MEMORY OF CHIRALITY IN THE ELECTROCHEMICAL OXIDATION OF *N-o*-PHENYLBENZOYLATED PROLINOLS[†]

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[†]Dedicated to the memory of Professor Dr. John Daly

Abstract – Memory of chirality in electrochemical carbon-carbon bond cleavage of *N-o*-phenylbenzoylated (*S*)-prolinol derivatives was observed. Substituents of the α-position affected the ee of the products. The reaction of α,α-diarylated (*S*)-prolinol derivatives proceeded smoothly to afford optically active α-methoxylated pyrrolidine with up to 73% ee.

The synthesis of optically active compounds on the basis of 'memory of chirality' continues to attract much attention in asymmetric synthesis.[1] In our previous study, we demonstrated that the decarboxylation of α-amino acids furnished iminium ions, which were quenched with nucleophiles to afford optically active compounds via memory of chirality.[2] The non-Kolbe electrolysis of *N*-acylated oxazolidine-4-carboxylic acid **1** afforded optically active *N,O*-acetals **3** with up to 83% ee,[3] while the electrochemical oxidation of the proline derivative **2** gave α-methoxylated pyrrolidine **4** in up to 46% ee (Scheme 1).[4]
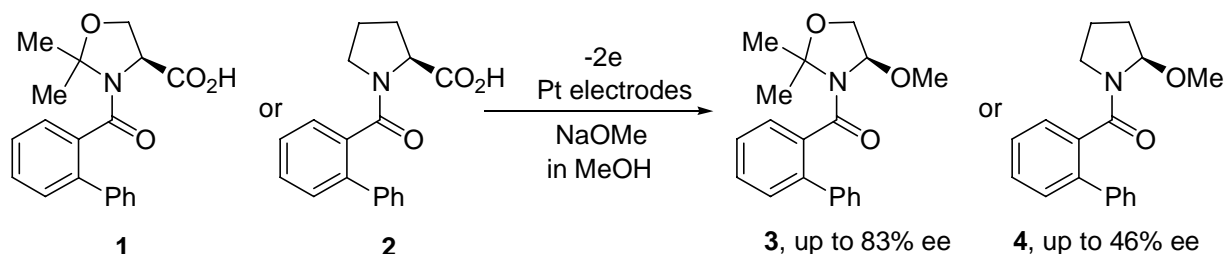

Scheme 1. Electrochemical oxidation of oxazolidine and proline derivatives

In our continuing study on memory of chirality, we anticipated that electrochemical oxidation of *N*-acylamino alcohols might bring about the carbon-carbon (C-C) bond cleavage between the α and β carbons[5] to give iminium ions (Scheme 2) similar to those anodically generated from amino acids and

trapping of these iminium ions intermediates with nucleophiles such as methanol could afford *N,O*-acetals with some memory of chirality. We report herein that the electrochemical C-C bond cleavage of several *N-o*-phenylbenzoyl prolinols **5** proceeds more efficiently than that of the proline derivative to afford **4** in good enantiomeric excess (Scheme 3). The ee (up to 73% ee) was better than that of the non-Kolbe reaction of proline derivative **2** (up to 46% ee).
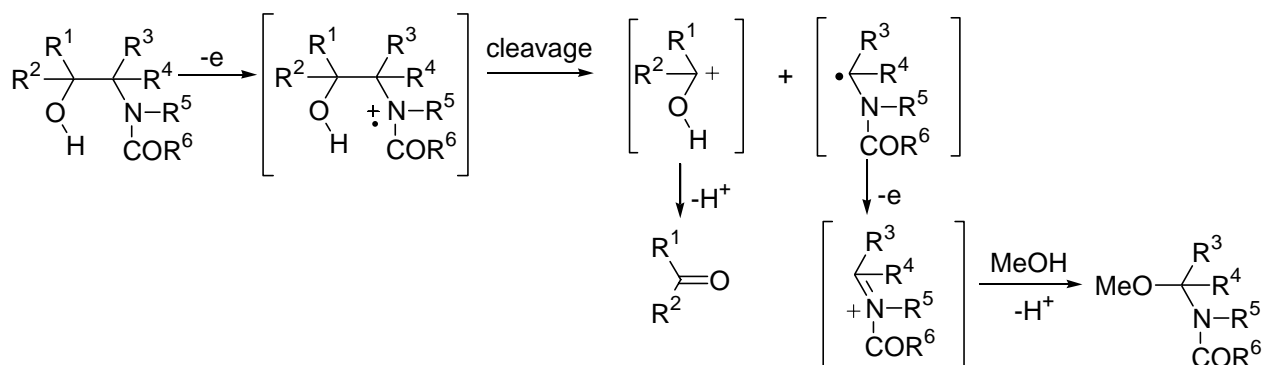
Scheme 2. Electrochemical C-C bond cleavage of *N*-acyl-β-hydroxylamines
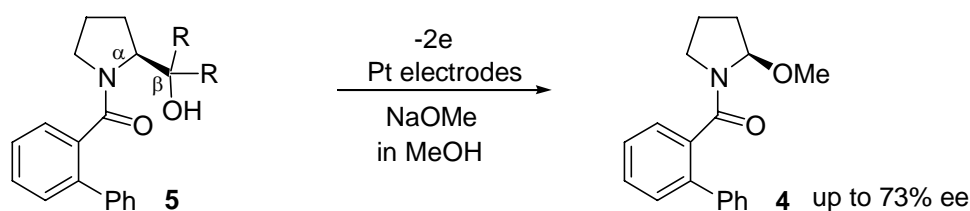
Scheme 3. Electrochemical C-C bond cleavage of prolinol derivatives

