

Metal Exchange between an Electrogenerated Organonickel Species and Zinc Halide: Application to an Electrochemical, Nickel-Catalyzed Reformatsky Reaction

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The mechanism of the electroreductive coupling of α -chloro esters or α -chloro nitriles with carbonyl compounds by the means of a sacrificial zinc anode and a nickel catalyst was elucidated by electroanalytical techniques. The mechanism involved reduction of a Ni(II) complex to a Ni(0) complex, oxidative addition of the α -chloro ester to the Ni(0) complex, and a Zn(II)/Ni(II) exchange, leading to an organozinc Reformatsky reagent. The electro-synthesis of various β -hydroxy esters, β -hydroxy nitriles, and 2,3-epoxy esters was successfully achieved under extremely mild conditions.

Introduction

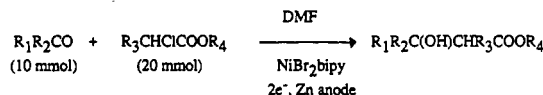
Recent research on the Reformatsky reaction, the reaction of an aldehyde or a ketone, an α -halo ester, and zinc metal to yield a β -hydroxy ester, has focused on the development of methods for the preparation of highly active forms of metallic zinc. This research has been the subject of several recent reviews.¹ Among the activation procedures that have been employed were the reduction of a zinc halide by an alkali metal to yield finely divided metallic zinc,² the use of Zn/Ag³ or Zn/Cu⁴ couples, and ultrasonic irradiation of the reaction mixture.⁵ The main problems encountered in the initiation and regulation of the reaction were related to the heterogeneity of the reaction mixture.

The convenient use of sacrificial magnesium, aluminum, or zinc anodes in the electroreductive coupling of organic halides with electrophiles has been recently reported, and the similarities to classical organometallic synthesis have been outlined.⁶

The electrosynthesis of alcohols from organic halides and carbonyl compounds has been described.⁷ For example, although the desired alcohol could be obtained in moderate yield from methyl α -chloropropionate and acetone by use of a magnesium anode, methyl α -chloroacetate coupled with carbonyl compounds only when a zinc anode was used. However, acid-base side reactions leading to epoxides and aldol condensation products and competitive zinc electrodeposition severely restricted the usefulness of the procedure. However, we found that the use of a zinc anode together with a catalytic amount of nickel(II)-bipyridine complex allowed the selective, high-yield coupling of methyl α -chloroacetate with carbonyl compounds.⁸

We now report the results of an investigation of the mechanism of this new reaction. An electrochemical study of the process gave evidence for a mechanism involving, as a key step, a metal exchange between anodically generated Zn(II) and a cathodically formed organonickel

Scheme I



complex. Such an exchange has been hypothesized to occur in the nickel-catalyzed electroreductive coupling of allylic chlorides with ketones.⁹ A Reformatsky reagent was easily obtained from α -chloro esters by this electrochemical process, which possessed all the advantages of reaction in a homogeneous medium.

The new procedure was applied to α -chloro esters, α,α -dichloroacetates, and α -chloro nitriles to yield, respectively, β -hydroxy esters, 2,3-epoxy esters, and β -hydroxy nitriles.

Results and Discussion

Mechanism of the Nickel-Catalyzed Electrochemical Coupling of α -Chloro Esters and Carbonyl Compounds. As has already been reported,⁸ the electrochemical system was characterized by two main features: an undivided electrolysis cell fitted with a zinc anode and a carbon cathode connected to a constant-current supply and an electrolysis solution containing a catalytic amount (5–10%) of NiBr₂(bipy) complex (bipy = 2,2'-bipyridine), α -chloro ester (2 equiv), and carbonyl compound (1 equiv), all dissolved in *N,N*-dimethylformamide (DMF) (Scheme I).

The effects of the solvent, the catalyst, and the metal of anode on the chemical and faradaic yields of methyl 3-ethyl-3-hydroxy-2-methylpentanoate (prepared from 3-pentanone and methyl α -chloropropionate) were determined. The metal of the anode was the critical factor in the process. Although the yield of hydroxy ester was 75% (based on ketone) with a zinc anode, only 8% yield was obtained with an aluminum anode and only traces of product were detected with a magnesium anode. Moreover, the presence in the reaction mixture of a small amount (5 mmol) of ZnBr₂ enhanced the yield to 82% when a zinc anode was employed. As the catalyst, Ni(bipy)₃(BF₄)₂ served as well as, or better than, NiBr₂(bipy). Changing the catalyst from a bipyridine complex to a phosphine complex such as NiCl₂(PPh₃)₂ or NiCl₂(Ph₂PCH₂CH₂PPh₂) or even omitting the catalyst caused only a modest decrease in the chemical yield. However, the faradaic yield was deeply affected, for an important competitive zinc deposition was observed. The electrolysis required a solvent that could readily dissolve inorganic salts and thus permit high electrical conductivity. Among the various

(1) (a) Fürstner, A. *Synthesis* 1989, 571. (b) Rathke, M. W. *Org. React.* 1975, 22, 423. (c) Gaudemar, M. *Organomet. Chem. Rev.* 1972, 8, 183.

(2) (a) Rieke, R. D.; Uhm, S. J.; Hudnall, P. M. *J. Chem. Soc., Chem. Commun.* 1973, 269. (b) Chao, L. C.; Rieke, R. D. *J. Org. Chem.* 1975, 40, 2253. (c) Rieke, R. D.; Uhm, S. J. *Synthesis* 1975, 452. (d) Rieke, R. D.; Li, P. T.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* 1981, 46, 4323.

(3) Bortolussi, M.; Seyden-Penne, J. *Synth. Commun.* 1989, 19, 2355.

(4) Santaniello, E.; Manzocchi, A. *Synthesis* 1977, 698.

(5) (a) Han, B. H.; Boudjouk, P. *J. Org. Chem.* 1982, 47, 5030. (b) Boudjouk, P.; Thompson, D. P.; Ohrbom, W. H.; Han, B. H. *Organometallics* 1986, 5, 1257.

(6) Chaussard, J.; Folest, J. C.; Nedelec, J. Y.; Périchon, J.; Sibille, S.; Troupel, M. *Synthesis* 1990, 5, 369.

(7) Sibille, S.; D'Incan, E.; Lepout, L.; Périchon, J. *Tetrahedron Lett.* 1986, 27, 3129.

(8) Sibille, S.; D'Incan, E.; Lepout, L.; Massebieau, M. C.; Périchon, J. *Tetrahedron Lett.* 1987, 28, 55.

(9) Durandetti, S.; Sibille, S.; Périchon, J. *J. Org. Chem.* 1989, 54, 2198.

