Catalytic C–C Bond Formation through Selective Activation of C–F Bonds **

Volker P. W. Böhm, Christian W. K. Gstöttmayr, Thomas Weskamp, and Wolfgang A. Herrmann*

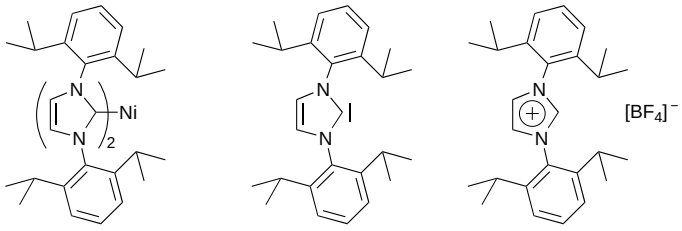
Dedicated to Professor Ludwig L. Böhm on the occasion of his 60th birthday

The activation of C–F bonds is of salient importance in organometallic chemistry and catalyst development because this reaction contributes to the fundamental understanding of the reactivity of very stable bonds, and because the selective replacement of fluorine atoms and the synthesis of partially fluorinated molecules is still a challenge.[1] Although the *stoichiometric* activation and functionalization of C–F bonds by soluble transition metal complexes has been shown to proceed under mild conditions,[2] homogeneous *catalytic* transformations of aromatic C–F bonds[3] are limited to defluorination reactions.[4–7]

From a synthetic point of view, the intermolecular formation of C–C bonds by cross-coupling reactions is of particular interest but possible to date only in stoichiometric reactions.[2] The zirconium-activated, radical homocoupling of hexafluorobenzene, which leads to a mixture of linear oligomers, is the only catalytic sp^2-C – sp^2-C bond formation to date.[8] The usefulness of cross-coupling chemistry to form unsymmetrical biaryls has been demonstrated and the interest in catalytic cross-coupling chemistry has undoubtedly been driven by the development of catalyst systems that have successively allowed the activation of aryl iodides, bromides, and finally chlorides even at ambient temperature.[9] However, aryl fluorides have been useless as substrates in these reactions due to their inertness. Only the coupling of an sp^3- with an sp^2-carbon center, as exemplified in the reaction of fluorobenzene with isopropylmagnesium chloride mediated by [Ni(dmpe)-Cl_2] (dmpe = 1,2-bis(dimethylphosphanyl)ethane), has been reported.[10]

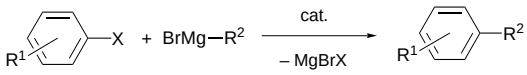
Based on general considerations, we therefore developed a strategy for the application of aryl fluorides in cross-coupling reactions: *Kinetically*, the catalyst must be able to 1) chemoselectively activate the aryl fluoride but still allow 2) the completion of the catalytic cycle by reductive elimination and C–C bond formation. *Thermodynamically*, the by-product of the reaction has to 3) incorporate the fluorine atom and thus provide a substantial part of the driving force of the reaction.

1) For the activation of C–F bonds, a highly electron-rich metal center is required. This criterion can be met by the use of strongly Lewis basic, electron-donating ligands combined with low-valent metals. For example, complexes of nickel(0) with triethylphosphane ligands are known to stoichiometrically activate aromatic C–F bonds.[11] Since N-heterocyclic carbenes are even stronger electron-donating ligands,[12] C–F bond activation should also be feasible with these ligands.
2) The catalytic cross-coupling with palladium and nickel catalysts is facilitated by sterically demanding ligands.[9] Therefore, we decided to use the complex bis[1,3-di(2′,6′-diisopropylphenyl)imidazolin-2-ylidene]nickel(0) (**1**), prepared by the reaction of [Ni(cod)$_2$] (cod = cyclooctadiene) and the free N-heterocyclic carbene **2**,[13] which is one of the most sterically demanding N-heterocyclic carbene ligands.[14]



1 **2** **3**

3) From the set of elements frequently used in cross-coupling chemistry, magnesium is known to form a strong bond to fluorine. The Kumada–Corriu cross-coupling reaction allows convenient and selective access to unsymmetrical biaryls [Eq. (1); OTf = trifluoromethanesulfonate].[15, 16] Therefore, we chose this reaction as the test system for our proposed catalyst **1**.



