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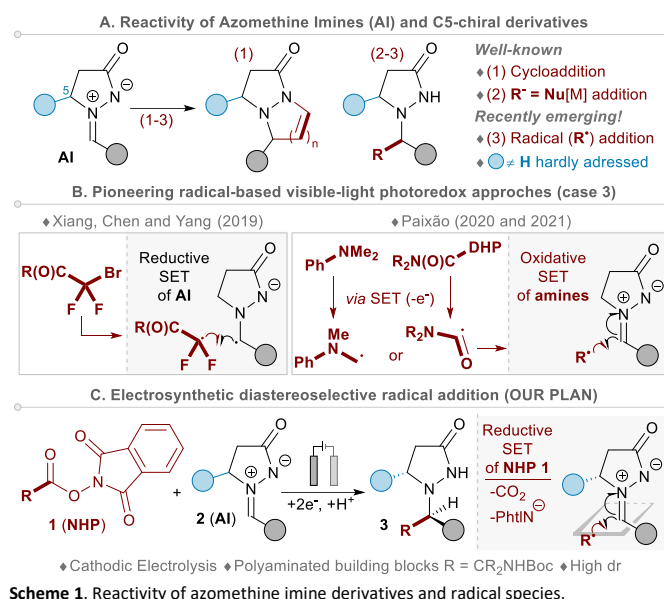
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Thanks to metal- and catalyst-free electrochemical conditions in an undivided cell, a series of readily available redox-active *N*-(acyloxy)phthalimide esters led to an efficient and highly stereoselective addition (85:15 to 95:5 dr) of putative radical species to chiral (racemic and enantioenriched) C5-substituted azomethine imines to provide an array of 31 polyaminated hydrazine derivatives as a single diastereoisomer.

Radical-based redox processes rapidly expanding in modern organic chemistry, thanks to the power of the renewal technology-driven synthesis by means of visible-light photoredox strategies and electrosynthesis.^{1,2} Beside ionic-based reagents approaches, the radical-promoted transformations have markedly enlarged the toolbox of organic chemists, by affording complementary selectivities and an exquisite functional group tolerance, although the transformation of important building blocks remain to be addressed.³ Azomethine imines (**AI**) have a versatile reactivity profile both for cycloadditions and nucleophilic additions of organometallic anionic-reagents (Scheme 1A), which opened routes to the construction of biologically important hydrazine derived architectures.⁴ Very recently, the radical-based transformation of these dipoles was also developed upon visible-light photoredox catalysis (Scheme 1B).^{5,6,7} Xiang, Chen and Yang and colleagues demonstrated the single-electron reduction of Dorn-Otto azomethine imines (**AI**) by an iridium-derived photocatalyst, followed by a radical-radical cross-coupling reaction of transient difluoroalkyl radicals originated from BrCF₂C(O)R partners.⁵ On the other hand, the group of Paixão developed radical α -amino alkylation and carbamoylation reactions of similar azomethine imines **AI**, triggered by the photocatalytic oxidative SET of either dimethylamine or dihydropyridine (DHP) precursors.⁶ Then, the obtained *N*-centered radical, or isomer derived thereof, undergoes a reductive SET by the reduced photocatalyst securing a redox-neutral process. In these pioneering and elegant achievements, a single example of a chiral C5-substituted azomethine imine was described but,

unfortunately, this led to low or not mentioned diastereoisomeric ratios. Thus, the complete potential of azomethine imines in radical and stereoselective transformations is still in its infancy.



Scheme 1. Reactivity of azomethine imine derivatives and radical species.