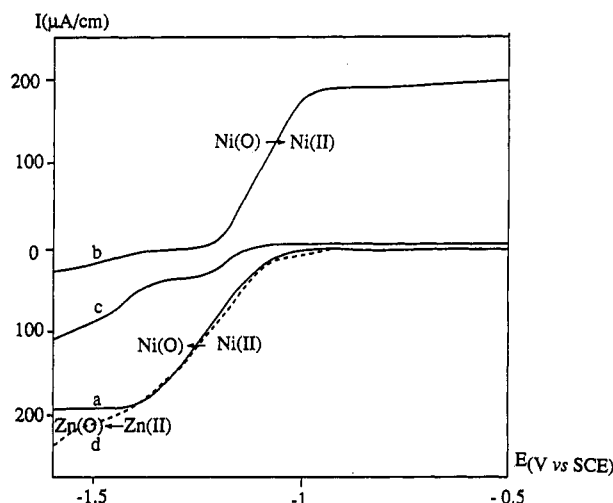
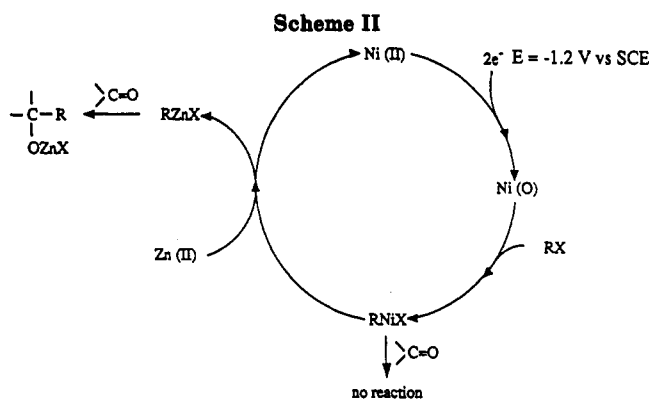
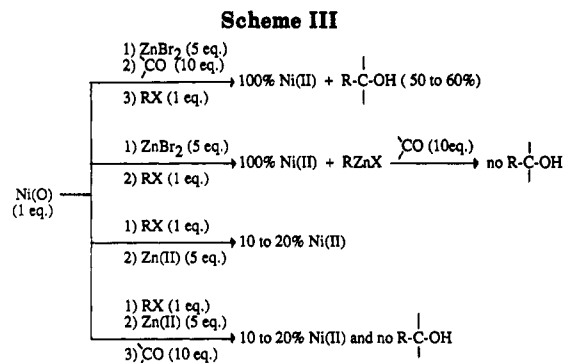


Figure 1. Rotating-disk voltammetry with a gold electrode of a solution of 0.1 M NBu_4BF_4 in DMF (30 mL): (a) $\text{NiBr}_2(\text{bipy})$ (0.5 mmol) + bipy (1 mmol); (b) Ni(0)(bipy)_2 (0.5 mmol) obtained by potentiostatic electrolysis at $E = 1.2$ V vs SCE [$Q = 2$ faradays/mol of Ni(II)]; (c) 1 equiv of α -chloro ester [relative to Ni(0)] added to the Ni(0) solution; (d) 2 equiv of ZnBr_2 and then 1 equiv of α -chloro ester [relative to Ni(0)] added to the Ni(0) solution.

solvents tested, neat DMF and 90:10 dichloromethane/DMF proved to be the most useful for a high-yield synthesis.

Voltammetric experiments were performed in DMF to determine the predominant roles of nickel catalyst and the Zn(II) species in the process. Of all the species present, the nickel(II)-bipyridine complex was the most readily reduced. Therefore, the first step of the reaction must have been a two-electron quasi-reversible reduction of Ni(II) to Ni(0) at -1.2 V vs SCE (Scheme II). In fact, during the electrolysis, the potential of the cathode was well-defined and ranged between -0.9 and -1.2 V vs SCE.

Therefore, to gain further insight into the catalytic process, a stoichiometric step-by-step procedure, using a two-compartment cell, was followed. Exhaustive potentiostatic electrolysis at -1.2 V vs SCE of the $\text{Ni(II)(bipy)}_3^{2+}$ solution (Figure 1a) gave a Ni(0) complex in 80–95% yield, as determined by amperometric measurements (Figure 1b). When an α -chloro ester, RX , was added to a solution of the Ni(0) complex, a fast bimolecular reaction,¹⁰ which could formally give an organonickel species, RNiX ¹¹ (Scheme II), ensued. As would be expected for such an



organonickel complex,¹² a reduction wave was observed at about -1.5 V vs SCE (Figure 1c). The nucleophilic addition of this organonickel species to the ketone was not observed, even when the ketone was present in the Ni(0) solution before RX was introduced.

Potentiostatic electrolyses were performed, in a divided cell, of solutions containing the Ni(II) complex, a 20-fold molar excess of methyl α -chloropropionate, and a 10-fold molar excess of ketone. At -1.2 V vs SCE, these electrolyses are not catalytic: only 2–2.5 faradays/mol of nickel was consumed. At the reduction potential of RNiX (-1.5 V vs SCE), up to 20 faradays/mol of nickel was consumed, but only traces of product β -hydroxy ester were detected.¹³ Therefore, neither RNiX nor its reduction product added to the ketone in the absence of zinc salts.

In contrast, when a stoichiometric amount of the α -chloro ester was added to a Ni(0) solution that also contained ZnBr_2 (5 equiv), a complete regeneration of $\text{Ni(II)(bipy)}_3^{2+}$ was observed, as indicated by its reduction wave (Figure 1d). The Ni(II) complex could be reduced further to Ni(0) , which accounted for the recycling of the catalyst and the invariability of the cathode potential during the electrolysis. These results suggested that there was a metal-exchange reaction between RNiX and ZnBr_2 to give Ni(II) and an organozinc species, RZnX (Scheme II). The latter was the real intermediate in the coupling reaction. If this reaction sequence was repeated with the ketone already present in the electrolysis solution, the desired β -hydroxy ester was obtained in good yield (50–60%).¹⁴

Thus, the reaction probably involved a catalytic cycle that included Ni(II) reduction to Ni(0) , oxidative addition of the α -chloro ester to the Ni(0) complex, transmetalation with regeneration of Ni(II) , and nucleophilic addition of RZnX so produced to the ketone (Scheme II). Such a mechanism would explain the paramount role of both the sacrificial zinc anode and the catalytic Ni(II) species in the electrochemical process.

It is intriguing that, in the stoichiometric step-by-step procedure, both Zn(II) and the ketone must be present in the reaction mixture before Ni(0) and α -chloro ester react further. Less than 20% of Ni(II) was recovered if Zn(II) was added after introduction of the α -chloro ester, and the alcohol did not form at all if the ketone was introduced at the end of the sequence (Scheme III). Also, no reaction was observed upon introduction of iodine, iodomethane,¹⁵

(12) a) Troupel, M.; Rollin, Y.; Sibille, S.; Périchon, J. *J. Organomet. Chem.* 1980, 202, 435. (b) Meyer, G.; Rollin, Y.; Périchon, J. *J. Organomet. Chem.* 1987, 333, 263.

(13) Note: Condensation between the reduced chloro ester and the ketone occurred, but the main product recovered was the alkene or the 2,3-epoxy ester.

(14) Note: The procedure was tested with methyl 2-chloropropionate or ethyl α -chloroacetate and either 3-pentanone, cyclohexanone, or acetophenone.

(10) Note: Amperometric titration of the Ni(0) complex after addition of a stoichiometric amount of methyl α -chloroacetate at 0°C gave a rate constant for the oxidative addition of ca. $150\text{ M}^{-1}\text{ s}^{-1}$.

(11) (a) Rollin, Y.; Troupel, M.; Tuck, D. G.; Périchon, J. *J. Organomet. Chem.* 1986, 303, 131. (b) Mabrouk, S.; Pellegrini, S.; Folest, J. C.; Rollin, Y.; Périchon, J. *J. Organomet. Chem.* 1986, 301, 391.

