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DEVELOPMENT OF NEW CROSS-COUPLING REACTIONS AND APPLICATIONS IN NATURAL PRODUCT SYNTHESIS

Summary of the Ph. D. thesis of Andreas Leitner

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1. Introduction

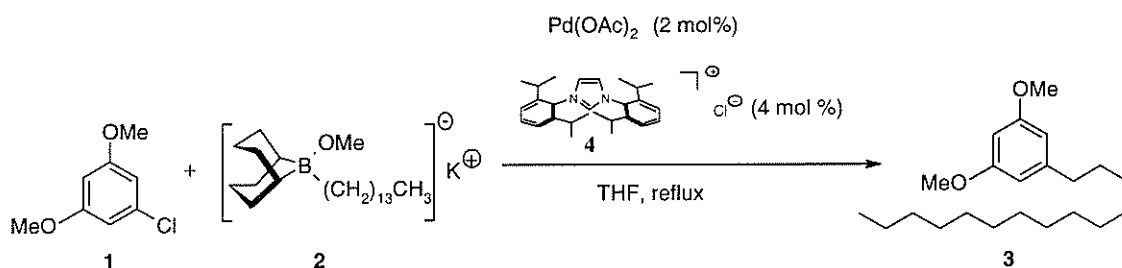
Despite the tremendous success of cross coupling reactions in general, most of them rely on the use of organic bromides, iodides and triflates as the substrates. Cheap and easy available organic chlorides were generally found to be unreactive under the standard reaction conditions.

The following summary documents the development of two new cross coupling methods using aryl chlorides and -sulfonates as the electrophiles. Furthermore, some applications of these procedures to target oriented synthesis will be presented.

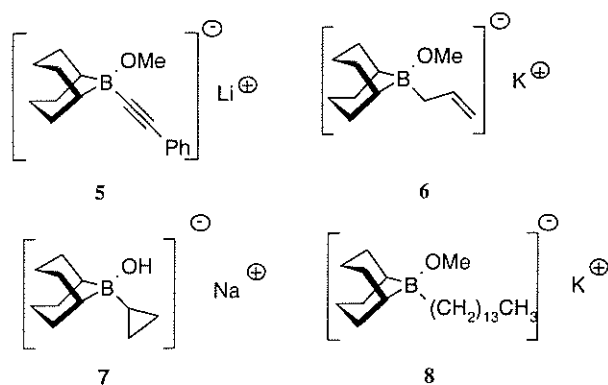
2. Palladium Catalyzed Suzuki Reactions with Aryl Chlorides

It was only recently that the replacement of palladium by nickel or the use of electron-rich and bulky ligands for palladium enabled the use of aryl chlorides for cross coupling reactions.¹ Thereby, bulky alkylphosphines and N-heterocyclic carbenes (NHC) turned out to be particularly successful. So far, however, these novel procedures have almost exclusively been applied to cross couplings with *aryl*boronic acids. Since Suzuki reactions are by no means restricted to such donors, we decided to study the reactivity of different organoboron derivatives.

An *in situ* system based on Pd(OAc)₂ and different N, N'-disubstituted imidazolium salts was used for a first catalyst screening. Upon deprotonation, the latter convert into an N-heterocyclic carbenes (NHC), a class of ligands that exhibits pronounced σ -donor but very poor π -acceptor properties.² These screenings showed that the imidazolium salt **4** (IPr•HCl) (4 mol%) is most efficient in the coupling reaction of the electron rich and demanding substrate **1** with borate complex **2** (Scheme 1).



Scheme 1



Scheme 2

Table 1 summarizes a set of representative cross-coupling reactions of electron rich and electron poor chloroarenes under the optimized reaction conditions.³ As can be seen, borate complexes **5-8** derived from B-alkyl-, B-allyl-, B-alkenyl-, B-alkynyl- or B-cyclopropyl-9-BBN-derivatives and KOMe or NaOH, perform such Suzuki couplings in excellent yields.

