ChemPubSoc Europe

DOI: 10.1002/chem.201303809

CHEMISTRY
A European Journal
Full Paper

Cross-Coupling Reactions

Nickel-Catalyzed Csp^2–Csp^3 Bond Formation by Carbon–Fluorine Activation

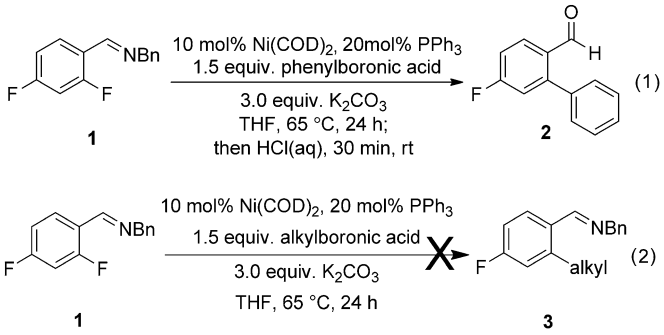
Alex D. Sun,[b] Kaylyn Leung,[a] Anita D. Restivo,[a] Nicole A. LaBerge,[a] Harumi Takasaki,[a] and Jennifer A. Love*[a]

Abstract: We report herein a general catalytic method for Csp^2–Csp^3 bond formation through C–F activation. The process uses an inexpensive nickel complex with either diorganozinc or alkylzinc halide reagents, including those with β-hydrogen atoms. A variety of fluorine substitution patterns and functional groups can be readily incorporated. Sequential reactions involving different precatalysts and coupling partners permit the synthesis of densely functionalized fluorinated building blocks.

Introduction

Fluorine atoms form the strongest carbon–element single bond, and the challenge of activating such strong C–F bonds has inspired considerable research effort, resulting in reports of both stoichiometric and catalytic C–F activation.[1,2] In particular, catalytic C–C bond formation through C–F activation has been reported for Kumada–Tamao–Corriu,[3] Suzuki–Miyaura,[4] Negishi,[5] and Stille[6] cross-coupling protocols, as well as C–H activation.[7] Notwithstanding these significant achievements, only a few of these processes permit the catalytic formation of Csp^2–Csp^3 bonds. Of these, all have significant limitations. For example, Csp^2–Csp^3 coupling was reported in Kumada's pioneering paper,[3a] but the highly basic Grignard reagents are incompatible with many functional groups. Moreover, some of these reactions involve partial or complete isomerization of the alkyl coupling partners.[3a,q] Although stoichiometric methylation has been achieved by sequential Ni-mediated C–F activation and transmetalation with dimethylzinc, the only catalytic reactions reported have very limited scope with respect to aliphatic nucleophiles.[3f,5i,8] In addition, 4-fluorostyrene can serve as a catalytic promoter for Ni-catalyzed Negishi coupling reactions, which suggests that the C–F bond is not reactive under the reported conditions.[9] We have recently reported Pt-catalyzed Negishi coupling reactions, but the coupling partner is mainly limited to the use of methyl nucleophiles. More recently, an aryl–alkyl Negishi cross-coupling has been reported, but the alkyl groups are still derived from Grignard reagents, which would significantly limit their functional group compatibility.[5i]

We have reported an efficient Ni-catalyzed Suzuki–Miyaura C–F cross-coupling of polyfluoroarenes as a means to synthesize a wide range of highly functionalized, fluorinated biaryl compounds under mild conditions [Eq. (1)].[4d] However, alkyl organoboron reagents are not reactive under those conditions and no alkyl–aryl coupling products, such as **3**, were produced [Eq. (2)].



Motivated by the increasing importance of catalytic C–F activation methods, we have developed a general catalytic method for Csp^2–Csp^3 bond formation through C–F activation. This process uses an inexpensive Ni complex with either dialkylzinc or alkylzinc halide reagents, including those with β-hydrogen atoms. The zinc reagents are significantly less reactive towards functional groups than many other organometallic reagents and therefore offer high synthetic utility.[10] In addition to the limited number of diorganozinc reagents that are commercially available, many organozinc halides can be either purchased or synthesized by using well-established protocols.[11] It is also worth noting that the aryl fluoride products of cross-coupling have potential use in the construction of pharma-

[a] K. Leung, A. D. Restivo, N. A. LaBerge, H. Takasaki, Prof. Dr. J. A. Love
Department of Chemistry, University of British Columbia
2036 Main Mall, Vancouver, British Columbia, V6T 1Z1 (Canada)
Fax: (+1) 604-822-2847
E-mail: jenlove@chem.ubc.ca

[b] Dr. A. D. Sun
WuXi AppTec (Shanghai) Co., Ltd., 288 Fute Zhong Road
Waigaoqiao Free Trade Zone, Shanghai 200131 (China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303809.

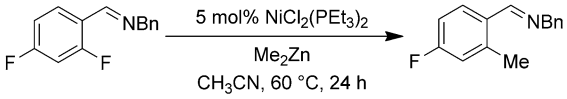
ceuticals, agrochemicals, and materials, many of which contain functionalized fluoroarenes.[12]

