Catalytic C−C Coupling Reactions at Nickel by C−F Activation of a Pyrimidine in the Presence of a C−Cl Bond: The Crucial Role of Highly Reactive Fluoro Complexes

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Treatment of $[Ni(COD)_2]$ (COD = 1,5-cyclooctadiene) with 5-chloro-2,4,6-trifluoropyrimidine (**1**) in the presence of P^iPr_3 or PPh_3 effects the formation of the fluoro complexes *trans*-$[NiF(4\text{-}C_4N_2ClF_2)(P^iPr_3)_2]$ (**3**) and *trans*-$[NiF(4\text{-}C_4N_2ClF_2)(PPh_3)_2]$ (**4**). The chloro complex *trans*-$[NiCl(4\text{-}C_4N_2ClF_2)(PPh_3)_2]$ (**5**) can be prepared by reaction of **4** with Me_3SiCl. In contrast, a reaction of **1** with $[Pd(PPh_3)_4]$ leads to the insertion of a $\{Pd(PPh_3)_2\}$ unit into the C−Cl bond yielding *trans*-$[PdCl(5\text{-}C_4N_2F_3)(PPh_3)_2]$ (**6**). Treatment of **4** with an excess of $TolB(OH)_2$ at 273 K results in the slow formation of *trans*-$[NiF(4\text{-}C_4N_2TolClF)(PPh_3)_2]$ (**7**) and subsequently 5-chloro-2-fluoro-4,6-ditolylpyrimidine (**8**). Quenching of a solution of **7** with Me_3SiCl leads to the chloro derivative *trans*-$[NiCl(4\text{-}C_4N_2TolClF)(PPh_3)_2]$ (**9**). Treatment of **4** with $PhB(OH)_2$ followed by addition of Me_3SiCl gives the complex *trans*-$[NiCl(4\text{-}C_4N_2PhClF)(PPh_3)_2]$ (**10**). In catalytic experiments, **1** is converted with the boronic acids $TolB(OH)_2$, $PhB(OH)_2$, and $p\text{-}F_3CC_6H_4B(OH)_2$ into the 5-chloro-2-fluoro-4,6-diarylpyrimidines **8**, **11**, and **12** in 73%, 88%, and 37% yield, respectively, when 10% of **4** is employed as catalyst. The molecular structures of the complexes **5**, **6**, and **10** have been determined by X-ray crystallography. The studies reported in this paper represent the first catalytic C−C coupling reactions involving the activation of a C−F bond in the presence of a thermodynamically weaker C−Cl bond. They provide a route to access 5-chloro-2-fluoro-4,6-diarylpyrimidines, which have not been described before. There is considerable evidence that the presence of the fluoro ligand in **4** is crucial for the transmetalation step to occur and for the catalytic cycle to proceed.

Introduction

In the past few years C−F activation at transition metal centers has been proven to be a useful tool to access fluoro-organics.[1−7] The strategy often involves the selective removal of a fluorine atom from readily available precursors sometimes providing routes to new building blocks and higher-value fluorinated compounds. Most of the investigations so far are concerned with hydrodefluorination reactions of highly fluorinated molecules.[1−3] Routes for the generation of fluoro-organics by the transition metal mediated conversion of an aromatic C−F bond into a C−C bond are barely developed.[1,5,8] W. D. Jones et al. demonstrated that upon heating of $[Cp_2Zr(C_6F_5)_2]$ in the presence of C_6F_6, linear chains of perfluoroarenes are generated.[5a] The selective functionalization of pentafluoropyridine at nickel and rhodium has been accomplished to give new methyl and acetyl derivatives.[5b,c] Note also that an example of an intramolecular and diastereoselective

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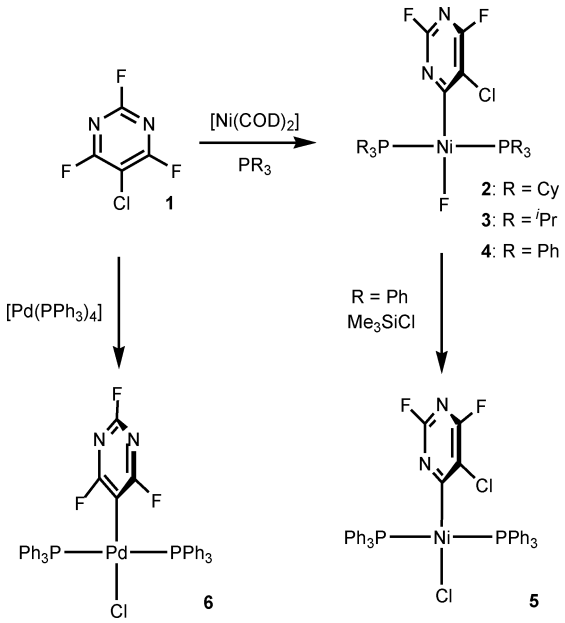
conversion of an α-C−F bond into a carbon−carbon bond at an iridium fluoroalkyl complex has been reported by R. P. Hughes and co-workers.[4a,4f]

Catalytic C−C coupling reactions based on C−F activation reactions of aryl fluorides are extremely rare.[8] Almost all of the transformations known consist of cross-coupling reactions to convert monofluoroarenes into nonfluorinated derivatives. Only one catalytic system has been described that can accomplish cross-couplings of highly fluorinated aromatics via C−F activation.[8a] The Stille type conversions transform fluorinated pyridines into vinyl derivatives and are most likely based on a concerted oxidative addition of a C−F bond at a nickel center.[1d,8a,9] In a comparable oxidative addition the activation of 5-chloro-2,4,6-trifluoropyrimidine (**1**) has been achieved at {$Ni(PCy_3)_2$} to give *trans*-[NiF(4-$C_4N_2ClF_2$)(PCy_3)$_2$] (**2**) (Scheme 1).[2] In this paper we report on the synthesis of a highly reactive nickel fluoro complex, which catalyzes Suzuki−Miyaura type[10] cross-coupling reactions of **1**. The analogous chloro complex is catalytically not active. The conversions represent the first catalytic reactions mediated by transition metals, which involve the cleavage of a C−F bond in the presence of a C−Cl bond.