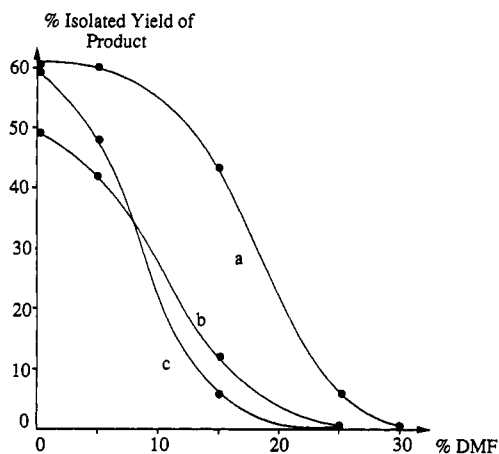


Figure 2. Influence of the DMF content of the solvent on the reaction of $\text{BrZnCH}_2\text{COOCH}_2\text{CH}_3$ with 3-pentanone or iodine: (a) reaction with 3-pentanone in $\text{CH}_2\text{Cl}_2/\text{DMF}$; (b) reaction with iodine in $\text{CH}_2\text{Cl}_2/\text{DMF}$; (c) reaction with 3-pentanone in methylal/DMF.

or allyl bromide¹⁶ to the RZnX solution.

Extensive studies have dealt with structure and reactivity of the Reformatsky reagent in various solvents, including methylal, tetrahydrofuran (THF), benzene, dimethyl sulfoxide (DMSO), and hexamethylphosphoramide (HMPA).¹⁷ However, the behavior of the reagent in *N,N*-dimethylformamide (DMF) has not been studied. So, in order to discover the reasons for the lack of reactivity of the electrogenerated organozinc species in DMF, the reactivity in that solvent of the classical chemical Reformatsky reagent, formed from ethyl α -bromoacetate and zinc powder, was investigated. The α -bromo ester readily reacted with the metal in DMF, and the desired β -hydroxy ester was obtained from 3-pentanone in 32% yield in one step. However in a two-step procedure, i.e., when the ketone or iodine was introduced after formation of the organozinc, no reaction occurred. In both cases, the only product recovered after acid hydrolysis was ethyl acetate. In contrast, in methylal or CH_2Cl_2 , the organozinc species did react with subsequently introduced 3-pentanone or iodine to give the expected products in good yield (Figure 2). Furthermore, various methylal/DMF or $\text{CH}_2\text{Cl}_2/\text{DMF}$ mixtures caused a decrease in yield, which could be related to the DMF content of the solvent (Figure 2). In solvents containing 20–25% DMF, the organozinc species no longer reacted with iodine or the ketone. No degradation product, other than ethyl acetate, was detected after acid hydrolysis.

Thus, in the presence of DMF, the behavior of both the electrogenerated and the chemical Reformatsky reagent was the same. The product β -hydroxy ester was obtained only if the ketone was present prior to organozinc formation. A strong coordination of zinc(II) in the organometallic compound with DMF could explain this loss of reactivity. This behavior may be related to the coexistence of C–Zn and O–Zn bonds arising from the bidentate nature of the ester anion.

α -Halo nitriles can also participate in Reformatsky reactions,¹⁸ but a nitrile group would be expected to behave differently from an ester group in a complex organometallic structure.

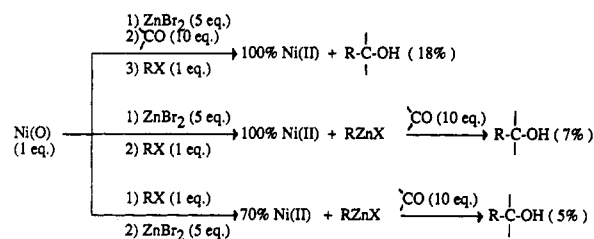
In contrast to α -bromo esters, the chemical reaction of α -bromoacetonitrile, zinc powder, and 3-pentanone could

Table I. Chemical and Electrochemical Reaction of α -Halo Nitriles with 3-Pentanone in DMF

entry	method ^a	α -halo nitrile	RX:CO	isolated yield (%)
1	A ₁	BrCH_2CN	1:3	32 ^b
2	A ₂	BrCH_2CN	1:3	28 ^b
3	B ₁	ClCH_2CN	4.5:1.0	20 ^c
4	B ₁	CH_3CHClCN	2.5:1.0	52 ^c
5	B ₂	ClCH_2CN	1:3	8 ^b
6	B ₂	CH_3CHClCN	1:3	12 ^b
7	C ₁	CH_3CHClCN		18 ^b
8	C ₂	CH_3CHClCN		7 ^b

^a(A) Chemical procedure: 1, one-step procedure; 2, two-step procedure. (B) Electrosynthetic procedure: 1, standard procedure; 2, standard procedure except that the ketone (60 mmol) was added after the α -chloro nitrile had been consumed (GC monitoring). (C) Stoichiometric step-by-step procedure: 1, standard procedure; 2, standard procedure except the ketone (60 mmol) was added after the α -chloro nitrile had been consumed (GC monitoring). ^b Isolated yield based on α -halo nitrile. ^c Isolated yield based on ketone.

Scheme IV



be performed in either one or two steps in DMF (Table I, entries 1 and 2). The organozinc BrZnCH_2CN appeared to be reactive in this solvent. The electrochemical procedure was also extended to include α -chloroacetonitrile and α -chloropropionitrile, which yielded β -hydroxy nitriles in moderate yield (Table I, entries 3 and 4).

The stoichiometric step-by-step electrochemical procedure described above was also carried out in DMF with essentially the same results as those obtained with α -chloro esters (Scheme IV). The main difference involved the reactivity of the two intermediate organometallic species. Ni(II) was recovered in large amounts (70% of the initially formed complex) even if ZnBr_2 was introduced after RNiX formation. When the ketone was introduced after nickel–zinc exchange, the alcohol was obtained in low but still significant yield (Table I, entry 8).

Moreover, the electrogenerated organozinc reagent was stable in DMF and reacted with the ketone introduced subsequently (Table I, entries 5 and 6).

The experiments with α -chloro nitriles clearly indicated that both RNiX and RZnX were involved as intermediates and, therefore, metal exchange did occur. It could be assumed that, in the case of the α -chloro esters, the lack of reactivity of the organometallic species was related to metal ion–solvent interactions and that Scheme II truly represented the catalytic cycle in the electrochemical Reformatsky reaction over the chemical process was mainly in the use, as reactants, of “ordinary” solid zinc rather than activated zinc and chloro derivatives rather than bromo derivatives. If, as pointed out in the preceding discussion, the solvents required by the electrochemical technique restricted the reactivity of the organometallic intermediates, they nevertheless were preferable to ethers and benzene. In fact, the lack of reactivity of the organozinc species in DMF could be overcome by the use of 2 equiv of α -chloro ester to 1 equiv of the ketone. It could be

(15) Orsini, F.; Pelizzoni, F.; Ricca, G. *Tetrahedron* 1984, 40, 2781.

(16) Orsini, F.; Pelizzoni, F. *Synth. Commun.* 1983, 13, 523.

(17) Gaudemar, G.; Martin, M. C. R. *Acad. Sci.* 1968, 267, 1053.

(18) Goasdoue, N.; Gaudemar, M. J. *Organomet. Chem.* 1972, 39, 17.