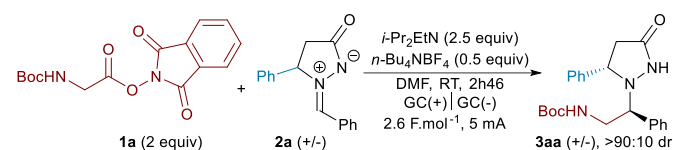
In that context, we devised an alternative plan from readily available chiral C5-substituted azomethine imines **2**⁴ based on an unprecedented electrochemical approach (Scheme 1C). The discovery in the 80's of *N*-(acyloxy)phthalimides (NHPs) **1** as potent redox-active esters (RAEs) has elicited a large array of developments in photoredox chemistry, capitalizing on the wide availability of acid starting materials.^{8,9} More recently, the alkyl NHP ester derivatives **1** emerged as versatile radical precursors upon a decarboxylative cathodic reductive SET event.^{9d,10,11} We reasoned that a sequential cathodic electrolysis,^{1,2c} advantageously occurring at the same electrode would be suited to our strategy.¹² Accordingly, the first addition of the radical species (stemming from the reduction of RAE **1**) to azomethine imine **2** would occur at the cathode-solution interface facilitating thereby the subsequent reductive SET of obtained *N*-centered radical followed by the final protonation. Based on this Electrochemical-Chemical-Electrochemical (ECEC) mechanism, we also assumed that the C5-chiral pyrazolidinone moiety could allow the steric-discrimination of the two diastereotopic faces of **2** during the approach of the radical species.

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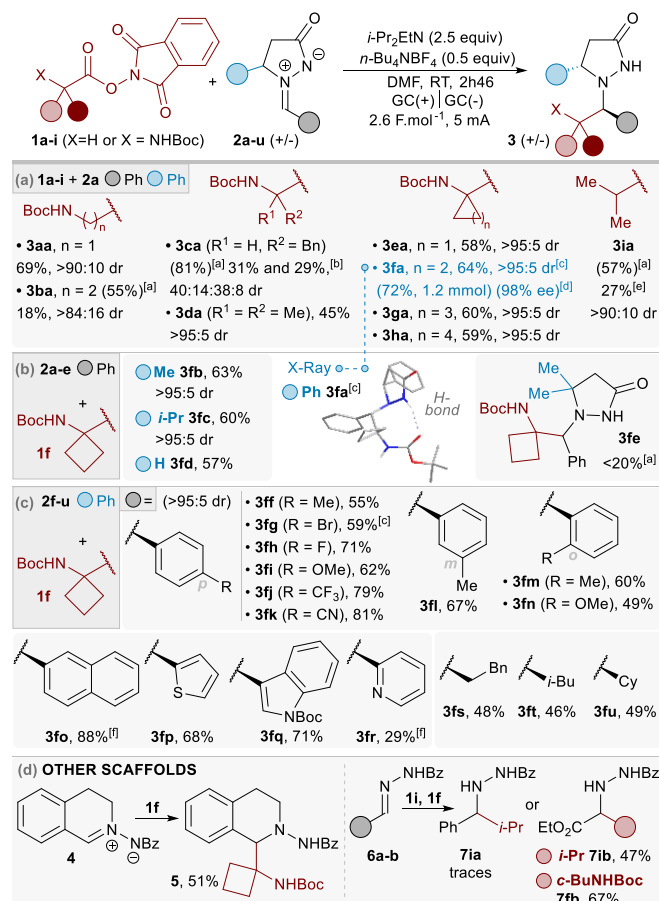
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1. Proof of principle and optimization.^a

Entry	Deviation from the standard conditions	Yield [%] 3aa
1	None	80
2	Cgraph(+)/Cgraph(-) as electrodes	27
3	Mg(+)/GC(-) as electrodes	60
4	SS(+)/SS(+) as electrodes	72
5	DMA or MeCN or THF or NMP as solvents	61-68
6	<i>i</i> -PrOH as solvent	0
7	No <i>n</i> -Bu ₄ NBF ₄ ^[a]	58
8	<i>n</i> -Bu ₄ NBr instead of <i>n</i> -Bu ₄ NBF ₄	67
9	No <i>i</i> -Pr ₂ EtN	16
10	Use of 1.5 equiv of <i>i</i> -Pr ₂ NEt	62
11	1.5 equiv of NHP ester 1a	47
12	2.2 F.mol ⁻¹ (2h21) at 5 mA	69
13	3.0 F.mol ⁻¹ (3h13) at 5 mA	70
14	No current ^[b]	0

Reaction conditions: carried out with **2a** (0.2 mmol), **1a** (2 equiv) in DMF (0.1 M) at RT in an undivided cell. Yield of the major diastereoisomer determined on the crude mixture by ¹H NMR with Bn₂O as internal standard. [a] High electrical resistance of the solution was observed without supporting electrolyte leading to a much longer reaction time to deliver 2.6 F.mol⁻¹. [b] 20% of **3aa** and 65% of **2a** estimated by ¹H NMR after 30 minutes of electrolysis and a stirring maintain during 2h17 afterwards.