Scheme 1. Activation of 5-Chloro-2,4,6-trifluoropyrimidine (1) at Palladium and Nickel



Results

1. Activation of 5-Chloro-2,4,6-trifluoropyrimidine (1). Reactions of [$Ni(COD)_2$] (COD = 1,5-cyclooctadiene) with 1 equiv of **1** in THF at room temperature produced in the presence of P^iPr_3 or PPh_3 the fluoro complexes *trans*-[NiF(4-$C_4N_2ClF_2$)(P^iPr_3)$_2$] (**3**) and *trans*-[NiF(4-$C_4N_2ClF_2$)(PPh_3)$_2$] (**4**) (Scheme 1). For **4** the NMR data of the reaction solutions reveal small amounts (5−10%) of *trans*-[NiCl(4-$C_4N_2ClF_2$)(PPh_3)$_2$] (**5**) as a second product.The substitution of the metal-bound fluorides by a chloro ligand can be explained by a reaction of the metal fluoride with the free pyrimidine as a source of chloride.[2] However, pure batches of **4** can be obtained by washing the crude product with cold hexane. Complex **5** can also be prepared independently by reaction of **4** with Me_3SiCl. In the ^{19}F NMR spectrum each of the fluoro complexes reveals a characteristic signal at high field (**3**: δ −379.3; **4**: δ −360.4), which can be assigned to the fluoro ligand.[2] The ^{31}P NMR spectra display doublets with couplings of the phosphorus nuclei to the metal-bound fluorine of 36.0 Hz (**3**) and 34.4 Hz (**4**). In contrast to the conversions described above, the activation of **1** with [$Pd(PPh_3)_4$] leads to the insertion of a {$Pd(PPh_3)_2$} unit into the C−Cl bond, yielding *trans*-[PdCl(5-$C_4N_2F_3$)(PPh_3)$_2$] (**6**) (Scheme 1). The ^{19}F NMR spectrum of **5** shows two resonances for the aromatic fluorines at δ −40.1 and −55.4 with an integral ratio of 2:1. The ^{31}P NMR spectrum exhibits a singlet at δ 23.1.

The molecular structures of **5** and **6** were confirmed by X-ray diffraction analysis at 100 K (Figures 1, 2; Tables 1, 2). Suitable crystals have been obtained from toluene solutions at 243 K. Selected bond lengths and angles are summarized in Tables 1 and 2. The molecular structures show the expected *trans* disposition of the phosphine ligands with approximately square-planar coordination at the metal. The dihedral angles between the plane defined by the pyrimidyl ring and the coordination plane of the metal are 93.7° for **5** and 104.5° for **6**. The pyrimidyl ligand in **5** is disordered on two positions (87:13). The nickel−carbon distance to the part with the higher occupation of 1.8541(17) Å is shorter than the comparable bond length in *trans*-[NiCl(3-C_5NF_4)(PEt_3)$_2$] [1.894(1) Å].[11] The palladium−carbon distance in **6** is 2.0032(17) Å. For comparison, the Pd−C separation in *trans*-[PdBr(4-C_5NH_4)(PEt_3)$_2$] of 2.030(17) Å is in a similar range.[12]

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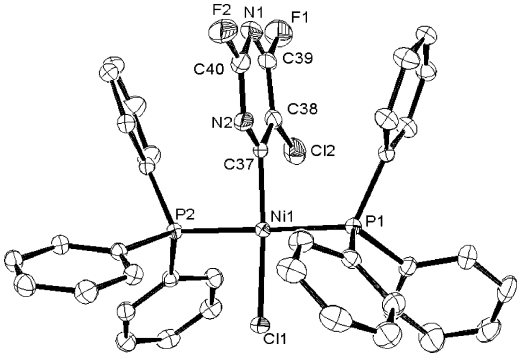


Figure 1. ORTEP diagram of **5** (ellipsoids at 50% probability level).

Table 1. Selected Bond Lengths (Å) and Angles (deg) of 5 with Standard Deviations in Parentheses[a]

bond	length	bond	length
Ni(1)−C(37)	1.8541(17)	N(1)−C(39)	1.300(4)
Ni(1)−Cl(1)	2.2097(4)	N(1)−C(40)	1.299(4)
Ni(1)−P(1)	2.2186(4)	N(2)−C(37)	1.345(3)
Ni(1)−P(2)	2.2166(4)	N(2)−C(40)	1.330(3)
C(38)−Cl(2)	1.726(2)	C(37)−C(38)	1.398(3)
C(39)−F(1)	1.335(3)	C(38)−C(39)	1.391(3)
C(40)−F(2)	1.344(3)		

bonds	angle	bonds	angle
C(37)−Ni(1)−Cl(1)	172.57(6)	Ni(1)−C(37)−N(2)	116.26(14)
P(1)−Ni(1)−P(2)	177.182(16)	N(2)−C(37)−C(38)	119.30(17)
C(37)−Ni(1)−P(1)	89.69(5)	C(37)−C(38)−C(39)	117.1(2)
C(37)−Ni(1)−P(2)	89.20(5)	C(38)−C(39)−N(1)	124.0(2)
Cl(1)−Ni(1)−P(1)	90.782(15)	C(39)−N(1)−C(40)	113.85(19)
Cl(1)−Ni(1)−P(2)	89.981(14)	N(1)−C(40)−N(2)	130.2(2)
Ni(1)−C(37)−C(38)	124.43(15)	C(40)−N(2)−C(37)	115.6(2)

[a] Note that the pyrimidyl ligand is disordered on two positions (87:13); data with the part with the higher occupation are given, only.

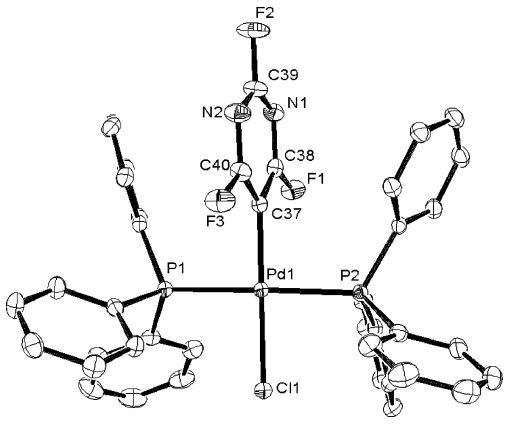


Figure 2. ORTEP diagram of **6** (ellipsoids at 50% probability level).

