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An Electrochemical Coupling of Organic Halide with Aldehydes, Catalytic in Chromium and Nickel Salts. The Nozaki–Hiyama–Kishi Reaction

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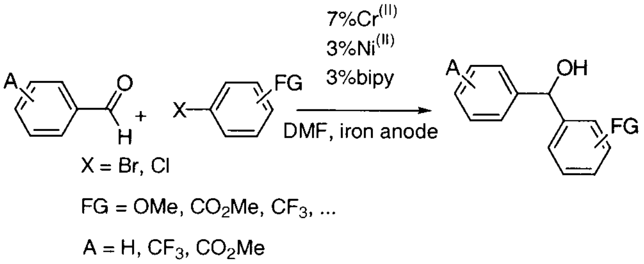
ABSTRACT



Electrochemical arylation of arenecarboxaldehydes using an iron sacrificial anode in the presence of chromium and nickel catalysts afforded the corresponding arylated secondary alcohols in moderate to good yields. The chromium and nickel salts as catalysts are obtained by oxidation of a stainless steel rod during a preelectrolysis in 7% and 3%, respectively. The process was also applied to the addition of vinyl halide, allyl acetate, or α-chloroester to aromatic aldehydes.

The addition of vinyl, allyl, or aryl halides to aldehydes (the Nozaki−Hiyama−Kishi reaction) via an intermediate chromium(III) species is generally achieved by $CrCl_2$ with a catalytic amount of nickel chloride. This reaction has been widely applied in organic synthesis.[1] As a matter of fact, it combines some rather unique features such as high aldehyde chemoselectivity. Also, organochromium(III) compounds are compatible with a large variety of functional groups. With regards to the nucleophile, a wide range of substrates including allyl, propargyl, aryl, or alkenyl halides, alkenyl triflates, or allyl phosphates[2] were found to be suitable precursors for the formation of organochromium intermediates.

This reaction, however, has serious drawbacks in that a large amount of toxic Cr^{II} reagent, sometimes up to 400 mol %, must be used. Since chromium salts are physiologically poisonous, this precludes any application of such transformations to industrial processes. Furthermore, the rather high cost of $CrCl_2$ makes large-scale syntheses less attractive. Several groups have already tried to minimize the amount of chromium reagent. Notably, the regeneration of Cr^{II} by electroreduction,[3] or by introduction of a reducing metal such as Mn[4] or Al,[5] was recently reported. The reaction, with 20% of chromium, has been applied to the alkenylation of aromatic aldehydes bearing electron-donating substituents,

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[1] Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1−36, and references cited therein.

[2] For the use of substrates other than halides, see the following. (a) For alkenyl triflates: Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048−6050. (b) For allylic phosphates: Nowotny, S.; Tucker, C. E.; Jubert, C.; Knochel, P. *J. Org. Chem.* **1995**, *60*, 2762−2772.

[3] (a) Grigg, R.; Putnikovic, B.; Urch, C. J. *Tetrahedron Lett.* **1997**, *38*, 6307−6308. (b) Kurobashi, M.; Tanaka, M.; Kishimoto, S.; Tanaka, H.; Torii, S. *Synlett* **1999**, 69−70.

[4] Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349−12357.

[5] Kurobashi, M.; Tanaka, M.; Kishimoto, S.; Goto, K.; Tanaka, H.; Torii, S. *Tetrahedron Lett.* **1999**, *40*, 2785−2788.

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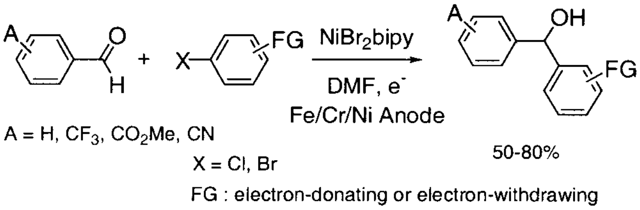
whereas electron-poor aromatic aldehydes gave poor results, affording the corresponding pinacol predominantly. Finally, although this reaction occurs with alkenyl halides, only a few examples with aryl halides have been reported and those are limited to aryl iodides. We report here an electrochemical arylation of an aromatic aldehyde using only 7% of chromium and applicable to aldehyde-bearing electron-withdrawing substituents. We have previously described an electrochemical version of the Nozaki−Hiyama−Kishi reaction, catalytic in both chromium and nickel, applied to aryl bromides and chlorides on one hand and to aromatic aldehydes bearing electron-withdrawing groups on the other.[6] We have shown that it is possible to realize this reaction with a nickel catalyzed and a sacrificial stainless steel rod anode, made in the weighting proportions Fe/Cr/Ni: 72/18/10 (Scheme 1).