The initial study was the electrolysis of *N-o*-phenylbenzoylated (*S*)-prolinol **5a** as described in (Scheme 4). The electrolysis proceeded to afford α-methoxylated pyrrolidine **4** in 7% ee (15% yield) by cleavage of the C-C bond. The major enantiomer of **4** had the same stereoconfiguration as the major enantiomer derived from *N-o*-phenylbenzoylated L-proline, albeit with low enantiomeric excess.
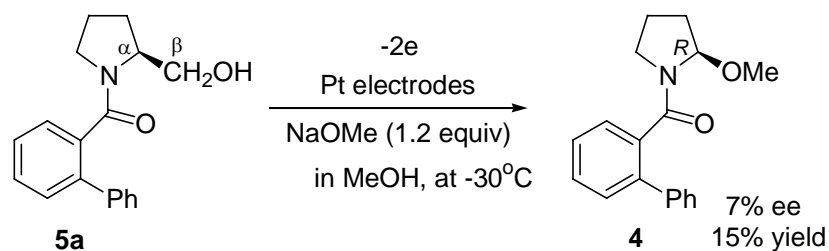
**Scheme 4.** Electrochemical oxidation of prolinol derivative **5a**

To deduce the absolute configuration of **4**, *racemic N-o*-phenylbenzoyl-*cis*-3-methylproline (**6**) was prepared.[6] The amino acid **6** was used instead of its β-amino alcohol since the oxidation products from both the proline **2** and the prolinols **5** were the same. The electrochemical oxidation of **6** afforded *cis*-**7**[7] as

a major product and *trans*-**8** as a minor product in 44% de (Scheme 5).
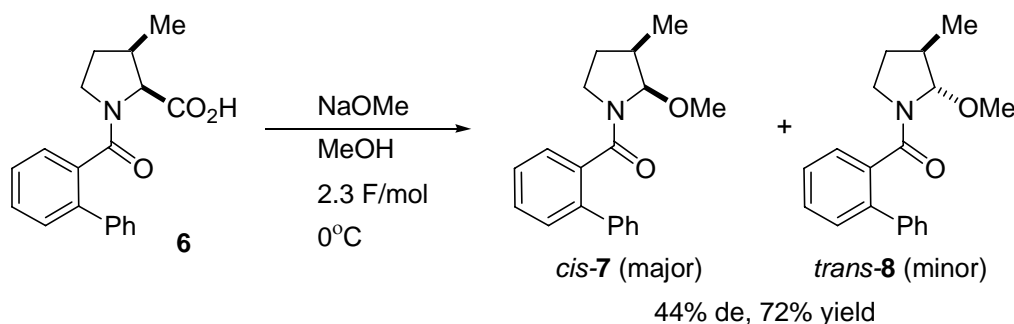

Scheme 5. Memory of chirality in the electrochemical oxidation of *cis*-3-methylproline **6**

Epimerization of *cis*-**7** (44% de) in methanol with catalytic amount of sulfuric acid afforded a mixture of *cis*-**7** (minor isomer) and *trans*-**8** (major isomer) in 17% de (Scheme 6). This implied that the initially formed *cis*-**7** was thermodynamically less stable and its formation was most likely achieved via memory of chirality.[8] It is on this basis of the results shown in Schemes 5 and 6 that the *R*-configuration of **4** was deduced.
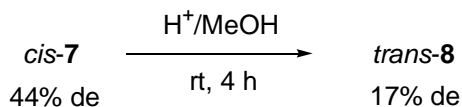
**Scheme 6.** Epimerization of *cis*-**7** to *trans*-**8** in acidic methanol

