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Electro-Organic Stereoselective Dehydrogenative Homo-Coupling of β-Naphthylamines Derivatives

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The electrochemical stereoselective dehydrogenative homocoupling of β-naphthylamine derivatives was investigated and successfully accomplished, the chiral diaryl amines being obtained in up to 60% yield. The use of an enantiopure β-naphthylamine featuring an aminoalcohol as chiral auxiliary led to the expected 2,2′-binaphthyl diamine derivative in up to 96/4 diastereoisomeric ratio. The application of the methodology to the intramolecular cross coupling of the enantiopure bis-*N*-β-naphthylamine 1,2-*trans*-diamino cyclohexane led to the formation of a single enantiopure diastereoisomer in 37% yield.

Introduction

Binaphthyl systems are pluripotent scaffolds present in biologically important natural products[1,2] and in numerous active pharmaceutical ingredients,[3,4] but they are also considered a privileged class of ligands in (organo)catalysis[5,6] and in material chemistry (Figure 1);[7] therefore, the development of efficient alternative methodologies to prepare such compounds is always attracting much attention. Traditional methods to synthetize these substrates are based on transition metal-catalysed coupling reactions, such as palladium or rhodium, involving nucleophilic organometallic species which show a notable environmental impact.[8]

In the last twenty years organic synthesis has witnessed a renewal of interest in the use of electrochemistry to tackle synthetic challenges and to propose innovative solutions for the preparation of functionalised organic molecules.[9–13] The strategy has been applied to electrocoupling reactions of phenols, anilines, naphthols and naphthylamines to afford biaryl systems.[14] Only a few enantioselective electrochemical organic reactions have been developed.[15–17]

However, while the coupling of phenols is widely studied,[18] the electrochemical synthesis of diaryl and binaphthyl diamines is much less explored. In 2017, Waldvogel and coworkers developed an efficient and metal-free electrochemical homo- and cross-coupling between protected anilines.[19] These pioneering studies were conducted in the presence of different protecting groups, the formyl derivative showing to be the most successful (Scheme 1).

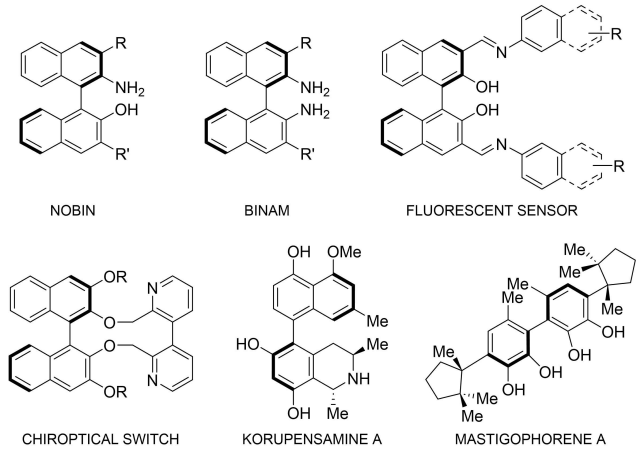

Figure 1. Binaphthol and binaphthyl diamines scaffolds of interest.

Different from the corresponding unprotected compounds, these aryl amides exhibit higher oxidation potentials (E_{ox} = 1.3–1.6 V) which improve the applicability and the selectivity of these substrates under electrochemical conditions. Furthermore, the use of tetrabutylammonium methyl sulphate as electrolyte, in a fluorinated media (hexafluoropropanol, HFIP), was able to stabilize the radical intermediate; the Glassy Carbon electrodes led to the synthesis of desired biaryl systems in up to 74% yield. (Scheme 1A).[20]

The authors also investigated the direct anodic cross-coupling between β-naphthylamines derivatives (E_{ox} = 0.32–0.55 V vs FcH/FcH+) and different-substituted phenols (E_{ox} = 0.96–1.42 V) and naphthols (Scheme 1B) under galvanostatic conditions.[21] When *N*-((S)-1-phenylethyl)- β-naphthylamines was used in the heterocoupling with β-naphthols, no stereoselectivity was observed and the products was isolated in 1:1 diasteroisomeric ratio and, in many cases, in low yields.

