Stereoselective Alkenylation of Activated Olefins via Nickel-Catalyzed Electroreductive Coupling

Sylvie Condon-Gueugnot,* Daniel Dupré, Jean-Yves Nédélec, Jacques Périchon

Laboratoire d'Electrochimie, Catalyse et Synthèse Organique (UMR No. 28), CNRS, 2 rue Henri Dunant, F-94320 Thiais, France
Fax +33(1)49781148

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Dedicated to Professor Hans Schäfer on the occasion of his 60th birthday.

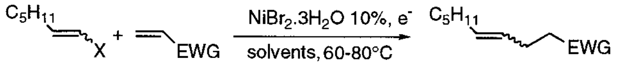
The nickel-catalyzed electroreductive conjugate addition of (*Z*)- or (*E*)-alkenyl halides to electron-deficient olefins in the presence of a sacrificial iron rod as the anode proceeds with complete retention of the stereochemistry of the alkenyl part and affords functionalized isomerically pure (*Z*)- or (*E*)-olefins in high yield.

Unsaturated compounds bearing functionalities are widely present as natural products, notably insect pheromones,[1] and a number of methods have been reported on the synthesis of such compounds with high stereocontrol. Alkenylcopper compounds[2] are now mostly used for the 1,4-addition of alkenyl groups to activated olefins. However, classic procedures for obtaining them require the preparation of moisture-sensitive organometallic precursors such as organomagnesium or organolithium reagents which are of restricted functional tolerance. It is also necessary to work at low temperature to ensure a high regioselectivity in the 1,4- vs. 1,2-addition. Recent approaches have, however, shown that functionalized alkenylcopper compounds can be generated from the less reactive alkenylzinc,[3] or alkenylzirconium[4] reagents by transmetalation using a copper salt. Organoboranes,[5] organoalanes,[6] and organozirconium[7] have also proved to be good candidates for introducing alkenyl moieties to activated olefins.

Easily stored and handled vinyl halides can be used as an alternative. Alkenyl halides are known to undergo stereoselective coupling reactions with alkenyl-[8] alkynyl-[9] or arylmetals[10] in the presence of a transition-metal catalyst, such as palladium or nickel complexes. However very few examples of their reaction with activated olefins in the presence of nickel-complex catalysts have been described.[11] In this paper, we report a highly stereoselective alkenylation method using a nickel-catalyzed electroreductive activation of alkenyl halides in the presence of activated olefins.

We have already reported that the electrochemical arylation[12] of activated olefins from aryl halides assisted by nickel catalysis can be achieved successfully with quite high regiocontrol using the sacrificial anode procedure.[13] We have shown that this reaction can be performed efficiently in mild reaction conditions and in one operation to give the addition products with high functional compatibility. We have now extended the method to the alkenylation of activated olefins with the aim of examining the scope of the reaction and its regio- and stereochemical features.

The reaction conditions used for performing the nickel-catalyzed electrochemical conjugate addition of alk-1-enyl halides are based on those used for the arylation reactions. They have, however, been optimized with methyl vinyl ketone (**2**, EWG = COMe) and (*Z*)- or (*E*)-1-halohept-1-ene **1** (X = Cl, Br, I) as model reagents.

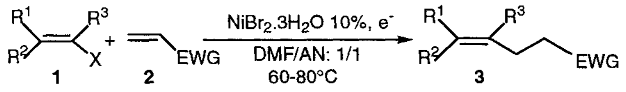


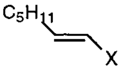
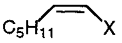
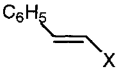
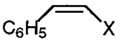
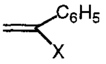
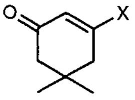
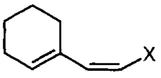
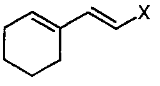
1 (1 eq.) **2** (2.5 eq.) **3**