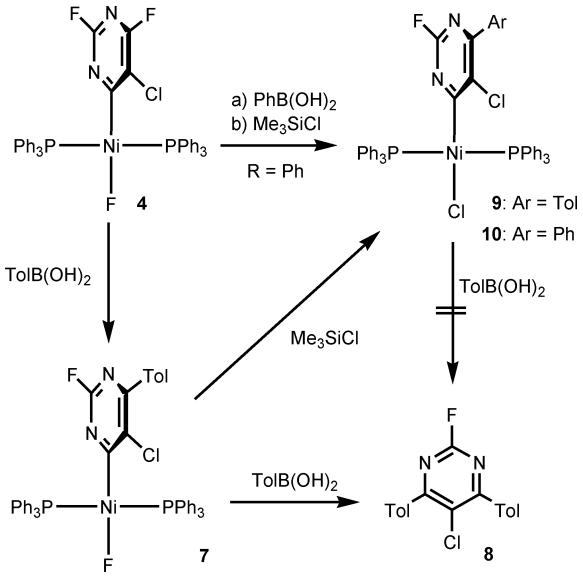
2. Reactivity of Nickel Fluorides toward Boronic Acids. Treatment of a solution of *trans*-[NiF(4-$C_4N_2ClF_2$)(PPh_3)$_2$] (**4**) with an excess of the boronic acid TolB(OH)$_2$ at 273 K results in the slow formation of the complex *trans*-[NiF(4-C_4N_2TolClF)(PPh_3)$_2$] (**7**) (Scheme 2). After 1 h the generation of the ditolylpyrimidine **8** and small amounts of [Ni(PPh_3)$_4$] is observed. The ^{31}P NMR spectrum of **7** exhibits a broad signal at δ 13.7, while the ^{19}F NMR spectrum shows one resonance for the pyrimidyl ligand at δ −53.3 and a broad signal at δ −358 indicating the nickel-bound fluorine. We tentatively attribute the broadness of the spectra to an interaction of free boronic acid with the fluoro ligand.[10,13] Addition of CsF to a reaction solution containing **7** diminishes that interaction, resulting in a sharp doublet in the ^{31}P NMR spectrum at δ 13.7 (J_{PF} = 34.4 Hz). We were not able to isolate **7**, but quenching of a solution with Me_3SiCl leads to the chloro derivative *trans*-[NiCl(4-C_4N_2TolClF)(PPh_3)$_2$] (**9**) (Scheme 2). In a comparable experiment, treatment of **4** with the boronic acid PhB(OH)$_2$ followed by addition of Me_3SiCl gives the complex *trans*-[NiCl(4-C_4N_2PhClF)(PPh_3)$_2$] (**10**). The molecular structure of **10** was confirmed by an X-ray diffraction analysis at low temperature (Figure 3, Table 3). Selected angles and bond lengths are depicted in Table 3. The dihedral angle between the plane defined by the pyrimidyl ring and the coordination plane of the metal is 89.6°. The nickel−carbon distance of 1.8640(16) Å is comparable with the separation found for compound **5**.

Table 2. Selected Bond Lengths (Å) and Angles (deg) of 6 with Standard Deviations in Parentheses

bond	length	bond	length
Pd(1)−C(37)	2.0032(14)	N(1)−C(38)	1.325(2)
Pd(1)−Cl(1)	2.3483(4)	N(1)−C(39)	1.306(2)
Pd(1)−P(1)	2.3310(4)	N(2)−C(39)	1.312(2)
Pd(1)−P(2)	2.3184(4)	N(2)−C(40)	1.328(2)
C(38)−F(1)	1.3413(17)	C(37)−C(40)	1.381(2)
C(39)−F(2)	1.3501(18)	C(37)−C(38)	1.381(2)
C(40)−F(3)	1.3446(18)		

bonds	angle	bonds	angle
C(37)−Pd(1)−Cl(1)	173.99(4)	Pd(1)−C(37)−C(40)	122.87(11)
P(1)−Pd(1)−P(2)	169.109(14)	C(38)−C(37)−C(40)	109.25(13)
C(37)−Pd(1)−P(1)	89.42(4)	C(37)−C(38)−N(1)	127.91(14)
C(37)−Pd(1)−P(2)	92.85(4)	C(38)−N(1)−C(39)	112.48(13)
Cl(1)−Pd(1)−P(1)	91.888(14)	N(1)−C(39)−N(2)	130.19(15)
Cl(1)−Pd(1)−P(2)	86.962(14)	C(39)−N(2)−C(40)	112.03(14)
Pd(1)−C(37)−C(38)	127.88(11)	N(2)−C(40)−C(37)	128.14(14)

Scheme 2. Reactivity of Nickel Pyrimidyl Compounds



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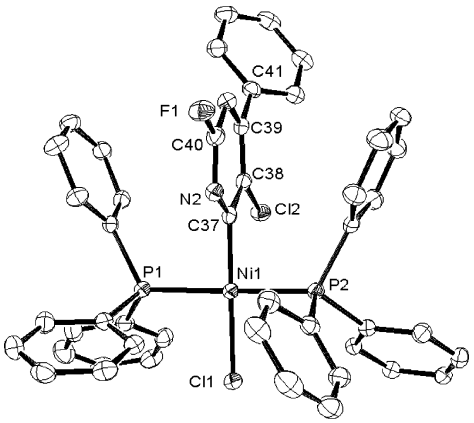

Figure 3. ORTEP diagram of **10** (ellipsoids at 50% probability level).

Table 3. Selected Bond Lengths (Å) and Angles (deg) of 10 with Standard Deviations in Parentheses

bond	length	bond	length
Ni(1)−C(37)	1.8640(16)	N(1)−C(39)	1.359(2)
Ni(1)−Cl(1)	2.2263(4)	N(1)−C(40)	1.308(2)
Ni(1)−P(1)	2.2250(5)	N(2)−C(37)	1.350(2)
Ni(1)−P(2)	2.2175(4)	N(2)−C(40)	1.317(2)
C(38)−Cl(2)	1.7415(17)	C(37)−C(38)	1.401(2)
C(39)−C(41)	1.484(2)	C(38)−C(39)	1.392(2)
C(40)−F(2)	1.3497(19)		

bonds	angle	bonds	angle
C(37)−Ni(1)−Cl(1)	177.76(5)	Ni(1)−C(37)−N(2)	118.91(12)
P(1)−Ni(1)−P(2)	167.964(18)	N(2)−C(37)−C(38)	118.85(14)
C(37)−Ni(1)−P(1)	89.40(5)	C(37)−C(38)−C(39)	120.59(15)
C(37)−Ni(1)−P(2)	88.19(5)	C(38)−C(39)−N(1)	119.14(15)
Cl(1)−Ni(1)−P(1)	91.587(16)	C(39)−N(1)−C(40)	114.79(14)
Cl(1)−Ni(1)−P(2)	90.434(16)	N(1)−C(40)−N(2)	131.44(16)
Ni(1)−C(37)−C(38)	122.24(12)	C(40)−N(2)−C(37)	115.13(14)

The complex converts into several unidentified products and only traces of **8**. An NMR experiment with *trans*-[NiF(4-$C_4N_2ClF_2$)(PCy_3)$_2$] reveals that initially a nickel fluoride is formed, which we assign as the compound comparable to **7**, *trans*-[NiF(4-C_4N_2TolClF)(PCy_3)$_2$] [δ(^{31}P) 17.0, J_{PF} = 40.2 Hz; δ(^{19}F) −50.2, −368].