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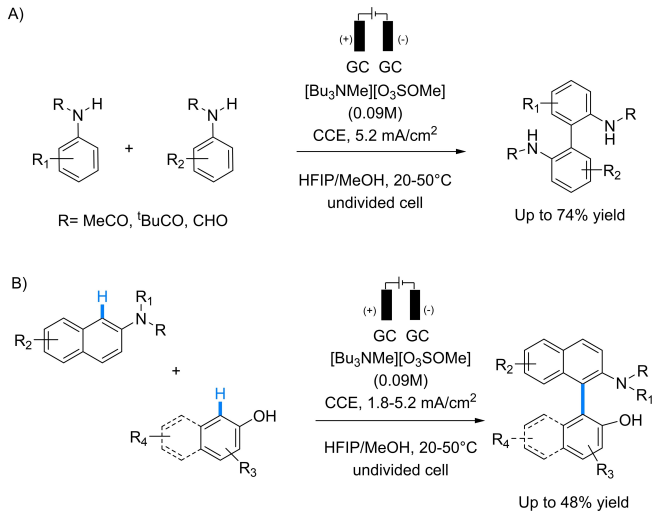
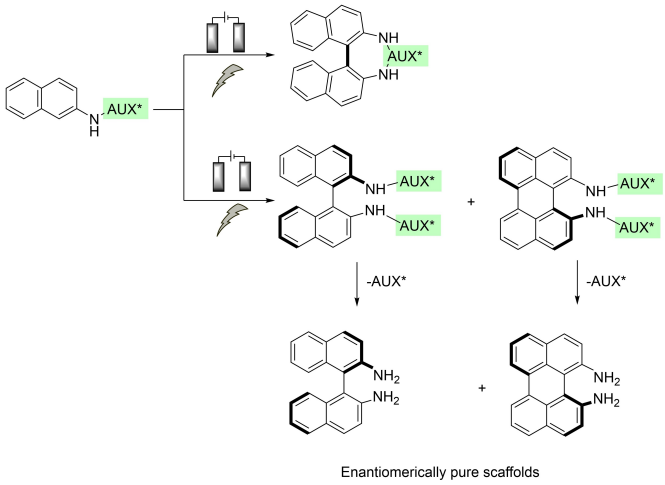


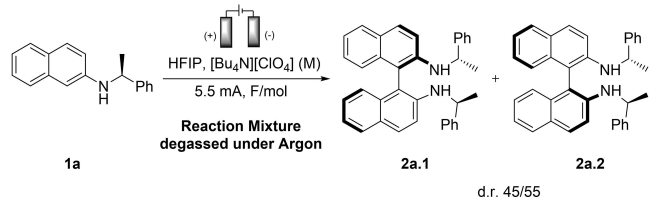
Scheme 1. A) Electrochemical homocoupling of aryl amines; B) Heterocoupling between 2-naphthyl amine and phenols or 2-naphthols.

Results and Discussion

Based on those works, we have decided to study the electro organic stereoselective dehydrogenative homo-coupling between aryl amines, exploiting the use of a chiral auxiliary. In particular, the oxidative coupling of naphthylamines derivatives bearing an enantiopure scaffold directly connected to the heteroatom was investigated (Scheme 2).



Scheme 2. Chiral auxiliary-driven strategy for the stereoselective synthesis of enantiopure binaphthyl diamine derivatives.



Scheme 3. Direct anodic homo-coupling of (S)-*N*-(1-phenylethyl)naphthalen-2 amine **1 a**.

Firstly, the electrochemical homo-coupling of the (S)-*N*-(1-phenylethyl)naphthalen-2-amine was investigated under different reaction conditions (Scheme 3). In all cases, two diastereoisomers were obtained and separated through a not trivial purification on column chromatography. Often, particularly in presence of a notable amount of unreacted starting material, two purification steps were required. Compounds **2 a.1** and **2 a.2** are respectively the first and the second isomer eluted during the chromatographic purification. The results of this preliminary investigation are collected in Table 1.

As expected, the electrodes material and the presence of oxygen in the reaction mixture seriously affected the reaction outcome. In particular, under electrochemical oxidative conditions, oxygen can form superoxides and peroxides radicals which can trap radical intermediates, favoring the formation of undesired side products. At 25 °C, operating with Glassy Carbon electrodes at constant current (5.5 mA), in undivided cell, and HFIP s solvent, without degassing, the reaction afforded the product **2 a** in low yields (Entry 1).

