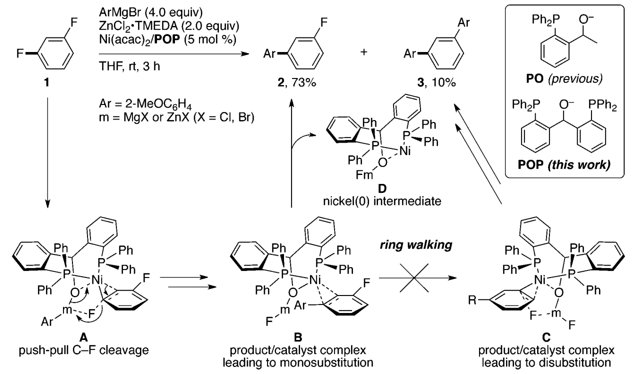
10.1021/ol301195x © 2012 American Chemical Society
Published on Web 06/12/2012

under widely used nickel catalysis,[5,12] we have designed a new diphosphine ligand (**POP**) that possesses two phosphine units and an alkoxide group. We report herein a nickel/**POP**-catalyzed selective monosubstitution reaction of polyfluoroarenes with aryl- and alkylzinc reagents.

We previously reported that installation of an alkoxide group in a phosphine ligand (**PO**) greatly enhances the efficiency of the C−F bond activation reaction of a polyfluoroarene.[13] We have also demonstrated that the alkoxide unit of the **PO** ligand coordinates to both nickel and magnesium and activates the C−F bond through push−pull mechanism. The catalytic system exhibited high efficiency toward C−F bond activation when mono- or polyfluoroarene was used as a substrate, which resulted in substitution of many C−F bonds due to the problematic "ring walking".[14,15] We considered that destabilization of the product/catalyst complex **C** through stabilization of a nickel(0) intermediate **D** should promote the product expulsion and hence promote the catalyst turnover in the reaction between 1,3-difluorobenzene (**1**) and a phenylzinc reagent (Scheme 1). We hence added an additional diphenylphosphino group to make a new tridentate ligand **POP** so that the nickel(0) species **D** can be stabilized. The **POP** ligand is expected to place the alkoxide group at an apical position of the nickel center and capture both the nickel and zinc (or magnesium) atoms to accelerate the C−F bond cleavage in a push−pull manner (**A**). The following transmetalation and reductive elimination would lead to the formation of a nickel/product complex **B** that gives monosubstituted product **2** upon product expulsion, whereas the ring walking would form complex **C**, a complex that gives disubstituted side product **3**.

A preligand, protonated **POP** was synthesized in 90% yield by coupling a commercially available 2-(diphenylphosphino)benzaldehyde with 2-(diphenylphosphino)phenyllithium prepared from the corresponding bromide, which is also commercially available.

Scheme 1. Typical Example and a Mechanistic Rationale



To investigate the efficiency of the **POP** ligand for the selective monosubstitution reaction, several reactions were carried out using **1** as a substrate (Table 1). In the reaction with 2.1 equiv of PhMgBr in the presence of 1 mol % of $Ni(acac)_2$ and **PO** ligand in diethyl ether, the **PO** ligand was converted in situ to its magnesium salt (**PO**-Mg)[13a] and quickly underwent nickel-catalyzed displacement of both of the fluorine atoms in **1** to give **3** exclusively (Table 1, entry 1). The reaction did not afford the monosubstitution product because of quick ring walking in the product complex.[11] The use of a diarylzinc reagent (prepared from ArMgBr and $ZnCl_2\cdot$TMEDA; Ar = 2-MeOC$_6$H$_4$) in THF at ambient temperature resulted in low conversion (entry 2).