Next we synthesized and investigated α,α-dimethylprolinol **5b** (Scheme 7). Electrolysis of **5b** under similar reaction conditions furnished α-methoxylated product **4** in 28% yield. The enantiomeric excess (12% ee) albeit low was relatively better than that of **5a** (7% ee) and the stereoconfiguration for the major enantiomer was the same as that of the products derived from **5a**.
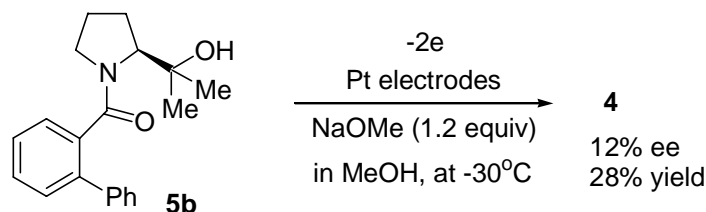
Scheme 7. Electrochemical oxidation of dimethylprolinol **5b**

The slight improvement in the enantiomeric excess (from 7% to 12%) was ascribed to the presence of two methyl groups, which are more bulkier than the protons for the prolinol. Furthermore, the improvement in yield (from 14% to 28%) was attributed to the faster chemical step for the dialkylated compound **5b** than for the primary prolinol **5a** due to relatively greater stability of the cationic side-product species.

Phenyl group are known to stabilize carbocations due to increased resonance of the cationic species. It was envisaged that the use of compounds with aryl substituents would increase the rate of the chemical bond fission step and thus improve the degree of enantioselectivity. In this perspective, we synthesized *N*-*o*-phenylbenzoyl-α,α-diphenylprolinol (**5c**) and electrolyzed it in methanol (Scheme 8).[9]
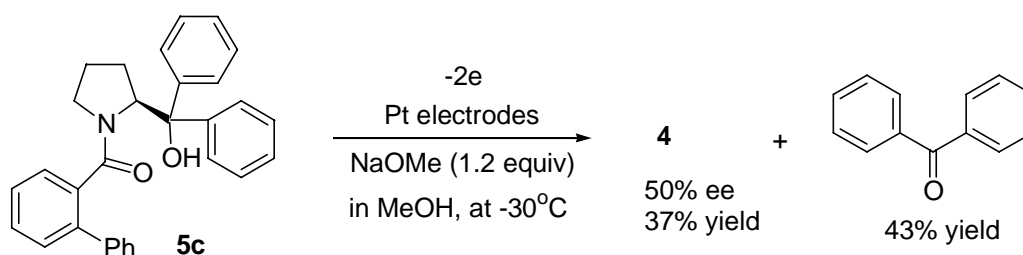
**Scheme 8.** Electrochemical oxidation of *N*-*o*-phenylbenzoyl-α,α-diphenylprolinol (**5c**)

C-C bond fission occurred with subsequent formation of the α-methoxylated compound **4** in 37% yield and benzophenone as the side-product in 43% yield. The enantioselectivity of **4** (50% ee) was much better than that from prolinol derivatives **5a** and 5b (7% and 12% ee, respectively, Schemes 4 and 7). The large improvement in the enantioselectivity could be ascribed to two factors; firstly, the enhanced stability of the $[Ph_2COH]^+$ intermediate ion, which could have improved the rate of C-C bond cleavage. Secondly, the bulkiness of the phenyl groups could have had a significant contribution to the conformational arrangement of the starting material especially the location of the *o*-phenyl group. These hypotheses were investigated by use of *para*- and/or *ortho*-substituted derivatives.[11]

To test which of the above-hypothesized factors contributed more to the memory of chirality, we investigated the effect of *para*- and/or *ortho*-substituents in the phenyl group on the ee. The results along with temperature effect are summarized in Table 1.

Electrolysis of all these compounds **5c-i** at -30 °C resulted into the cleavage of the C-C bond on the side chain and the formation of α-methoxylated product **4** in 28-44% yield. The enantiomeric excesses (34-42% ee) obtained for all **4** derived from the derivatives bearing substituents at the *para*-position (Entries 2-4) were smaller than that of the unsubstituted compound **5c** (50% ee) (Entry 1). However, the electron donating groups (OMe, Me), which are known to stabilize carbocation, afforded slightly lower enantioselectivities than the derivative with electron withdrawing group (CF_3). This was contrary to our expectations. We deduced from these results that the stability of the intermediate $[Ar_2COH]^+$ did not have a direct correlation with the observed ee. To investigate the effect of *ortho*-substitutents on the ee, compounds **5g-i** were electrochemically oxidized to afford **4** in 56-73% ee. The *o*-methyl substituted compound **5g** afforded **4** in 56% ee (Entry 5), the *o*-methoxyl substituted derivative **5h** afforded **4** in 73% ee (Entry 6), whereas the *ortho*, *para* di-substituted compound **5i** afforded **4** in 66% ee (Entry 11). These enantiomeric excesses from *ortho*-substituted compounds **5g-i** were higher than those from either the