Therefore, in a typical set up, the mixture was degassed with Argon before the electrolysis and the reaction carried out under Argon atmosphere. In order to keep the cell potential between 1.5–2.5 V, in entries 2 and 3 the conductivity of the reaction mixture was increased and the electrochemical coupling was carried out in presence of Glassy Carbon electrodes and Platinum foil electrodes respectively. The latter option proved to be optimal, since **2 a** products were isolated in 37% overall yield with minimal side products. Thus, using Platinum foil electrodes, F/mol parameter was taken into account. Notably, when 1.3 F/mol was applied to the reaction mixture, **2 a** was obtained in up to 47% yield (entry 5), whereas the use of 1.7 F/mol was detrimental, since product was isolated in 34% yield only (entry 6).

With the aim to increase the diastereoselectivities, enantiopure β-naphthylamino amines **1 b–1 e** each incorporating different chiral amino alcohols at the nitrogen atom, were synthesized using conventional Bucherer reaction conditions.[22] Compounds **1 b–1 e** were reacted under the optimized conditions reported in entry 5, Table 1 (Scheme 4).

The reactivity of the t-leucinol derivative **1 b** was first investigated, and gratefully, the electrocoupling occurred with good yield (50%) and 83/17 diastereoselectivity. Moreover, the two diastereoisomers **2 b.1** and **2 b.2** were easily separated by column chromatography and no unreacted starting material was observed. The reaction of the *N*-valinol naphthyl amine **1 c** led to a higher yield of **2 c** mixture (60% isolated yield) although with lower diastereoselectivity (**2 c.1**:**2 c.2** 71/29), probably due to the decreasing steric hindrance of the R group. To understand the possible role of hydrogen bonding interactions in the improved selectivity and diastereocontrol of the reaction in presence of the aminoalcohol auxiliaries, we decided to protect the hydroxy group of valinol as methyl ether (compound **1 d**). The electrochemical coupling afforded two diasteroisomers **2 d.1** and **2 d.2** with comparable yield and diastereoselectivity of **2 c** and **2 c.1**, even if more byproducts were observed. Last, the

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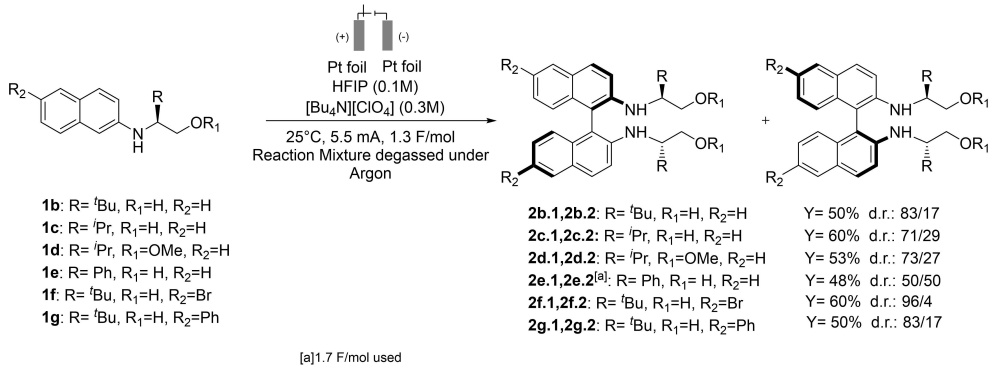
Table 1. Reaction conditions explored for the (S)-*N*-(1-phenylethyl)naphthalen-2 amine homo-coupling.

Entry[a]	Electrodes	Electrolyte (M)	Charge (F/mol)	**1a** (M)	**2a** Yield (%)
1	**Glassy Carbon**	0.2	1	0.15	25[b,c]
2	**Glassy Carbon**	**0.3**	1	0.15	25[c]
3	**Platinum foil**	**0.3**	1	0.15	37
4	**Platinum foil**	0.3	1.3	0.15	45
5	**Platinum foil**	0.3	1.3	0.10	47
6	**Platinum foil**	0.3	1.7	0.15	34[c]
7	**Platinum foil**	0.3	0.5	0.15	n.d.[d]

[a] Electrolysis conditions: 25 °C, constant current (5,.5 mA), undivided cell, solvent: HFIP. Reaction mixture degassed with Argon before the electrolysis. Reaction carried out under Argon atmosphere.
[b] No degassing and no Argon atmosphere.
[c] Formation of significant amounts of by-products.
[d] Crude not purified since a large amount of unreacted starting material was detected by TLC.