3. Catalytic Cross-Coupling Reactions of 5-Chloro-2,4,6-trifluoropyrimidine (1). Next we turned our attention to catalytic cross-coupling reactions for the synthesis of new fluoropyrimidines by C−F activation. Representative results are summarized in Table 4. The coupling of 5-chloro-2,4,6-trifluoropyrimidine (**1**) with boronic acids in the presence of *trans*-[NiF(4-$C_4N_2ClF_2$)-(PPh_3)$_2$] (**4**) as catalyst, PPh_3, and Cs_2CO_3 was investigated. For the boronic acids Tol$B(OH)_2$, Ph$B(OH)_2$, and *p*-$F_3CC_6H_4B(OH)_2$ the diarylpyrimidines **8**, **11**, and **12** are obtained as products in 73%, 88%, and 37% yield, respectively, when 10% catalyst is employed (Scheme 3). NMR investigations show that the corresponding fluoroboronic acids are also formed. In the case of Mes$B(OH)_2$ as coupling reagent we observed the generation of **13** and 5-chloro-4-mesityl-2,6-difluoropyrimidine (**14**) in a ratio of 1:2 (yields: 16%, 32%; Table 4). The best results are achieved at 323 K in THF as a solvent. By altering the solvent to benzene or DME the yields are lower. For the formation of **11**, the influence of the base has also been investigated, revealing that CsF and Et_3N have no effect, while Na_2CO_3 or K_3PO_4 can be employed, but leading to lower yields. Employment of Ni$(COD)_2$/PPh_3 as precatalytic system also yields with Ph$B(OH)_2$ the pyrimidine **11**, but in low yields. We did not observe any reaction of Ph$B(OH)_2$ with **1** without adding complex **4**, even in the presence of CsF or Cs_2CO_3.

Scheme 3. Catalytic Cross-Coupling Reactions of 1; for Ar = Mes 5-Chloro-4-mesityl-2,6-difluoropyrimidine (14) is also Formed

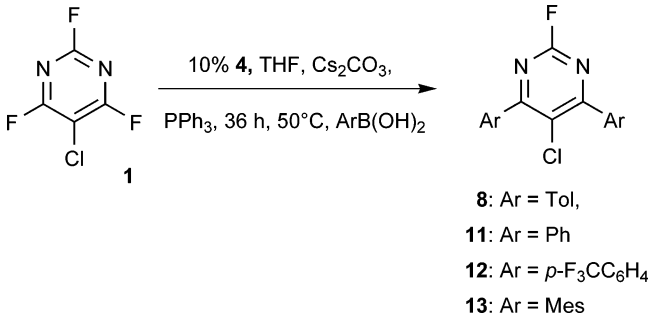

Table 4. Coupling of 1 with Boronic Acids Using 10% 4 as a Catalyst[a]

entry	boronic acid	product	base	yield (%)
1	Tol$B(OH)_2$	**8**	Cs_2CO_3	73
2	Ph$B(OH)_2$	**11**	Cs_2CO_3	88
3	Ph$B(OH)_2$	**11**	Na_2CO_3	20
4	Ph$B(OH)_2$	**11**	K_3PO_4	14
5	*p*-$F_3CC_6H_4B(OH)_2$	**12**	Cs_2CO_3	37
6	Mes$B(OH)_2$	**13**, **14**	Cs_2CO_3	16, 32

[a] The reactions have been performed in THF at 323 K for 36 h; yields based on **1** have been determined by ^{19}F NMR spectroscopy using a capillary containing 4-fluorotoluene as external standard.

Notably, on employing the palladium compound *trans*-[PdCl(5-$C_4N_2F_3$)(PPh_3)$_2$] (**6**) as catalyst, no formation of an arylpyrimidine has been observed. Although Suzuki coupling reactions of 5-chloropyrimidines have proven to be difficult, an example has recently been reported.[14,15] The chloro complexes **5**, **9**, **10**, *trans*-[NiCl-(4-$C_4N_2ClF_2$)(PCy_3)$_2$], and *trans*-[NiCl(4-$C_4N_2ClF_2$)-(PEt_3)$_2$][2] did not react with Ar$B(OH)_2$ (Ar = Ph, Tol) under stoichiometric or catalytic conditions, not even in the presence of Cs_2CO_3 or CsF. Therefore, the tendency of the catalyst **4** to form **5** in the presence of **1** might be one decomposition pathway for the catalyst **4**, among other possiblities such as electron transfer reactions.[11,16] In accordance with the stoichiometric observations, we also did not find any catalytic activity on using the fluoro compound **2** or **3** as catalyst.

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(15) For Suzuki coupling reactions of aryl chlorides see for example: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed*. **2002**, *41*, 4176. (b) Littke, A. F.; Fu, G. C. *Angew. Chem.* **2002**, *114*, 4350. (c) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc*. **2003**, *125*, 16194. (d) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2003**, 38. (e) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem., Int. Ed*. **2002**, *41*, 4120. (f) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem.* **2002**, *114*, 4294. (g) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *41*, 1363. (h) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem.* **2002**, *114*, 1421. (i) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (j) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem.* **1999**, *111*, 2570.