Results and Discussion

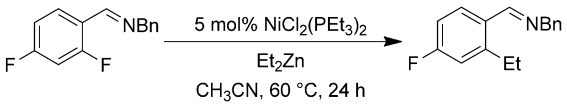
Reactions with diorganozinc reagents

We began our investigation by looking at the reaction between 2,4-difluorophenyl imine **1** and dimethylzinc in CH_3CN with catalytic amounts of various nickel salts. To our delight, a number proved to be competent precatalysts for this transformation. For instance, with 5 mol% $[NiCl_2(PEt_3)_2]$ as the pre-catalyst, the signal in the $^{19}F\{^1H\}$ NMR spectrum corresponding to the 2-position C–F bond in 2,4-difluorophenyl imine **1** disappeared completely after 8 h, and the methylated product **4** was formed quantitatively according to $^{19}F\{^1H\}$ NMR spectroscopic analysis [Eq. (3)]. The same pre-catalyst was also able to catalyze the reaction between **1** and diethylzinc, producing the ethyl-substituted product **5** [Eq. (4)]. There was no evidence of any β-hydride elimination from presumed Ni-alkyl intermediates, which preludes a significant problem in cross-coupling reactions involving alkyl coupling partners with β-hydrogen atoms. In addition, the phenyl-substituted product was obtained from the reaction of **1** and diphenylzinc. After hydrolysis and column chromatography, aldehyde **2** was isolated in 76% yield [Eq. (5)] and shown to be identical to the compound obtained from the reaction between **1** and phenylboronic acid in Ni-catalyzed Suzuki–Miyaura cross-coupling [Eq. (1)].[4d] Overall, however, the Negishi reaction conditions are more user-friendly than those of our previously reported Suzuki–Miyaura protocol. Rigorously dried solvents are not required because commercially available solvents were successfully employed without compromising the yields. Furthermore, these reactions do not require the rigorous exclusion of air. It is noteworthy that no products from potential imine-assisted C–H activation were observed, despite well-established selective catalytic and stoichiometric C–H bond activation of fluoroarenes.[13,14] C–H activation may indeed be occurring, but could be reversible.[14]

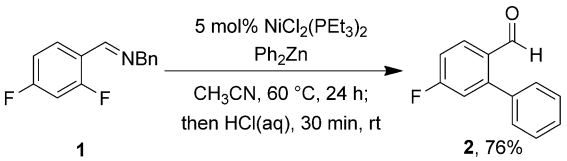
Whereas in the case of diphenylzinc the product could easily be isolated in the form of an aldehyde after hydrolysis and purification, the same procedure could not be extended to the methylated and ethylated aldehydes, because of their high volatility. We were also unable to isolate the imine products by column chromatography because of gradual decomposition.



1 **4**, quant. conv. (3)



1 **5**, quant. conv. (4)



1 **2**, 76% after column chromatography (5)

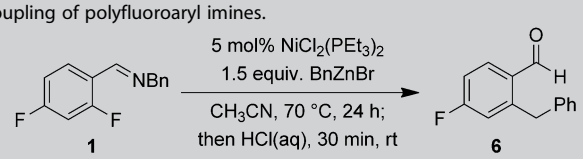
Nevertheless, these preliminary experiments established the feasibility of Ni-catalyzed Negishi coupling of aryl fluorides with organozinc reagents. We were thus poised to explore the substrate scope of this reaction.

Reactions with preformed organozinc halides

Compared with diorganozinc reagents, organozinc halide reagents are more readily available from commercial sources. Benzylzinc bromide was selected for initial optimization studies, because it is relatively stable and inexpensive. $[NiCl_2(PEt_3)_2]$ catalyzed the reaction between 2,4-difluorophenyl imine **1** and benzylzinc bromide, generating benzyl-substituted compound **6** in 85% yield after hydrolysis and column chromatography. C–F activation took place exclusively at the ortho position and no C–H activation was observed. Encouraged by this result, we modified a number of parameters with the hope of optimizing the reaction conditions so as to maximize the yield; the results are summarized in Table 1.

A variety of Ni complexes were found to catalyze the Negishi cross-coupling reaction. One significant discovery was that, unlike our previously reported Suzuki–Miyaura reaction, in which only Ni^0 complexes were competent precatalysts, both Ni^0 and Ni^{II} complexes could be employed. We also found that the reaction yields were significantly influenced by the nature of the ligand. Triethylphosphine had a significant advantage over other ligands, both as a preformed complex (Table 1, entry 1) and when reacted with $[Ni(COD)_2]$ in situ (Table 1, entry 4); triphenylphosphine (Table 1, entry 3) and an *N*-hetero-

Table 1. Exploration of reaction conditions for Ni-catalyzed Negishi cross-coupling of polyfluoroaryl imines.



1 **6**

Entry	Changes from conditions listed above	Yield [%][a]
1	no change	85
2	no NiCl2(PEt3)2	0
3	NiCl2(PPh3)2 instead of NiCl2(PEt3)2	27
4	5 mol % Ni(COD)2/ 10 mol % PEt3	82
5	1 mol % NiCl2(PEt3)2	53
6	5 mol % Ni(COD)2, 1,3-diisopropyl-imidazol-2-ylidene	17
7	60 °C instead of 70 °C	0
8	aldehyde instead of imine	0

[a] Isolated yields.

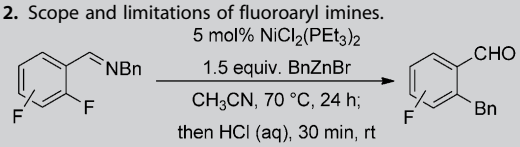
cyclic carbene (Table 1, entry 6) were not as effective. For practical purposes, we chose [$NiCl_2(PEt_3)_2$] as our preferred precatalyst because it was easy to synthesize, relatively stable, and afforded excellent results.