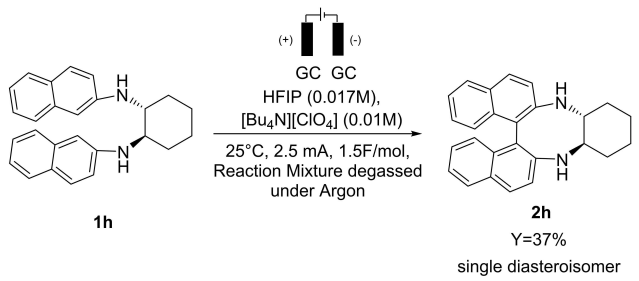


Scheme 4. Direct anodic Homo-coupling between β-naphthylamines **1b–1g** featuring a chiral amino alcohol unit as chiral auxiliary.

electrochemical coupling of **1e** using 1.7 F/mol led to products **2e.1** and **2e.2** in 45% yield and in 50/50 ratio. With the aim to investigate the reactivity of functionalised BINAM scaffolds in the coupling reaction, we synthetized compound **1f** and **1g** using *t*-leucinol as chiral auxiliary. Noteworthy, the diastereoisomers **2f.1** and **2f.2** were achieved with good yields and excellent diastereoselectivity, upto 96/4 ratio.

Based on these experimental results, we performed a preliminary investigation of an intramolecular electrochemical coupling, employing (1R,2R)-(+)-1,2-Diaminocyclohexane as the chiral unit for the reaction of chiral diamine **1h** (Scheme 5).

A brief reaction condition optimization was carried out by adjusting the electrode material and substrate concentration.[23]

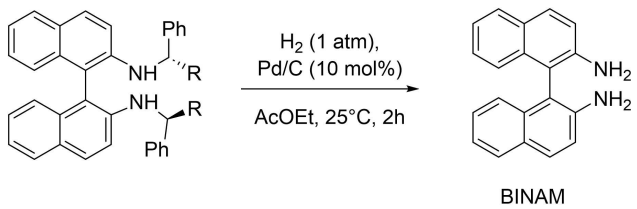


Scheme 5. Direct anodic intramolecular homo-coupling of diamine **1h**.

As in the case of the intermolecular electrochemical coupling, it was noted that the presence of oxygen significantly impacted on the reaction yields, promoting the formation of by-products. This undesirable effect was mitigated by employing argon atmosphere. Under these conditions, the electrolysis of **1h** afforded product **2h** as a single diastereoisomer in 37% yield.

As the synthesis of enantiopure [1,1′-Binaphthalene]-2,2′-diamine scaffolds (BINAM) as chiral ligands is highly desirable, the chiral auxiliary of compounds **2a** and **2e** was effectively removed through hydrogenation on Pd/C (Scheme 6 and Table 2).

Hydrogenation proved to be a successful approach for obtaining enantiopure forms of BINAM. Specifically, compounds **2a.1** and **2e.2** led to the selective formation of the (R) enantiomer, while hydrogenation of **2a.2** and **2e**.1 yielded the



Scheme 6. Chiral auxiliary removal.

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Table 2. Hydrogenation of **2a** and **2e** to afford enantiopure BINAM.

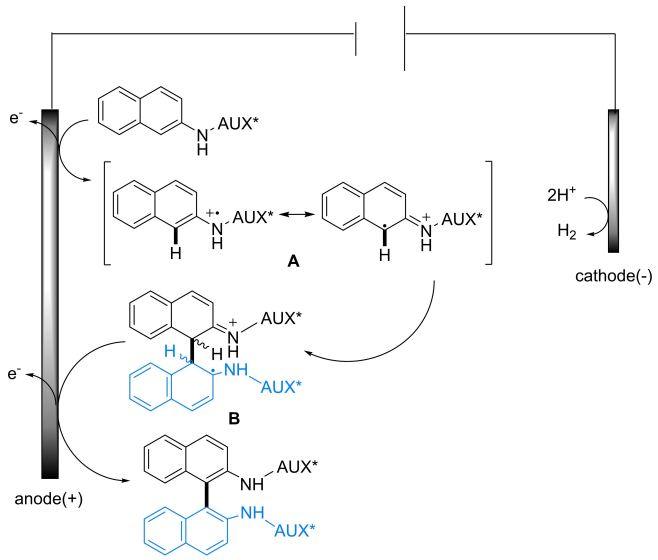
Entry	Starting material	R	BINAM configuration	BINAM yield (%)	$[a]_D$
1	**2a.1**	CH_3	(*R*)	47	(+)
2	**2a.2**	CH3	(S)	40	(−)
3	**2e.1**	CH_2OH	(S)	48	(−)
4	**2e.2**	CH_2OH	(*R*)	48	(+)

(S) enantiomer. The optical purity and absolute configuration of the isolated compounds were determined using HPLC on a chiral stationary phase and by measuring their optical rotation.[23]

Following previous publications in the field,[19–22] a tentative mechanism has been proposed (Scheme 7). After a single electron oxidation of the amine, the radical cation **A** reacts with another molecule of naphthyl amine to afford intermediate **B** that by a further anodic oxidation is converted in the binaphthyl diamine.

