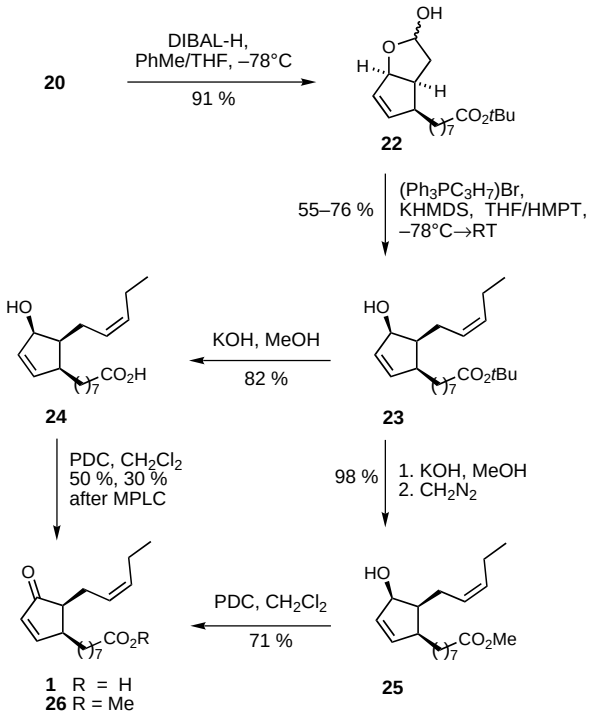

Scheme 5. Synthesis of 12-OPDA (**1**) and 12-OPDA methyl ester (**26**). DIBAL-H = diisobutylaluminum hydride, KHMDS = potassium hexamethyldisilazanide, HMPT = hexamethylphosphoric acid triamide, PDC = pyridinium dichromate.

dioica tendril coiling assay.[14] This allowed us to confirm that **26** is more active than *rac*-**1**.

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Palladium-Catalyzed Coupling of Alkyl Chlorides and Grignard Reagents**

Anja C. Frisch, Nadim Shaikh, Alexander Zapf, and Matthias Beller*

Organometallic cross-coupling reactions have proven extremely important in recent years for the synthesis of organic building blocks, and pharmaceutical and agrochemical derivatives. A topic of current interest in this area is the catalytic activation and subsequent functionalization reactions of C–Cl bonds not only for laboratory-scale synthesis but also for industrial applications.[1] To date the main focus has been the refinement of aryl and vinyl chlorides. Important contributions have been made, for example, in the area of Heck, Suzuki, and amination reactions of aryl chlorides.[2–8]

While catalytic nucleophilic substitution of $C(sp^2)$–Cl bonds is nowadays well established, the palladium-catalyzed refinement of alkyl chlorides has been largely neglected so far. The difficulty of catalytic nucleophilic substitution at $C(sp^3)$–Cl has been attributed to the ease of β-hydride elimination reactions of the corresponding alkylpalladium complexes. Nevertheless, Suzuki et al.[9] and Knochel et al.[10] demonstrated the possibility of palladium- and nickel-catalyzed coupling of alkyl bromides and alkyl boranes as well as organozinc derivatives. Furthermore, we were also able to show that palladium-catalyzed carbonylations of in situ generated α-amidoalkyl bromides proceed in good yields to the corresponding amino acid derivatives.[11]

Fu et al.[12] recently described the first catalytic coupling reactions of alkyl chlorides through a palladium-catalyzed Suzuki reaction. Kambe et al.[13] developed the efficient

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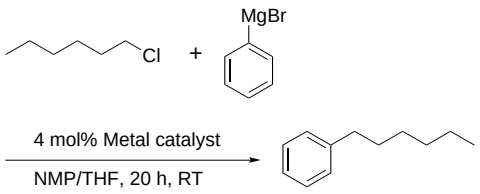
nickel-catalyzed Kumada coupling of 1-chlorooctane with butylmagnesium chloride in the presence of 50 mol% of butadiene. As most arylboronic acids are synthesized from the corresponding Grignard reagents, the Kumada coupling reaction offers a more direct access to the desired products than the Suzuki reaction. Therefore, we have studied the Grignard coupling of alkyl halides (Kumada coupling) in the presence of various metal catalysts. Herein, we describe the first successful development of such a palladium-catalyzed method using alkyl chlorides.

