

# Simplifying Access to Targeted Protein Degraders via Ni-Electrocatalytic Cross-Coupling

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**ABSTRACT:** C–C linked glutarimide-containing structures with direct utility in the preparation of cereblon-based degraders (PROTACs, CELMoDs) can be assessed in a single step from inexpensive, commercial  $\alpha$ -bromoglutaramide through a unique Brønsted-acid assisted Ni-electrocatalytic approach. The reaction tolerates a broad array of functional groups that are historically problematic and can be applied to the simplified synthesis of dozens of known compounds that have only been procured through laborious, wasteful, multistep sequences. The reaction is scalable in both batch and flow and features a trivial procedure wherein the most time-consuming aspect of reaction setup is weighing out the starting materials.

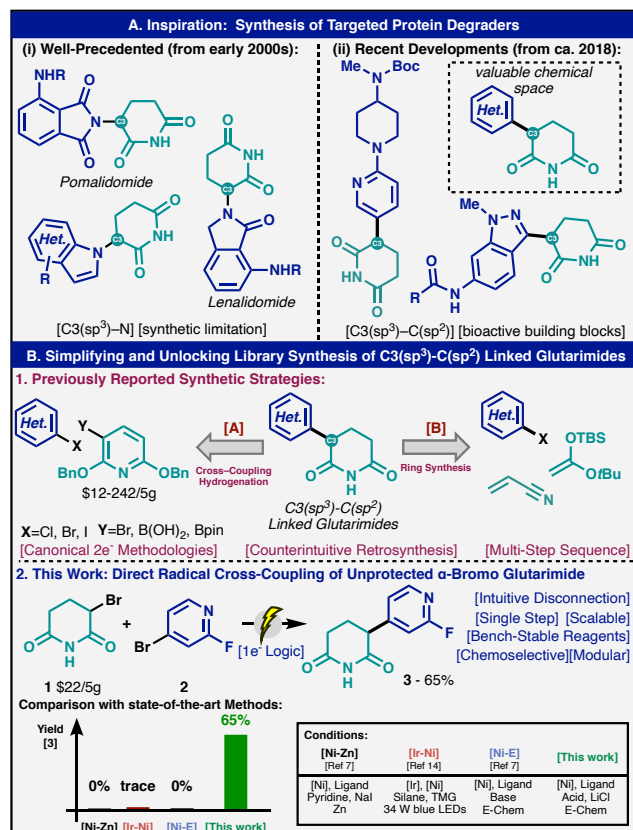
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Targeted protein degraders have found widespread utility in clinical treatments for various diseases, including cancer, immune disorders, viral infections, and neurodegenerative diseases since their first disclosure in 2001.<sup>1</sup> Molecular Glues (e.g. cereblon E3 ligase modulating drugs; CELMoDs) and bifunctional degraders (e.g. proteolysis targeting chimeras; PROTACs) trigger the rapid, selective degradation of targeted proteins by concurrently binding the E3 ligase and the protein targeted for degradation.<sup>2</sup> Traditional degraders possess C3(sp<sup>3</sup>)-N substituted glutarimides (e.g. Pomalidomide, Lenalidomide), which have proven to be valuable structural motifs for their ability to bind E3 ligase/CRBN (Figure 1A).<sup>3</sup> Recent developments in this area have explored alternative binding vectors and linkage modes to the glutarimide motif. Chief amongst these novel architectures are C3(sp<sup>3</sup>)-C(sp<sup>2</sup>) substituted glutarimides, which have seen increasing use in academic and patent literature.<sup>4-6</sup> Whereas the demand for such structures has increased, their respective syntheses remain a vexing problem to date, heavily relying on canonical 2e<sup>-</sup> methodologies which suffer from poor selectivity, modularity, and functional group tolerance (Figure 1B-1). Surprisingly, only two distinct synthetic strategies have been employed: (A) Pd-catalyzed cross-coupling of often cost-prohibitive 2,6-bis(benzyloxy)pyridine units with (hetero)aryl halides followed by exhaustive hydrogenation, or (B) heterocyclic synthesis of the glutarimide ring via a Pd-enolate coupling followed by harsh cyclization conditions.<sup>4</sup> Counterintuitive retrosyntheses and low-yielding, multi-step sequences characterize both strategies. A far more direct and inexpensive approach would enlist  $\alpha$ -bromoglutarimide **1**, a widely available building block, in a cross-coupling with (hetero)aryl halides. The capricious nature of unpro-