Table II. Nickel-Catalyzed Electrolytic Coupling of Methyl α -Chloropropionate with Ketones and Aldehydes

R_1R_2CO		α -chloro ester:ketone or aldehyde	isolated yield ^a (%)
R_1	R_2		
CH_3CH_2	CH_3CH_2	2.5:1.0	82.5
$CH_3(CH_2)_2$	CH_3	2:1	87.5 ^c
$-(CH_2)_5-$	CH_3	2:1	64
$-CH=CH(CH_2)_3-$	CH_3	2:1	72
C_6H_5	CH_3	2:1	50
C_6H_5	CH_3	2:1	89
C_6H_5	C_6H_5	2:1	71 ^c
$(CH_3)_2C=CH(CH_2)_2$	CH_3	2:1	60
$(CH_3)_3C$	CH_3	2:1	83
$(CH_3)_2CH$	$(CH_3)_2CH$	5:1	trace ^b
C_6H_5	H	2:1	trace ^b
$(CH_3)_3C$	H	2:1	80
$(CH_3)_2CH$	H	2:1	59
		2:1	55

^a Isolated yield based on ketone or aldehyde. ^b The ketone was recovered. ^c 90:10 CH_2Cl_2 /DMF as solvent.

Table III. Nickel-Catalyzed Electrolytic Coupling of Ethyl α -Chloroacetate with Ketones and Aldehydes

R_1R_2CO		α -chloro ester:ketone or aldehyde	isolated yield ^a (%)
R_1	R_2		
CH_3CH_2	CH_3CH_2	3:1	77
$CH_3(CH_2)_2$	CH_3	3:1	71 ^b
$-(CH_2)_5-$	CH_3	2.5:1.0	89
$-CH=CH(CH_2)_3-$	CH_3	2:1	86
C_6H_5	CH_3	2:1	50
C_6H_5	CH_3	2:1	84
C_6H_5	C_6H_5	2:1	84 ^b
$(CH_3)_2C=CH(CH_2)_2$	CH_3	3:1	77
$(CH_3)_3C$	CH_3	2.5:1.0	76
$(CH_3)_2CH$	CH_3	5:1	38
	$(CH_3)_2CH$	7:1	10
			11 ^b
C_6H_5	H	2:1	46
$(CH_3)_3C$	H	2:1	37

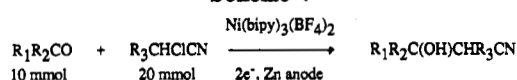
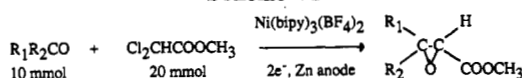
^a Isolated yield based on ketone or aldehyde. ^b 90:10 CH_2Cl_2 /DMF as solvent.

assumed that the excess α -chloro ester was present in DMF solution in the form of an unreactive zinc derivative and that it was recovered as a chlorine-free ester upon hydrolysis.

Synthetic Applications. (a) α -Chloro Esters. The results of the electrochemical addition of methyl α -chloropropionate to various ketones under optimum reaction conditions are presented in Table II. Aromatic as well as aliphatic ketones gave good yields of β -hydroxy esters. Lower yields were obtained with 2-cyclohexen-1-one due to a polymerization side reaction. No conjugate addition was observed. With a hindered ketone (pinacolone and diisopropyl ketone), coupling failed and the ketone was recovered at the end of the electrolysis.

Ethyl α -chloroacetate also gave good yields of β -hydroxy esters (Table III). The lower steric requirements of the chloroacetate compared to the chloropropionate allowed coupling with pinacolone and diisopropyl ketone, although in low yield. Comparable results were obtained with neat DMF and CH_2Cl_2 /DMF mixtures.

Difficulties were encountered when the of coupling α -chloroacetate or α -chloropropionate with aldehydes was attempted. The reaction was not selective, and a variety of products was obtained. Besides the expected β -hydroxy esters, dehydration products, epoxides, and, in some cases, aldol condensation products were all formed in significant yield. In fact, the byproducts were the same as those obtained when the electroreductive coupling was per-

Scheme V**Scheme VI****Table IV. Nickel-Catalyzed Electrolytic Coupling of α -Chloro Nitriles with Ketones**

R_1R_2CO		$R_3CH(Cl)CNH$	isolated yield ^a (%)
R_1	R_2		
CH_3CH_2	CH_3CH_2	H	20
C_6H_5	CH_3	H	36
		H	36 ^b
$-(CH_2)_5-$		H	24
CH_3CH_2	CH_3CH_2	CH_3	52
C_6H_5	CH_3	CH_3	72
		CH_3	57 ^b
C_6H_5	C_6H_5	CH_3	50
$-(CH_2)_5-$		CH_3	59

^a Isolated yield based on ketone. ^b 90:10 CH_2Cl_2 /DMF as solvent.

formed in the absence of nickel catalyst. The main side reaction apparently resulted from the basicity of the anion derived from the ester. Ni(0) species are known to form complexes with aldehydes¹⁹ and to catalyze aldol condensation reactions.²⁰ Indeed, electrochemical experiments showed that Ni(0)(bipy)₂ reacted with benzaldehyde or trimethylacetaldehyde and that the resulting complexes still reacted with the α -chloro ester, but at a slower rate than Ni(0)(bipy)₂ ($k = 15\ M^{-1}\ s^{-1}$ instead of $k = 150\ M^{-1}\ s^{-1}$). It was believed that a lower electrolysis intensity (100 mA instead of 200 mA) or a higher Ni(II) complex concentration would allow better recycling of the catalyst. Indeed, with such modifications, the side reactions were suppressed (Tables II and III). However, the product β -hydroxy esters were partially esterified. Acetates, chloroacetates, propionates, and chloropropionates were all obtained in significant yield. Although the electrocoupling of aldehydes was less selective than that of ketones, it confirmed the importance of the oxidative addition step in the proposed mechanism.

(b) α -Chloro Nitriles. α -Chloroacetonitrile and α -chloropropionitrile were able to participate in the catalytic cycle. The yields of β -hydroxy nitriles (Scheme V), collected in Table IV, were only moderate to good. As in the chemical synthesis from Zn metal and α -bromo nitriles,¹⁸ better results were obtained with α -chloropropionitrile than with α -chloroacetonitrile. The organozinc derivatives of the α -chloro nitriles seemed to be more alkaline than those of the α -chloro esters, because the ketone was not recovered at the end of the electrolysis, but rather underwent base-catalyzed polymerization. As a solvent, CH_2Cl_2 /DMF mixtures were as suitable as neat DMF.

(c) Methyl α,α -Dichloroacetate. Although the chemical Reformatsky reaction apparently fails with polyhaloesters,²¹ the electrochemical process, when applied to methyl α,α -dichloroacetate and ketones, gave 2,3-epoxy esters in high yield (Table V; Scheme VI). With aldehydes, employment of the same procedural modifications as used for the monochloro esters (low electrolysis intensity

(19) Walther, D. Z. Chem. 1975, 15, 490.

(20) Walther, D.; Dinjus, E. Z. Anorg. Allg. Chem. 1978, 440, 22.

(21) Miller, R. E.; Nord, F. F. J. Org. Chem. 1951, 16, 728.

Table V. Nickel-Catalyzed Electrosynthesis of 2,3-Epoxy Esters from Methyl α,α -Dichloroacetate and Carbonyl Compounds as a Function of Solvent

R ₁ R ₂ CO		neat DMF		90:10 CH ₂ Cl ₂ /DMF	
		isolated yield ^a (%)	isomer ratio Z:E	isolated yield ^a (%)	isomer ratio Z:E
R ₁	R ₂				
CH ₃	CH ₃ CH ₂	73	60:40		
CH ₃ CH ₂	CH ₃ CH ₂			91	
	-(CH ₂) ₅ -	86		92	
C ₆ H ₅	CH ₃	58	82:18	84	62:38
C ₆ H ₅	C ₆ H ₅	65		65	
C ₆ H ₅	H	54	69:31	60	51:49
(CH ₃) ₃ C	H	61	39:61		
(CH ₃) ₂ CH	H	59	55:45		

^a Isolated yield based on ketone or aldehyde.

and high catalyst concentration) ensured selective coupling. The reaction could be performed in neat DMF or CH₂Cl₂/DMF mixtures.