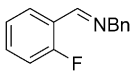
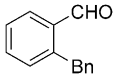
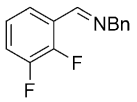
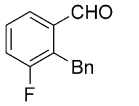
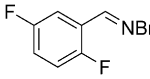
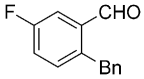
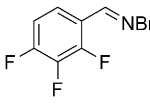
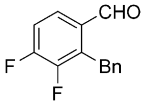
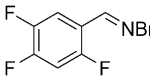
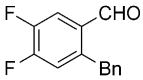
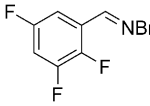
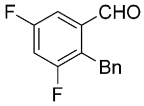
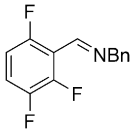
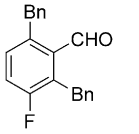
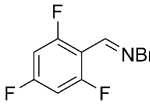
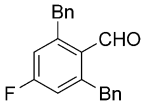
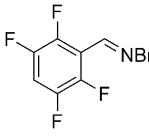
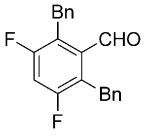
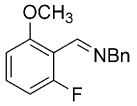
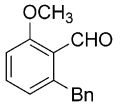
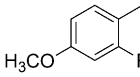
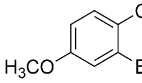
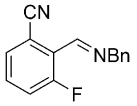
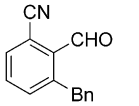
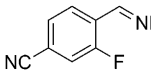
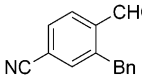
We discovered a rather unexpected strong influence of the reaction temperature in this cross-coupling reaction. Whereas 60 °C was the optimal temperature for Ni-catalyzed Negishi cross-coupling of diorganozinc reagents [Eqs. (3)–(5)], no reaction was observed at this temperature with benzylzinc bromide as the coupling partner. The temperature must be raised to 70 °C for C–F cross-coupling to take place (Table 1, entry 7). At present, we do not have an explanation for this observation. Reactions were generally completed overnight (12–14 h), but certain substrates required longer reaction times. Therefore, reactions were allowed to continue for 24 h to ensure that all were completed with satisfactory yields. It is noteworthy that we did not observe product decomposition with longer reaction times. Further extension of reaction duration offered no additional benefits. It is also clear that a sufficiently strong directing group must be used, because no reaction took place in the absence of a directing group. Likewise, an aldehyde directing group was unable to promote C–F activation. However, other directing groups could be used (see below), although we preferred an imine directing group because of its synthetic versatility (via the aldehyde).

We then turned our attention to the scope of the fluorine substitution pattern on these polyfluoroaryl imines. The results with benzylzinc bromide as coupling partner are summarized in Table 2. As expected, only the products derived from ortho C–F cross-coupling were isolated, and there was no evidence of C–H activation or C–F activation/C–H formation. Most substrates underwent smooth cross-coupling reactions, resulting in high yields. However, in the case of 2,5-difluorophenyl imine (Table 2, entry 3), the yield was considerably lower than those of other substrates, providing aldehyde **9** in only 33% yield. It is worth noting that this substrate showed no reactivity at all under Suzuki–Miyaura reaction conditions. At this point, we do not have a definitive answer for why this particular substrate is so problematic in Ni-catalyzed C–F activation. One possible explanation is that this substrate underwent irreversible C–H bond activation, which would consume the Ni complex rapidly. It has been suggested that the imine directing group and the fluorine substituent adjacent to the C–H bond could facilitate C–H activation.[15] The same 2,5-difluoro-substitution pattern can also be found in Table 2, entries 5 and 6, but these imines reacted without difficulty, suggesting that if C–H activation is occurring for those substrates, perhaps it is more easily reversible for them than for 2,5-difluoroimine. More kinetic and mechanistic studies are underway.

Dialkylation took place with substrates containing two chemically equivalent ortho C–F bonds (Table 2, entries 8 and 9). The monoalkylated compounds for each substrate could be detected as minor products by $^{19}F\{^1H\}$ NMR spectroscopy and mass spectrometry at incomplete conversion, but could not be isolated due to their very similar physical and chemical properties. Dialkylation was also observed for a 2,3,6-trifluoroaryl imine (Table 2, entry 7). This result was very intriguing because only the C–F bond at the 2-position was activated under the Suzuki–Miyaura conditions. In other words, Ni-catalyzed Negishi cross-coupling was able to achieve the second C–F activation whereas Ni-catalyzed Suzuki–Miyaura cross-coupling was only good for the first, for yet unknown reasons. We an-

Table 2. Scope and limitations of fluoroaryl imines.



Entry	Imine	Product		Isolated yield [%]
1			**7**	84
2			**8**	91
3			**9**	33
4			**10**	88
5			**11**	84
6			**12**	79
7			**13**	90[a]
8			**14**	86[a]
9			**15**	83[a]
10			**16**	71
11			**17**	75
12			**18**	–
13			**19**	–

[a] 3.0 equiv benzylzinc bromide was used.

ticipated that this difference in reactivity between the two catalytic systems would provide a valuable opportunity for sequential cross-coupling reactions (see below).

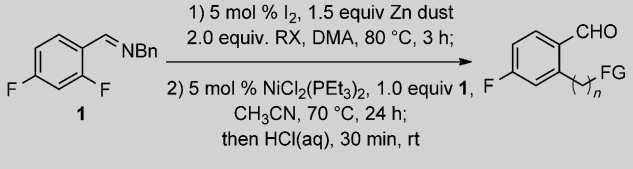
The chemoselectivity on the fluoroaryl rings is worth mentioning. As expected, C–Br and C–Cl bonds are reactive under Negishi conditions, and coupling reactions would take place preferentially at these bonds. Despite reports of Ni-catalyzed C–O activation reactions,[16] an aryl–OMe moiety was tolerated under the reaction conditions, both at the ortho- (Table 2, entry 10) and para-positions (Table 2, entry 11). In contrast, aryl–CN bonds either ortho- or para- to the directing group, were not tolerated.