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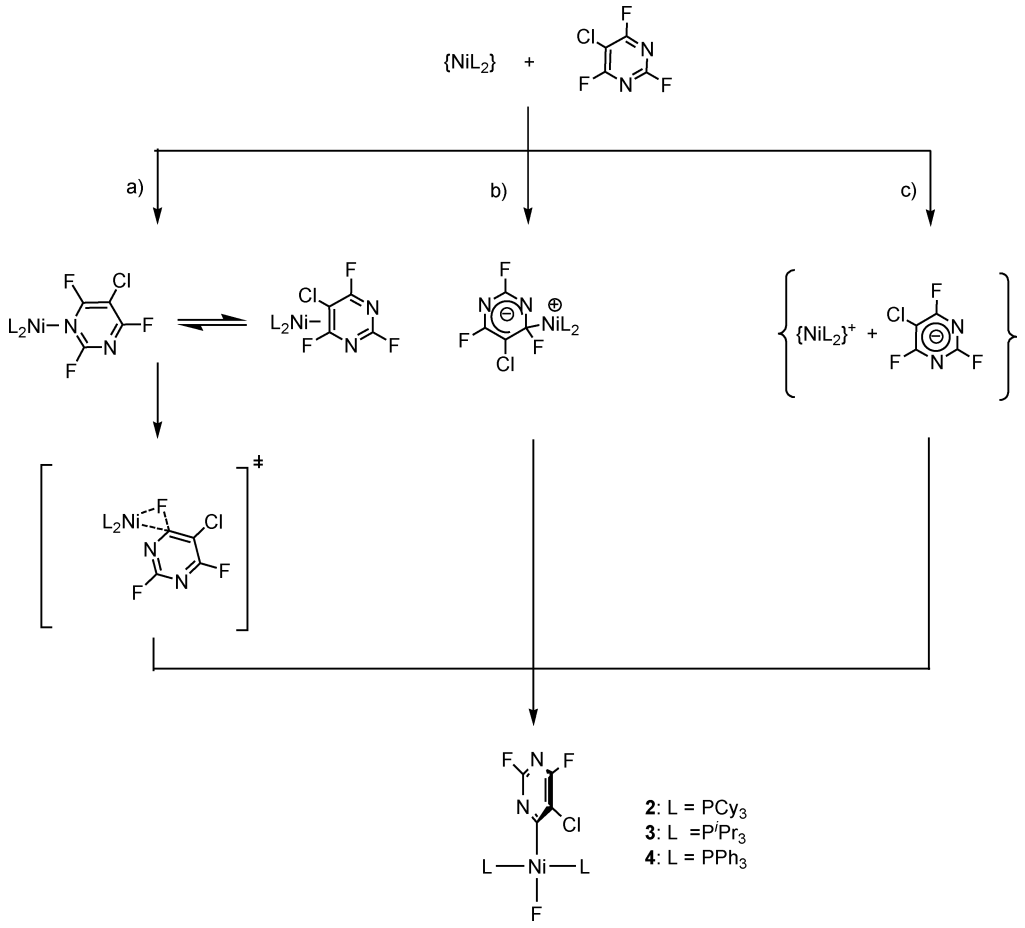
Scheme 4. Conceivable Reaction Pathways for the C−F Activation of 1



Discussion

Activation reactions of 5-chloro-2,4,6-trifluoropyrimidine (**1**) at nickel and palladium are shown in Scheme 1. The selective cleavage of the C−F bond in **1** at $\{Ni(PPh_3)_2\}$ is particularly intriguing. For comparison, not only the treatment of **1** with $[Pd(PPh_3)_4]$ but also a reaction with $[Ni(COD)_2]/PEt_3$ lead to a C−Cl activation of **1**.[2] Together with the C−F activations at $\{Ni(PR_3)_2\}$ (R = Cy, ^{i}Pr), the findings suggest that the chemospecifity found at nickel is controlled by steric factors. The only other example for the activation of a C−F bond in the presence of a C−Cl bond by a transition metal is the activation of the imine $(C_6F_5)CH{=}NCH_2(2\text{-}ClC_6H_4)$ at a Pt(II) center, but with the carbon−halogen bonds at different rings.[17] Note also that for 2,4,6-trifluoropyrimidine C−F activation at $\{Ni(PEt_3)_2\}$ in the 2-position is preferred over C−H activation.[6c,6d] 3-Chlorotetrafluoropyridine, 3,5-dichlorotrifluoropyridine, and chloropentafluorobenzene show C−Cl activation at $\{Ni(PCy_3)_2\}$ or $\{Ni(PEt_3)_2\}$.[11,18]

A conceivable mechanism for the C−F activation reactions consists of a precordination of the pyrimidine at nickel followed by a concerted oxidative addition at the nickel center.[9,19] Unfortunately we were not able to identify any intermediate by NMR spectroscopy, such as a complex with a coordinated pyrimidine at nickel (pathway a; Scheme 4). An alternative reaction pathway proceeds via a nucleophilic substitution, which is initiated by a nucleophilic attack of a $\{NiL_2\}$ unit (L = PPh_3, PCy_3, P^iPr_3) at the electrophilic site at the aromatic system as the rate-determining step (pathway b; Scheme 4).[20,21] Note that 5-chloro-2,4,6-trifluoropyrimidine (**1**) and 5-chloro-2,4-difluoropyrimidines are vulnerable for nucleophilic attack at the 4-position.[22] Both mechanisms are compatible with the observed cleavage of the C−Cl bond at $\{Ni(PEt_3)_2\}$, because less steric hindrance can result in a different reaction pathway.[21a] We have no

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(19) One reviewer asked for the reversibility of the C−F activation reactions at higher temperature. So far reductive elimination of an aromatic C−F bond has never been observed, although the reductive elimination of other aryl halides at palladium has been reported. However, note also that Grushin et al. demonstrated the reductive elimination of benzoic fluoride from *trans*-$[PdF\{C(O)Ph\}(PPh_3)_2]$: (a) Grushin, V. V. *Chem. Eur. J.* **2002**, *8*, 1007. (b) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944.

(20) If the formation of the Meisenheimer intermediate is the rate-determining step, 5-chloro-2,4,6-trifluoropyrimidine (**1**) will be attacked at the more electrophilic site, leading to a cleavage of the C−F bond, which is stronger than the aromatic C−Cl bond. The activation of the C−F bond in **1** is then presumably the kinetic pathway.[1d,21]

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direct evidence for a pathway induced by electron transfer giving initially a tight ion pair (pathway c; Scheme 4).[16] In this case, the fluoro complexes would be formed after irreversible dissociation of F^- from the pyrimidyl anion. Radical trapping experiments with 9,10-dihydroanthracene showed no formation of anthracene or 5-chloro-2,4-difluoropyrimidine.[16,23]

Some rare examples for cross-coupling reactions that involve the cleavage of a C−F bond have been reported.[8] While the nickel fluoro complex *trans*-[NiF(4-$C_4N_2ClF_2$)-(PPh_3)$_2$] (**4**) is an active catalyst for the conversions, comparable chloro compounds are not. The stoichiometric C−F activation of **1** as well as NMR investigations suggests the presence of metal fluoro intermediates such as *trans*-[NiF(4-$C_4N_2ClF_2$)(PPh_3)$_2$] (**4**) and *trans*-[NiF(4-C_4N_2TolClF)(PPh_3)$_2$] (**7**) as catalytic intermediates (Scheme 2). We believe that within the catalytic cycle the presence of such complexes bearing a fluoro ligand is crucial for the introduction of the second aryl ligand at the metal center. It is conceivable that the fluorophilicity of boron facilitates the transmetalation by stabilizing a transition state.[10,24] However, the identification of the intermediate **7** indicates that, at least for the second coupling reaction, the transmetalation step is slower than the oxidative addition.[10] A stabilization of the nickel halogen complexes occurs presumably by a push−pull interaction. For the fluoro compounds **2**−**4** and **7** this can be rationalized by a M−F d_π−p_π filled/filled repulsion, which is alleviated by the π-acceptor pyrimidyl group in the position *trans* to the halogeno ligand.[25] Nevertheless, d^8 metal fluoro complexes are usually much more reactive compared to their chloro counterparts.[19a,24−26] This is reflected by the unique properties of the fluoro compounds **4** and **7**, which exhibit a considerable higher reactivity than **5**, **9**, or **10**.