In most cases, 2-chloro-3-hydroxy ester intermediates were detected. Addition of pyridine at the end of the electrolysis cleaved the alcoholate-Zn(II) bond and brought about ring closure. With unsymmetrical ketones, the reaction appeared to be no more stereoselective than the Darzens reaction. The slight changes in stereoselectivity between reactions performed in neat DMF and those performed in CH₂Cl₂ may have reflected only difficulties in effecting intramolecular cyclization of one of the diastereoisomeric chlorohydrins.

Conclusion

The important part played by the sacrificial zinc anode in the nickel-catalyzed electroreductive coupling of α -chloro esters and nitriles with aldehydes and ketones has been clearly demonstrated. That a metal exchange occurred between an organonickel species and zinc salts generated by the anodic oxidation has been substantiated by electrochemical analysis. Clear evidence for the existence of an organozinc species has been presented, at least for the case involving α -chloro nitriles, because reaction with iodine or carbonyl compounds did occur in a multistep manner. The transmetalation enabled the synthesis of a Reformatsky reagent from α -chloro esters and nitriles and a solid zinc anode. 2,3-Epoxy esters are readily obtained from methyl α,α -dichloroacetate, by the electrochemical process, which did not require the alkaline conditions of the Darzens synthesis.

The facile workup, the simplicity of the electrolysis system, and the possibility for large scale-up of the process have been reported.^{6,22} The electrosynthesis of β -hydroxy esters, β -hydroxy nitriles, and 2,3-epoxy esters thus appears to be an attractive alternative to the use of the classical Reformatsky reaction, for which careful activation of zinc is always necessary.

Experimental Section

Nickel bromide, nickel tetrafluoroborate, and zinc bromide were obtained from Alfa. ZnBr₂ was dried by heating overnight at 150 °C in a vacuum oven. Tetrabutylammonium bromide (Fluka) and 2,2'-bipyridine (Janssen) were commercially available. Zinc rod (Alfa), magnesium rod (Prolabo), aluminum rod (Alfa), and nickel wire (Alfa) served as anodes. The cathode was of carbon fiber. Other reagents were obtained from Aldrich or Janssen and were generally used as received. *N,N*-Dimethylformamide (Prolabo) was distilled from calcium hydride and then from copper sulfate under reduced pressure and was dried over molecular sieves

(4 Å). Dichloromethane (Prolabo) was stored over molecular sieves (4 Å). The reaction products were identified by the usual techniques. ¹H NMR spectra were recorded with a Varian EM 360L instrument at 200 and 300 MHz. TMS served as an internal standard. Mass spectra were recorded with an ITD Finnigan spectrometer coupled to a gas chromatograph (column 25 m CP Sil 5 capillary). Microanalyses were performed by the Service Central de Microanalyses (CNRS, Lyon).

Preparation of Ni(II) Complexes. NiBr₂(PPh₃)₂,^{23a} NiCl₂-(Ph₂PCH₂CH₂PPh₂),^{23b} NiBr₂(bipy),^{24a} and Ni(bipy)₃(BF₄)₂^{24b} were prepared according to literature methods.

General Procedure for the Electrosynthesis. The electrolysis cell has been described elsewhere.⁶ It was fitted with a carbon fiber cathode (20 cm²) and a zinc rod (1-cm diameter, immersed to 2 cm) anode. To neat DMF or 90:10 CH₂Cl₂/DMF mixture (30 mL) containing 1 mmol of NBu₄Br, 5 mmol of dry ZnBr₂, and 0.5 mmol of Ni(bipy)₃(BF₄)₂ (1 mmol for the coupling with aldehydes) were added α -chloro ester, α -chloro nitrile, or methyl α,α -dichloroacetate (20 mmol, or 10 mmol for the coupling with aldehydes) and the aldehyde or ketone (10 mmol, or 5 mmol for the coupling with aldehydes). Reactions were performed at room temperature, under argon. The electrolysis (*i* = 200 mA, or 100 mA for the coupling with aldehydes) was monitored by GC until complete (4–6 h). Additional halide was added if necessary. Then the reaction mixture was poured into 100 mL of 3% aqueous HCl and was extracted with diethyl ether (3 × 60 mL). The combined extracts were washed with water (3 × 20 mL) to ensure complete removal of DMF. The extracts were dried (MgSO₄), and solvent was removed under reduced pressure. The crude product was purified by column chromatography on 60–200- μ m silica gel (pentane/ether). Isolated yields based on aldehyde, ketone, or halo ester or nitrile are reported.

General Procedure for the Stoichiometric Step-by-Step Reactions. The reactions were performed under argon at 0 °C in a two-compartment cell (sintered glass No. 4) equipped with a gold cathode, a nickel wire anode, and a saturated calomel reference electrode (SCE) in the cathodic compartment. The anodic compartment contained a DMF solution (30 mL) of NBu₄BF₄ (10 mmol) and NBu₄Br (2 mmol). The cathodic compartment contained 35 mL of the same solution, to which 3 mmol of NiBr₂(bipy) and 6 mmol of 2,2'-bipyridine had been added. The electrolysis (cathode potential -1.2 V vs SCE) was stopped when the current reached 5% of its initial value (2 faradays/mol of Ni). Then, 15 mmol of ZnBr₂, 30 mmol of ketone, and 3 mmol of RX (RX:Ni(0) = 1) were added. For the two-step procedure, the ketone was added after the reaction between Ni(0) and RX. The dark green solution changed color to red. The solution was then stirred until the product alcohol concentration remained constant (GC monitoring). The cathodic and anodic solutions were put together to minimize the effect of diffusion through the separator. The workup was the same as described above.

General Procedure for the Chemical Reformatsky Reaction. (a) α -Bromo Esters. A stirred mixture of 120 mmol of zinc powder, 2 mL of solvent, and 20 mmol of BrCH₂COOCH₂CH₃ protected from atmospheric moisture by CaCl₂ tubes was warmed to 50 °C, and a solution of 38 mL of solvent and 40 mmol of BrCH₂COOCH₂CH₃ (plus 120 mmol of 3-pentanone for the one-step reaction) was added drop by drop over ca. 30 min. When the ethyl α -bromoacetate was consumed (as determined by GC analysis), the mixture was cooled in an ice bath. In the two-step procedure 3-pentanone (60 mmol) was then added, and the solution was stirred until the product alcohol concentration remained constant (GC monitoring). The workup was the same as described above. For the reaction with iodine, the reaction mixture was decanted from excess zinc powder into a 100-mL flask containing 20 mmol of iodine and 20 mL of solvent. If necessary, iodine was added until the color of the solution remained violet. The solution was then stirred until the iodoester concentration remained constant (GC monitoring). Saturated aqueous sodium thiosulfate

(23) (a) Browning, M. C.; Davies, R. F. B.; Morgan, D. J.; Sutton, L. E.; Vananzi, L. M. *J. Chem. Soc.* 1961, 4816. (b) Booth, G.; Chatt, J. *J. Chem. Soc.* 1965, 3238.

(24) (a) Uchino, M.; Asagi, K.; Yamamoto, A.; Ikeda, S. *J. Organomet. Chem.* 1975, 84, 93. (b) Duñach, E.; Périchon, J. *J. Organomet. Chem.* 1988, 352, 239.