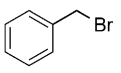
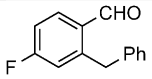
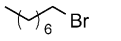
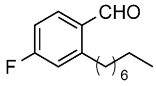
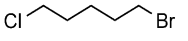
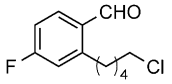
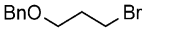
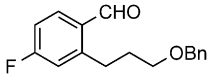
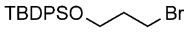
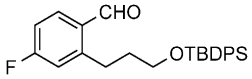
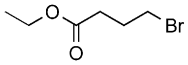
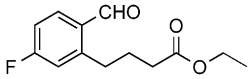
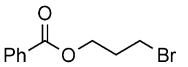
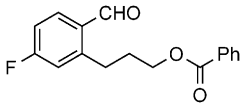
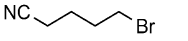
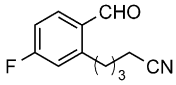
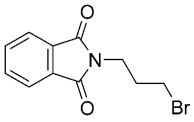
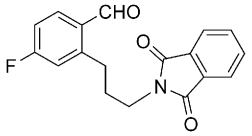
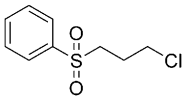
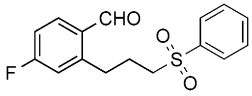
Reactions with organozinc halides generated in situ

Zinc reagents used in Negishi cross-coupling reactions are significantly more tolerant towards functional groups than lithium or magnesium-based reagents. In addition to the limited number of diorganozinc and organozinc halide that are commercially available, there are well-established protocols to synthesize organozinc reagents with diverse functional groups. We decided to utilize the Huo protocol, which is a highly efficient, general method for the preparation of alkylzinc halide reagents from unactivated alkyl bromides and chlorides under mild conditions.[11c] Table 3 summarizes the results from the reactions between alkylzinc halides and imine **1** under the catalytic conditions. In general, this procedure offered good-to-excellent yields and great functional group compatibility. For example, benzylzinc bromide was prepared in situ by using 5 mol% I_2, 2.0 equiv benzyl bromide, and 1.5 equiv zinc dust in dimethylacetamide (DMA) at 80 °C for 3 h. The resulting mixture was then transferred to a solution of 1.0 equiv 2,4-difluoroimine and 5 mol% [$NiCl_2(PEt_3)_2$] in CH_3CN, while maintaining the temperature at 70 °C for 24 h. After hydrolysis, workup and column chromatography, the same aldehyde **6** was isolated in comparable yields (87 vs. 85% from commercially available BnZnBr solution, Table 3, entry 1).

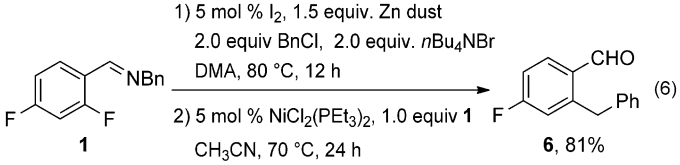
The use of octylbromide resulted in high yield (Table 3, entry 2). A potentially reactive C–Cl bond did not react under the reaction conditions and the chlorine-containing product was successfully isolated (Table 3, entry 3). Two types of protected alcohols were tested. Both benzyl (Table 3, entry 4) and *tert*-butyldiphenylsilyl (Table 3, entry 5) groups survived under the reaction conditions and the desired products were isolated in excellent yields. Likewise, both of the tested ester-containing substrates (Table 3, entries 6 and 7) generated their corresponding products. An alkyl cyano group was also tolerated (Table 3, entry 8). This methodology could be further extended to phthalimide-protected amino groups, as well as sulfones (Table 3, entries 9 and 10), respectively. Notably, alkylzinc chlorides could be also be used, which is particularly significant when the corresponding alkyl bromides are not readily available (Table 3, entry 10). Likewise, by using benzyl chloride and *n*-tetrabutylammonium bromide as the halide transfer agent, aldehyde **6** could be isolated in 81% yield [Eq. (6)], which is comparable to those obtained by using either commercially available benzylzinc bromide (85%; Table 1, entry 1) or benzylzinc bromide generated in situ (87%; Table 3, entry 1). A few functional groups were not tolerated. Not surprisingly, acidic functionalities were incompatible with the reaction conditions, presumably because of quenching of the organozinc reagent. Alkyl halides bearing a leaving group attached to the β-carbon could not be used because of instability of the zinc reagent. As with our previously reported Suzuki–Miyaura cross-coupling,[4d] some sulfur-containing functional groups were not compatible.

Table 3. Scope of in situ-generated organozinc reagents.



Entry	R–X	Product		Isolated yield [%]
1			**6**	87
2			**20**	90
3			**21**	86
4			**22**	84
5			**23**	92
6			**24**	83
7			**25**	81
8			**26**	75
9			**27**	78
10[a]			**28**	69

[a] 2.0 equiv *n*-tetrabutylammonium bromide was added, heated for 12 h in DMA.

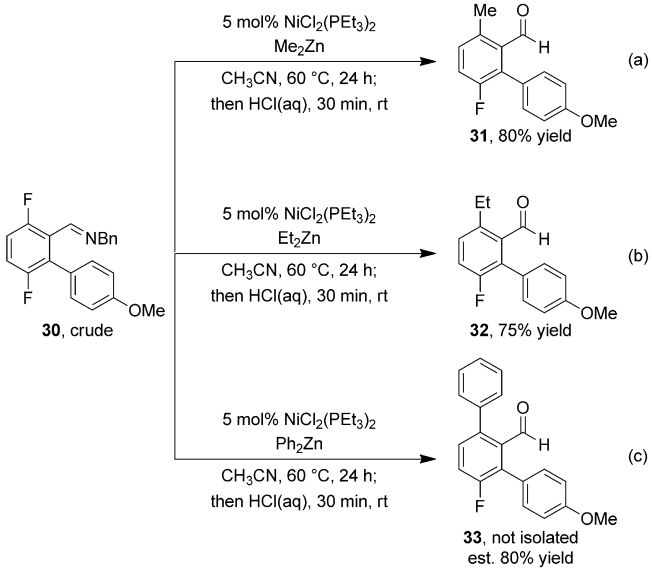


(6)

Whereas a sulfone was tolerated (see above), sulfide and sulfoxide groups shut down the reactions completely and the polyfluoroimines were recovered. At present, our explanation is that the Ni complex reacts preferentially with the C–S bonds of sulfide and sulfoxide substrates, precluding C–F activation.