Scheme 1. Addition of Aryl Halides to Aromatic Aldehydes via a Nickel and Chrome Catalysis



A charge of 4−5 F/mol was necessary to consume benzaldehyde. A 5 F/mol charge corresponded to the release of 50% of chromium and 25% of nickel vs PhCHO. We have shown that it was possible to reduce the amount of chromium and nickel released to 20% and 10%, respectively, by replacing an iron rod for the stainless steel rod after passing 2 F/mol and then continuing the electrolysis until 4−5 F/mol. In all cases, chemical yields are good (50−80%) and approximately the same as those obtained with the other process.

With the intent to further reduce the amount of chromium, we found that it is possible to make a preelectrolysis with the stainless steel rod to obtain 7% of chromium and 3% of nickel. This solution is used as catalyst with 3% of 2,2′-bipyridine, while the electrolysis is run with an iron rod. We obtained thus the same yield of addition products as when the electrolysis was run with the stainless steel rod anode, as illustrated in Table 1 for the cross-coupling reaction between benzaldehyde and bromobenzene.

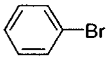
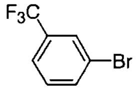
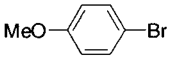
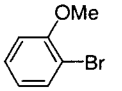
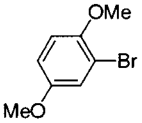
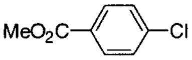
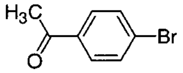
This led us to a typical procedure: in an one-compartment cell fitted with a nickel sponge as the cathode (20 cm^2) and a stainless steel rod (Fe/Cr/Ni 72/18/10) as the anode[7] was introduced DMF (40 mL) as solvent, NBu_4BF_4 (0.2 g 0.6 mmol) as supporting electrolyte, and CH_2Br-CH_2Br (220 μL 2.5 mmol). The preelectrolysis was run under argon, at room temperature, at a constant current density of 0.3 A for 500 C. Afterward, the stainless steel rod was replaced by an iron rod, and 3% of 2,2′-bipyridine (0.039 g 0.25 mmol) was added along with 7.5 mmol of ArCHO and a portion of ArX (0.3 mmol). The electrolysis was then conducted at constant current density (0.15 to 0.25 A) so that the potential of the working electrode remained = −1.2 V/SCE. During the electrolysis ArX was constantly added in the solution via a syringe pump at a rate of 2−2.5 mmol/h, to minimize its dimerization. A charge of 3−4 F/mol was necessary to consume the aldehyde. The amount of chromium and nickel released during the preelectrolysis was obtained by weighing the stainless steel rod anode before and after the preelectrolysis. In all cases, 0.150 g of the sacrificial anode were consumed. The weighting proportions of Fe/Cr/Ni were 72/

Table 1. Electroreductive Cross-Coupling between Bromobenzene and Benzaldehyde

entry	method[a] (%Cr/%Ni released)	% alcohol[b]	% ketone[b,c]
1	**A** (50/25)	50	6
2	**B** (20/10)	52	5
3	**C** (7/3)	65	3

[a] Method **A**: the electrolysis was totally conducted with the stainless steel anode (Fe/Cr/Ni 72/18/10). Method **B**: the electrolysis was conducted with the stainless steel anode for 1500 C and then continued with an iron rod. Method **C**: a preelectrolysis is run with the stainless steel rod for 500 C and then the stainless steel rod is replaced by an iron rod. [b] Isolated yields, based on the initial benzaldehyde. [c] Ketone is obtained by a Meerwein−Pondorf−Verley reduction between PhCHO and $Ph-CHO^--Ph$.