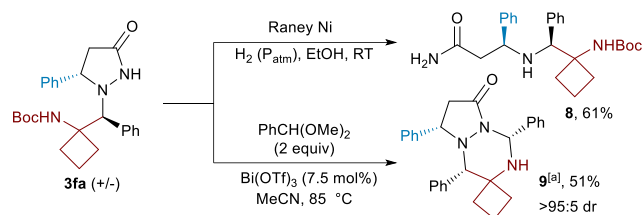
To our delight, and based on these working hypotheses, a mixture of *N*-Boc glycine-derived NHP **1a** (2 equiv) and azomethine imine **2a**, upon constant current electrolysis with Glassy Carbon (GC) electrodes, led rapidly (less than 3 hours at room temperature) to the corresponding product **3aa** in 80% NMR yield for the major diastereoisomer (determined with an internal standard, Table 1, entry 1).^{9b} Thanks to ¹H NMR and HPLC/MS analyses, a diastereoisomeric ratio (dr) of 90:10 have been estimated on the crude reaction mixture. Interestingly, among the screening of electrodes (entries 2-4, see SI for the complete investigation), the cheap Stainless Steel (SS) electrodes could be used as well with a slight decreased in yield (72%, entry 4). The reaction performed at best (1) in polar aprotic solvent such as DMF (entries 5-6), (2) in the presence of both 0.5 equivalent of *n*-Bu₄NBF₄ as supporting electrolyte (entries 7-8), and (3) with 2.5 equivalents of Hunig base as a sacrificial oxidable species (entries 9-10). An excess of NHP ester **1a** (2 equiv, entry 1) was required in order to improve the yield (1.5 equiv of **1a** gave 47% yield, entries 1 *versus* 11), likely due to a competitive dimerization of the transient α -amino radical species (see ESI). Eventually, the delivery of 2.6 F.mol⁻¹ proved to be the optimal charge at 5 mA to get the maximum yield of 80% (Entry 1 *versus* entries 12-14).



Scheme 2. Scope and limitation. Reaction conditions: carried out with **2** (0.2 mmol), RAEs **1** (2 equiv) in DMF (0.1 M) at RT in an undivided cell. Isolated yields (%) of the major diastereoisomer after purification by column chromatography; diastereoisomeric ratio determined by ¹H NMR, and HPLC/MS if required, on the crude product. [a] Yield determined by ¹H NMR on the crude mixture with Bn₂O as internal standard. [b] Isolated yields of the two major diastereoisomers. [c] Structures **3fa** (CCDC2154728), **2g**-(Z) (CCDC2154729) were ascertained by X-ray analyses. [d] Starting from **2a**-(S) (0.2 mmol, 99% ee) giving **3fa** in 57% yield and >98% ee. [e] Product **3ia** unstable on silica gel and was purified as a stable derivative after *N*-Boc formation (**3ia'**, 27% over two steps). [f] The reaction was performed in diluted conditions (0.05 M) for solubility issue.