Conclusions

In summary, a stereoselective electrochemical dehydrogenative homocoupling of β-naphthylamine derivatives, featuring a chiral, enantiopure unit, has been successfully accomplished. By tuning the experimental conditions, good yields (up to 60%) and stereoselectivities, up to 96/4, have been achieved.[24] After separation of the two diastereoisomers, the chiral auxiliary could be removed to afford enantiomerically pure BINAM (2,2′-binaphthyl diamine) scaffold. Further studies aimed to improve the stereoselectivity of the reaction, to identify new, easily removable and recyclable chiral auxiliaries, and to apply the methodology to the naphthyl amine/naphthol cross coupling are currently ongoing. The possibility to perform the reaction under continuous flow conditions will be also studied, thus offering new opportunities to a large scale preparation of chiral compounds.[25]



Scheme 7. Proposed reaction mechanism.

Experimental Section

General Methods and Materials

NMR Spectra: 1H-NMR and 13 C-NMR spectra were recorded with instruments Bruker Avance 300. The chemical shifts are reported in ppm (δ), with the solvent reference relative to tetramethylsilane (TMS).

Mass Spectra: Mass spectra were registered on Synapt G2-S*i*(Waters) equipped with an ESI ion source.

$[\alpha]T_D$: Optical rotations were measured on a JASCO P-1030 polarimeter (Series: A014060839) at 589 nm using a 1 mL cell, with a length of 1 dm, at 14 °C

HPLC: HPLC analyses were performed using an Agilent Technologies 1260 Infinity. The specific operative conditions for each products are reported in the SI.

TLC: Reactions and chromatographic purifications were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates and visualized using UV light.

Chromatographic Purification: Purification of the products was performed by column chromatography with flash technique (according to the Still method) using as stationary phase silica gel 230–400 mesh.

Solvent and Reagents: All chemicals were obtained from standard commercial suppliers and were used without any further purification.

Electrochemical reactions were carried out in an IKA ElectraSyn 2.0.

General Protocol for the Electrochemical Intermolecular Homo-Coupling

In a 5 mL IKA ElectraSyn 2.0 vial, equipped with a stir bar, the chiral amine (0.5 mmol, 1 eq.) and Lithium Perchlorate (1.5 mmol, 3 eq) were dissolved in 5 ml of 1,1,1,3,3,3-Hexafluoro-2-propanol. The electrochemical cell was assembled with IKA Platinum foil anode and cathode and the reaction mixture was degassed with Argon for two minutes. Under Argon Atmosphere, the solution was electrolyzed with a constant current of 5.5 mA (Cell potential 1.5–2.5 V). After 1.3 F/mol were furnished, the reaction mixture was diluted with ethyl acetate and washed two times with brine. The organic phase was than dried over magnesium sulphate and the solvent evaporated under reduced pressure. The crude was purified by column chromatography on flash silica gel to separate the diastereoisomers.

Supporting Information Summary

See the Supporting Information for: synthetic procedures of starting materials, experimental details on electrochemical reactions, characterization data for products, NMR spectra for all described compounds, HPLC chromatograms. Additional references cited within the Supporting Information.[26,27]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Electrochemistry · Chiral diamines · Stereoselective coupling · Chiral auxiliary · Chemoselectivity

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[23] For further details please see the Supporting Information.
[24] General Procedure: In a 5 mL IKA ElectraSyn 2.0 vial, equipped with a stir bar, the chiral amine (0.5 mmol, 1 eq.) and Lithium Perchlorate (1.5 mmol, 3 eq) were dissolved in 5 ml of 1,1,1,3,3,3-Hexafluoro-2-propanol. The electrochemical cell was assembled with IKA Platinum foil anode and cathode and the reaction mixture was degassed with Argon for two minutes. Under Argon atmosphere, the solution was electrolyzed with a constant current of 5.5 mA (cell potential 1.5–2.5 V). After 1.3 F/mol were furnished, the reaction mixture was diluted with ethyl acetate and washed two times with brine. The organic phase was than dried over magnesium sulphate and the solvent evaporated under reduced pressure. The crude was purified by column chromatography on flash silica gel to separate the desired diasteroisomers.
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