We found notably that a preelectrolysis involving the oxidation of the anode along with the reduction of 1,2-dibromoethane, followed by the electrolysis of the reagent mixture of **1** and **2** enabled the reaction yields to be improved by ca. 10–15% as compared to the electrolyses conducted without this preelectrolysis. The reactions were, thus, conducted in an undivided electrochemical cell fitted with an iron rod as the anode and a nickel grid as the cathode. A solution of 1,2-dibromoethane (0.90 mmol) in 28 mL of 1:1 mixture of dimethylformamide and acetonitrile was first electrolyzed for 0.5 hours at constant current density (ca. 0.3 Adm^{-2}) at room temperature. After addition of $NiBr_2 \cdot 3H_2O$ (0.80 mmol), the activated olefin (20 mmol), and the alkenyl halide (8 mmol), the solution was heated at 70 °C and the electrolysis was run at constant current density (ca. 0.3 Adm^{-2}) under argon until the halide had been consumed. In most cases, the faradaic yield for the conversion of the alkenyl halide was close to 100% on the basis of an overall two- electron reduction process.

Reactions were best conducted at ca. 70 °C; at a lower temperature (30–40 °C), the organic halide was consumed, but a lower yield of the addition product was obtained (Table 1, entry 5[c]) along with the reduction product of the alkenyl halide. During the course of the reaction the current density was kept relatively low (0.3 Adm^{-2}) in order to drive the catalytic process selectively and thus avoid direct reduction of the starting reagents. Two solvent mixtures were tested. The alkenylation reaction occurs cleanly and affords the conjugate addition product in high and identical isolated yield in either a mixture of DMF/pyridine in 9:1 (v/v) ratio or DMF/acetonitrile in 1:1 (v/v) ratio. We previously found that the DMF/pyridine mixture was the most satisfactory combination for the arylation of activated olefins from aryl halides.[12] Since yields are similar for the alkenylation reaction, we only give in this paper the results obtained in DMF/acetonitrile. It is noteworthy that no emulsion forms during the work up when pyridine is replaced by acetonitrile. In addition, it should be noted that pyridine is hardly acceptable in industrial processes. Acetonitrile, as well as pyridine, most probably stabilizes the electrochemically formed low-valent nickel essential for the course of the reaction. In the absence of a nickel salt alkenylation can only occur if the iron consumable anode is replaced by a stainless steel (Fe/Ni% = 64:36) rod (entry 5[d]). Indeed, the small amount of $NiBr_2$ released by the oxidation of the stainless steel rod during the preelectrolysis stage can catalyze, in

Table 1. Stereoselective Alkenylation of Electron-Deficient Olefins



Entry	Haloalkene 1	X	EWG in 2	Product	Isomeric Purity[a] (Z/E)	Yield[b] (%)
1		Cl	COMe	3a[14]	0:100	49
2		Br	–		0:100	77
3		I	–		0:100	80
4		Br	COMe	3b[15]	100:0	77
5[c,d]		I	–		100:0	81
6[e]		Br	COMe	3c[16]	7:93	73
7		Br	COMe	3d	97:3	84
8			CN	3e[17]	98:2	68
9			CO$_2$Et	3f	95:5	76
10		Br	COMe	3g[18]	–	61
11			CO$_2$Et	3h	–	60
12		Cl	COMe	3i	–	60
13		Br			–	75
14		I	COMe	3j	94:6	50
15		I	COMe	3k	0:100	71

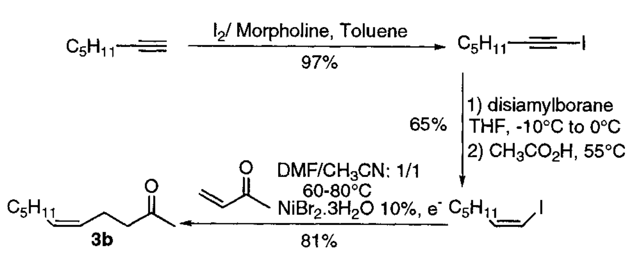
[a] Crude product. [b] Isolated yield of isomerically pure 3. [c] Yield 52 %, when performed at 30 °C. [d] Yield 52 %, in the presence of a stainless steel rod as a nickel ions supplier. [e] β-Bromostyrene is a commercial product of Z/E-isomers in ratio 10 : 90.

the next stage, the alkenylation after addition of the reagents. However, the continuous release of NiBr$_2$ from the stainless steel rod is not effective enough to perform the reaction in good yield.