Conclusions

In conclusion, the transformations that have been reported in this paper represent the first catalytic C−C coupling reactions involving the activation of a C−F bond in the presence of a thermodynamically weaker C−Cl bond. The reactions lead to previously unknown diarylpyrimidines. It is striking that even two C−F bonds can be cleaved catalytically. The C−F activation reactions represent a crucial step within the catalytic cycle, because they lead to the generation of very reactive nickel fluoro complexes. There is considerable evidence that the presence of the fluoro ligand is crucial for the transmetalation step to occur and for the catalytic cycle to proceed. Studies on a more general applicability of the transformations described are in progress.

Experimental Section

General Methods. All solvents were purified and dried by conventional methods and distilled under argon before use. Benzene-d_6 and CD_2Cl_2 were dried by stirring over potassium or CaH_2, respectively. PPh_3, [$Pd(PPh_3)_4$], and the boronic acids were obtained from Aldrich and ABCR. 5-Chloro-2,4,6-trifluoropyrimidine (**1**) was purchased from ABCR and distilled before use. [$Ni(COD)_2$] and P^iPr_3 were prepared according to the literature.[27,28]

The NMR spectra were recorded with a Bruker DRX 500 spectrometer. The ^{1}H NMR chemical shifts were referenced to residual C_6D_5H at δ 7.15 and $CDHCl_2$ at δ 5.3. The ^{19}F NMR spectra were referenced to external C_6F_6 at δ −162.9. The $^{31}P\{^1H\}$ NMR spectra were referenced externally to H_3PO_4 at δ 0. Mass spectra were recorded on a MS QP5050A fitted with a Shimadzu GC 17a.

***trans*-[NiF(4-$C_4N_2ClF_2$)(P^iPr_3)$_2$] (3).** A suspension of [$Ni(COD)_2$] (414 mg, 1.51 mmol) in THF (10 mL) was treated with P^iPr_3 (610 μL, 3.20 mmol). After 10 min 5-chloro-2,4,6-trifluoropyrimidine (**1**) (166 μL, 1.60 mmol) was added and the solution was stirred for 2 h at room temperature. The volatiles were removed under vacuum. The residue was extracted with hexane (5 mL), and the volatiles were removed from the extract in vacuo, yielding a yellow solid. Yield: 345 mg (42%); ^{1}H NMR (500 MHz, C_6D_6, 300 K) δ 1.84 (m, 6 H, CH), 1.24 (m, d in $^1H\{^{31}P\}$ NMR, $^3J_{H,H}$ = 6.7 Hz, 18 H, CH_3), 1.11 (m, d in $^1H\{^{31}P\}$ NMR, $^3J_{H,H}$ = 6.1 Hz, 18 H, CH_3); ^{19}F NMR (470.4 MHz, C_6D_6, 300 K) δ −50.8 (s, 1 F, CF), −72.9 (s, 1 F, CF), −379.3 (t, $^2J_{P,F}$ = 36 Hz, 1 F, NiF); ^{31}P NMR (202.4 MHz, C_6D_6, 300 K) δ 27.3 (d, $^2J_{P,F}$ = 36.0 Hz). Anal. Calcd (%) for $CHN_2ClF_3NiP_2$: C 48.25, H 7.68, N 5.12. Found: C 48.25, H 7.54, N 5.07.

***trans*-[NiF(4-$C_4N_2ClF_2$)(PPh_3)$_2$] (4).** A suspension of [$Ni(COD)_2$] (315 mg, 1.15 mmol) in THF (10 mL) was treated with PPh_3 (706 mg, 2.69 mmol). The dark red solution was stirred for 5 min at room temperature. After adding 5-chloro-2,4,6-trifluoropyrimidine (**1**) (119 μL, 1.15 mmol) the solution was stirred for 4 h and the volatiles were removed under vacuum. The residue was washed with cold hexane (10 mL) and dried in vacuo. Yield: 270 mg (31%); ^{19}F NMR (470.4 MHz, C_6D_6, 300 K) δ −51.2 (s, 1 F, CF), −73.3 (s, 1 F, CF), −360.4 (t, $^2J_{P,F}$ = 34 Hz, 1 F, NiF); ^{31}P NMR (202.4 MHz, C_6D_6, 300 K) δ 14.0 (d, $^2J_{P,F}$ = 34.4 Hz). Anal. Calcd (%) for $C_{40}H_{30}N_2ClF_3NiP_2$: C 63.91, H 4.02, N 3.73. Found: C 63.58, H 4.14, N 3.54.

***trans*-[NiCl(4-$C_4N_2ClF_2$)(PPh_3)$_2$] (5).** A solution of **4** (210 mg, 0.28 mmol) in THF (5 mL) was treated with Me_3SiCl (39 μL, 0.30 mmol). After the yellow solution was stirred for 1 h at room temperature, the volatiles were removed in vacuo. The residue was extracted with hexane (10 mL), and the volatiles were removed from the extract in vacuo, yielding a yellow solid. Yield: 192 mg (96%); ^{19}F NMR (470.4 MHz, C_6D_6, 300 K) δ −50.8 (s, 1 F, CF), −72.9 (s, 1 F, CF); ^{31}P NMR (202.4 MHz, C_6D_6, 300 K) δ 21.3 (s). Anal. Calcd (%) for $C_{40}H_{30}N_2Cl_2F_2NiP_2$: C 62.50, H 3.91, N 3.65. Found: C 62.31, H 4.13, N 3.52.

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***trans*-[PdCl(5-$C_4N_2F_3$)(PPh_3)$_2$] (6).** A solution of [Pd(PPh_3)$_4$] (406 mg, 0.35 mmol) in toluene (40 mL) was treated with 5-chloro-2,4,6-trifluoropyrimidine (**1**) (55 μL, 0.35 mmol). The solution was heated to reflux for 2 h. The solution was then cooled to room temperature and filtered. The volatiles were removed from the filtrate under vacuum. The residue was washed twice with hexane (10 mL) and dried in vacuo. Yield: 208 mg (73%); ^{19}F NMR (470.4 MHz, C_6D_6, 300 K) δ −40.1 (s, 2 F, CF), −55.4 (s, 1 F, CF); ^{31}P NMR (202.4 MHz, C_6D_6, 300 K) δ 23.1 (s). Anal. Calcd (%) for $C_{40}H_{30}N_2ClF_3PdP_2$: C 60.09, H 3.78, N 3.50. Found: C 59.63, H 3.92, N 3.87.