ted **1** makes it virtually unusable in cross-coupling approaches and no metal-mediated cross-coupling of **1** have been reported to date. In our hands, all known cross-coupling methods failed to react **1** with pyridine **2** in more than traces (chemical, photochemical, or electrochemical).<sup>7, 8</sup> Herein we report a direct, electrochemically enabled nickel-catalyzed cross-coupling of unprotected  $\alpha$ -bromoglutarimide with various (hetero)aryl halides to forge the essential C3(sp<sup>3</sup>)-C(sp<sup>2</sup>) glutarimide linkage (Figure 1B-2). This radical cross-coupling strategy succeeds when other cutting-edge methods fail and is characterized by operational simplicity, intuitive retrosynthesis, and high chemoselectivity, enabling the modular synthesis of targeted protein degraders.

The invention of a direct electrochemical-promoted Glutarimide Cross-Coupling (GCC) using **1** was initially explored with bromopyridine **4** – (Table 1). Although other radical precursors were considered and evaluated, **1** is the least expensive and most convenient. In its fully optimized form, GCC is extraordinarily simple and convenient to conduct open to the air in an undivided cell without regard to residual moisture and air: After mixing **1** (1.5 equiv, \$9.00/g) and aryl halide **4** in NMP, NiCl<sub>2</sub>·6H<sub>2</sub>O (20 mol%, \$0.02/g), bipy (20 mol%, \$0.08/g), TBABF<sub>4</sub> (1.0 equiv, \$0.96/g), LiCl (2.5 equiv, \$0.05/g), and AcOH (1.5 equiv, \$0.26/l) are added. Subsequent electrolysis at room temperature for 5 hours results in a 78% isolated yield of **5** (entry 1). Not surprisingly, rudimentary control studies (entries 2-4) demonstrate the need for Ni, ligand, and electricity. One of the two main breakthroughs of

this study, however, was the finding that a Brønsted-acid enabled this transformation as shown in entry 5.



**Figure 1.** (A) Valuable synthetic building blocks for Proteolysis Targeting Chimeras (PROTACs). (B) State-of-the-art strategies for the synthesis of C3(sp<sup>3</sup>)-C(sp<sup>2</sup>) linked glutarimides.

While numerous proton-sources can facilitate the reaction, AcOH was chosen due to its low cost, ease of removal, broad functional group tolerance and highest performance of acids screened (see SI). The use of acid additives is rare in Ni-based cross-couplings and, to our knowledge, without precedent for Ni-electrocatalysis. Indeed, this unusual inclusion is counterintuitive due the potential of undesired proto-dehalogenation and/or reduction reactions. As the resistance is low due to the acid additive, an electrolyte is not necessary but its inclusion increases overall conversion by 10-20% (entry 6). The addition of LiCl, however, is essential to achieve reasonable catalyst turnover and may serve a variety of roles (entry 7).<sup>9</sup> It is interesting to note that the use of NiBr<sub>2</sub> in place of NiCl<sub>2</sub> (in the absence of LiCl) completely shuts down the reaction (entry 8). Increasing the catalyst loading to 40 mol% in the absence of LiCl results in only a single turnover of the catalyst (entry 9). The use of AgNO<sub>3</sub>, an additive that is quite beneficial in the coupling of redox-active esters, has no beneficial effect in this reaction (entry 10).<sup>10, 11</sup> Lowering the catalyst loading to 10 mol% only has a modest effect on the yield (entry 11) and a full 6 F/mol of electrons results in the highest conversion (entry 12).

With a robust set of optimized conditions in hand, the substrate scope was explored as depicted in Table 2 with a focus only on 23 known structures from the medicinal chemistry literature (9 patents,<sup>5, 12, 2</sup> publications<sup>4, 13</sup>). Strikingly, all of these disclosures use only two general strategies for synthesis, both of which rely on classic 2-electron disconnections: (1) Pd-cross-coupling of protected pyridine **7** (itself requiring a 3-step synthesis), and (2) stepwise glutarimide ring synthesis through condensation, hereby referred to as [Lit. A] and [Lit. B],

respectively. For instance, seemingly simple structures **10** and **14** were previously prepared by either [Lit. A] for **10** or [Lit. B] for **14** in 2-4 steps and 4-75% overall yield respectively. In contrast the same structures were accessed via GCC in a single step when coupled with the corresponding aryl iodide in 42-84% yield. For completeness sake, several known radical cross-couplings (chemical, electrochemical, photochemical)<sup>7, 14</sup> were benchmarked on seven different substrates (**3**, **15-20**) and the highest yield observed for any substrate or condition was less than 5% (compound **16** & **17**) with most entries giving no observable product. In all cases debrominated glutarimide was observed as the major product.