para-substituted compounds **5d-f** or the unsubstituted compound **5c**. It was deduced from those results that the *ortho* substituents enhanced the enantiomeric excesses possibly due to increased bulkiness of the starting material. Effect of temperature is shown in Entries 6-10. -30 °C was the optimum temperature affording the best ee value.

Table 1. Effect of *para*- and/or *ortho*-substituents and temperature on ee of **4**[a]
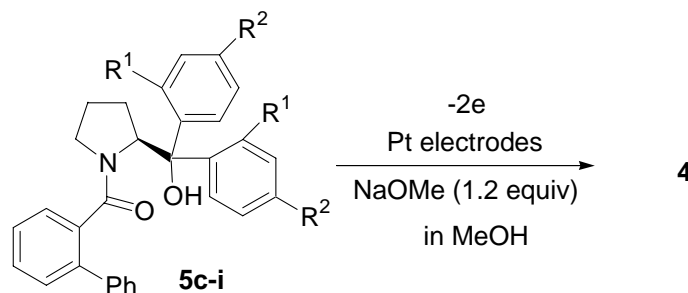
| Entry	Substrate	R^1	R^2	Reaction temp (°C)	α-Methoxypyrrolidine **4** % ee	yield (%)[b]
1	**5c**	H	H	-30	50	37
2	**5d**	H	Me	-30	34	35
3	**5e**	H	OMe	-30	37	34
4	**5f**	H	CF$_3$	-30	42	44
5	**5g**	Me	H	-30	56	35
6	**5h**	OMe	H	-30	73	32
7	**5h**	OMe	H	-40	68	28
8	**5h**	OMe	H	-20	67	35
9	**5h**	OMe	H	0	64	40
10	**5h**	OMe	H	+15	54	42
11	**5i**	OMe	Me	-30	66	28

[a] 2 F/mol of electricity was passed. [b] Isolated yield.

For the purpose of gaining a better understanding on this C-C bond cleavage, the role of the hydroxyl group was investigated. This was achieved by synthesis of compound **9** that did not have the hydroxyl group and subjecting it to the same electrolysis process as discussed above. The electrochemical oxidation of **9** in methanol cleaved the C-C bond of the side chain in a similar fashion as for the carbinols to afford α-methoxylated product **4** (Scheme 9). Surprisingly, the enantiomeric excess, 55% ee obtained was relatively better than that from diphenylprolinol **5c**.
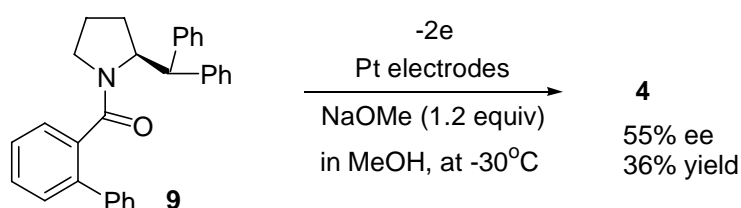
Scheme 9. Electrochemical oxidation of diphenylpyrrolidine derivative **9**

This indicated that the electrochemical oxidation of **9** proceeded via retention mechanism. That is, the methoxyl group was introduced predominantly from the same side of the carboxyl group for the non-Kolbe reaction of **2**.[3,4] Similarly, it can be deduced that the methoxylation of the prolinols **5a-i** and diphenylmethylated pyrrolidines **9** proceeded via retention mechanism to afford (*R*)-**4** as the main product (Scheme 10).