Although the role of the iron ions released by the oxidation of the iron rod during the preelectrolysis is not very clear, no retardation was observed in the conversion of the organic halide at the very beginning of the electrolysis. These ions, which are continuously generated during the electrolysis, may play the role of a Lewis acid in activating the electron-deficient olefin to facilitate the carbon–carbon bond formation.

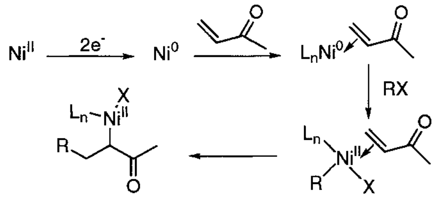
In order to compare the reactivity of various halides and study the stereochemistry of the alkenylation, geometrically pure alkenyl halides were prepared according to classical procedures (Table 1). Alkenyl bromides gave the same yields as alkenyl iodides (entries 2–3) and higher yields than alkenyl chlorides (entry 1). No differences in the course of the reaction or in the yield were observed between (*Z*)- or (*E*)-alkenyl halides (entries 2–5). A single stereoisomer was formed with the same double-bond stereochemistry as that of the reagent. A slight loss of stereoselectivity, as determined by GC analysis, was observed only in the case of (*Z*)-β-bromostyrene (entries 7–9). Conjugate addition to acrylonitrile (entry 8) and ethyl acrylate (entry 9) was also readily achieved. Several other alkenyl halides including β-halogenated enones were tested in the reaction with methyl vinyl ketone and were thus attached stereoselectively in good to high yields (entries 10–13). Functionalized conjugated dienes were also prepared with high stereoselectivity from (*Z*)- and (*E*)-halodienes (entries 14–15).

A straightforward preparation of (*Z*)-undec-5-en-2-one (**3b**), a pheromone from the pedal gland of the Bontebok (*Damaliscus dorcas dorcas*),[14] illustrates the usefulness of the method.



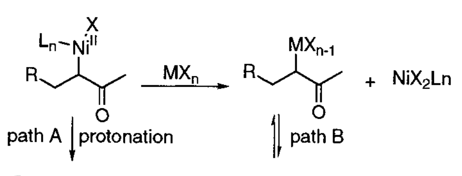
Upon reaction with the iodine–morpholine complex, heptyne was converted into the nearly pure 1-iodohept-1-yne (97 % crude product) which was then readily reduced by disiamylborane to afford (*Z*)-1-iodohept-1-ene (65 % overall yield). The pure (*Z*)-1-iodohept-1-ene underwent an alkenylation reaction in the presence of methyl vinyl ketone and NiBr$_2$ · 3H$_2$O by the consumable anode procedure to give compound **3b** (81 %) with high stereoisomeric purity.

Although the mechanism of the addition process remains to be elucidated, a possible reaction mechanism (Scheme 1) would involve the coordination of the activated olefin to the electrochemically formed nickel(0) species. Then an organonickel complex arises by oxidative addition of the vinyl halide to the catalyst, followed by an insertion reaction.



Scheme 1

The fate of this new organonickel complex is still unclear. Either protonation by residual water (path A) occurs to afford the addition product, or the ions released by the oxidation of the anode undergo a transmetalation reaction (path B), these two routes contributing to the recycling of Ni(II) (Scheme 2).