Table 1 Representative Suzuki Reactions with Chloroarenes^a

Entry	Substrate	Product	t (h)	Yield (%)	Entry	Substrate	Product	t (h)	Yield (%)
1			2	98 ^b	6			4	86
2			14	96	7			65	85 ^d
3			21	61	8			14	82
4			2	91 ^c	9			16	84
5			10	82	10			2	83

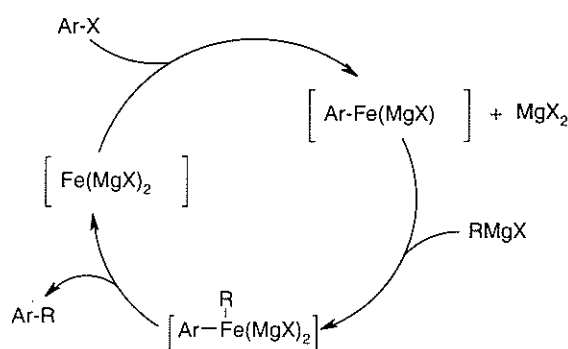
^a All reactions were carried out using Pd(OAc)₂ (2 mol%) and IPr•HCl (4 mol%) in THF reflux unless stated otherwise. ^b Using only 1 mol% Pd(OAc)₂ and 2 mol% of IPr•HCl. ^c In toluene/aq. NaOH (3M) as the reaction medium. ^d Using 4 mol% of Pd(OAc)₂ and 8 mol% of IPr•HCl

These examples illustrate the generality and scope of this method which accommodates substantial variations in both reaction partners without significant effects on the yields. The procedure can easily be carried out on a multigram scale, uses Pd(OAc)₂ as the cheapest palladium source, KOMe as the base, and a ligand precursor (IPr•HCl) which is easy to make on a large scale and now also commercially available.

3. Iron Catalyzed Cross Coupling Reactions

Although scattered reports on iron catalyzed cross coupling of *alkenyl* derivatives and Grignard reagents can be found in the literature,⁴ a publication of Bogdanović in the field of “inorganic Grignard reagents” encouraged us to *re-evaluate* such processes in a broader context.

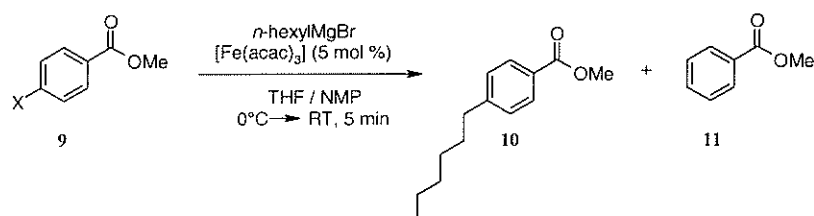
Bogdanović described the conversion of FeCl₂ with 4 equiv. of R–MgX into a species of the *formal* composition [Fe(MgX)₂], an “inorganic Grignard reagent” that is soluble in ethereal solvents such as THF.⁵ The formation of this *formally negatively charged iron species* implies that the reduction process does not stop once a zerovalent “Fe⁰” is formed, but rather generates Fe^{-II} centers which are capable of oxidatively adding to aryl halides due to their highly nucleophilic character. We anticipated that the ensuing Fe⁰ complexes might again be alkylated by the excess of the Grignard reagent. Subsequent reductive elimination should then form the desired product and regenerate the catalytically active [Fe(MgX)₂] species (Scheme 3).⁶ This scenario might form the basis for new iron catalyzed cross coupling reactions of aromatic compounds.



Scheme 3

Initial attempts to verify this concept with aryl iodide **9a** (X = I, Scheme 4) and aryl bromide **9b** (X = Br, Scheme 4) were rather disappointing. Although we were able to detect the cross-coupling product **10** in the reaction mixture, the reduction of the substrates with formation of

compound **11** prevailed. Gratifyingly, however, a very rapid (< 5 min) and essentially quantitative conversion of chloride **9c** (X = Cl, Scheme 4) has been observed without competing attack of the Grignard reagent on the methyl ester function. No special ligand is necessary to enable this conversion.



Scheme 4. Optimization of the iron-catalyzed cross-coupling reaction of substrate **9**, (see Table 2). NMP = *N*-Methylpyrrolidone.

Table 2. Screening of different substrates in the iron catalyzed cross coupling reaction depicted in Scheme 4.

Entry	X	Yield [GC, %]	
		10	11
1	I	27	46
2	Br	38	50
3	Cl	>95	-
4	OTf	>95	-
5	OTs	>95	-

It also turned out that the corresponding triflate **9d** (X = OTf, Scheme 4) and even tosylates **9e** (X = OTs, Scheme 4) perform equally well, providing product **10** in excellent yields and high reaction rates. Further investigations showed that the reaction is virtually independent of the chosen iron salt. Therefore Fe(acac)₃ is usually employed as a non-hygroscopic and very cheap precatalyst.

With regard to the substrate scope, the iron-catalyzed cross coupling process of alkylmagnesium halides and aromatic electrophiles turned out to be widely applicable. As can be seen from the results in Table 3, moderately electron-deficient aryl chlorides and tosylates react with good to excellent yields.⁷ This includes various benzene derivatives substituted with electron-withdrawing groups such as esters, nitriles, sulfonates, sulfonamides, or -CF₃ groups as well as many heterocyclic compounds. Also electron-rich aryl triflates are easily converted to the corresponding cross coupling products. Acidic N – H protons (entry 40, 42, Table 3) as well as acetyl protecting groups on alcohols (entry 43, Table 3) are tolerated without significant influence on the efficiency of the reaction.