Addition of Ph_3P (1.0 equiv) to 1.0 equiv of **PO** did not change the selectivity (entry 3). By contrast, the use of **POP** in the reaction of **1** with PhMgBr (2.0 equiv) increased the selectivity toward **2** to give **2** and **3** in a 3:2 ratio (entry 4) and the use of the Grignard-derived diarylzinc greatly increased the selectivity to give **2** and **3** in 73 and 10% yields, respectively (entry 5). When 1.3 equiv[16] of the organometallic reagent was used, the yield decreased, while the selectivity remained the same (**2**: 54% yield, **3**: 6% yield). Interestingly, the use of diphenylzinc led to higher selectivity; however, the conversion was low (entry 6). Moreover, the organozinc reagent prepared from PhLi or Ph_2Zn gave no desired product (entries 7 and 8), and **1** was largely recovered. When $MgBr_2$ was added to the reaction with Ph_2Zn and TMEDA, **2** was obtained in trace amounts (4%, data not shown). The necessary presence of both magnesium and zinc to achieve high reactivity and high selectivity suggests cooperation of nickel, zinc, and magnesium,[17,18] thus making the picture in Scheme 1 too simplistic.

Many other mono- and diphosphine ligands were found to be inferior to **POP**. For instance, the diphosphine ligand DPEphos, in which two 2-(diphenylphosphino)phenyl

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Table 1. Effect of the Ligand and of the Organometallic Reagent on the Nickel-Catalyzed Phenylation of 1,3-Difluorobenzene **1**[a]

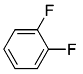
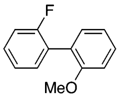
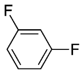
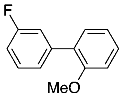
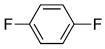
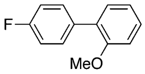
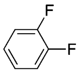
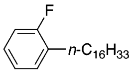
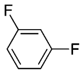
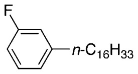
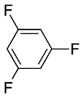
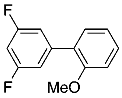
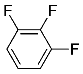
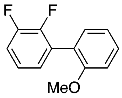
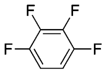
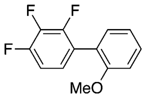
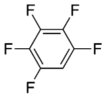
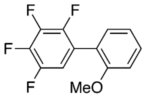
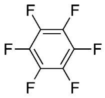
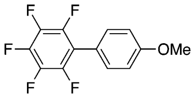
entry	ligand[b]	organometallic reagent	**2**[c] (%)	**3**[c] (%)
1[d]	**PO**	PhMgBr	0	92
2	**PO**	$ZnCl_2 \cdot TMEDA/2ArMgBr$	3	2
3[e]	**PO**/PPh_3	$ZnCl_2 \cdot TMEDA/2ArMgBr$	0	8
4	**POP**	PhMgBr	27	17
5	**POP**	$ZnCl_2 \cdot TMEDA/2ArMgBr$	73	10
6	**POP**	$ZnCl_2 \cdot TMEDA/2PhMgBr$	34	2
7	**POP**	$ZnCl_2 \cdot TMEDA/2PhLi$	0	0
8	**POP**	$Ph_2Zn/TMEDA$	0	0
9	DPEphos	$ZnCl_2 \cdot TMEDA/2ArMgBr$	4	0
10	dppe	$ZnCI_2 \cdot TMEDA/2ArMgBr$	1	0
11	dppp	$ZnCl_2 \cdot TMEDA/2ArMgBr$	14	0
12	dppb	$ZnCl_2 \cdot TMEDA/2ArMgBr$	8	<1
13	XPhos	$ZnCl \cdot TMEDA/2ArMgBr$	<1	0

[a] Reaction conditions: 1,3-difluorobenzene (**1**, 0.30 mmol) was reacted with diarylzinc reagent (2.0 equiv) prepared from 2-$MeOC_6H_4MgBr$ (4.0 equiv) and $ZnCl_2 \cdot TMEDA$ (2.0 equiv) unless otherwise noted in the presence of 5 mol % of $Ni(acac)_2$ and 5 mol % of ligand in THF for 3 h. See the Supporting Information for details. [b] **PO** = alkoxyphosphine (or 1-(2-(diphenylphosphino)phenyl)ethanolate); DPEphos = 2,2′-bis(diphenylphosphino)diphenyl ether; dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane; dppb = 1,4-bis(diphenylphosphino)butane; XPhos = 2-dicyclohexylphosphine-2′,4′,6′-triisopropylbiphenyl. [c] Yields were determined by gas chromatography (GC) using *n*-tridecane as an internal standard. [d] Reaction was carried out with 1 mol % each of $Ni(acac)_2$ and **PO** with PhMgBr (2.1 equiv) at ambient temperature for 2 h. [e] **PO** and Ph_3P (5 mol % each) were added as ligands.

groups are connected by an ether bridge instead of the CH_2O group as in **POP**, was entirely ineffective (entry 9), and the diphosphine ligands used in the literature in a related context (entries 10–12) uniformly performed poorly. Sterically hindered XPhos, which is known to be useful for chloride displacement, was entirely ineffective (entry 13).