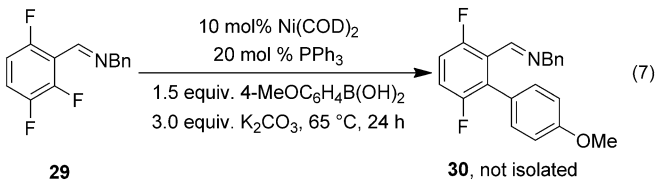
Ni-catalyzed sequential C–F cross-coupling of polyfluoroaryl imines

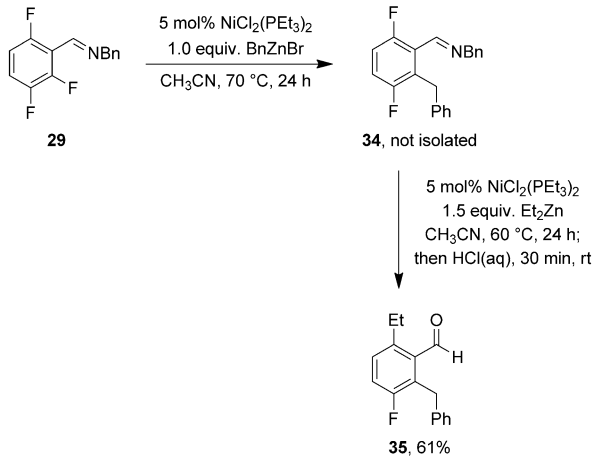
We have become interested in the possibility of Ni-catalyzed sequential cross-coupling reaction with unsymmetrically-substituted substrates. We selected 2,3,6-trifluorophenyl imine **29** as the substrate, given that monoarylation prevailed under Suzuki–Miyaura conditions, but dialkylation occurred under Negishi conditions. We hypothesized that after selective activation of the C–F bond in the 2-position under Suzuki–Miyaura conditions, Negishi coupling would be possible for functionalization at the 6-position, resulting in the generation of highly functionalized fluorine-containing building blocks. Imine **29** was subjected to Suzuki–Miyaura cross-coupling conditions with 4-methoxyphenylboronic acid in tetrahydrofuran (THF). As expected, C–F activation took place exclusively at the 2-position, resulting in the formation of imine **30** [Eq. (7)]. After rapid workup, the crude material was dissolved in CH_3CN and subjected to Negishi cross-coupling conditions with dimethylzinc, diethylzinc, and diphenylzinc (Scheme 1 a, b, and c), respectively. Upon hydrolysis, aldehydes **31** and **32** were isolated in 80 and 75%, respectively. The phenyl-substituted aldehyde **33** was generated in approximately 80% conversion with diphenylzinc (based on integration of the $^{19}F\{^1H\}$ NMR spectrum), but could not be fully separated from the aldehyde derived from remaining starting material.



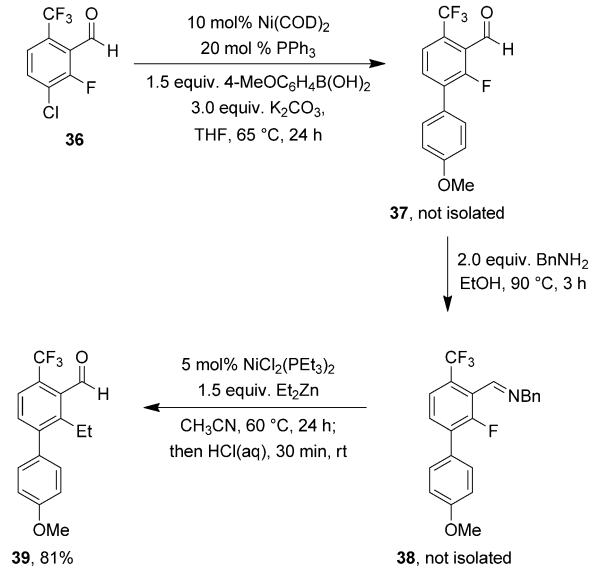
Scheme 1. Sequential Ni-catalyzed Suzuki–Miyaura/Negishi cross-coupling.

Imine **29** could also be reacted with two different alkyl zinc reagents, added sequentially. For example, use of 1.0 equiv benzylzinc bromide provided 80–85% monoalkylated product **34**, along with 15–20% unreacted starting material (Scheme 2). Fortunately, by controlling the reaction stoichiometry, no dialkylated product was detected. Excess diethylzinc was added to the crude mixture, along with an additional 5 mol% [$NiCl_2(PEt_3)_2$], which was necessary for the reaction to proceed. The remaining ortho C–F bonds of **29** and **34** were replaced with an ethyl group, according to ^1H and $^{19}F\{^1H\}$ NMR spectroscopy, as well as mass spectrometry. Upon hydrolysis, aldehyde **35**





Scheme 2. Sequential Ni-catalyzed Negishi/Negishi cross-coupling with different organozinc reagents.



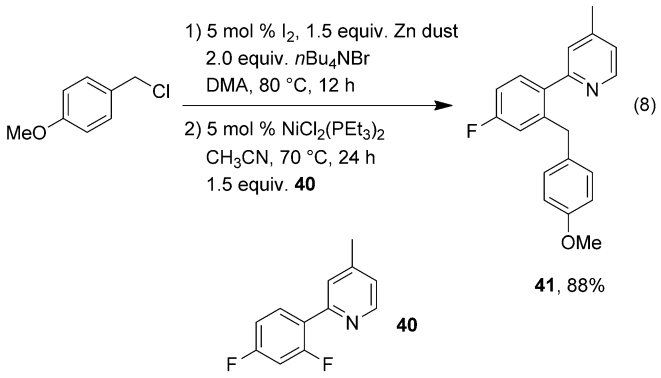
Scheme 3. Sequential Ni-catalyzed C–Cl/C–F cross-coupling.

was isolated from the diethyl byproduct (derived from **29**) in 61% yield after column chromatography.