Table 3. Cross-Coupling Reactions of Alkyl Grignard Reagents R-MgBr with Aryl and Heteroaryl Chlorides, Tosylates, and Triflates (Ar-X)^a













Entry	Ar-X	R-MgBr	Ar-R (Yield)	Entry	Ar-X	R-MgBr	Ar-R (Yield)
1 2 3		<i>n</i> -C ₆ H ₁₃ MgBr	91% (X = Cl) 87% (X = OTf) 83% (X = Ts)	27		<i>n</i> -C ₁₄ H ₂₉ MgBr	81%
4			91%	28		<i>n</i> -C ₁₄ H ₂₉ MgBr	93%
5			88%	29		<i>n</i> -C ₁₄ H ₂₉ MgBr	41%
6			85%	30		<i>n</i> -C ₁₄ H ₂₉ MgBr	68%
7 8 9		<i>n</i> -C ₁₄ H ₂₉ MgBr	91% (X = Cl) 80% (X = OTf) 74% (X = OTs)	31		<i>n</i> -C ₁₄ H ₂₉ MgBr	89%
10 11 12		<i>n</i> -C ₁₄ H ₂₉ MgBr	94% (X = Cl) 72% (X = OTf) 75% (X = OTs)	32		<i>n</i> -C ₁₄ H ₂₉ MgBr	84%
13 14		<i>n</i> -C ₁₄ H ₂₉ MgBr	0% (X = Cl) 81% (X = OTf)	33		<i>n</i> -C ₁₄ H ₂₉ MgBr	95%
15		<i>n</i> -C ₆ H ₁₃ MgBr	85%	34		<i>n</i> -C ₁₄ H ₂₉ MgBr	95%
16		<i>n</i> -C ₆ H ₁₃ MgBr	94%	35		<i>n</i> -C ₁₄ H ₂₉ MgBr	94%
17 18		<i>n</i> -C ₁₄ H ₂₉ MgBr	0% (X = Cl) 90% (X = OTf)	36		<i>n</i> -C ₁₄ H ₂₉ MgBr	67%
19		<i>n</i> -C ₁₄ H ₂₉ MgBr	81%	37		<i>n</i> -C ₁₄ H ₂₉ MgBr	68%
20		<i>n</i> -C ₁₄ H ₂₉ MgBr	81%	38		<i>n</i> -C ₁₄ H ₂₉ MgBr	60%
21 22 23		<i>n</i> -C ₁₄ H ₂₉ MgBr	92% (X = Cl) 74% (X = OTf) 82% (X = OTs)	39		<i>n</i> -C ₁₄ H ₂₉ MgBr	84%
24		<i>n</i> -C ₆ H ₁₃ MgBr	68%	40		C ₂ H ₅ MgBr	67%
25 26		<i>n</i> -C ₁₄ H ₂₉ MgBr	95% 56% ^b	41 42		<i>n</i> -C ₁₄ H ₂₉ MgBr	90% (R = Me) 85% (R = H)
				43		<i>n</i> -C ₁₄ H ₂₉ MgBr	72%

^a All reactions were carried out in THF / NMP using Fe(acac)₃ (5 Mol %) as the catalyst. ^b Using Fe(salen)Cl (5 Mol %) as catalyst.

In contrast to alkylations, the corresponding iron-catalyzed arylation is limited to various π -electron-deficient heterocycles. As shown in Table 4 a broad variety of such heterocycles can

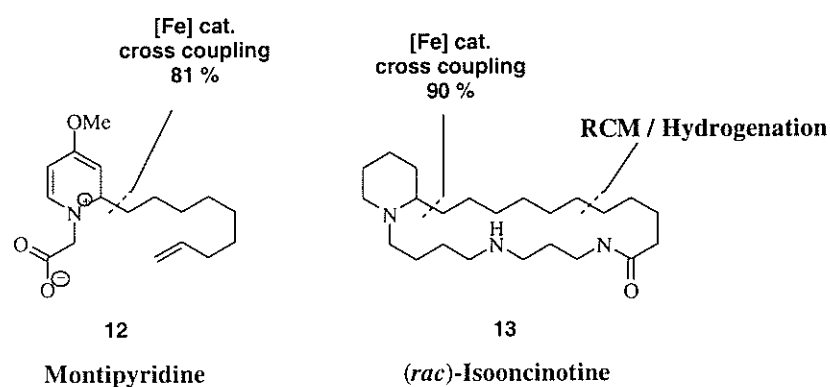
be converted to the desired biaryls in reasonable yields. In all cases, varying amount of biphenyl is formed as byproduct, which is easily separated by flash chromatography.

