Asymmetric Induction in the Electrochemical Cross-Coupling of Aryl Halides with α-Chloropropionic Acid Derivatives Catalyzed by Nickel Complexes

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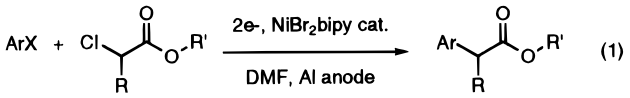
Several 2-arylpropanoic acids are known as important nonsteroidal pharmaceuticals exhibiting antiinflammatory activity,[1] and many methods of preparation of these acids have been developed.[1,2] These methods lead generally to racemic compounds, but it has been shown[3] that a higher activity is associated with the *S* configuration at the chiral center of, for example, 2-(3-phenoxyphenyl)-propanoic acid (fenoprofen) or 2-(6-methoxy-2-naphthyl)-propanoic acid (naproxen).[3] Different approaches described[2] so far to obtain the most active enantiomer include chemical resolution,[4] microbial transformation,[5] and various asymmetric syntheses.[6]

We have previously described the electroreductive cross-coupling of α-halogeno esters with aryl halides[7] catalyzed by nickel complexes in combination with the sacrificial anode process and leading to α-arylpropionic esters in one operation in good to high yields (eq 1). The scope and the mechanism[8] of these reactions have already been reported. In this paper, we now report on a remote asymmetric induction in this reaction using chiral auxiliaries.



X = I, Br

We first tried to obtain chiral products by using the commercially available chiral methyl (*R*)- or (*S*)-2-chloropropanoates in the coupling with iodobenzene but we only obtained the racemic α-arylpropionic ester. We then attempted to induce the chirality remotely using chiral auxiliaries attached to the carboxylic group. There are some reports in the literature on the successful use of chiral auxiliaries in anodic or cathodic syntheses such as the electrohydrodimerization of cinnamate esters,[9] the Kolbe electrolysis of malonic acids derivatives,[10] or the reduction of glyoxylic acid derivatives.[11,12]

Table 1. Nickel-Catalyzed Electroreductive Coupling between α-Chloropropionic Acid Derivatives Bearing Chiral Auxiliaries and Iodobenzene or *m*-Bromo-α,α,α-trifluorotoluene[a]

entry	chiral auxiliary (Y*) in $ClCH(CH_3)COY^*$	ArX	isolated yields[b] (%) of coupling product	ee (%) (de (%))[c]	major confign
1	**1**	**11**	60	19 (30)	*S*
2	**1**	**12**	50	24	*S*
3	**2**	**12**	70	45 (50)	*S*
4	**3**	**11**	50	5 (10)	*S*
5	**3**	**12**	70	3 (6)	*S*
6	**4**	**11**	41	1 (6)	*R*
7	**5**	**11**	45	5	*R*
8	**5**	**12**	50	13	*R*
9	**6**	**11**	60	6 (6)	*R*
10	**7**	**11**	57	90 (96)	*R*
11	**7**	**12**	51	87 (92)	*R*
12	**8**	**12**	51	80 (92)	*S*
13	**9**	**11**	64	17 (20)	*R*
14	**10**	**11**	50	52 (63)	*R*

[a] For experimental conditions, see text. [b] Based on initial ArX, after conversion of the product into the corresponding 2-arylpropanoic acid methyl ester. All products gave satisfactory NMR and mass spectra. [c] Ee was obtained by polarimetry on the methyl ester derivative; de was determined by GC of the crude product.

The auxiliaries used in this study are given in Chart 1. Compounds **1**−**6** are commercially available. Compound **7** was prepared in one step by fusing (−)-ephedrinium chloride with urea[13] (yield 50%; $[\alpha]_D = -45$ (c = 3.5, methanol) (lit. $[\alpha]^{25}_D = -44.5$[13])). The same procedure was applied to prepare **8**, **9**, and **10**, from (+)-ephedrine, (2*S*,3*R*)-norephedrine, and (*R*)-2-phenylglycinol, respectively. The 2-chloropropanoic acid derivatives were obtained in 70−100% yield by reacting (*rac*)-2-chloropropanoyl chloride with either the alcohols **1** to **6** or with the lithium salts of **7** to **10**. We used either iodobenzene (**11**) or *m*-bromo-α,α,α-trifluorotoluene (**12**), which are reactive enough for the coupling reaction to be conducted at room temperature.

The general procedure is as follows, on the basis of our previous investigations: freshly distilled DMF (40 mL), Bu_4NBF_4 (0.6 mmol), $NiBr_2$bipy (1 mmol), the arylhalide ArX (10 mmol), and a portion of the α-chloropropionic acid derivative RX (ca. 0.3 mmol) were introduced in a one-compartment cell fitted with an aluminum rod as the anode and a nickel sponge as the cathode (cathode area: ca. 20 cm^2). The electricity was supplied at constant current intensity of 0.25 A, and RX was added constantly to the solution via a syringe pump at a rate of 4 mmol/h.