Capitalizing on the greater reactivity of aryl C–Cl bonds relative to aryl C–F bonds, we were able to achieve a sequential C–Cl/C–F cross-coupling. Consistent with our expectations, activation of the chloro-substituent does not require a directing group, allowing for selective C–Cl Suzuki–Miyaura cross-coupling of aldehyde **36** to generate intermediate **37** (Scheme 3). Addition of 2.0 equiv benzyl amine provided imine **38**, which was then subjected to Negishi coupling with diethylzinc to generate, after hydrolysis, aldehyde **39**.

Ni-catalyzed Negishi cross-coupling of polyfluoroarenes with different directing groups

The synthetic versatility of aldehydes means that aldehyde-derived directing groups are among the most desirable. Nevertheless, we were interested in determining whether or not other directing groups could function under the Negishi coupling conditions. Whereas oxygen-based directing groups were ineffective (presumably due to the inability to promote C–F activation), other nitrogen-based directing groups permitted cross-coupling. For example, pyridine-based 2,4-difluoroarene **40** reacted smoothly with 4-methoxybenzylzinc chloride to produce **41** in 88% yield [Eq. (8)].



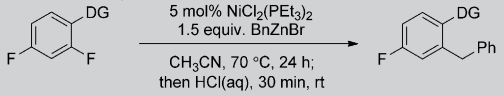
(8)

In comparison, lower yields were found when preformed benzylzinc bromide was used. Pyridine **40** provided 21% yield of the corresponding benzylated product (Table 4, entry 1). Likewise, an oxazoline-based 2,4-difluoroarene reacted with benzylzinc bromide to generate the corresponding benzylated product in 27% yield, with the remaining mass balance being recoverable starting material (Table 4, entry 2). An isooxazole (Table 4, entry 3) was ineffective at promoting the transformation.

Conclusion

We have reported a new way to generate alkyl-substituted aryl fluorides through Ni-catalyzed Negishi cross-coupling reactions. A diverse array of polyfluoroaryl imines are able to react with organozinc reagents, with high functional-group compatibility. Sequential reactions involving different precatalysts and coupling partners permit the synthesis of densely functionalized fluorinated building blocks, and the catalytic procedure can be applied to other directing groups. Mechanistic analysis of this reaction will be reported in due course.

Table 4. Scope and limitations of directing groups in Nickel catalyzed Negishi cross-coupling.



DG = directing group

Entry	Directing group (DG)	Isolated yield [%]
1		21
2		27
3		0

Experimental Section

Reaction between 2,4-difluoroimine and benzylzinc bromide solution

In a glovebox, imine (116 mg, 0.5 mmol, 1.0 equiv), [$NiCl_2(PEt_3)_2$] (9.1 mg, 0.025 mmol, 5 mol%), and benzylzinc bromide (0.5 M in THF, 1.5 mL, 0.75 mmol, 1.5 equiv) were dissolved in acetonitrile (10 mL) in a 20 mL vial. The vial was capped, removed from the glovebox and subsequently heated to 70 °C for 24 h. The solution was cooled to RT, aqueous hydrochloric acid (3 M) was added, and the mixture was stirred at RT for 30 min. The mixture was then extracted with diethyl ether (3×25 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated by rotary evaporation to provide the crude aldehyde product. Further separation by column chromatography (SiO_2, 230–400 mesh; *n*-pentane/EtOAc = 100:1) provided clean product.

Reaction between 2,4-difluoroimine and benzylzinc bromide generated in situ

A dry 25 mL one-neck round-bottom flask was charged with anhydrous DMA (5 mL), I_2 (7 mg, 0.025 mmol, 5 mol%), and zinc dust (50 mg, 0.75 mmol, 1.5 equiv) under N_2. The mixture was stirred at RT for 5 min until the iodine color disappeared. Benzyl bromide (171 mg, 1.0 mmol, 2.0 equiv) was added by using a syringe and the resulting mixture was heated for 3 h at 80 °C. The mixture was then added to a solution of 2,4-difluoroimine (116 mg, 0.5 mmol, 1.0 equiv) and [$NiCl_2(PEt_3)_2$] (9.1 mg, 0.025 mmol, 5 mol%) in CH_3CN (10 mL), while maintaining the temperature at 70 °C for 24 h. The mixture was cooled to RT and stirred for 30 min following the addition of aqueous hydrochloric acid (3 M). The mixture was then extracted with diethyl ether (3×25 mL) and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated by rotary evaporation to provide the crude aldehyde product. Further separation by column chromatography (SiO_2, 230–400 mesh; *n*-pentane/EtOAc = 100:1) provided clean product.

Acknowledgements

We thank the following for support of this research: NSERC (Collaboration Research and Development Grant, Research Tools and Instrumentation Grant), AstraZeneca Canada (2008 Award in Chemistry to J. A. L.) and the University of British Columbia. We thank Nicholas Cowper and Philip Provencher for preliminary investigations, and Matthew Wathier for analyzing NMR spectra.

Keywords: cross-coupling · fluorine · nickel · synthetic methods · zinc

[1] For early reviews on C–F activations, see: a) J. L. Kiplinger, T. G. Richmond, C. E. Osterberg, *Chem. Rev.* **1994**, *94*, 373 – 413; b) T. G. Richmond, *Angew. Chem.* **2000**, *112*, 3378 – 3380; *Angew. Chem. Int. Ed.* **2000**, *39*, 3241 – 3244; c) T. Braun, R. N. Perutz, *Chem. Commun.* **2002**, 2749 – 2757.