Table 4. Cross-Coupling Reactions of Aryl Grignard Reagents R – MgBr with Heteroaryl Chlorides Ar – Cl^c

Entry	Ar-X	R-MgBr	Ar-R (Yield)	Entry	Ar-X	R-MgBr	Ar-R (Yield) ^a
1		PhMgBr	73% ^b	7		PhMgBr	71%
2		PhMgBr	82%	8		PhMgBr	63%
3		PhMgBr	69%	9		PhMgBr	63%
4		PhMgBr	53%	10		PhMgBr	57%
5		PhMgBr	64%	11		PhMgBr	60%
6		PhMgBr	63%	12		PhMgBr	66%

^a Isolated yield. ^b Using Fe(salen)Cl as the catalyst. ^c All reactions were carried out in THF using Fe(acac)₃ (5 mol %) as the catalyst unless stated otherwise.

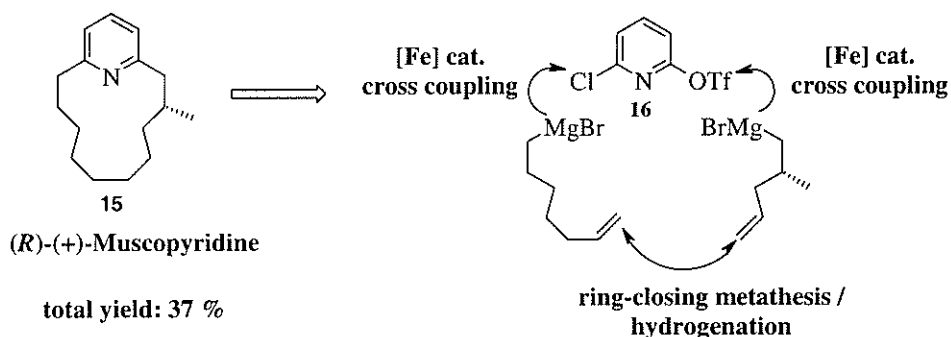
This novel method was also applied to target oriented synthesis of the cytotoxic marine natural product montipyridine **12** (Scheme 5) and the macrocyclic spermidine alkaloid isoconcinotine **13** (Scheme 5). In the later case, the macrocyclic ring was formed *via* a one pot ring-closing metathesis / hydrogenation sequence using a single ruthenium pre-catalyst to accomplish both steps (Scheme 5).⁸



Scheme 5

Furthermore, a highly integrated catalytic approach to the odoriferous musk alkaloid (*R*)-(+)-muscopyridine **15** (Scheme 6) has been established based on the consecutive addition of two different Grignard reagents to the difunctional substrate **16**. The resulting diene was subjected

to the one-pot metathesis-hydrogenation manifold giving rise to muscopyridine in a single operation.⁹



Scheme 6

4. Summary

Two new and highly versatile methods for the cross coupling of cheap and readily available chloroarenes and –sulfonates have been developed. The palladium catalyzed Suzuki-Miyaura reaction shows high yields with electron-rich as well as electron-poor electrophiles in alkylation-, alkenylation-, alkynylation-, as well as cyclopropylation reactions.

The use of environmentally benign and cheap Fe(acac)₃ as pre-catalyst for coupling reactions of electron deficient aryl chlorides and -tosylates as well as electron-rich aryl triflates with alkyl- and aryl Grignard reagents nicely complements the well known nickel- and palladium based protocols.

¹ A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

² W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342; *Angew. Chem. Int. Ed.* **2002**, *41*, 1291.

³ A. Fürstner, A. Leitner, *Synlett* **2002**, 292.

⁴ G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199 and literature cited therein.

⁵ B. Bogdanović, M. Schwickardi, *Angew. Chem.* **2000**, *112*, 4788; *Angew. Chem. Int. Ed.* **2000**, *39*, 4610.

⁶ A. Fürstner, A. Leitner, *Angew. Chem.* **2002**, *114*, 632; *Angew. Chem. Int. Ed.* **2002**, *41*, 609.

⁷ A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856.

⁸ A. Fürstner, A. Leitner, unpublished results.

⁹ A. Fürstner, A. Leitner, *Angew. Chem.* **2003**, *115*, 320; *Angew. Chem. Int. Ed.* **2003**, *42*, 308.