Expedited Aminoglutarimide C-N Cross-Coupling Enabled by High-Throughput Experimentation

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Supporting Information Placeholder

ABSTRACT: A simple protocol for the direct Buchwald-Hartwig cross-coupling of (hetero)aryl halides with unprotected aminoglutarimide to afford diverse Cereblon Binding Motifs is disclosed. This C-N cross-coupling method development was enabled by high throughput combinatory screening of key reaction parameters namely solvents, temperatures and ligands. Scope studies revealed generality across various heteroaryl and aryl halides, with the reaction proceeding under mild conditions. In comparison, this method demonstrated strategic superiority over previously reported approaches, as evidenced by a significant step count reduction from known syntheses in the patent literature.

INTRODUCTION

Targeted Protein Degradation (TPD) has emerged as a powerful new mechanism to leverage against previously undruggable disease targets.[1, 2] Key to this approach is the recognition of the putative small molecule degrader by Cereblon. In this space, two such modalities have emerged; Ligand Directed Degraders (LDD's)[3] wherein a target recognition molecule is linked to a cereblon binding motif (CBM) and molecular glues or CELMoDs (Cereblon E3 Ligase Modulatory Drugs)[4] that create a suitable protein-protein interaction between Cereblon and the target protein. In both cases, Cereblon helps mediate ubiquitin transfer and subsequent proteasomal degradation (Figure 1A). Many chemical motifs have emerged as competent CBM, but none is more ubiquitous than glutarimide. Indeed, one of the most clinically successful degraders, Revlimid (Lenalidomide), involves such a motif appended to an isoindolinone core.[5, 6] While this scaffold has enjoyed a range of success against many targets, medicinal chemists have branched out beyond the isoindolinone in the development of novel degraders. The exploration of novel glutarimide-containing CBMs can alter the activity, depth of degradation, pharmacokinetic/pharmacodynamic properties, and off-target neosubstrate selectivity, which can impact the overall success of a potential degrader in the clinic.[7]

One emerging class of CBM's is the N-(hetero)aryl glutarimide, which has begun to find applications in a range of disease targets.[8, 9] Despite the promise of this CBM in degrader drug discovery, efforts to rigorously explore structure-activity relationships (SAR) have been limited by the inefficient and bespoke synthetic strategies currently employed (Figure 1B). Such strategies fall into two categories: 1) alkylation of anilines with an α-halo glutarimide and 2) C-N cross-coupling of a dibenzoyl pyridine which reveals the glutarimide after high-pressure hydrogenation. These strategies suffer from scope limitations and ideality for large-scale process development and manufacture. The alkylation approach requires a reasonably nucleophilic aniline, which limits the scope to electron-neutral and rich arenes. Such alkylation results in a low yield when an electron-deficient arene is employed, as shown in a recent patent,[10] where aniline **1** undergoes alkylation with bromoglutarimide to afford **2** in a poor 19% yield. While enabling the initial activity studies, such a strategy is unfit for process scale deliveries. On the other hand, while the C-N cross-coupling of anilines and aryl halides may incorporate a broader substrate scope, this mitigative approach is still stymied by the subsequent hydrogenation step, whose selectivity and efficiency depends on compatibility any appended functional group and the electronic properties of substrates. As an example, **4** was prepared with only 20% yield over 4 steps from commercially available starting material **3**.[11] The aforementioned limitations lead to an unmet need in medicinal chemistry for a robust and

general approach to explore this promising new CBM. An approach that leverages readily available starting materials and intuitive retrosynthetic logic would enable access to a broader scope of potential CBMs, which in turn further enables degrader drug discovery campaigns.

In this work, a direct Pd-catalyzed Buchwald-Hartwig C-N cross-coupling of a wide range of (hetero)aryl halides with a simple unprotected amino glutarimide is realized via high-throughput experimentation (HTE), thus offering medicinal chemists a reliable tool to expedite the CBM SAR exploration from commercially available starting materials in a single step (Figure 1C).