The selective monofunctionalization of various polyfluoroarenes in the presence of the nickel/**POP** was investigated using the optimized conditions (Table 2). 1,2-Difluorobenzene was monoarylated with complete selectivity, and 1,3- and 1,4-difluorobenzene also gave the monoarylated product with good selectivity (entries 1–3). The alkylation of 1,2- and 1,3-difluorobenzene with *n*-octylzinc reagent also proceeded selectively to give the corresponding monoalkylated products (entries 4 and 5). 1,3,5-Trifluorobenzene reacted with excellent selectivity to give the monoarylated product in 58% yield, together with a trace amount (4%) of diarylated product (entry 6), while a triarylation reaction took place as a major pathway when **PO** was used.[13] 1,2,3-Trifluorobenzene, 1,2,3,4-tetrafluorobenzene, and pentafluorobenzene reacted selectively on the 1-fluoro carbon rather than on the internal C–F bond (entries 7–9).[19]

Table 2. Ni/**POP**-Catalyzed Monofunctionalization of Polyfluoroarenes with Organozinc Reagents[a]

entry	ArF	R in "R_2Zn"[b]	product	yield (%)[c]
1		2-$MeOC_6H_4$		68(0)
2		2-$MeOC_6H_4$		73(10)
3		2-$MeOC_6H_4$		51(17)
4		*n*-$C_{16}H_{33}$		47(0)
5		*n*-$C_{16}H_{33}$		65(5)
6		2-$MeOC_6H_4$		58(4)
7[d]		2-$MeOC_6H_4$		75(4)
8[d]		2-$MeOC_6H_4$		32(3)
9		2-$MeOC_6H_4$		67(3)
10		4-$MeOC_6H_4$		52(2)

[a] Reactions were performed on a 0.30–0.50 mmol scale. Substrates were reacted with the diorganozinc reagent (2.0 equiv) in the presence of 5 mol % each of $Ni(acac)_2$ and **POP** ligand in THF at rt (80 °C for alkylzinc reagent) for 3 h. See the Supporting Information for details. [b] Prepared in situ from $ZnCl_2 \cdot TMEDA$ and 2RMgBr. [c] Isolated yields. Yields in parentheses are those of the corresponding diarylated or dialkylated byproducts, and were estimated by GC using *n*-tridecane as an internal standard. [d] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [e] Reaction was carried out at 70 °C for 1 h.

Hexafluorobenzene is a challenging substrate, and to the best of our knowledge there has been only one report on tantalum-catalyzed benzylation of this substrate.[20] **POP** effected this transformation in 52% yield with high selectivity for monoarylation (entry 10).

The reaction also allows the coupling of a variety of fluoroaromatics with aryl- and alkylzinc reagents, β-hydrogen-possessing alkylzinc reagents, and functionalized alkyl reagents (Table 3). Arylzinc reagents bearing an *ortho*-substituent smoothly took part in the coupling reaction (entries 1, 2, 8, 10, and 12). Both dimethylzinc (entry 4)[8] and dialkylzinc reagents possessing a β-hydrogen (entries 5,