Scheme 2

In conclusion, we have reported a new efficient method for the preparation of unsaturated functionalized olefins in one operation from alkenyl halides and activated olefins (Table 1). This reaction proceeds under mild conditions and is highly regio- and stereoselective: no traces of 1,2-addition product were observed and the main stereoisomer was formed with the same configuration as the starting material. Application of this procedure has been illustrated by the short synthesis of the pheromone of Bontebok which is very competitive as compared to the known syntheses.[15]

GC analysis was carried out using a 25-m DB-1 capillary column. Column chromatography was performed on silica gel, 70–230 mesh. NMR samples were recorded in $CDCl_3$. Elemental analyses were made by the Service Central de Microanalyses (CNRS, Lyon).

The electrochemical cell has been described previously.[13]

Unless indicated, all solvents and reagents were purchased and used without further purification. DMF and MeCN were stored under argon.

(*E*)-1-Bromo-, (*E*)-1-iodohept-1-ene and (*E*)-2-cyclohex-1-enyl-1-iodoethene were prepared from the commercially available corresponding alkynes via hydroalumination reaction.[19] (*E*)-1-Chlorohept-1-ene was obtained by reaction of (*E*)-1-iodohept-1-ene with copper(I) chloride.[20] (*Z*)-1-Iodohept-1-ene and (*Z*)-2-cyclohex-1-enyl-1-iodoethene were prepared from the corresponding 1-iodoalk-1-yne[21] followed by hydroboration reaction[22] and acidic work-up. (*Z*)-β-Bromostyrene and (*Z*)-1-bromohept-1-ene were prepared respectively by bromination of cinnamic acid and (*E*)-oct-2-enoic acid followed by decarboxylative elimination in alkaline conditions.[23] 3-Bromo- and 3-chloro-5,5-dimethylcyclohex-2-en-1-one were prepared by a new procedure[24] developed in this laboratory. β-Bromostyrene (Table 1, entry 6) and α-bromostyrene are commercial products and were used without any purification. β-Bromostyrene was a mixture of *Z*/*E*-isomers in 10:90 ratio.

All vinyl halides prepared were isomerically pure. The vinylic signals in the ^{1}H and ^{13}C NMR spectra for the (*Z*)- or (*E*)-stereoisomers were different enough to allow the stereochemical assignment. The measure of the *Z*/*E*-stereoisomer ratio of the product was made by GC analysis of crude samples.

Table 2. Compounds **3d–k** Prepared[a]