Initially, we performed the coupling of 1-chlorohexane (**1**) and phenylmagnesium bromide (**2**) in the presence of different metal catalysts as a model reaction [Eq. (1)]. Selected



(1)

results are shown in Table 1. In general, all reactions were run with 4 mol% of metal catalyst at room temperature. A commercially available solution of phenylmagnesium bromide in THF was added to a solution of **1** and catalyst in such a way that the reaction temperature does not exceed 40 °C. No conversion was observed in the absence of catalyst. Simple salts of Cu,[14] Ni, or Fe, which have been shown to be active in Grignard coupling reactions of alkyl bromides or aryl chlorides, did not catalyze the desired reaction to an appreciable amount (Table 1, entries 1–3). For palladium as catalyst metal, we studied the effect of different phosphane ligands, solvents, and substrate concentration. Although a high conversion was observed in the presence of $Pd(OAc)_2$ and triarylphosphanes, the selectivity of the reaction was low (Table 1, entries 4 and 5). Side products were hexene and hexane. In agreement with the results reported by Fu et al. for Suzuki reactions, tricyclohexylphosphane (PCy_3) proved to be the best ligand for the Grignard coupling of **1** (Table 1, entries 7–9). However, the ligand effect was not pronounced, as $Pd/PtBu_3$ also gave a significant amount of product. Further optimization of the amount of Grignard reagent (Table 1, entries 13–18) led to excellent yield (96%) of 1-phenylhexane in the presence of 1.5 equivalents of **2**. Apart from the influence of the ligand, the efficiency of the reaction was found to be largely dependent on the solvent (Table 1, entries 10–12). So far, only *N*-methylpyrrolidinone (NMP) and dimethylacetamide (DMAc) gave good yields of the coupling product.

Table 1. Coupling of 1-chorohexane (**1**) and phenylmagnesium bromide (**2**).[a]

Entry	Solvent	**2** [equiv]	Metal compound	Ligand	Conversion [%]	Yield [%]
1	NMP	1.2	$CuCl_2$·LiCl	–	27	3
2	NMP	1.2	$[Fe(acac)_3]$	–	44	7
3	NMP	1.2	$[Ni(acac)_2]$	–	45	2
4	NMP	1.2	$Pd(OAc)_2$	PPh_3	88	9
5	NMP	1.2	$Pd(OAc)_2$	$P(o\text{-tol})_3$	92	11
6	NMP	1.2	$Pd(OAc)_2$	$PtBu_3$	70	27
7	NMP	1.2	$Pd(OAc)_2$	PCy_3	99	68
8[b]	NMP	1.2	$Pd(OAc)_2$	PCy_3	99	70
9[b,c]	NMP	1.2	$Pd(OAc)_2$	PCy_3	76	34
10	THF	1.2	$Pd(OAc)_2$	PCy_3	1	1
11	dioxane	1.2	$Pd(OAc)_2$	PCy_3	1	2
12	DMF	1.2	$Pd(OAc)_2$	PCy_3	70	3
13	NMP	1.0	$Pd(OAc)_2$	PCy_3	91	61
14	NMP	1.5	$Pd(OAc)_2$	PCy_3	99	73
15	NMP	2.0	$Pd(OAc)_2$	PCy_3	99	71
16	NMP	3.0	$Pd(OAc)_2$	PCy_3	99	72
17	DMAc	1.5	$Pd(OAc)_2$	PCy_3	95	84
18	NMP[d]	1.5	$Pd(OAc)_2$	PCy_3	99	96

[a] Reaction conditions: **1** (2 mmol), metal complex (4 mol%), ligand (4 mol%), solvent (5 mL; NMP was distilled over CaH_2, the other solvents were used as received from Aldrich (water-free, over molecular sieves)), 20 h, room temperature; NMP = *N*-methylpyrrolidinone, DMAc = *N*,*N*-dimethylacetamide, PCy_3 = tricyclohexylphosphane. [b] 40 °C. [c] 1 mol% $Pd(OAc)_2/PCy_3$, 1/1. [d] NMP from Aldrich water-free 99.5%, sure/seal bottle, used as received.