[2] For reviews of transition-metal-catalyzed C–F bond activation, see: a) H. Torrens, *Coord. Chem. Rev.* **2005**, *249*, 1957 – 1985; b) G. Meier, T. Braun, *Angew. Chem.* **2009**, *121*, 1575 – 1577; *Angew. Chem. Int. Ed.* **2009**, *48*, 1546 – 1548; c) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119 – 2183; d) A. D. Sun, J. A. Love, *Dalton Trans.* **2010**, *39*, 10362 – 10374; e) T. Braun, F. Wehmeier, *Eur. J. Inorg. Chem.* **2011**, 613 – 625.

[3] For examples of Kumada–Tamao–Corriu type aryl fluorine cross-coupling reactions, see: Ni a) Y. Kiso, K. Tamao, M. Kumada, *J. Organomet. Chem.* **1973**, *50*, C12 – 14; b) V. P. W. Böhm, C. W. K. Gstottmayr, T. Weskamp, W. A. Hermann, *Angew. Chem.* **2001**, *113*, 3500 – 3503; *Angew. Chem. Int. Ed.* **2001**, *40*, 3387 – 3389; c) F. Mongin, L. Mojovic, B. Guillamet, F. Trecourt, G. Queguiner, *J. Org. Chem.* **2002**, *67*, 8991 – 8994; d) J. W. Dankwardt, *J. Organomet. Chem.* **2005**, *690*, 932 – 938; e) L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angew. Chem.* **2005**, *117*, 7382 – 7386; *Angew. Chem. Int. Ed.* **2005**, *44*, 7216 – 7219; f) N. Yoshikai, H. Mashima, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 17978 – 17979; g) T. Saeki, Y. Takashima, K. Tamao, *Synlett* **2005**, 1771 – 1774; h) L. Ackermann, R. Born, J. H. Spatz, A. Althammer, C. J. Gschrei, *Pure Appl. Chem.* **2006**, *78*, 209 – 214; i) K. Inamoto, J. Kuroda, T. Sakamoto, K. Hiroya, *Synthesis* **2007**, 2853 – 2861; j) T. Ramnial, S. A. Taylor, M. L. Bender, B. Gorodetsky, P. T. K. Lee, D. A. Dickie, B. M. McCollum, C. C. Pye, C. J. Walsby, J. A. C. Clyburne, *J. Org. Chem.* **2008**, *73*, 801 – 812; k) B.-T. Guan, S.-K. Xiang, T. Wu, Z.-P. Sun, B.-Q. Wang, K.-Q. Zhao, Z.-J. Shi, *Chem. Commun.* **2008**, 1437 – 1439; l) N. Yoshikai, H. Matsuda, E. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 9590 – 9599; m) J.-R. Wang, K. Manabe, *Org. Lett.* **2009**, *11*, 741 – 744; n) Z. Jin, Y.-J. Li, Y.-Q. Ma, L.-L. Qiu, J.-X. Fan, *Chem. Eur. J.* **2012**, *18*, 446 – 450; o) W.-J. Guo, Z.-X. Wang, *J. Org. Chem.* **2013**, *78*, 1054 – 1061; Pd: p) K. Manabe, S. Ishikawa, *Synthesis* **2008**, 2645 – 2649; Ta/Ti: q) H. Guo, F. Kong, K.-I. Kanno, J. He, K. Nakajima, T. Takahashi, *Organometallics* **2006**, *25*, 2045 – 2048; Co: r) T. J. Korn, M. A. Schade, S. Wirth, P. Knochel, *Org. Lett.* **2006**, *8*, 725 – 728; s) T. J. Korn, M. A. Schade, M. N. Cheemala, S. Wirth, S. A. Guevara, G. Cahiez, P. Knochel, *Synthesis* **2006**, 3547 – 3574.

[4] For examples of Suzuki–Miyaura type aryl fluorine cross-coupling reaction, see: Ni: a) A. Steffen, M. I. Sladek, T. Braun, B. Neumann, H.-G. Stammler, *Organometallics* **2005**, *24*, 4057; b) J. Liu, M. J. Robins, *Org. Lett.* **2005**, *7*, 1149 – 1151; c) T. Schaub, M. Backes, U. Radius, *J. Am. Chem. Soc.* **2006**, *128*, 15964 – 15965; d) A. D. Sun, J. A. Love, *Org. Lett.* **2011**, *13*, 2750 – 2753; e) M. Tobisu, T. Xu, T. Shimasaki, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 19505 – 19511; Pd; f) D. A. Widdowson, R. Wilhelm, *Chem. Commun.* **1999**, 2211 – 2212; g) R. Wilhelm, D. A. Widdowson, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3808 – 3814; h) Y. M. Kim, S. Yu, *J. Am. Chem. Soc.* **2003**, *125*, 1696 – 1697; i) D. A. Widdowson, R. Wilhelm, *Chem. Commun.* **2003**, 578 – 579; j) K. Mikami, T. Miyamoto, M. Hatano, *Chem. Commun.* **2004**, 2082 – 2083; k) S. Bahmanyar, B. C. Borer, Y. M. Kim, D. M. Kurtz, S. Yu, *Org. Lett.* **2005**, *7*, 1011 – 1014; l) M. R. Cargill, G. Sandford, A. J. Tadeusiak, D. S. Yufit, J. A. K. Howard, P. Kilickiran, G. Nelles, *J. Org. Chem.* **2010**, *75*, 5860 – 5866; m) J. R. Ruiz, C. Jimenez-Sanchidrian, M. Mora, *J. Fluorine Chem.* **2006**, *127*, 443 – 445; n) B. J. Gallon, R. W. Kojima, R. B. Kaner, P. L. Diaconescu, *Angew. Chem.* **2007**, *119*, 7389 – 7392; *Angew. Chem. Int. Ed.* **2007**, *46*, 7251 – 7254; o) D. Yu, Q. Shen, L. Lu, *J. Org. Chem.* **2012**, *77*, 1798 – 1804; Ru: p) K. Kawamoto, T, Kochi, M. Sato, E. Mizushima, F. Kakiuchi, *Tetrahedron Lett.* **2011**, *52*, 5888 – 5890.