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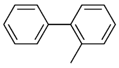
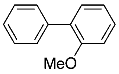
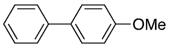
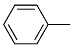
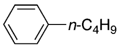
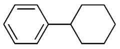
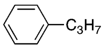
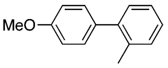
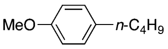
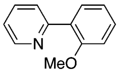
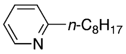
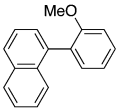
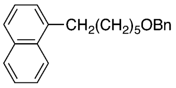
Table 3. Ni/**POP**-Catalyzed Cross-Coupling of Aryl Fluorides with Organozinc Reagents[a]

entry	Ar in ArF	R in "R_2Zn"[b]	product	yield (%)[c]
1	Ph	2-MeC_6H_4		94
2	Ph	2-$MeOC_6H_4$		85
3	Ph	4-$MeOC_6H_4$		96
4	Ph	CH_3		92
5	Ph	*n*-C_4H_9		57
6	Ph	*n*-C_6H_{11}		32
7	Ph	*i*-C_3H_7		37[d]
8	4-$MeOC_6H_4$	2-MeC_6H_4		90
9	4-$MeOC_6H_4$	*n*-C_4H_9		57
10	2-pyridyl	2-$MeOC_6H_4$		90
11	2-pyridyl	*n*-C_8H_{17}		86
12	1-naphthyl	2-$MeOC_6H_4$		88
13	1-naphthyl	$BnO(CH_2)_5CH_2$		62

[a] Reactions were performed on a 0.50–1.0 mmol scale. Substrates were reacted with the diphenylzinc reagent (1.3–1.8 equiv, unless otherwise noted) in the presence of 5–10 mol % each of $Ni(acac)_2$ and **POP** ligand in THF at 60–80 °C. See the Supporting Information for details. [b] Prepared in situ from $ZnCl_2 \cdot TMEDA$ and 2RMgBr. [c] Isolated yield except for entries 1 and 4–7 (GC yield based on *n*-tridecane internal standard). [d] Product ratio: *i*/*n* = 51:49.

6, 7, 9, 11, and 13) reacted well. The reaction of *i*-Pr_2Zn gave the coupling products with an *i*-Pr/*n*-Pr ratio of 1:1, in contrast to the 1:7 ratio reported in a previous nickel catalysis (entry 7).[5a] We speculate that the hydroxy group in the **POP** ligand placed at the apical position of nickel may inhibit the undesired β-hydride elimination, to induce the smooth reaction of these alkylzinc reagents. A benzyloxy group remained intact during the reaction (entry 13). An aryl fluoride possessing an electron-donating group (entries 8 and 9) and naphthyl fluoride (entries 12 and 13) reacted smoothly. 2-Fluoropyridine reacted well with *o*-anisylzinc (entry 10) and also with *n*-octylzinc (entry 11). The **POP** ligand was also effective for the reaction of aryl iodides, bromides, and chlorides (data not shown).

In summary, we have developed a new ligand, **POP**, for nickel catalysis that has provided a highly efficient system for the C–F bond arylation and alkylation of mono- to polyfluoroarenes. A selective C–F monofunctionalization reaction was achieved for polyfluoroarenes, where product expulsion was promoted when **POP** was used as a ligand. This tripodal, tridentate ligand differs from the popular tridentate pincer ligands[21] for its noncoplanarity of the three coordinating groups relative to the main skeleton of the ligand. The two phosphine groups stabilize the nickel(0) complex and accelerate the product expulsion at the end of the catalytic cycle, thus suppressing multisubstitution of polyfluoroarenes caused by ring walking. The alkoxide coordinating group is located in the apical position of the nickel(II) intermediate and captures a Lewis acidic metal to accelerate the C–F bond cleavage. We consider that the present strategy to preserve fluorine atoms in the cross-coupling product provides a valuable new methodology for the chemistry of fluorous compounds.

Acknowledgment. We thank MEXT for financial support (KAKENHI Specially Promoted Research No. 22000008 to E.N., and Grant-in-Aid for Young Scientists (B) No. 23750100 to L.I.). Y.N. thanks the Japan Society for the Promotion of Science for the Research Fellowship for Young Scientists (21·8591). We thank Sobi Asako for helpful mechanistic discussions.

Supporting Information Available. Experimental procedures and physical properties of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Reviews on metal pincer complexes: (a) Selander, N.; Szabó, K. J. *Chem. Rev.* **2011**, *111*, 2048–2076. (b) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759–1792.

The authors declare no competing financial interest.