(22) Chaussard, J.; Troupel, M.; Jacob, G.; Juhasz, J. P. *J. Appl. Electrochem.* 1989, 19, 345.

was then added to discharge the violet color. The workup was the same as described above, except that hydrolysis was performed with water instead of aqueous HCl.

(b) α -Bromo Nitriles. A stirred mixture of 60 mmol of zinc powder, 1 mL of solvent, and 5 mmol of BrCH_2CN was warmed (50 °C) in a water bath. When reaction commenced, the mixture was cooled to 20 °C and a solution of 9 mL of solvent and 15 mmol of BrCH_2CN (plus 60 mmol of 3-pentanone for the one-step reaction) was added, drop by drop, over ca. 30 min. In the two-step procedure, 60 mmol of 3-pentanone was then added when the halo nitrile had disappeared (GC monitoring). The solution was stirred until the product alcohol concentration remained constant (GC monitoring). The workup was the same as described above.

Characterization of Products. (a) **Methyl α -Chloropropionate.** The identities of the following products were confirmed by comparison of their spectra with spectral data from the literature: methyl 3-hydroxy-2-methyl-3-phenylbutyrate,²⁵ methyl 1-hydroxy- α -methylcyclohexaneacetate,²⁶ methyl 3-hydroxy-2-methyl-3-phenylpropanoate,²⁷ methyl 3-hydroxy-2,4,4-trimethylpentanoate,²⁷ methyl 2,4-dimethyl-3-hydroxy-pentanoate.²⁷

Methyl 3-ethyl-3-hydroxy-2-methylpentanoate: ¹H NMR (CDCl_3 , 300 MHz) δ 3.72 (s, 3 H), 3.35 (s, 1 H), 2.6 (q, $J = 7.16$ Hz, 1 H), 1.35–1.65 (m, 4 H), 1.18 (d, $J = 7.16$ Hz, 3 H), 0.89 (t, $J = 7.44$ Hz, 3 H), 0.82 (t, $J = 7.54$ Hz, 3 H); MS 157 (M – 17), 145 (M – 29), 113, 97, 88, 57 (base peak). Anal. Calcd for $\text{C}_9\text{H}_{18}\text{O}_3$: C, 62.04; H, 10.41. Found: C, 61.75; H, 10.43.

Methyl 3-hydroxy-2,3-dimethylhexanoate: GC analysis, two diastereoisomers isolated as a mixture, relative configurations unknown; ¹H NMR (CDCl_3 , 300 MHz) δ 3.77 and 3.76 (2 s, 3 H), 3.12 (s, 1 H), 2.56 and 2.53 (q, $J = 7.18$ Hz, 1 H), 1.47 (m, 4 H), 1.19 (d, $J = 7.18$ Hz, 3 H), 1.18 and 1.13 (2 s, 3 H), 1.0–0.93 (m, 3 H); MS 157 (M – 17), 131, 99, 88, 57 (base peak). Anal. Calcd for $\text{C}_9\text{H}_{18}\text{O}_3$: C, 62.04; H, 10.41. Found: C, 61.85; H, 10.44.

Methyl 1-hydroxy- α -methyl-2-cyclohexaneacetate: GC analysis, two diastereoisomers isolated as a mixture, relative configurations unknown; ¹H NMR (CDCl_3 , 300 MHz) δ 5.89–5.49 (m, 2 H) (a + b), 3.70 and 3.68 (2 s, 3 H), 3.3 and 2.95 (2 s, OH), 2.61 (q, $J = 7.15$ Hz, 1 H_a), 2.58 (q, $J = 7.22$ Hz, 1 H_b), 2.07–1.56 (m, 6 H), 1.2 (d, $J = 7.15$ Hz, 3 H_a), 1.16 (d, $J = 7.22$ Hz, 3 H_b); MS 167 (M – 17), 156, 147, 133, 107, 97 (base peak), 88, 79, 68, 55. Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_3$: C, 65.19; H, 8.76. Found: C, 64.89; H, 8.88.

Methyl 3-hydroxy-2-methyl-3,3-diphenylpropanoate: ¹H NMR (CDCl_3 , 300 MHz) δ 7.61–7.23 (m, 10 H), 4.75 (s, OH), 3.67 (q, $J = 7.1$ Hz, 1 H), 3.61 (s, 3 H), 1.23 (d, $J = 7.1$ Hz, 3 H); MS 253 (M – 17), 239, 183, 105 (base peak), 77, 51. Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$: C, 75.53; H, 6.71. Found: C, 75.34; H, 6.87.

Methyl 3-hydroxy-2,3,7-trimethyl-6-octenoate: GC analysis, two diastereoisomers isolated as a mixture, relative configurations unknown; ¹H NMR (CDCl_3 , 300 MHz) δ 5.12–5.08 (m, 1 H), 3.72 (s, 3 H), 3.18 (s, OH), 2.58 (q, $J = 7.21$ Hz, H_a), 2.56 (q, $J = 7.21$ Hz, H_b), 2.08–1.90 (m, 2 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.54–1.4 (m, 2 H), 1.21 (s, 3 H_a), 1.2 (d, $J = 7.21$ Hz, 3 H), 1.15 (s, 3 H_b); MS 215 (M + 1), 197 (M – 17), 165, 137, 109 (base peak), 69, 57. Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{O}_3$: C, 67.25; H, 10.35. Found: C, 67.01; H, 10.22.

(b) **Ethyl Choroacetate.** The identities of the following products were confirmed by comparison of their spectra with spectral data from the literature: ethyl 1-hydroxycyclohexaneacetate,²⁸ ethyl 3-hydroxy-3-phenylbutanoate,²⁸ ethyl 3,7-dimethyl-3-hydroxy-6-octenoate,²⁸ ethyl 3-hydroxy-3-isopropyl-4-methylpentanoate,²⁸ ethyl 3-hydroxy-3-phenylpropanoate,³⁰ ethyl 3-hydroxy-4,4-dimethylpentanoate.³¹

Ethyl 3-ethyl-3-hydroxypentanoate:²⁸ ¹H NMR (CDCl_3 , 200 MHz) δ 4.15 (q, $J = 7.05$ Hz, 2 H), 3.52 (s, 1 H), 2.44 (s, 2 H), 1.54 (q, $J = 7.48$ Hz, 4 H), 1.26 (t, $J = 7.05$ Hz, 3 H), 0.88 (t, $J = 7.48$ Hz, 6 H); MS 147 (M – 17), 145 (M – 29), 117, 104, 99, 83, 69, 57 (base peak).

Ethyl 3-hydroxy-3-methylhexanoate:²⁶ GC analysis, two diastereoisomers, isolated as a mixture, relative configurations unknown ¹H NMR (CDCl_3 , 200 MHz) δ 4.16 (q, $J = 7.1$ Hz, 2 H), 3.61 (s, OH), 1.98 (d, $J = 2.42$ Hz, 2 H diastereotopic), 1.54–1.31 (m, 4 H), 1.27 (t, $J = 7.1$ Hz, 3 H), 1.23 (s, 3 H), 0.91 (t, $J = 6.86$ Hz, 3 H); MS 175 (M + 1), 157 (base peak) (M – 17), 131, 103, 85, 71.

Ethyl 3,3-diphenyl-3-hydroxypropanoate:³² ¹H NMR (CDCl_3 , 200 MHz) δ 7.72–7.07 (m, 10 H), 5.17 (s, OH), 3.96 (q, $J = 7.2$ Hz, 2 H), 3.2 (s, 2 H), 1.01 (t, $J = 7.2$ Hz, 3 H); MS 253 (M – 17), 225, 183, 115, 105 (base peak), 77, 51.