Table 2. Electroreductive Cross-Coupling between Benzaldehyde and Aryl Halides

entry	ArX	n eq.	% alcohol[a]	% ketone[a]
1		1.4	65	3
2		1.1	50	< 1
3		1.3	62	7
4		1.5[b]	74	9
5		1.5[c]	63	6
6		1.3	58	< 1
7		1.4	56	1

[a] Isolated yield, based on initial PhCHO; spectroscopic data for all products are in agreement with the given structures. [b] 1.6 mmol of ArBr is initially introduced. [c] 8 mmol of ArBr is initially introduced.

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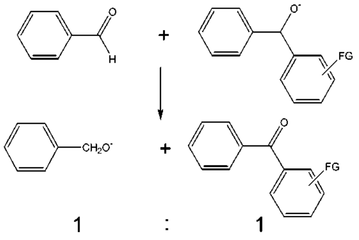
[6] Durandetti, M.; Périchon, J.; Nédélec, J.-Y. *Tetrahedron Lett.* **1999**, *40*, 9009−9013.

[7] Stainless steel was purchased from Weber (ref. 304L) and nickel sponge from Nitech (ref. Mn110.050.020, grade 110).

18/10, corresponding to 0.52 mmol of chromium (7%) and 0.26 mmol of nickel (3.5%). We applied this method to a large variety of aryl halides. The results with benzaldehyde are reported in Table 2.

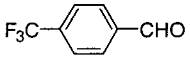
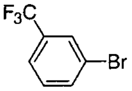
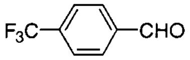
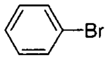
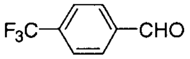
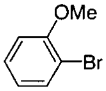
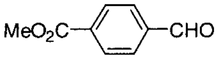
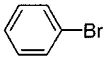
Chemical yields are moderate to good and approximately the same as those obtained with the stainless steel rod used as the anode. Therefore, the use of chromium and nickel salts obtained during the preelectrolysis allows the cross-coupling between benzaldehyde and aryl halides using a catalytic amount of chromium (7% based on initial PhCHO). This method is efficient with aryl halides bearing electron-donating as well as electron-withdrawing substituents. With electron-donating substituents, aryl bromides must be used (no cross-coupling occurs with aryl chloride), and with an ortho-substituent, a larger amount of ArX is introduced (Table 2, entries 4−5). With electron-withdrawing groups aryl chlorides (Table 2, entry 6) or bromides (Table 2, entries 2, 7) could be used. The reaction is highly aldehyde selective, as no addition products with ester or ketone groups are detected (Table 2, entries 6−7). During the electrolysis, the formation of benzyl alcohol in the same amount as the ketone indicates that a Meerwein−Pondorf−Verley reduction occurs between PhCHO and the alkoxide $PhCHO^-$−Ar leading to benzyl alkoxide $PhCH_2O^-$ and the ketone Ph-CO-Ar (Scheme 2). It is interesting to note that this reaction occurs mainly with alkoxides bearing electron-donating substituents (Table 2, entries 3−5).

Scheme 2. The Meerwein−Pondorf−Verley Reduction



We also applied this process to the cross-coupling reaction of aldehydes bearing electron-withdrawing substituents (Table 3). As these aldehydes are more reactive than benzaldehyde, the aromatic halide can be introduced in the cell, before the electrolysis, with only a small excess with respect to the aldehyde. The reduction of aromatic aldehydes bearing electron-withdrawing groups occurs before that of PhCHO (−1.55 V/SCE for *p*-CF_3-PhCHO, −1.45 V/SCE for *p*-MeOCO-PhCHO compared to −1.95 V/SCE for PhCHO). Therefore, the addition of aromatic aldehyde in several portions to the reaction mixture avoids pinacolization. This requires also the portionwise addition of the aryl halide. So the initial mixture is prepared with 1 mmol of ArCHO and 1.5−2 mmol of Ar′Br and the syringe pump. Aryl bromides must be used (only a small amount of cross-coupling is detected with an aryl chloride, with a large amount of pinacol). Yields are moderate to good and do not seem to depend on the substituent of the aromatic halide provided that the excess of the aryl halide is larger with electron-donating substituents than with electron-withdrawing groups. For all the reactions reported in Table 3, only 3 F/mol were necessary and ketone Ar−CO−Ar′ is always < 1%.