Formation of *trans*-[NiF(4-C_4N_2TolClF)(PPh_3)$_2$] (7) and *trans*-[NiCl(4-C_4N_2TolClF)(PPh_3)$_2$] (9). A solution of **4** (129 mg, 0.17 mmol) in THF (6 mL) was treated with TolB(OH)$_2$ (8.8 mg, 0.07 mmol) at 263 K. After the reaction mixture has been warmed to 273 K CsF was added (15.0 mg, 0.10 mmol). The ^{19}F and ^{31}P NMR spectroscopic data of the suspension reveal the presence of **7**. Me_3SiCl (22 μL, 0.17 mmol) was added, and the solution was stirred for 2 h at room temperature. The volatiles were removed under vacuum. The remaining residue was extracted with toluene (15 mL), and the volatiles were removed from the extract under vacuum, yielding a yellow solid, which consisted of **9** and minor amounts (5−10%) of **7**. Spectroscopic data for **7**: ^{19}F NMR (470.4 MHz, THF/C_6D_6, 273 K) δ −53.3 (s, 1 F, CF), −358 (s, br, 1 F, NiF); ^{31}P NMR (202.4 MHz, THF/C_6D_6, 273 K) δ 13.7 (d, $^2J_{P,F}$ = 34.4 Hz). Spectroscopic data for **9**: ^{1}H NMR (500 MHz, C_6D_6, 300 K) δ 7.43 (m, 4 H, CH), 2.47 (s, 3 H, CH_3); ^{19}F NMR (470.4 MHz, C_6D_6, 300 K) δ −53.2 (s); ^{31}P NMR (202.4 MHz, C_6D_6, 300 K) δ 20.7 (s).

***trans*-[NiCl(4-C_4N_2PhClF)(PPh_3)$_2$] (10).** A solution of **4** (338 mg, 0.45 mmol) in THF (10 mL) was treated with PhB(OH)$_2$ (55.3 mg, 0.45 mmol). After 10 min Me_3SiCl (57 μL, 0.45 mmol) was added and the solution was stirred for 2 h at room temperature. The volatiles were removed under vacuum. The remaining residue was washed with hexane (5 mL) and then extracted with toluene (15 mL). The extract was concentrated under vacuum to ca. 5 mL, and yellow crystals formed at −40 °C after 1 week. The supernatant was removed, and the resulting crystals were dried under vacuum. Yield: 146 mg (43%); ^{1}H NMR (500 MHz, C_6D_6, 300 K) δ 7.73−7.38 (m); ^{19}F NMR (470.4 MHz, C_6D_6, 300 K) δ −52.7 (s); ^{31}P NMR (202.4 MHz, C_6D_6, 300 K) δ 21.1 (s). Anal. Calcd (%) for $C_{46}H_{35}N_2Cl_2FNiP_2\cdot 1.5\ C_7H_8$: C 70.36, H 4.91, N 2.90. Found: C 70.15, H 4.97, N 3.00.

5-Chloro-2-fluoro-4,6-ditolylpyrimidine (8). A Schlenk tube was charged with a solution of **4** (106 mg, 0.14 mmol) in THF (10 mL), 5-chloro-2,4,6-trifluoropyrimidine (**1**) (146 μL, 1.40 mmol), TolB(OH)$_2$ (344 mg, 2.80 mmol), PPh_3 (184 mg, 0.70 mmol), and Cs_2CO_3 (150 mg, 0.46 mmol). The tube was sealed and put in an oil bath at 323 K. After 36 h the mixture was cooled to room temperature and analyzed by ^{19}F NMR spectroscopy using 4-fluorotoluene as external standard to determine the yield of **8** before workup (73%). The volatiles were then removed under vacuum. The remaining residue was extracted with hexane (3 × 5 mL). The extracts were combined and the volatiles removed under vacuum. The residue was dissolved in ether/hexane (1:1, 2 mL), and the solution was chromatographed on silica (length of column 8 cm). A colorless fraction was eluted, from which the solvents were removed in vacuo. The residue was recrystallized from toluene (5 mL) at 233 K to give a colorless solid. Yield: 210 mg (48%); ^{1}H NMR (500 MHz, C_6D_6, 300 K) δ 7.73 (d, $^3J_{H,H}$ = 8.2 Hz, 4 H, CH), 6.99 (d, $^3J_{H,H}$ = 8.2 Hz, 4 H, CH), 2.07 (s, 6 H, CH_3); ^{19}F NMR (470.4 MHz, C_6D_6, 300 K) δ −48.1 (s); MS (70 eV): *m/z* (%) 312 (100) [M^+], 277 (55) [M^+ − Cl]. Anal. Calcd (%) for $C_{18}H_{14}N_2ClF$: C 69.12, H 4.51, N 8.95. Found: C 69.04, H 4.77, N 8.96.

5-Chloro-2-fluoro-4,6-diphenylpyrimidine (11). A Schlenk tube was charged with a solution of **4** (814 mg 0.85 mmol) in THF (60 mL), 5-chloro-2,4,6-trifluoropyrimidine (**1**) (883 μl, 8.50 mmol), PhB(OH)$_2$ (1.95 g, 17.0 mmol), PPh_3 (1.01 g, 3.85 mmol), and Cs_2CO_3 (793 mg, 2.40 mmol). The tube was sealed and put in an oil bath at 323 K. After 36 h the mixture was cooled to room temperature and analyzed by ^{19}F NMR spectroscopy using 4-fluorotoluene as external standard to determine the yield of **11** before workup (88%). The volatiles were then removed under vacuum. The remaining residue was extracted with hexane (3 × 3 mL). The extracts were combined and the volatiles removed under vacuum. The residue was dissolved in ether/hexane (1:1, 2 mL), and the solution was chromatographed on silica (length of column 10 cm). A colorless fraction was eluted, from which the solvents were removed in vacuo, yielding a colorless solid. Yield: 1.54 g (64%); ^{1}H NMR (500 MHz, C_6D_6, 300 K) δ 7.32 (m); ^{19}F NMR (470.4 MHz, C_6D_6, 300 K) δ −47.7 (s); MS (70 eV) *m/z* (%) 227 (100) [M^+]. Anal. Calcd (%) for $CHN_2ClF_3NiP_2$: C 67.49, H 3.52, N 9.84. Found: C 67.12, H 3.75, N 9.68.