Ethyl 3-hydroxy-3,4,4-trimethylpentanoate:³² ¹H NMR (CDCl_3 , 200 MHz) δ 4.18 (q, $J = 7.12$ Hz, 2 H), 3.54 (s, OH), 2.60 (d, $J = 14.6$ Hz, 1 H), 2.42 (d, $J = 14.6$ Hz, 1 H), 1.28 (t, $J = 7.12$ Hz, 3 H), 1.21 (s, 3 H), 0.96 (s, 9 H); MS 171 (M – 17), 155, 143, 131 (base peak), 103, 85, 57.

(c) **α -Chloroacetoneitrile.** The identities of the following products were confirmed by comparison of their spectra with spectral data from the literature: 3-hydroxy-3-ethylpentanenitrile,³³ 3-hydroxy-3-phenylbutanenitrile.³³

1-Hydroxycyclohexaneacetoneitrile:³⁴ ¹H NMR (CDCl_3 , 200 MHz) δ 2.52 (s, 2 H), 2.37 (s, OH), 1.75–1.23 (m, 10 H); MS 140 (M + 1), 122 (M – 17), 110, 99, 81 (base peak), 68, 55.

(d) **α -Chloropropionitrile.** The identity of the following product was confirmed by comparison of its spectrum with spectral data from the literature: 1-hydroxy- α -methylcyclohexaneacetoneitrile.³⁵

3-Ethyl-3-hydroxy-2-methylpentanenitrile:³⁶ ¹H NMR (CDCl_3 , 200 MHz) δ 2.79 (q, $J = 7.25$ Hz, 1 H), 2.26 (s, OH), 1.74–1.44 (m, 4 H), 1.31 (d, $J = 7.25$ Hz, 3 H), 0.93 (t, $J = 7.4$ Hz, 3 H), 0.90 (t, $J = 7.6$ Hz, 3 H); MS 142 (M + 1), 124 (M – 17), 112, 87, 69, 56 (base peak).

3-Hydroxy-2-methyl-3-phenylbutanenitrile:¹⁸ GC analysis, two diastereoisomers, isolated in pure form, relative configurations unknown; MS 176 (M + 1), 158 (M – 17), 149, 121 (base peak), 105, 77. Diastereoisomer a: ¹H NMR (CDCl_3 , 200 MHz) δ 7.52–7.28 (m, 5 H), 2.99 (q, $J = 7.08$ Hz, 1 H), 2.7 (s, OH), 1.74 (s, 3 H), 1.15 (d, $J = 7.08$ Hz, 3 H). Diastereoisomer b: ¹H NMR (CDCl_3 , 200 MHz) δ 7.45–7.21 (m, 5 H), 3.15 (s, OH), 2.93 (q, $J = 7.1$ Hz, 1 H), 1.72 (s, 3 H), 1.17 (d, $J = 7.1$ Hz, 3 H).

3,3-Diphenyl-3-hydroxypropanenitrile:³⁷ ¹H NMR (CDCl_3 , 200 MHz) δ 7.78–7.28 (m, 10 H), 3.67 (q, $J = 7.05$ Hz, 1 H), 2.91 (s, OH), 1.19 (d, $J = 7.05$ Hz, 3 H); MS 220 (M – 17), 183, 105 (base peak), 77, 55.

(e) **Methyl Dichloroacetate.** The identities of the following products were confirmed by comparison of their spectra with spectral data from the literature: methyl 3,3-diphenyl-2-oxiranecarboxylate,³⁸ methyl 3-ethyl-3-methyl-2-oxiranecarboxylate,³⁸ methyl 1-oxaspiro-2,5-octane-2-carboxylate,³⁹ methyl 3-methyl-3-phenyl-2-oxiranecarboxylate.⁴⁰

Methyl 3,3-diethyl-2-oxiranecarboxylate: ¹H NMR (CDCl_3 , 200 MHz) δ 3.79 (s, 3 H), 3.38 (s, 1 H), 1.78–1.58 (m, 4 H), 1.01–0.92 (m, 6 H); MS 141 (M – 17), 129, 101, 41 (base peak). Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_3$: C, 60.74; H, 8.92. Found: C, 60.85; H, 8.89.

Methyl 3-phenyl-2-oxiranecarboxylate:⁴⁰ GC analysis, two diastereoisomers, isolated in pure form; MS 178 (M), 121 (base

(31) Namy, J. L.; Collin, J.; Zhang, J.; Kagan, H. B. *J. Organomet. Chem.* 1987, 328, 81.

(32) Curé, J.; Gaudemar, M. *Bull. Soc. Chim.* 1969, 7, 2471.

(33) Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* 1968, 33, 3402.

(34) Ivanov, C.; Angelova, G. *C.R. Acad. Bulg. Sci.* 1966, 19, 739.

(35) Funabiki, T.; Yamazaki, Y.; Sato, Y.; Yoshida, S. *J. Chem. Soc., Perkin Trans.* 1983, 1915.

(36) Beak, P.; Kempf, D. J.; Wilson, K. D. *J. Am. Chem. Soc.* 1985, 107, 4745.

(37) Richard, T. C. *J. Labelled Compd. Radiopharm.* 1978, 15, 591.

(38) Johnson, C. R.; Bade, T. R. *J. Org. Chem.* 1982, 47, 1205.

(39) Rodriguez, J. G.; Benito, Y.; Temprano, F. *J. Heterocycl. Chem.* 1985, 22, 1207.

(40) Ayi, A. I.; Remli, M.; Condom, R.; Guedj, R. *J. Fluorine Chem.* 1981, 17, 565.

(25) Wooten, J. B.; Houminer, Y. *J. Org. Chem.* 1982, 47, 5102.

(26) Watanabe, S.; Suga, K.; Fujita, T.; Fujiyoshi, K. *Isr. J. Chem.* 1970, 8, 731.

(27) (a) Hofstraat, R. G.; Scheeren, H. W.; Nivard, J. F. *J. Chem. Soc., Perkin Trans.* 1985, 561. (b) Meyers, A. I.; Reider, P. J. *J. Am. Chem. Soc.* 1979, 101, 2501.

(28) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* 1983, 48, 4108.

(29) Koller, M.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* 1986, 69, 560.

(30) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H. *Nozaki, H. Bull. Chem. Soc. Jpn.* 1980, 53, 3301.

peak), 105, 91. Diastereoisomer *Z*: ^1H NMR (CDCl_3 , 200 MHz) δ 7.4-7.25 (m, 5 H), 4.25 (d, $J = 4.6$ Hz, 1 H), 3.83 (d, $J = 4.6$ Hz), 3.55 (s, 3 H). Diastereoisomer *E*: ^1H NMR (CDCl_3 , 200 MHz) δ 7.4-7.25 (m, 5 H), 4.1 (d, $J = 1.8$ Hz, 1 H), 3.82 (s, 3 H), 3.52 (d, $J = 1.8$ Hz, 1 H).

Methyl 3-(1,1-dimethylethyl)-2-oxiranecarboxylate.⁴¹ GC analysis, two diastereoisomers, isolated in pure form; MS 141 (M - 17), 115, 101, 70, 55 (base peak). Diastereoisomer *Z*: ^1H NMR (CDCl_3 , 200 MHz), δ 3.78 (s, 3 H), 3.47 (d, $J = 4.7$ Hz, 1 H), 2.95 (d, $J = 4.7$ Hz, 1 H), 0.97 (s, 9 H). Diastereoisomer *E*: ^1H NMR (CDCl_3 , 200 MHz), δ 3.78 (s, 3 H), 3.32 (d, $J = 1.9$ Hz, 1 H), 2.98 (d, $J = 1.9$ Hz, 1 H), 0.97 (s, 9 H).