(1)

X = Hal, OTf

When aryl fluorides are used under standard conditions in the Kumada–Corriu cross-coupling reaction[17] employing catalyst **1**, biaryls are formed even at ambient temperature. Compared to well-defined and isolated **1**, an in situ catalyst system using [Ni(acac)$_2$] (acac = acetylacetonate) and the imidazolium salt **3** in a 1:1 ratio combines enhanced performance with easier handling. To evaluate the scope of this reaction, experiments employing different aryl fluorides and aryl Grignard reagents were conducted.[13] Activated, elec-

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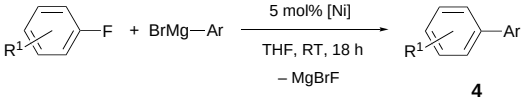
tron-poor 4-trifluoromethylfluorobenzene as well as deactivated, electron-rich 4-fluoroanisole are both converted in high yields (Table 1). Steric congestion on the organometallic reagent like in the case of mesitylmagnesium bromide is tolerated (entries 16–19, Table 1). That the yields with **1** are

Table 1. Nickel-catalyzed cross-coupling of aryl fluorides with aryl Grignard compounds.[a]



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Entry	R^1	Ar	[Ni][b]	Yield **4** [%][c]
1	4-CF_3	C_6H_5	**1**	95
2	4-CF_3	C_6H_5	in situ	98
3	4-CH_3	C_6H_5	**1**	82
4	4-CH_3	C_6H_5	in situ	92
5	2-CH_3	C_6H_5	**1**	38
6	2-CH_3	C_6H_5	in situ	53
7	4-OCH_3	C_6H_5	in situ	58[d]
8	4-CF_3	4-*t*BuC_6H_4	**1**	95
9	4-CF_3	4-*t*BuC_6H_4	in situ	97
10	H	4-*t*BuC_6H_4	**1**	83
11	H	4-*t*BuC_6H_4	in situ	86
12	4-CH_3	4-*t*BuC_6H_4	in situ	95
13	2-CH_3	4-*t*BuC_6H_4	in situ	69
14	4-OCH_3	4-*t*BuC_6H_4	**1**	59[d]
15	4-OCH_3	4-*t*BuC_6H_4	in situ	73[d]
16	4-CF_3	2,4,6-$Me_3C_6H_2$	in situ	75
17	H	2,4,6-$Me_3C_6H_2$	in situ	68
18	4-CH_3	2,4,6-$Me_3C_6H_2$	in situ	65
19	4-OCH_3	2,4,6-$Me_3C_6H_2$	in situ	65[d]
20	4-CH_3	C_6H_5	$NiCl_2$	23
21	4-CH_3	C_6H_5	**3**[e]	0

[a] 1.0 equiv aryl fluoride, 1.5 equiv Grignard reagent, 5 mol% Ni catalyst, THF, RT, $t = 18$ h. Reagents were used as received. [b] in situ: 5 mol% [Ni(acac)$_2$] + 5 mol% **3**. [c] GC yield of product **4** based on the aryl fluoride; diethyleneglycol-di-*n*-butylether as internal standard. [d] Plus *p*-terphenyl by additional activation of the C_{Ar}–OCH_3 bond. [e] No nickel added.

poorer than those obtained by using [Ni(acac)$_2$]/**3** can be rationalized on the basis of mechanistic considerations: As we were unable to observe stoichiometric oxidative addition of aryl fluorides to complex **1** and because the 1:1 mixture of [Ni(acac)$_2$] and **3** works as well as or even better than a 1:2 mixture, we propose that the catalytically active species is zero-valent nickel coordinated by only *one* N-heterocyclic carbene ligand **2**.[18] The formation of this 12-electron complex is evidently favored in the in situ system. If $NiCl_2$ is used without a ligand, poorer yields are obtained accompanied by the formation of C–H activated by-products. Conversely, no turnovers can be achieved by using only the imidazolium salt **3** (entries 20 and 21, Table 1). Homocoupling of the Grignard reagents is observed as a major by-product in variable amounts. With $NiCl_2$ as the catalyst the amount of the homocoupling product increases significantly and terphenyls are formed in major quantities.

With respect to the mechanism of the reaction, four different possibilities of C–F bond transformations have to be taken into account:[2] 1) nucleophilic aromatic substitution,[19] 2) elimination–addition via aryne intermediates,[20] 3) radical reactions,[21] and 4) polar pathways probably through oxidative addition.[16] The first two possibilities are very unlikely considering the selectivities of the reaction. The presence of terphenyls as minor by-products in some reactions (<1%) suggests the participation of radical intermediates. The increase in the formation of these by-products upon use of $NiCl_2$ supports this idea, in particular for the ligand-free system. However, the low amounts of these by-products formed by using catalysts **1** and [Ni(acac)$_2$]/**3** as well as the electronic influence of the aryl fluorides on the reaction rate as demonstrated by the Hammett correlation to σ^--values[22] is a strong indication for a polar pathway (Figure 1). The