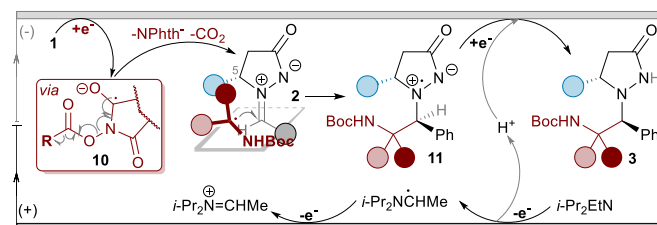
With these efficacious electrosynthesis conditions in hand, we investigated the scope of this reaction with regard to various NHP esters **1a-i** (Scheme 2a). Beside the model glycine derived REA **1a**, providing product **3aa** in 69% isolated yield of the major diastereoisomer and >90:10 dr, the homologated β -alanine derivative **1b** also led to the corresponding addition product **3ba** in a 84:16 dr and a modest yield of 18% due to purification issue (55% yield estimated by NMR). The addition of the secondary radical intermediate derived from phenyl alanine derivative **1c** occurred smoothly to the dipole **2a** in a likely similar diastereoinduction, but the relative configuration of the second stereocenter α to *R*² was not controlled affording 4 diastereoisomers (**3ca**, 40:14:38:8 dr) in 31% (**3ca'**) and 29% (**3ca''**) isolated yields respectively of the two major stereoisomers. Pleasingly, disubstituted acyclic (*R*¹ = *R*² = Me, **1d**) and cyclic (cyclopropyl to cyclohexyl, **1e-h**) *N*-Boc glycine derivatives, *via* a putative tertiary radical species, gave rise to the formation of the original products **3da-3ha** in 45-64% yields and an excellent stereoinduction (> 95:5 dr, minor stereoisomer hardly seen by ¹H NMR or HPLC/MS). The reaction with the

cyclobutyl precursor was uneventfully performed to 1.2 mmol scale with a slight improvement of the isolated yield (from 64% of 72%) or the faraday efficiency (from 50% of 55%, see SI for details) for **3fa**. Most importantly, the reaction starting from readily available enantioenriched azomethine imine **2a** (99% ee)^{4,13} led to the corresponding addition product **3fa** in similar enantiomeric excess (>98% ee). Thereby, no significant racemization event takes place during this radical process. Beside amino acid derivatives, this electrosynthesis reaction could also be applied to various alkyl residues. For instance, *iso*-propyl NHP ester **1i** furnished **3ia** in 57% NMR yield (> 90:10 dr). However, the obtained product turned out to be unstable during purification on silica gel, but was eventually isolated after a *N*-Boc protection in moderate 27% yield over two-steps. Although further investigation would be required to explain this phenomenon, deshydrogenated products were identified by MS-analyses of the crude mixture, which could stem from the formation of an azomethine imine after loosing of hydrogen. Furthermore, a crystal of the diastereoisomer **3fa** suitable to X-ray diffraction analysis revealed an intramolecular hydrogen bonding between the NH of the pyrrolidinone and the *N*-Boc group which might account for the higher stability of addition products derived from aminoacids. Subsequently, making use of the cyclobutyl-glycine precursor **1f** (Scheme 2b), the addition reaction was performed on various azomethine imines either unsubstituted derivatives (**3fd**, 57%) or flanked on the pyrrolidinone part with a methyl (**3fb**, 63%) and a bulkier *iso*-propyl moiety (**3fc**, 60%) with high dr in both cases. A limitation was reached with the more sterically hindered dimethyl azomethine imine affording product **3fe** in a low estimated yield (<20%). As long as the iminium moiety of the azomethine imine is concerned (Table 1c), variously *ortho*, *meta* and *para*-substituted aryl (**3ff-3fn**, 49-81%), a naphthyl (**3fo**, 88%) and heterocycles such as thiophene and indole derivatives (**3fp-3fq**, 68-71%) underwent highly stereoselective C-C bond formation (> 95:5 dr). Pyridine-derived precursor **2r** turned out to be poorly soluble in the reaction media, and even in diluted conditions led to **3fr** in a modest yield of 29%. Eventually, the azomethine imines derived from linear (**2s**) or branched aliphatic aldehydes (**2t-2u**) proved to be compatible with these electrochemical conditions leading to the corresponding products **3fs-3fu** in high stereoselectivities (> 95:5 dr) but slightly lower yields (46-49%). Being interested in extrapolating these electrochemical conditions to other substrates, without further optimization, it was also demonstrated that the NHP ester **1f** could be added to isoquinoline derived *C,N*-cyclic azomethine imine **4** to form **5** in 50% yield (Scheme 2d). Eventually, the hydrazone **6b**, having an ester pendant, was also transformed into the products **7ib** and **7fb** in 47% and 67% yields respectively as stable products. Most notably, the analogous hydrazone **6a** derived from a benzaldehyde was resistant to these conditions which highlights the complementary reactivity with azomethine imines **2**.