After having optimized the model reaction, we were interested in extending the scope of the coupling reaction. As shown in Table 2, the coupling reactions of 1-chlorohexane and 1-chlorobutane with different tolyl, anisyl, and 4-fluorophenyl Grignard reagents proceeded in good to excellent yields (77–99%; Table 2, entries 1–5). Isobutyl chloride led to a slightly lower yield (72%). Unfortunately, *sec*-butyl chloride, and *tert*-butyl chloride did not react under the conditions described. On the other hand, the method was applicable to functionalized alkyl chlorides. 5-Chloropentanenitrile, methyl 6-chlorohexanoate, and 3-chloropropionaldehyde diethyl acetal gave the corresponding products (58–99%; Table 2, entries 7–9). Even coupling reactions with 2-phenylethyl chloride, which is amenable to elimination of HCl to give styrene, proceeded with significant yields (43–76%; Table 2, entries 10, 11). The coupling of **1** and **2** exhibited complete conversion within 30 min; the reaction times for the other reactions have not been optimized (in general 20 h).

Interestingly, the palladium-catalyzed coupling of organozinc reagents proceeded under similar conditions as described for the Kumada coupling. For example, the reaction of **1** with phenylzinc bromide proceeded in the presence of a Pd/PCy_3 catalyst at 60 °C in 41% yield (44% conversion).

In conclusion, we have developed a novel method for the palladium-catalyzed cross-coupling of alkyl chlorides and Grignard reagents. Good to excellent yields of the coupling products were obtained at room temperature, and functional groups such as ethers, esters, acetals, fluorides, nitriles, aryl and benzyl were tolerated by the procedure. We are currently investigating extensions of this methodology to alkyl–alkyl coupling reactions.

Experimental Section

General procedure: A 25-mL Schlenk flask was charged with $Pd(OAc)_2$ (0.0180 g, 0.080 mmol) and PCy_3 (0.0224 g, 0.080 mmol), sealed with a septum, and

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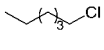
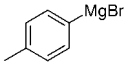
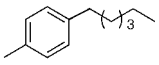
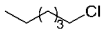
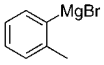
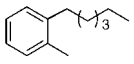
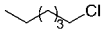
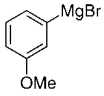
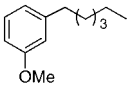
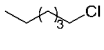
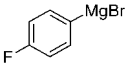
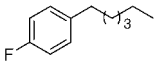
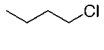
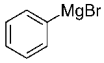
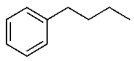
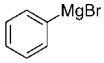
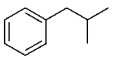
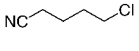
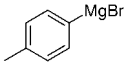
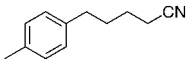
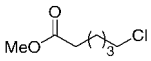
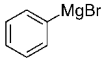
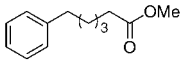
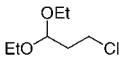
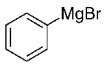
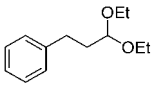
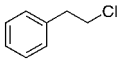
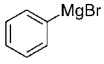
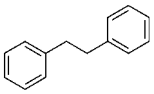
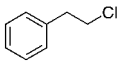
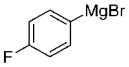
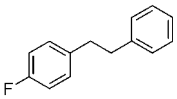
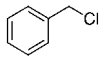
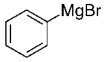
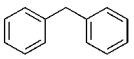
Table 2. Palladium-catalyzed cross-coupling of alkyl chlorides with aryl Grignard reagents.