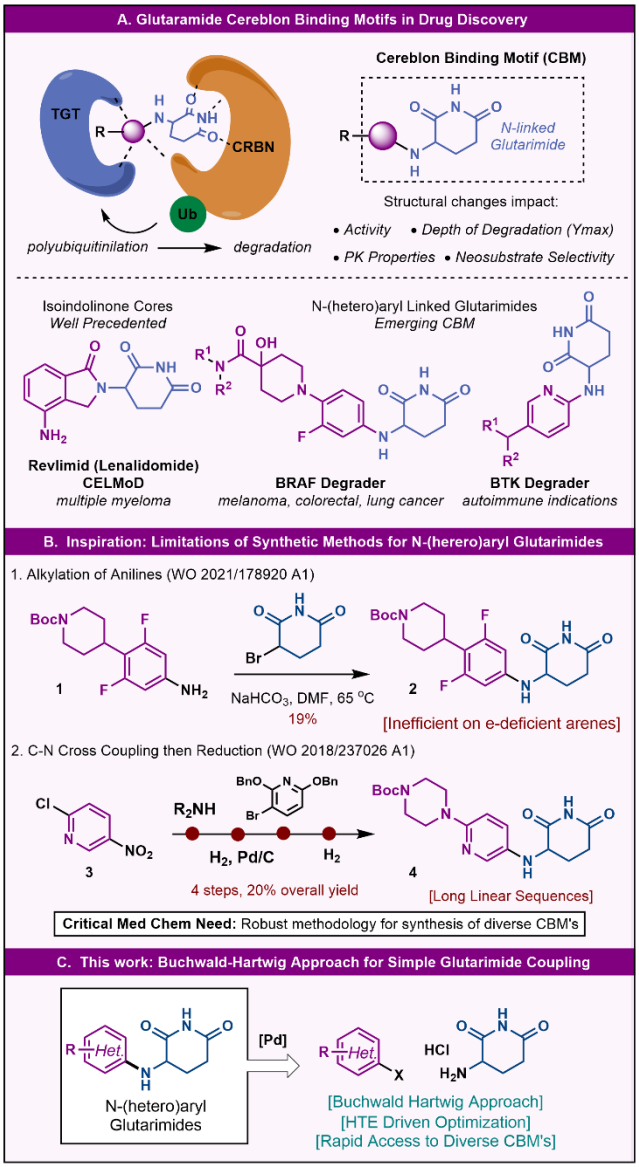

Figure 1: A) Cereblon binding motifs represent an important structural variable in degrader drug discovery. B) Current approaches to N-(hetero)aryl glutarimides lack generality or suffer from lengthy synthetic sequences. C) This work: A direct Buchwald Hartwig method enabled by high-throughput experimentation.

Reaction Optimization by High-Throughput Experimentation

The Pd-catalyzed Buchwald-Hartwig C-N cross-coupling has revolutionized medicinal chemistry and synthetic drug discovery efforts in the past three decades. In particular, the last decade has witnessed remarkable advances in ligand design, which have improved the efficiency and generality of Pd-catalyzed C-N cross-coupling in pharmaceutics research and development of drug molecules.[12] Given the significant advances in ligands design and mechanistic understanding of the Buchwald-Hartwig coupling, countless optimization tools are now available to synthetic chemists. High-throughput experimentation is a valuable tool for rapidly exploring and optimizing the broad, multivariate experimental space endemic to this transformation.[13-15] Following a literature survey, we identified several ligand classes that have been utilized for the cross-coupling of (hetero)aryl chlorides and primary amines, opting to evaluate the competence of bidentate bisphosphines, trialkylphosphines, and biaryldialkylphosphines ligands in the C-N cross-coupling of chloropyridine **5** and aminoglutarimide **6** (Figure 2).[16-19] When selecting an appropriate Pd precatalyst for a given transformation, it is important to consider the binding affinity of the chosen ligand to the metal center and the ability of the resulting complex to undergo reliable reduction (activation of $Pd^{(II)}$) to the on-cycle $Pd^{(0)}$ complex.[20-22] To accommodate the bulky phosphine ligands under investigation, we utilized the cationic Pd complex "[(crotyl)Pd]OTf" (generated *in situ* from an 0.5:1 molar ratio of $[(crotyl)PdCl]_2$ dimer and AgOTf).[23, 24]

With regards to solvent choice, we considered 1) the solubility of the principal reaction components, 2) the precedented efficiency of the given solvent medium in related Buchwald-Hartwig couplings, and 3) the chemical compatibility of the solvent with the hydrolytically labile glutarimide group. Broad solubility screening indicated that the hydrochloride salt of the 2-aminoglutarimide possesses exceedingly low solubility in most organic solvents. Aside from water, 2-aminoglutarimide•HCl is soluble in DMSO (>50 mg/mL) and MeOH (8 mg/mL) (see SI). In addition, we evaluated the performance of more traditional solvents such as *t*-AmOH, THF, and *i*PrOAc in the HTE platform. The combination of soluble organic bases and NaOTf as the halide scavenger has been documented to be effective for the amination of aryl halides bearing hydrolytically sensitive functionality, a desirable feature for this specific transformation. Thus, the combination of BTMG and NaOTf was included in the base screening alongside the standard NaO^{t}Bu base commonly employed in C-N cross-coupling.[25]