**Table 1.** Optimization of synthesis of C3(sp<sup>3</sup>)-C(sp<sup>2</sup>) linked glutarimides via Ni-electrocatalytic cross-coupling.<sup>a</sup>

**Optimization on Radical Cross-Coupling of Unprotected  $\alpha$ -Bromo Glutarimide**

Reaction scheme: **1** (1.5 equiv.) + **4** (0.4 mmol) → **5** (Yield 78%)  
Conditions: NiCl<sub>2</sub>·6H<sub>2</sub>O (20 mol%), 2,2'-bipy (20 mol%), AcOH (1.5 equiv.), TBABF<sub>4</sub> (1.0 equiv.), LiCl (2.5 equiv.), NMP, r.t., 12 mA, 6.0 F/mol, Mg(+)/RVC(-), 5 h

Entry	Modification	Yield (%) <sup>a</sup>
1	none	78
2	No [Ni]	0
3	No Ligand	0
4	In presence of (+)Mg but no electricity (16 h)	0
5	No AcOH	<5
6	No TBABF <sub>4</sub>	53
7	No LiCl	16
8	NiBr <sub>2</sub> instead of NiCl <sub>2</sub> ·6H <sub>2</sub> O	0
9	Entry 7, 40 mol% of [Ni] and 2,2'-bpy	37
10	Entry 9, with AgNO <sub>3</sub> instead of TBABF <sub>4</sub>	41
11	10 mol% of [Ni] and 2,2'-bpy	71
12	4.0 F/mol instead of 6.0 F/mol	59

**Standard Procedure:**

- Dissolve [Ni], bpy, Glu-Br Ar-X, TBABF<sub>4</sub> and LiCl in NMP
- Add AcOH
- Electrolyze open to air

<sup>a</sup>Yields determined by <sup>1</sup>H-NMR with 1,3,5-trimethoxybenzene as an internal standard.

GCC tolerates numerous functional groups and displays a high degree of chemoselectivity that appears to be not only superior to other radical methods tested but also the more laborious literature conditions. Thus, unactivated aryl fluorides (**3**, **22**), electron-rich arenes (**15**, **21**, **23**), free alcohols (**20**, **33**), pyridines (**14**, **3**, **16**, **17**, **22**, **27**), pyrimidines (**20**), indoles (**19**), labile acetate (**28**), indazoles (**29**), isoquinolines (**32**), quinolones (**30**), oxazolidinones (**31**), and even aryl bromides (**34**) were successfully employed. Remarkably, even a nitro-containing arene was tolerated under these mildly reductive conditions (**18**) with no reduction to the amine. The choice of aryl halide coupling partner with **1** in the GCC deserves further comment. In general, for electron-rich (hetero)arenes, an aryl iodide is preferable whereas aryl bromides are acceptable when using electron-poor (hetero)arenes. For medicinal chemistry explorations this is advantageous for orthogonal synthesis as the iodide can react preferentially in GCC followed by conventional metal(Pd/Ni/Cu/Fe)-couplings of the remaining aryl bromide (**34**). In terms of limitations, electron-rich (hetero)aryl bromides, imidazoles, pyridinones, and isoindolinones are so far not amenable to GCC (see SI for listing of the currently known problematic coupling partners).

The ease with which Ni-electrocatalytic cross-couplings can be scaled up has been demonstrated on numerous occasions.<sup>11, 15</sup> As such, GCC could be scaled up on gram-scale in batch or flow modes without any yield diminishment (Figure 2). The only modification made to the

**Table 2:** Scope of C3(sp<sup>3</sup>)-C(sp<sup>2</sup>) linked glutarimides and comparison with canonical methods.<sup>a,b</sup>

