

# Nickel-Catalyzed Arylation of Acrolein Diethyl Acetal: A Substitute to the 1,4-Addition of Arylhalides to Acrolein

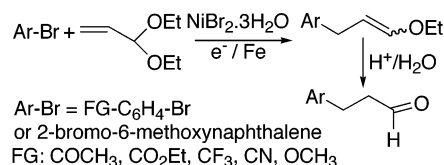
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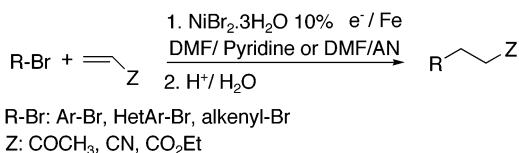
## ABSTRACT



In the presence of catalytic amount of NiBr<sub>2</sub> as catalyst precursor, organic halides are reductively coupled at 70 °C with acrolein diethyl acetal to give (Z)- and (E)-enolethers by allylic displacement of an alkoxy group. Subsequent hydrolysis affords β-arylated aldehydes.

We have already reported a very easy and efficient method of introduction of aryl,<sup>1,2</sup> heteroaryl,<sup>3</sup> or alkenyl<sup>4</sup> groups onto an activated olefin in a 1,4-addition manner (Scheme 1). This

### Scheme 1. Nickel-Catalyzed Addition of Organic Halides onto Electron-Deficient Olefins



reaction is catalyzed by nickel complexes in combination with cathodic reduction, which allows performance of the reaction by electrolysis of the reagent mixture in the presence of the catalyst precursor. In addition, the process is based on the use of a sacrificial anode, which in the case of an

iron anode thus provides iron ions that interestingly cooperate with the coupling process to improve the yield as compared to metals. Some features of the process are worth mentioning. The reaction is a one-operation process easily carried out in an undivided electrochemical cell and without the need of preparing an unstable organometallic intermediate. This explains the high functional tolerance observed. Also, the reaction is regiospecific and no 1,2-addition product is formed. When applied to conjugated aldehydes, we could have expected the occurrence of 1,2-addition as a side reaction, as it is observed commonly in organometallic chemistry. However, this was not observed, the main reaction being the polymerization of the substrate. It has already been shown<sup>5</sup> that nucleophilic addition of organometallics onto α,β-ethylenic acetals can avoid the peculiar behavior of α,β-unsaturated aldehydes. The enol ether formed by S<sub>N</sub>2' displacement of one alkoxy group can be hydrolyzed to form the β-substituted aldehyde. Herein, we wish to show that α,β-ethylenic acetals, as substrates equivalent to conjugated aldehydes, can be used in the nickel-catalyzed electroreductive arylation of olefins, according to Scheme 2.

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**Table 1.** Nickel-Catalyzed Arylation of Acrolein Diethyl Acetal: An Easy Access to Enol Ethers and  $\beta$ -Arylated Aldehydes

$\text{Ar-Br (1 equiv, 7.5 mmol)} + \text{Acetal (2, 2.5 equiv)} \xrightarrow[\text{DMF/pyridine: 9/1, 70 °C, } I = 0.1 \text{ A}]{10\% \text{ NiBr}_2 \cdot 3\text{H}_2\text{O, e}^-} \text{Enol ether (3)} \xrightarrow{\text{H}^+/\text{H}_2\text{O}} \text{Aldehyde (4)}$

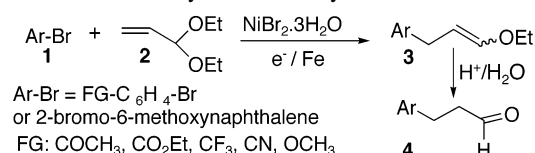
entry	Ar-Br <b>1</b>	anode	reaction time <sup>a</sup>	% Z/E <sup>b</sup>	enol ether <b>3</b> isolated yield %	aldehyde <sup>c,d</sup> <b>4</b> isolated yield %
1		Fe	5.5h	60 / 40	58.5	52
2		Fe/Ni/Cr	5.5h	59 / 41	59	
3		Zn	16h <sup>e</sup>	43 / 57	traces	
4		Al	16h <sup>f</sup>	58 / 42	traces	
5		Mg	7h	63 / 37	30	
6		Fe	6h	59 / 41	n/a	45
7		Fe	5h	63 / 37	55	47
8		Fe	7h	61 / 39	n/a	28
9		Fe	4h	67 / 33	28	24
10		Fe	4.5h	63 / 37	56	45
11		Fe	5.5h	56 / 44	n/a	40
12		Fe	5.5h	71 / 29	54.5	81 <sup>g</sup>