Scheme 3. Chemical transformations. [a] Relative configuration proposed from NOE experiment.

Mindful of taking advantage of the obtained and original chiral products such as **3fa** (Scheme 3), we were pleased to observe that an uneventfully N-N bond reductive cleavage took place in the presence of Raney Nickel to afford the polyaminated derivative **8** in 61% yield (as a single diastereoisomer). Next, owing to the significance of hydrazine derived fused-bicyclic heterocycles as bioactive compounds in the literature,¹⁴ we undertook a cyclization strategy of **3fa**. The acetal derived from benzaldehyde in the presence of Bi(OTf)₃, furnished the original spirocyclic heterocycle **9** in 51%, due to partial conversion of 57%, with more than 95:5 dr along with an *in-situ* *N*-Boc deprotection.



♦ Inhibition reaction: + TEMPO (3 equiv) → traces of **3fa** (conditions of Table 1, entry 1)
♦ Cyclic Voltammetry experiments (V vs SCE in DMF): **1a**, *E* = -1.25 V; **1f**, *E* = -1.27 V, **2a**, *E*_{red} = -1.66 V and *E*_{ox} = +1.56 V; **3af**, *E*_{ox} = +1.12 V and +1.56 V; *i*-Pr₂EtN, *E* = +0.88 V

Scheme 4. Mechanistic proposal.

We carried out preliminary model reactions to get insight into this electrochemical process. The TEMPO (3 equivalents), used as a radical scavenger, largely inhibited the formation of product **3fa** in the optimized conditions. Next, *N*-Boc glycine-derived NHP **1a** without azomethine imine yielded the (BocNHCH₂)₂ dimer likely stemming from the recombination of the formed radical species. Accordingly, based on both cyclic voltammetry (CV) experiments (see ESI for further details) and a background literature on the use of NHP ester as RAE in electrosynthesis,^{10,11} we propose the possible mechanism depicted in Scheme 4. The transformation would start by the SET from the cathode to the NHP ester **1**, leading to the radical species **10**, thus triggering the subsequent fragmentation/decarboxylation events. The thus obtained α-amino radical would add diastereoselectively to the less shielded face of the azomethine imine **2**, at the opposite to substituent at C5 (as depicted in Scheme 4). For this induction model, the initial *Z*-configuration of **2g** was proven from X-ray analyses. Actually, CV experiments clearly showed that NHP esters **1** (**1a**, *E* = -1.25 V; **1f**, *E* = -1.27 V vs SCE in DMF) is more easily reduced than the azomethine imine partner such as **2a** (*E*_{red} = -1.66 V), ruling out *a priori* a radical-radical coupling-mechanism similar to the one reported by Yang and colleague.⁵ Then, the obtained radical **11**, or an isomer derived thereof,^{6a}

would undergo a second reductive SET, followed by a protonation, along with a sequential cathodic electrolysis. This cathodic sequence was balanced at the counter electrode by the two electrons oxidation of the Hunig base ($E = +0.88$ V), as a sacrificial reaction, while furnishing the proton atoms required to obtain **3**. Furthermore, it is believed that *i*-Pr₂EtN protects the obtained product **3** or azomethine imine **2** (**2a** and **3fa**, $E_{ox} = +1.56$ V) to anodic oxidative events, albeit some decomposition at the end of the electrolysis cannot be ruled out, especially when more than 2.6 F.mol⁻¹ is applied (see Table 1, entries 9–10 and 13).

In conclusion, we demonstrated that a likely sequential cathodic electrolysis process leads to an efficient way to add alkyl acid-derived redox active *N*-(acyloxy)phthalimide esters to chiral C5-substituted azomethine imines with excellent diastereoselectivities, to provide versatile and original hydrazine heterocycles. This strategy opens new opportunities for radical-based transformation of these dipoles upon electrochemical metal- and catalyst-free conditions, while expanding the scope of the growing cathodic-based transformations.^{2c}

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Conflicts of interest

There are no conflicts to declare.

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