Methyl 3-(1-methylethyl)-2-oxiranecarboxylate.⁴¹ GC analysis, two diastereoisomers, isolated as a mixture; ^1H NMR (CDCl_3 , 200 MHz) δ 3.80 (s, 3 H_Z), 3.78 (s, 3 H_E), 3.56 (d, $J = 4.6$ Hz, 1 H_Z), 3.28 (d, $J = 1.9$ Hz, 1 H_E), 2.98 (dd, $J = 1.9$ and 7 Hz, 1 H_E), 2.86 (dd, $J = 4.6$ and 9.2 Hz, 1 H_Z), 1.70-1.53 (m, 1 H), 1.15-0.9 (m, 6 H); MS 127 (M - 17), 113, 101, 85 (base peak).

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Supplementary Material Available: ^1H NMR spectra of all compounds described (24 pages). Ordering information is given on any current masthead page.

(41) Mulzer, J.; Lammer, O. *Chem. Ber.* 1986, 119, 2178.

New Synthesis of Nitrogen Heterocycles through Amide-Directed Hydrocarbonylation of Alkenamides Catalyzed by Rhodium Complexes

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Amide-directed hydrocarbonylation of 3-butenamide (1) catalyzed by rhodium complexes such as $\text{RhCl}(\text{PPh}_3)_3$, $\text{RhCl}(\text{CO})(\text{PPh}_3)_2$, $\text{HRh}(\text{CO})(\text{PPh}_3)_3$, and $\text{Rh}_4(\text{CO})_{12}$ gives a mixture of 3,4-dihydro-2-pyridone (2), 4-methyl-3-pyrrolin-2-one (3), and a unique heterodimer, 6-(4-methyl-2-oxo-3-pyrrolin-1-yl)-2-piperidone (4). Dihydropyridone (2) is obtained in 88% yield with 98% selectivity by using $\text{HRh}(\text{CO})(\text{PPh}_3)_3$ -dppb (2 equiv) catalyst system while 4 is yielded in 90% yield with 94% selectivity with the use of $\text{RhCl}(\text{PPh}_3)_3$ - $\text{P}(\text{O}i\text{Pr})_3$ (10 equiv) as the catalyst. Control experiments revealed that this crossed coupling only proceeds in the copresence of rhodium catalyst, carbon monoxide, and hydrogen. The reactions of *N*-benzyl-3-butenamide (1a) gives a mixture of 1-benzyl-dihydropyridone (2a), 1-benzyl-4-methylpyrrolinone (3a), and 1-benzyl-6-formyl-3,4-dihydropyridone (5) and its 5-formyl isomer (6). The formation of 5 and 6 is suppressed by the addition of PPh_3 , and 2a is selectively isolated (72%) in the reaction using $\text{RhCl}(\text{CO})(\text{PPh}_3)_2$ - PPh_3 (20 equiv) as the catalyst. The hydroformylation of 2a catalyzed by $\text{RhCl}(\text{PPh}_3)_3$ gives 5 in 80% isolated yield. The reaction of *N*-*tert*-butyl-3-butenamide (1b) gives a nearly 1:1 mixture of 1-*tert*-butyl-4-methylpyrrolinone (3b) and uncyclized *N*-*tert*-butyl-4-formylbutanamide (7) accompanied by a small amount of 1-*tert*-butyl-dihydropyridone (2b). In the reaction of *N*-trityl-3-butenamide (1c), no dihydropyridone (2c) was formed, and a mixture of 1-trityl-4-methylpyrrolinone (3c) (major) and *N*-trityl-4-formylbutanamide (8) (minor) is yielded. The reaction of 4-pentenamide gives 4-methyl-3,4-dihydro-2-pyridone (9) exclusively regardless of the structure of the rhodium catalysts used. Possible mechanisms for these reactions are discussed.

Dihydro-2-pyridone and 2-pyrrolinone skeletons are among the important nitrogen heterocycles for pharmaceutical and agrochemical agents.² Dihydro-2-pyridones and 2-pyrrolinones also serve as key intermediates for the syntheses of biologically active alkaloids.² Simple dihydro-2-pyridones have been synthesized by the direct reaction of 2,4-pentadienoic acid or sorbic acid with ammonia³ and by the sodium borohydride reduction of glutarimide.⁴ The former reaction gives a mixture of 3,6-dihydro- and 5,6-dihydro-2-pyridones, while the latter yields 3,4-dihydro-2-pyridones selectively. Substituted 3,4-dihydro-2-pyridones and 5,6-dihydro-2-pyridones have been synthesized selectively, for example, through hetero-Diels-Alder cycloaddition of 1-aza-1,3-butadienes with

ketenes⁵ and cyclocondensation of vinylketene silyl acetals with imines promoted by Lewis acids,⁶ respectively. 2-Pyrrolinones have been synthesized in 25-30% yields by oxidation of the corresponding pyrroles with hydrogen peroxide in water,⁷ by dehydration of 4-hydroxypyrrolidin-2-one,⁸ by the condensation of furan with diazofornate,⁹ or by alkaline hydrolysis of 4-(chloromethyl)azetid-2-one¹⁰ by ferrous sulfate promoted rearrangement of bicyclic oxaziridines which were obtained through photolysis of 2*H*-pyrroles.¹¹

In the course of our study on chelation-controlled regio- and stereoselective carbonylations in organic syntheses, we have found that amide function can serve as a strong "directing group" in regioselective hydrocarbonylations.^{12,13}

(1) Postdoctoral Research Associate, 1988-1990, on leave from the Institute of Organic Chemistry, Polish Academy of Sciences, ul Kasprzaka 44, 01-224 Warsaw, Poland.

(2) (a) E.g.: Jones, R. A.; Bean, G. P. In *The Chemistry of Pyrroles*; Academic Press: London, 1977; pp 209-238. (b) Coutts, R. T.; Casy, A. F. *Pyridines and Reduced Pyridines of Pharmacological Interests*. In *Heterocyclic Compounds. Pyridine and Its Derivatives*; Abramovitch, R. A., Ed.; John Wiley Interscience: New York, 1975; pp 445-524.

(3) Kheddis, B.; Bahibah, D.; Hamdi, M.; Périé, J. J. *Bull. Soc. Chim. Fr.* 1981, 3-4, 135.

(4) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* 1975, 31, 1437.

(5) Krishnan, K.; Singh, A.; Singh, B.; Kumar, S. *Synth. Commun.* 1984, 14, 219.

(6) (a) Brandstadter, S. M.; Ojima, I.; Hirai, K. *Tetrahedron Lett.* 1987, 28, 613. (b) Ojima, I.; Brandstadter, S. M. In *Selectivities in Lewis Acid Promoted Reactions*; NATO ASI Series; Schinzer, D., Ed.; Kluwer Academic Publishers: Dordrecht, 1989; pp 37-52.

(7) Bocchi, V.; Gardini, G. P.; Chierici, L. *Tetrahedron* 1970, 26, 4073.

(8) Baker, J. T.; Sifniades, S. J. *Org. Chem.* 1979, 44, 2798.

(9) Bordner, J.; Rapoport, H. *J. Org. Chem.* 1965, 30, 3824.

(10) Claus, K. *Tetrahedron Lett.* 1974, 1271.

(11) Black, D. S. C.; Blackman, N. A. *Aust. J. Chem.* 1979, 32, 2035, 2041.