Scope of Reductive Radical Cross-Coupling: Comparison of Different Methods for the Synthesis of C3(sp <sup>3</sup> )-C(sp <sup>2</sup> ) Linked Glutarimides	
<p><b>[Ni]-Electrocatalytic Access to C-Linked Glutarimides</b></p> <p>[Operationally Simple] [PROTAC Building Blocks] [Open to Air] [Undivided Cell] [Patent Literature Applications]</p> <p><b>Methods used for comparison:</b> [Ni-Zn] [Ref 7] [Ir-Ni] [Ref 14] [Ni-E] [Ref 7]</p>	<p>NiCl<sub>2</sub>·6H<sub>2</sub>O, bpy, AcOH, LiCl, TBABF<sub>4</sub>, NMP, r.t., 12 mA, 6.0 F/mol, (+)Mg/(-)RVC</p>
<p><b>[Lit. A] 2e<sup>-</sup> Strategy - Pd cat. Cross-Coupling</b></p> <p><b>[Lit. B] 2e<sup>-</sup> Strategy - Glutarimide Ring Synthesis</b></p>	<p><b>10 (X=I)</b> [Ni] 84% [Lit. A] 75% (2)</p> <p><b>14 (X=I)</b> [Ni] 42% [Lit. B] 4% (4)</p>
<p><b>3 (X=Br)</b> [Ni] 65% [Lit. A] 41% (2) [Ni-Zn] 0%<sup>c</sup> [Ir-Ni] trace<sup>d</sup> [Ni-E] 0%<sup>c</sup></p> <p><b>15 (X=I)</b> [Ni] 81% [Lit. B] 57% (3) [Ni-Zn] 0%<sup>c</sup> [Ir-Ni] 0%<sup>d</sup> [Ni-E] trace<sup>c</sup></p> <p><b>16 (X=I)</b> [Ni] 61% [Lit. A] 17% (2) [Ni-Zn] 0%<sup>c</sup> [Ir-Ni] 0%<sup>d</sup> [Ni-E] &lt;5%<sup>c</sup></p> <p><b>17 (X=Br)</b> [Ni] 42% [Lit. A] 8% (2) [Ni-Zn] 0%<sup>c</sup> [Ir-Ni] trace<sup>d</sup> [Ni-E] &lt;5%<sup>c</sup></p> <p><b>18 (X=Br)</b> [Ni] 65% [Lit. B] 51% (4) [Ni-Zn] 0%<sup>c</sup> [Ir-Ni] 0%<sup>d</sup> [Ni-E] 0%<sup>c</sup></p> <p><b>19 (X=I)</b> [Ni] 40% [Lit. B] 3% (4) [Ni-Zn] 0%<sup>c</sup> [Ir-Ni] 0%<sup>d</sup> [Ni-E] trace<sup>c</sup></p> <p><b>20 (X=I)</b> [Ni] 13% [Lit. A] 9% (2) [Ni-Zn] 0%<sup>c</sup> [Ir-Ni] 0%<sup>d</sup> [Ni-E] 0%<sup>c</sup></p>	<p><b>21 (X=I)</b> [Ni] 48% [Lit. A] 20% (2)</p> <p><b>22 (X=Br)</b> [Ni] 36% [Lit. A] 88% (2)</p> <p><b>23 (X=I)</b> [Ni] 48% [Lit. A] 88% (2)</p> <p><b>24 (X=I)</b> [Ni] 46% [Lit. A] 4% (2)</p> <p><b>25 (X=I)</b> [Ni] 70% [Lit. A] 91% (2)</p> <p><b>26 (X=I)</b> [Ni] 44% [Lit. A] 16% (2)</p> <p><b>27 (X=I)</b> [Ni] 71% [Lit. A] 14% (2)</p> <p><b>28 (X=I)</b> [Ni] 58% [Lit. B] 57% (3)</p> <p><b>29 (X=I)</b> [Ni] 34% [Lit. A] 43% (2)</p> <p><b>30 (X=Br)</b> [Ni] 14% [Lit. A] 2% (2)</p> <p><b>31 (X=I)</b> [Ni] 33% [Lit. A] 18% (2)</p> <p><b>32 (X=I)</b> [Ni] 24% [Lit. B] 4% (3)</p> <p><b>33 (X=I)</b> [Ni] 19% [Lit. A] 58% (2)</p> <p><b>34 (X=I)</b> [Ni] 49% [Lit. B] 34% (4)</p>
<p><b>Limitations:</b></p>	