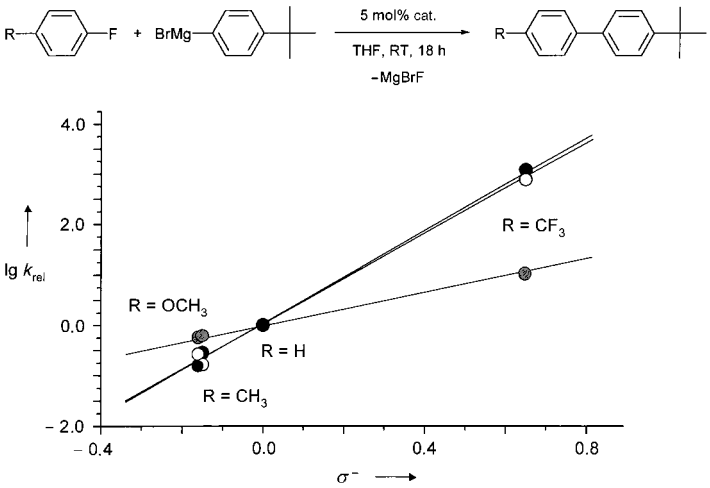

Figure 1. Hammett correlation of relative rate constants of the nickel-catalyzed cross-coupling of aryl fluorides against the σ^- constants of the aryl substituents R. ○: **1**, $\rho = 4.55 \pm 0.43$; ●: [Ni(acac)$_2$]/**3**, $\rho = 4.56 \pm 0.38$; ●: $NiCl_2$, $\rho = 1.56 \pm 0.58$.

reaction of 4-*tert*-butylphenylmagnesium bromide with various aryl fluorides results in $\rho = 4.55 \pm 0.43$ for **1** and $\rho = 4.56 \pm 0.38$ for [Ni(acac)$_2$]/**3**.[13, 23] This similarity indicates that both catalysts probably furnish the same active species during catalysis. The ρ values in these cases are much higher than any value expected for radical reactions. Thus, the activation of the aryl fluorides must proceed here via intermediates bearing a strong negative polarization on the aromatic ring. This is the case for the oxidative addition of aryl fluorides to a nickel(0) complex formed under the reaction conditions. The value of $\rho = 1.56 \pm 0.58$ for $NiCl_2$ indicates, however, a major participation of radicals and demonstrates that the application of ligand **2** is responsible for opening up the polar pathway and allowing the switch of mechanism for this system resulting in a highly selective transformation.

In summary, a highly active, cheap and easy-to-prepare nickel catalyst for the selective cross-coupling reaction of aryl fluorides and aryl Grignard reagents at room temperature was described. This is the first time that a catalytic C–F bond activation has been achieved in conjunction with a selective C–C bond forming reaction. Both the product selectivity and the Hammett correlation clearly suggest a polar reaction and disfavor radical pathways as seen to participate in the case of $NiCl_2$.

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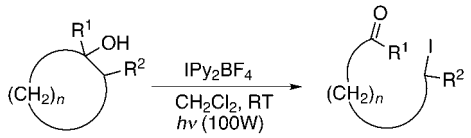
Oxidative Opening of Cycloalkanols: An Efficient Entry to ω-Iodocarbonyl Compounds**

José Barluenga,* Francisco González-Bobes, Sreenivasa R. Ananthoju, Miguel A. García-Martín, and José M. González

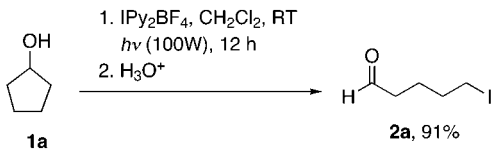
The development of new approaches to elaborate the carbon backbone of organic compounds is among the central issues in organic synthesis. In this regard, a general method for the direct conversion of readily available cyclic alcohols to bifunctional derivatives, such as ω-iodocarbonyl compounds, is an attractive synthetic goal.[1] Herein, we report on a powerful method for synthesizing iodinated derivatives of both, aldehydes and ketones.[2] Thus, bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4)[3] promotes a regioselective opening reaction of **1** upon irradiation leading to compounds **2** (Scheme 1).[4]



1 **2**

Scheme 1. IPy_2BF_4-promoted regioselective opening of cycloalkanols. R^1, R^2: H, CH_3; n: 2, 3, 4, 10; nine examples (76 – 94 %).

In preliminary studies, cyclopentanol (**1a**) was recovered unreacted upon treatment with IPy_2BF_4. Moreover, NMR experiments revealed that in the absence of visible light no change had taken place even after several days at room temperature. Interestingly, when the mixture was photoactivated (irradiation, 100 W lamp) a clean transformation took place affording 5-iodopentanal (**2a**)[5] in excellent yield after hydrolysis [Eq. (1)].



1a **2a**, 91% (1)

This is an elusive transformation for a secondary alcohol, only accomplished previously for cyclopentanol derivatives.[6] Our method offers a more efficient entry to achieve this scission reaction even from **1a**.[7] This stimulated us to further investigate its scope and convenience, in search for a clean

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