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(12) Other approaches have been reported for asymmetric electrosyntheses such as use of chiral electrodes or chiral solvents or chiral supporting electrolytes. For rewiews, see: Tallec, A. *Bull. Soc. Chim. Fr.* **1985**, *15*, 743. Nonaka, T. In *Organic Electrochemistry*, 3rd ed.; Baizer, M. M., Ed.; Marcel Dekker: New York, 1991; p 1131.
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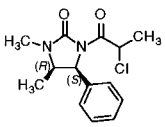
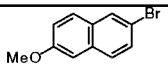
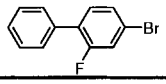
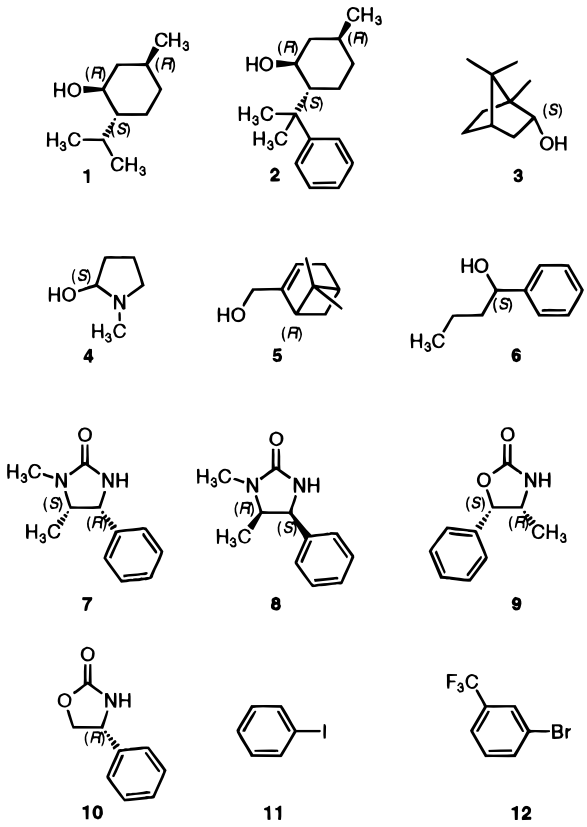
Table 2. Nickel-Catalyzed Electroreductive Coupling between the Chiral Imide Prepared from 8 and Aromatic Bromides[a]

Entry	mmol of 	ArX (10 mmol)	Isolated yields[b] of coupling product	ee (de)[c]	major configuration
1	10		62%	85% (93%)	*S*
2	12		58%	82% (92%)	*S*

[a] For experimental conditions, see text. [b] Based on initial ArX, after conversion of the product into the corresponding 2-arylpropanoic acid methyl ester. All products gave satisfactory NMR and mass spectra. [c] Ee was obtained by polarimetry on the methyl ester derivative; de was determined by GC of the crude product.

Chart 1

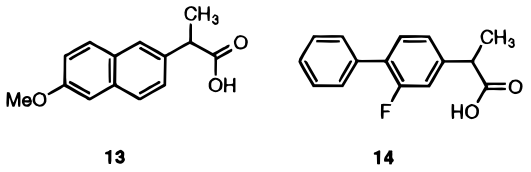


The electrolyses were run at room temperature under argon until the aromatic halide was totally consumed. Results are given in Table 1.

The diastereomer ratio (de) was determined by gas chromatography and by NMR. The enantiomeric excess was determined by polarimetry after conversion of the product, either an ester (entries 1−9, Table 1) or an imide (entries 10−14, Table 1), into the corresponding 2-arylpropanoic acid methyl ester by reaction in methanol in the presence of K_2CO_3. No racemization occurred during this reaction. The measured rotation for the methyl ester derivative of the 2-arylpropanoic acid obtained was compared to the value found in the literature, i.e., +103.5° for (*S*)-methyl α-phenyl propionate[14] and +53° for (*S*)-methyl α-[*m*-(trifluoromethyl)phenyl]propionate.[5a] The product was also obtained in the carboxylic acid form, without racemization, by reaction of the crude product with LiOH in THF and then hydrolysis.

Chemical yields are moderate to good and were not optimized for these model reactions. The auxiliaries **3**−**6** are poor inductors in this coupling reaction, since the product was obtained with low (<15%) diastereomeric excess (entries 4−9, Table 1). With a menthol skeleton a higher de can be obtained providing that a phenyl group is on C_8 (entries 2 and 3, Table 1), in keeping with other studies.[15,16] Medium de was obtained with the oxazolidinone as chiral auxiliary, and with a phenyl group close enough to the α-position to the propionic acid derivative (**10** in Chart 1). The best results were, however, obtained from imidazolidinone derivatives. In addition to the high asymmetric induction obtained, the easy access to both enantiomers **7** and **8** of the imidazolidinone from (−)- or (+)-ephedrine, respectively, makes this process efficient to obtain the *R* or *S* isomer of the desired α-arylpropionic acid.

Chart 2



We have previously shown[7b] that when aryl bromides are used in this type of coupling the reaction may be best conducted at 60 °C. So we carried out the coupling between *m*-bromo-α,α,α-trifluorotoluene and the chiral imidazolidinone from **8** at 60 °C in order to check the possible effect of the temperature on de. We obtained 68% of α-[*m*-(trifluoromethyl)phenyl]propionic acid derivative, with a de of 88% (*S* major isomer), compared to a de of 92% at room temperature (entry 12, Table 1). Therefore, an increase of the reaction temperature does not significantly affect the diastereoselectivity of the cross-coupling reaction.

We finally applied the reaction to the preparation of two commonly used drugs (*S*)-naproxen (**13**) and (*S*)-flurbiprofen (**14**). Results are reported in Table 2. These compounds were obtained in good yield and high diastereomeric excess at room temperature using only 1 equiv of α-chloroimide prepared from **8**. Since the diastereomers can be easily separated by silica gel column chromatography, the acid can thus be obtained enantiomerically pure.

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