[5] For examples of Negishi type aryl fluorine cross-coupling reactions see: Pt: a) T. Wang, B. J. Alfonso, J. A. Love, *Org. Lett.* **2007**, *9*, 5629 – 5631; b) T. Wang, J. A. Love, *Organometallics* **2008**, *27*, 3290 – 3296; c) H. L. Buckley, A. D. Sun, J. A. Love, *Organometallics* **2009**, *28*, 6622 – 6624; d) A. D. Sun, J. A. Love, *J. Fluorine Chem.* **2010**, *131*, 1237 – 1240; e) L. Keyes, A. D. Sun, J. A. Love, *Eur. J. Org. Chem.* **2011**, 3985 – 3994; f) T. Wang, L. Keyes, B. O. Patrick, J. A. Love, *Organometallics* **2012**, *31*, 1397 – 1407; Ni: g) B.-J. Li, Y.-Z. Li, X.-Y. Lu, J. Liu, B.-T. Guan, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 10278 – 10281; *Angew. Chem. Int. Ed.* **2008**, *47*, 10124 – 10127 (a Ni-catalyzed C–F activation was discussed on page 10126, Table 3); h) L.-G. Xie, Z.-X. Wang, *Angew. Chem.* **2011**, *123*, 5003 – 5006; *Angew. Chem. Int. Ed.* **2011**, *50*, 4901 – 4904 (Ni-catalyzed C–F activation was discussed on page 4902, Table 3); i) Y. Nakamura, N. Yoshikai, L. Llies, E. Nakamura, *Org. Lett.* **2012**, *14*, 3316 – 3319.

[6] For examples of Stille type aryl fluorine cross-coupling reactions, see: Ni: a) T. Braun, R. N. Perutz, M. I. Sladek, *Chem. Commun.* **2001**, 2254 – 2255; Pd: b) T. Braun, J. Izundu, A. Steffen, B. Neumann, H.-G. Stammler, *Dalton Trans.* **2006**, 5118 – 5123.

[7] For an example of C–F/C–H activation, see: D. Yu, L. Lu, O. Shen, *Org. Lett.* **2013**, *15*, 940 – 943.

[8] For stoichiometric reactivity, see: a) T. Braun, S. Parsons, R. N. Perutz, M. Voith, *Organometallics* **1999**, *18*, 1710 – 1718; For catalytic methylation, see: b) X. Yang, H. Sun, S. Zhang, X. Li, *J. Organomet. Chem.* **2013**, *723*, 36 – 42.

[9] a) M. Piber, A. E. Jensen, M. Rottlander, P. Knochel, *Org. Lett.* **1999**, *1*, 1323 – 1326; b) A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79 – 85.

[10] a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117 – 2188; b) R. D. Rieke, *Aldrichimica Acta* **2000**, *33*, 52 – 60; c) P. Knochel, M. A. Schade, S. Bernhardt, G. Manolikaes, A. Metzger, F. M. Piller, C. J. Rohbogner, M. Mosrin, *Beilstein J. Org. Chem.* **2011**, *7*, 1261 – 1277.

[11] a) C. Jubert, P. Knochel, *J. Org. Chem.* **1992**, *57*, 5425 – 5431; b) T. D. Blümke, F. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082 – 4084; c) S. Huo, *Org. Lett.* **2003**, *5*, 423 – 425.

[12] a) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886; b) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369; c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308 – 319; d) S. Purser, P. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; e) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071 – 1081.

[13] For recent examples of Ni-catalyzed preferential activation of C–H over C–F bonds, see: a) Y. Nakao, N, Kashihara, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 16170 – 16171; b) K. S. Kanyiva, N. Kashihara, Y. Nakao, T. Hiyama, M. Ohashi, S. Ogoshi, *Dalton Trans.* **2010**, *39*, 10483 – 10494.

[14] For mechanistic studies of Ni-promoted C–H versus C–F activation, see: a) S. A. Johnson, C. A. Huff, F. Mustafa, M. Saliba, *J. Am. Chem. Soc.* **2008**, *130*, 17278 – 17280; b) S. A. Johnson, E. T. Taylor, S. J. Cruise, *Organometallics* **2009**, *28*, 3842 – 3855; c) M. E. Doster, J. A. Hatnean, T. Jeftic, S. Modi, S. A. Johnson, *J. Am. Chem. Soc.* **2010**, *132*, 11923 – 11925; d) J. A. Hatnean, R. Beck, J. D. Borrelli, S. A. Johnson, *Organometallics* **2010**, *29*, 6077 – 6091; e) S. A. Johnson, N. M. Mroz, R. Valdizon, S. Murray, *Organometallics* **2011**, *30*, 441 – 457.

[15] E. Clot, O. Eisenstein, N. Jasim, S. A. Macgregor, J. E. McGrady, R. N. Perutz, *Acc. Chem. Res.* **2011**, *44*, 333 – 348.

[16] For a review, see: B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A. Resmerita, N. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346 – 1416. For a recent example of Ni-catalyzed Negishi coupling of aryl methyl ethers, see: C. Wang, T. Ozaki, R. Takita, M. Uchiyama, *Chem. Eur. J.* **2012**, *18*, 3482 – 3485.

Received: September 29, 2013
Published online on February 12, 2014