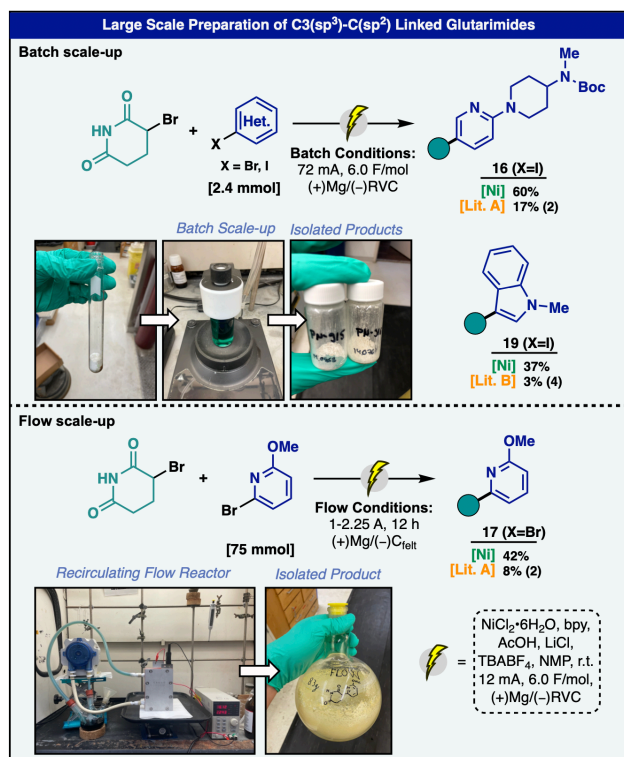
<sup>a</sup>Yields of isolated products are indicated unless otherwise specified. <sup>b</sup>Number of steps for literature comparisons are given in parentheses. For [Lit. A] only the Pd-catalyzed cross-coupling of the protected pyridine and subsequent hydrogenation were considered. <sup>c</sup>Yields determined by <sup>1</sup>H-NMR with 1,3,5-trimethoxybenzene as an internal standard. <sup>d</sup>Observations based on UPLC-MS analysis (see SI).

general procedure was scaling the current linearly to the amount of substrate employed (30 mA/mmol). In a batch setting, structures **16** and **19** could be easily procured on gram scale. When conducting the reaction of decagram scale under flow conditions, GCC proceeded smoothly to deliver **17** in 42% yield. Due to the polar nature of the solvents and additives both modes of scale-up operated under very low potential due to the low resistance of the media.

Therapeutics based on protein targeting degraders have become an extremely hot area for study in both academic and industrial arenas. The demand for rapid methods to append a glutarimide to various fragments through a C-C linkage at C3 is apparent given the sheer number of patents and publications in the area. It is striking that only two general methods were available to chemical practitioners for con-

structing such compounds, both wedged to laborious polar-bond based retrosynthetic disconnections. This is due to the peculiar reactivity and physical properties of free glutarimides that render their direct cross-couplings problematic. The most inexpensive functionalized glutarimide,  $\alpha$ -bromo derivative **1**, was found to be an unwilling coupling partner in all precedented radical cross-coupling conditions. The present work illustrates how a unique Brønsted-acid assisted Ni-electrocatalytic approach can tame the reactivity of **1** and render it a viable coupling partner in C-C bond formation with simple (hetero)arylhalides. While the role of the Brønsted-acid additive is speculative at the moment, it is postulated that it may serve to protect and attenuate the tendency of **1** to rapidly dehalogenate. The utility of this finding is proven by benchmarking it with state-of-the-art radical cross-coupling chemistries and implementing it to dramatically simplify the way a multitude of known PROTAC-precursors and candidates can be

prepared. The reaction is operationally trivial to conduct (insensitive to air, moisture tolerant, and conducted in an undivided cell), can be easily scaled up, and has already been field tested in a demanding pharmaceutical context.



**Figure 2.** Scale-up of synthesis of C3(sp<sup>3</sup>)-C(sp<sup>2</sup>) linked glutarimides in batch and flow reactor.

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P.N. and L.M. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Funding Sources

Financial support for this work was provided by the NSF Center for Synthetic Organic Electrochemistry (CHE-2002158). P.N. thanks the Kellogg Family for the Graduate Research Fellowship. L.M. thanks the Swedish Research Council (Vetenskapsrådet, VR-2023-00499) and the Stiftelsen Bengt Lundqvists Minne for postdoctoral fellowships. Á.P. acknowledges the European Union's Horizon Europe research and innovation programme for a Marie Skłodowska-Curie postdoctoral fellowship (MSCA-GF Grant No. 101110288).

## ACKNOWLEDGMENT

We thank L. Pasternack and G.J. Kroon for assistance with NMR spectroscopy; J. Chen, B. Sanchez, Q. N. Wong, and J. Lee (Scripps Automated Synthesis Facility) for assistance with HRMS; M. Nassir,

G. Laudadio A. Pollatos, M. D. Palkowitz, A. Garrido-Castro, M. Mandler, J. Richter, B. P. Vokits, S. A. Shaw and M. Costantini for helpful discussions.

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