Product	IR (NaCl) ν (cm^{-1})	^{1}H NMR (250 MHz, $CDCl_3$) δ, J (Hz)	^{13}C NMR (50.32 MHz, $CDCl_3$) δ	MS m/z (%)
3d	3080, 3030, 1730, 1600, 1500, 1450, 770, 700	1.94 (s, 3H), 2.34–2.51 (m, 4H), 5.45 (dt, 1H, J = 11.6, 6.9), 6.69 (d, 1H, J = 11.6), 7.05–7.23 (m, 5H)	22.8, 29.7, 43.5, 126.7, 128.2, 128.7, 129.8, 130.7, 137.2, 207.7	175 (100), 174 (95), 131 (43), 117 (48)
3f	3080, 3060, 1740, 1600, 1450, 770, 700	1.40 (t, 3H, J = 7.1), 2.59 (t, 2H, J = 7.1), 2.85 (q, 2H, J = 7.1), 4.29 (q, 2H, J = 7.1), 5.81 (dt, 1H, J = 11.6, 7.1), 6.65 (d, 1H, J = 11.6), 7.34–7.54 (m, 5H)	13.9, 23.8, 34.0, 60.0, 125.8, 127.9, 128.4, 129.8, 130.1, 136.9, 172.4	205 (14), 204 (20), 130 (62), 117 (53), 115 (100), 91 (88)
3h	3080, 2980, 1740, 1630, 1490, 1450, 1380, 1160, 900, 770, 710	1.21 (t, 3H, J = 7.1), 2.45 (t, 2H, J = 7.7), 2.84 (t, 2H, J = 7.7), 4.09 (q, 2H, J = 7.1), 5.08 (s, 1H), 5.30 (s, 1H), 7.20–7.42 (m, 5H)	14.0, 30.3, 33.0, 60.1, 112.5, 125.9, 127.4, 128.2, 140.4, 146.8, 172.6	204 (33), 159 (10), 131 (100)
3i	1720, 1670, 1640, 910	0.58 (s, 6H), 1.73 (m, 7H), 1.99 (m, 2H), 2.24 (m, 2H), 5.33 (s, 1H)	27.9 (2C), 29.6, 31.0, 33.2, 39.9, 43.7, 50.7, 123.9, 162.1, 199.1, 206.2	195 (52), 194 (21), 179 (16), 151 (64), 95 (100)
3j	3020, 1720, 1620, 920, 840, 730	1.38–1.59 (m, 4H), 2.02–2.09 (m, 7H), 2.46 (m, 4H), 5.13 (m, 1H), 5.57 (br s, 1H), 5.71 (d, 1H, J = 11.7)	22.0, 22.7, 23.1, 25.4, 28.8, 29.6, 44.0, 127.0, 127.4, 132.6, 134.9, 207.8	178 (9), 161 (20), 135 (28), 91 (100), 77 (70)
3k	3030, 1720, 960, 920, 780	1.47–1.63 (m, 4H), 1.98–2.03 (m, 4H), 2.07 (s, 3H), 2.29 (m, 2H), 2.46 (m, 2H), 5.43 (dt, 1H, J = 15.6, 6.7), 5.57 (br s, 1H), 5.97 (d, 1H, J = 15.6)	22.3, 22.4, 24.3, 25.5, 26.8, 29.6, 43.3, 124.1, 127.6, 134.2, 135.13, 207.7	178 (8), 161 (10), 135 (23), 91 (94), 77 (100)

[a] All products are oils.

Nickel-Catalyzed Electroreductive Coupling; General Procedure:
In an undivided cell equipped with a nickel grid (area 30 cm^2) as the cathode and an iron rod as the anode, under argon, Bu_4NBr (0.34 mmol) and Bu_4NI (0.21 mmol) were dissolved as supporting electrolytes in a mixture of DMF (14 mL) and MeCN (14 mL). 1,2-Dibromoethane (0.90 mmol) was introduced. A short electrolysis was run at constant current density (0.3 Adm^{-2}) and at r.t. over 30 min to generate a small amount of iron ions. Then the current was turned off. $NiBr_2 \cdot 3\ H_2O$ (0.80 mmol) and activated olefin **2** (20 mmol) were added; the mixture was heated at 70 °C and alkenyl halide **1** (8 mmol) was added. The electrosynthesis was run at constant current density (0.3 Adm^{-2}). The reaction was monitored by GC and stopped after alkenyl halide **1** was consumed (ca. 4.5 h). A charge of 2 Fmol^{-1} was used in most reactions described in this paper. The mixture was then hydrolyzed with 1 M HCl (20 mL) and diluted with Et_2O (40 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL), the combined organic layers were washed with H_2O and sat. NaCl, dried ($MgSO_4$), and the solvent was evaporated. The oil thus obtained was purified by column chromatography to give compounds **3a–k**.

Anal. Calcd for **3d**: C, 82.72; H, 8.10. Found: C, 82.82; H, 8.09.
Anal. Calcd for **3f**: C, 76.44; H, 7.79. Found: C, 76.45; H, 8.15.
Anal. Calcd for **3h**: C, 76.44; H, 7.89. Found: C, 76.70; H, 8.04.
Anal. Calcd for **3i**: C, 74.19; H, 9.34. Found: C, 74.16; H, 9.42.
Anal. Calcd for **3k**: C, 80.85; H, 10.17. Found: C, 80.61; H, 10.45.

Spectal data are given in Table 2.

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