Entry	Alkyl chloride	Aryl Grignard Compound	Product	Conversion [%]	Yield [%]
1				99	91
2				99	83
3				100	99
4				99	77
5				nd[a]	89
6				100	72
7				100	99
8				80	58
9				85	74
10				90	76
11				96	43
12				100	84

[a] nd = not determined.

purged with argon for 15 min. NMP (5 mL) and **1** (0.27 mL, 2 mmol) were added by syringe. Then, **2** (3 mL, 3 mmol, 1M in THF) was added dropwise over 1 min to the stirred mixture. After 20 h at room temperature, the reaction was quenched with MeOH (1 mL) and water (1 mL). The solution was concentrated to about 6 mL by rotary evaporation, and subjected to silica gel column chromatography (heptane) to give a colorless liquid (0.276 g, 1.7 mmol, 85 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$–7.00 (m, 5H; Ar), 2.51 (t, $^3J(H,H) = 7.7$ Hz, 2H; CH_2), 1.58–1.47 (m, 2H; CH_2), 1.30–1.15 (m, 6H; CH_2), 0.80 ppm (t, $^3J(H,H) = 6.4$ Hz, 3H; CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 143.4$, 128.9, 128.7, 126.0, 36.5, 32.2, 32.0, 29.5, 23.1, 14.6 ppm; MS (EI, 70 eV): *m*/*z* (%): 162 (33) [M^+], 105 (11) [Ph-$C_2H_4^+$], 91 (100) [Ph-CH_2^+], 77 (4) [Ph^+], 43 (16) [$C_3H_7^+$].

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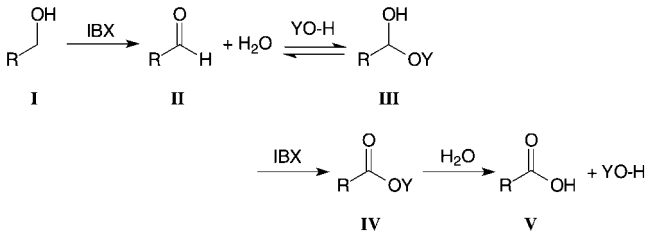
IBX-Mediated Oxidation of Primary Alcohols and Aldehydes To Form Carboxylic Acids**

Ralph Mazitschek, Marcel Mülbaier, and Athanassios Giannis*

Dedicated to Professor Peter Welzel on the occasion of his 65th birthday

During recent years the hypervalent iodine reagent 1-hydroxy-1,2-benziodoxole-3(1*H*)-one-1-oxide (IBX) was utilized for numerous novel and synthetically valuable oxidative transformations, including, among others, the cyclization of anilides,[1] the preparation of amino desoxy sugars from glycals,[2] the benzylic oxidation of aromatic compounds,[3] and the synthesis of α,β-unsaturated aldehydes and ketones from homologous, saturated precursors.[4]

IBX is safe and easily accessible, and is especially suited to the oxidation of alcohols in homogenous solution to yield the corresponding aldehydes and ketones.[5,6] Recently, analogous reactions using polymer-supported IBX have been reported.[7,8] The transformation of primary alcohols to carboxylic acids has never been observed using IBX. For the first time, we report here that primary alcohols are oxidized easily in the presence of IBX and certain O nucleophiles to give carboxylic acids at ambient temperature in high yields. Starting from the hypothesis that the aldehyde **II**, which is generated from a primary alcohol **I** and an excess of IBX, reacts with suited O nucleophiles (YO-H) to form the intermediate **III**. This intermediate can be oxidized to the corresponding active ester **IV**, which in turn is hydrolyzed to give the desired carboxylic acid **V** (Scheme 1).



Scheme 1. Mechanism of the IBX-mediated oxidation of primary alcohols to give the carboxylic acids.

In our initial attempt 2-hydroxypyridine (**1**, HYP) was used as an O nucleophile. We were pleased to find that, in the presence of 2 equivalents of IBX and 4 equivalents of 2-hydroxypyridine, 1-decanol was oxidized to form decanoic acid in 48 h in 92% yield. A series of other aliphatic alcohols (and aldehydes) was oxidized under the same reaction conditions in high yields to give the carboxylic acid analogues (Table 1). That only catalytic amounts of hydroxypyridine are

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[**] IBX = 1-hydroxy-1,2-benziodoxole-3(1*H*)-one-1-oxide.

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