<sup>a</sup> After consumption of aryl halide, unless otherwise indicated. <sup>b</sup> Z/E ratio determined by GC are consistent with <sup>1</sup>H NMR data. <sup>c</sup> All of these substances are fully characterized by satisfactory spectral data (NMR and MS) and isolated yields are based on aryl bromide, unless otherwise indicated. <sup>d</sup> Aldehydes are directly obtained by HCl (6 N, 20 mL) hydrolysis of the electrolytic crude mixture at 20 °C. <sup>e</sup> 33% of unconsumed aryl halide. <sup>f</sup> At *t* = 5 h only traces of the expected product are detected. <sup>g</sup> The aldehyde is obtained after deprotection of the purified enol ether in AcOH/H<sub>2</sub>O (20 mL; 3:1) refluxing solution.

The reaction conditions have been tuned with *p*-*t*-Bu-bromobenzene and acrolein diethyl acetal as model reagents. We found that the 1:1 DMF/acetonitrile solvent mixture<sup>2–4</sup> used previously with activated olefins is not suitable here, since the aryl halide was not transformed. On the contrary, in DMF containing 10% of pyridine, the consumption of the

aryl halide is complete after 2 equiv of electrons have been passed. This solvent effect may indicate that the acrolein diethyl acetal is not as much coordinated to the reduced nickel species as  $\alpha,\beta$ -unsaturated carbonyls; the required stabilization of the reduced form of the catalyst is thus better ensured by pyridine. The reactions were conducted at 70 °C, in the presence of an iron or stainless steel anode (Fe/Cr/Ni, 72/18/10) and at constant current intensity (entries 1 and 2). The expected enol ether **3** was isolated after quenching of the reaction mixture with 1 N HCl. Results obtained with various aryl halides are reported in Table 1.

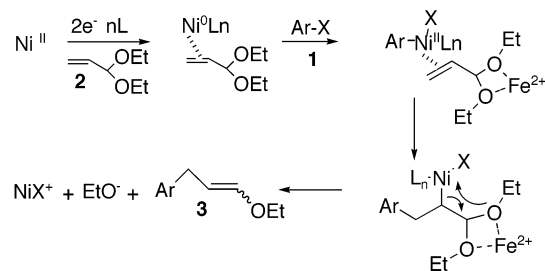
The isolated products are the  $\gamma$ -arylated-enol ethers **3**, which are regioselectively formed by allylic displacement of one alkoxy group. No S<sub>N</sub>2 substitution product was observed. Also the formation of the Z isomer is slightly favored, the isomer ratio being constant over all the reaction.

**Scheme 2.** Syntheses of  $\beta$ -Arylated Aldehydes via Electrochemical Arylation of Acrolein Diethyl Acetal Mediated by Nickel Catalysis

Isolated yields of **3** are in the range of 50–60% with both electron-withdrawing and electron-releasing groups on the aryl halide, though unexpectedly lower with CF<sub>3</sub> and CN substituents (Table 1, entries 8 and 9). The main byproduct is the reduced form of the starting aryl compound. We found that **3** is also formed when magnesium is used as the anode but in lower yield (entry 5), whereas only traces of **3** were found with zinc and aluminum (entries 3 and 4).

The product formation can be accounted for by the following mechanism (Scheme 3). The reduced nickel

**Scheme 3.** Proposed Mechanism for the Present Catalytic Reaction



species, which is stabilized by both pyridine and the acrolein acetal, first reacts with the aryl halide before inserting the

unsaturated substrate into the Ar–Ni bond; this ends with the  $\beta$ -elimination of Ni<sup>II</sup> and the ethoxy moiety, assisted by Fe<sup>2+</sup> ions.

The aldehyde form **4** can be generated either by acid hydrolysis (6 N HCl) of the crude mixture and then isolation by chromatography on silica gel, or by hydrolysis of the isolated enol ether by 3:1 AcOH/H<sub>2</sub>O.<sup>6</sup>

We have described in this paper a new procedure for the arylation of acrolein diethyl acetal with the aim of obtaining  $\beta$ -arylated aldehydes. The yields are only fair, but the process makes possible the use of functionalized (ketone, ester, nitrile) aryl bromide and thus represents an interesting improvement over previous analogous organometallic pathways.<sup>5</sup> The Heck arylation reaction of allylic alcohols is, however, a more efficient alternative.<sup>7</sup>

**Supporting Information Available:** General procedures for the preparation of  $\beta$ -arylated aldehydes and for  $\gamma$ -arylated enolethers and characterization of selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(6) The cleanliness of this last procedure makes further purification unnecessary.

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