Scheme 10. Reaction mechanism for electrochemical oxidation of **5c**
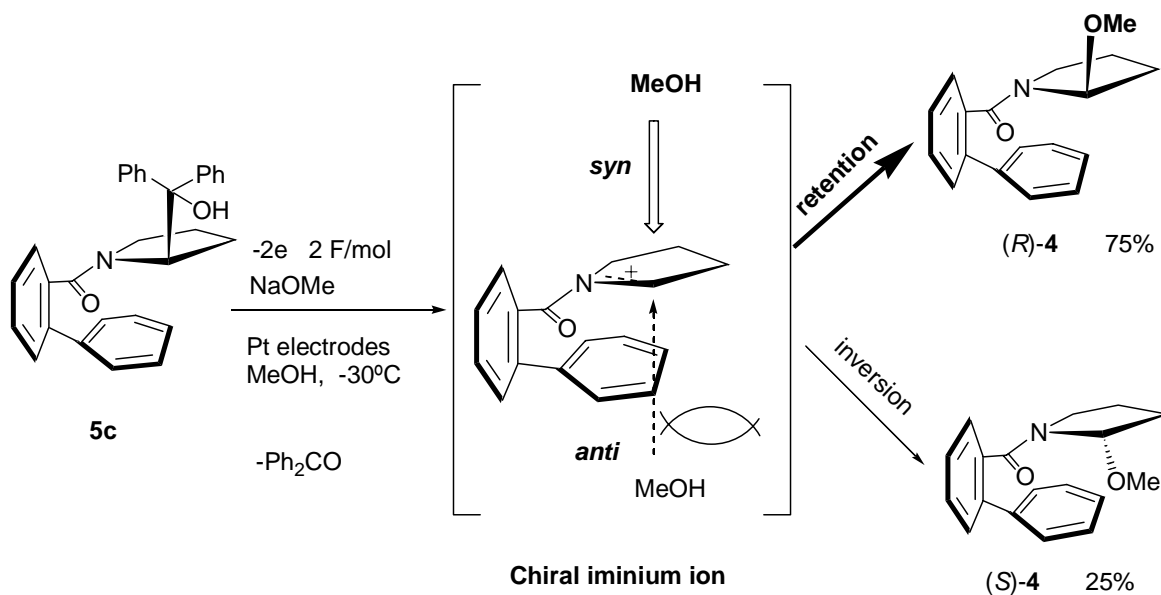
In conclusion, the electrochemical oxidation of *N-o*-phenylbenzoylated prolinols proceeded with C-C bond cleavage to generate iminium ions that were trapped with methanol to furnish optically active *N,O*-acetals. The α,α-diarylated prolinols afforded α-methoxylated product with better enantiomeric excess (up to 73% ee). In the prolinol derivatives, the C-C bond fission and the methoxylation steps occurred via retention mechanism as deduced from the derivatization reactions.

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6. Methyl *racemic-cis*-3-methylprolinate was prepared by reported method, see: E. Lorthiois, I. Marek, and J. F. Normant, *J. Org. Chem.*, 1998, **63**, 2442.

7. Strong NOESY peaks illustrated in Figure 1 were observed between 3-methyl protons and the 2-methoxyl protons. No cross peaks were observed between the methoxyl protons and the proton at 3-carbon. On the basis of this result, the stereochemistry of the major diastereomer was deduced to be a *cis* configuration.
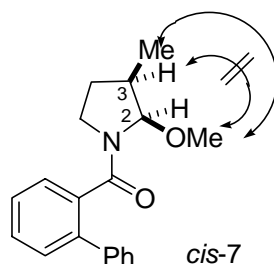
Figure 1. NOESY for major oxidation product derived from **6**

8. It can not be overruled that the repulsion of 3-methyl group and *N-o*-phenylbenzoyl group in iminium ion intermediate generated from **6** partially contributed the *cis*-methoxylation.

9. Electrochemical oxidation of **5c**: A solution of serine derivative **5c** (0.5 mmol) and NaOMe (0.6 mmol) in MeOH (10 mL) was put into an undivided cell equipped with platinum plate electrodes (1 cm x 2 cm), and then the solution was subjected to constant current (50 mA) electrolysis at –30°C. After 2 F/mol of electricity was passed,[10] the solvent was removed. The residue was subjected to silica gel chromatography to give **4** (37% yield, 50% ee) as a colorless oil and benzophenone (40 % yield). The optical purity of **4** was determined by HPLC analysis using Daicel Chiralcel OD (0.46 cmφ x 25 cm). Condition: *n*-hexane : 2-propanol=9 : 1; wavelength, 254 nm; flow rate 1.0 mL/min; retention time, 6.6 min for (*R*)-**4**, 8.7 min for (*S*)-**4**.

10. Excess amount of electricity (2.5 or 3.0 F/mol) did not improve the yield and % ee of **4**.

11. *N-o*-Phenylbenzoyl-α,α-diarylprolinol **5c-i** were prepared by the Grignard reaction of *N-o*-phenyl-benzoyl-L-proline methyl ester with 2.2 equiv of the corresponding arylmagnesium bromide in THF (over 70% yields).