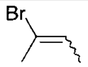
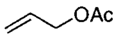
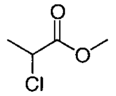
Table 3. Electroreductive Cross-Coupling between Aromatic Aldehyde Bearing EWG and Aryl Halides

entry	ArCHO	Ar’Br	n eq. Ar'Br	% alcohol[a]
1			1.4[b]	38
2			1.3[c]	47
3			1.3[d]	42
4			1.6[c]	62

[a] Isolated yield, based on initial ArCHO; spectroscopic data for all products are in agreement with the given structures. [b] 1.4 mmol of Ar′Br is initially introduced. [c] 2 mmol of Ar′Br is initially introduced. [d] 3.2 mmol of Ar′Br is initially introduced.

We also applied this process to the cross-coupling reaction of benzaldehyde with vinyl bromide, allyl acetate, and α-chloroester (Table 4), and we have found that the cross-coupling between vinyl halides and benzaldehyde can be performed using the general procedure described for the coupling between benzaldehyde and aryl halides, except that 2 equiv of vinyl bromide is initially introduced. Under these conditions yields are moderate (Table 4, entries 1−2). The

Table 4. Electro Reductive Cross-coupling between Aldehyde and Different Subsituents

entry	RCHO	RX	n eq. RX	% alcohol[a]
	PhCHO			
1		Z/E = 75/25	2[b]	54 Z/E = 66/34
2		Z/E = 31/69	2[b]	46 Z/E = 35/65
3		Z/E = 31/69[c]	2[b]	62 Z/E = 42/58
4	PhCHO		2	78
5	PhCHO		1.1	77[d] *erythro*/*threo* = 68/32
6	*p*-CF_3-PhCHO	"	1.1	76[d] *erythro*/*threo* = 67/33
7	CH_3-$(CH_2)_7$-CHO	"	1	60[d] *erythro*/*threo* = 61/39

[a] Isolated yield, based on initial RCHO; spectroscopic data for all products are in agreement with the given structures. [b] 15 mmol of RX is initially introduced. [c] Reaction is carried out at 50 °C. [d] 4% of the corresponding ketone is equally obtained.

reaction also seems stereoselective. Thus, starting from commercial (*Z*)-2-bromo-2-butene which contains 25% of the *E*-isomer, the *Z*/*E* isomer ratio in the coupling product is 66/34 (Table 4, entry 1). If the starting material has mainly an *E* geometry ($Z/E = 31/69$), it is the same for the cross-coupling product ($Z/E = 35/65$) (Table 4, entry 2), thus indicating that the reaction is stereoselective. Chemical yield could be increased by heating the solution at 50 °C, but unfortunately at this temperature stereoselectivity is lost (Table 4, entry 3).

This method can also be applied to allyl acetate or methyl 2-chloropropanoate: these yields of these products is as good as the yield of the aryl halide. In the case of 2-chloropropanoate, we obtained the two diastereoisomers with moderate diastereoselectivity (Table 4, entries 5−7), depending on the nature of the aldehyde. The reaction is efficient with benzaldehyde (Table 4, entry 5) as well as aromatic aldehydes bearing electron-withdrawing groups (Table 4, entry 6) or aliphatic aldehydes (Table 4, entry 7). In the three cases, only 1.1 equiv of 2-chloropropanoate was used, and only 2 F/mol were necessary to consume the aldehyde.

In conclusion, various substituted benzhydrols can be prepared in good yields in one step by a very simple electrochemical method where chromium salts are released by oxidation of the anode, thus avoiding the use of $CrCl_2$, which is toxic, air and moisture sensitive, and expensive. The reaction is catalytic in chromium salt (only 7%/PhCHO). This process was extended to the alkenylation of aromatic aldehydes as well as to the coupling with allyl acetate or methyl 2-chloropropanoate.

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