5-Chloro-2-fluoro-4,6-bis(α,α,α-trifluortolyl)pyrimidine (12). A Schlenk tube was charged with a solution of **4** (83 mg, 0.11 mmol) in THF (10 mL), 5-chloro-2,4,6-trifluoropyrimidine (**1**) (121 μl, 1.17 mmol), *p*-$F_3CC_6H_4B(OH)_2$ (446 mg, 2.34 mmol), PPh_3 (181 mg, 0.69 mmol), and Cs_2CO_3 (221 mg, 0.68 mmol). The tube was sealed and put in an oil bath at 323 K. After 36 h the mixture was cooled to room temperature and analyzed by ^{19}F NMR spectroscopy using 4-fluorotoluene as external standard to determine the yield of **12** before workup (37%). The volatiles were then removed under vacuum. The remaining residue was extracted with a mixture of hexane/ether (1:1; 3 × 3 mL). The extracts were combined and the volatiles removed under vacuum. The residue was dissolved in ether/hexane (1:1, 2 mL), and the solution was chromatographed on silica (length of column 10 cm). A light yellow fraction ontaining **12** and small amounts of *p*-$F_3CC_6H_4B(OH)_2$ (9%) was eluted, from which the solvents were removed in vacuo. Yield of **12**: 156 mg (31%); ^{1}H NMR (500 MHz, CD_2Cl_2, 300 K) δ 8.00 (d, $^3J_{H,H}$ = 8.2 Hz, 4 H, CH), 7.83 (d, $^3J_{H,H}$ = 8.2 Hz, 4 H, CH); ^{19}F NMR (470.4 MHz, CD_2Cl_2, 300 K) δ −48.5 (s, 1 F, CF), −63.3 (s, 6 F, CF_3) (s); MS (70 eV) *m/z* (%) 420 (100) [M^+], 385 (70) [M^+ − Cl].

5-Chloro-2-fluoro-4,6-dimesitylpyrimidine (13) and 5-Chloro-2,6-difluoro-4-mestitylpyrimidine (14). A Schlenk tube was charged with a solution of **4** (90 mg, 0.12 mmol) in THF (10 mL), 5-chloro-2,4,6-trifluoropyrimidine (**1**) (127 μl, 1.23 mmol), MesB(OH)$_2$ (402 mg, 2.46 mmol), PPh_3 (149 mg, 0.57 mmol), and Cs_2CO_3 (147 mg, 0.45 mmol). The tube was sealed and put in an oil bath at 323 K. After 36 h the mixture was cooled to room temperature and analyzed by ^{19}F NMR spectroscopy using 4-fluorotoluene as external standard to determine the yields of **13** (16%) and **14** (32%) before workup. The volatiles were then removed under vacuum. The remaining residue was extracted with a mixture of hexane (3 × 3 mL). The extracts were combined and the volatiles removed under vacuum. The residue was dissolved in ether/hexane (1:1, 2 mL), and the solution was chromatographed on silica (length of column 10 cm). A colorless fraction containing **13** and **14** was eluted, from which the solvents were removed in vacuo. Yield of **13**: 55 mg (12%). Yield of **14**: 97 mg (29%). Analytical data for **13**: ^{1}H NMR (500 MHz, CD_2Cl_2, 300 K) δ 6.80 (s, 4 H, CH), 2.31 (s, 12 H, CH_3), 2.24 (s, 6 H, CH_3); ^{19}F NMR (470.4 MHz, CD_2Cl_2, 300 K) δ −48.5 (s); MS (70 eV) *m/z* (%) 368 (40) [M^+], 333 (100) [M^+ − Cl]. Analytical data for **14**: ^{1}H NMR (500 MHz, CD_2Cl_2, 300 K) δ 6.81 (s, 2 H, CH), 2.32 (s, 6 H, CH_3), 2.25 (s, 3 H, CH_3); ^{19}F NMR (470.4 MHz, CD_2Cl_2, 300 K) δ −46.2 (s, 1 F), −58.8 (s, 1 F); MS (70 eV) *m/z* (%) 268 (55) [M^+], 233 (100) [M^+ − Cl].

Crystal Structures. Crystallographic data for **5**, **6**, and **10** are listed in Table 5. All diffraction data were collected on a Nonius Kappa CCD diffractometer at 100 K. The structures were solved by direct methods (SHELXTL PLUS or SIR 97) and refined with the full matrix least-squares methods on F^2

Table 5. Crystallographic Data

	5	6	10
cryst dimens/mm^3	0.30 × 0.23 × 0.14	0.30 × 0.28 × 0.23	0.25 × 0.17 × 0.07
empirical formula	$C_{40}H_{30}Cl_2F_2N_2NiP_2$	$C_{40}H_{30}ClF_3N_2P_2Pd$	$C_{46}H_{35}Cl_2FN_2NiP_2 + 1.5C_7H_8$
fw	768.21	799.45	964.51
cryst syst	triclinic	monoclinic	triclinic
space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
a/Å	10.6520(2)	15.85800(10)	12.4360(2)
b/Å	11.73400(10)	11.67700(10)	13.1960(2)
c/Å	16.1210(2)	20.0380(2)	15.3180(3)
α/deg	103.5350(9)		77.1590(11)
β/deg	96.2150(9)	99.2740(4)	72.6010(9)
γ/deg	110.8670(9)		83.7340(10)
V/Å^3	1789.33(4)	3464.18(5)	2336.30(7)
Z	2	4	2
density(calcd)/Mg m^{-3}	1.426	1.533	1.371
μ(Mo Kα)/mm^{-1}	0.823	0.754	0.643
θ range/deg	3 to 30	3 to 30	3 to 27.5
no. of reflns collected	70 204	99 333	75 788
no. of indep reflns	10 408	10 090	10 678
R_{int}	0.045	0.045	0.048
no. of reflns with $I_o > 2\sigma(I_o)$]	8276	8536	8743
completeness to max. θ	99.8%	99.8%	99.7%
R_1, wR_2 on all data	0.0487, 0.0847	0.0350, 0.0636	0.0453, 0.0808
goodness-of-fit on F^2	1.046	1.030	1.023
R_1, wR_2 [$I_o > 2\sigma(I_o)$]	0.0339, 0.0792	0.0259, 0.0605	0.0328, 0.0748
max. diff peak hole/e Å^{-3}	0.598 and −0.459	0.638 and −0.631	0.372 and −0.419
CCDC	276019	276020	232995

(SHELX-97).[29] The disorder of the pyrimidyl ligand in **5** was refined on two positions (87:13). For the ring atoms the part with the lower occupation was restrained with the same distances as the other part. For **10** one toluene molecule is disordered on an inversion center.

(29) (a) *SHELXTL-PLUS*, Siemens Analytical X-Ray Instruments Inc.: Madison, WI, 1990. (b) Sheldrick, G. M. *SHELX-97*, program for crystal structure refinement; University of Göttingen, 1997. (c) Cascarano, G.; Altomare, A.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Sigli, D.; Burla, M. C.; Polidori M G.; Camalli, M. *Acta Crystallogr.* **1996**, *A52*, C-79.

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Supporting Information Available: Crystallographic data are available in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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