In our final high-throughput experimental design, we treated (**5**) and 1.25 equivalent of 2-aminoglutarimide•HCl (**6**) with 4.5 mol% "[(crotyl)Pd]OTf", 5 mol% phosphine ligand, and 3.5 equivalent base in 0.1 M solvent at 40 °C. Sixteen ligands, five solvents, and two base/halide scavenger combinations were interrogated for a total of 96 reactions. Among the selected ligands bisphosphine ligands, DPPF and SL-J009-1 and monophosphine ligands BrettPhos, and *t*BuBrettPhos constituted highly reactive catalyst systems, providing the desired product (**7**) in >95 relative area percent (RAP). While EtOH has been demonstrated to be a competent solvent for Pd-catalyzed aminations, exclusively alcoholysis and S_NAr products were observed.[26] *i*PrOAc similarly yielded complex mixtures of undesired products. While an excellent solvent for the glutarimide salt, DMSO provided moderate conversion of starting material and yield of the desired product. THF was the most effective solvent for this transformation, providing clean reaction profiles and excellent conversion for the top ligands. Surprisingly, *t*-amyl alcohol, a green solvent, provided a similar level of

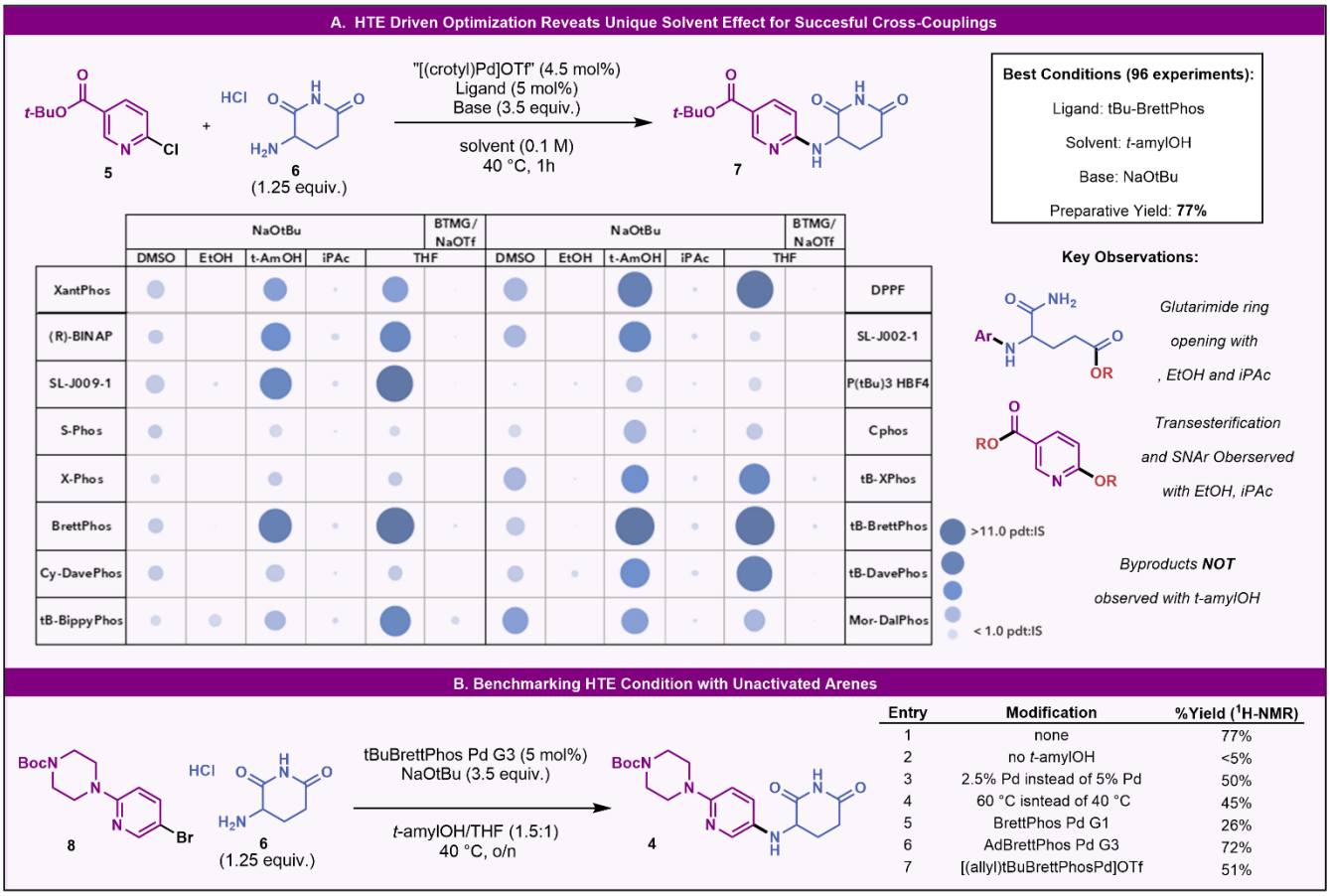

Figure 2: A) HTE optimization overview and common observations. The size and color of the sphere correspond to UPLC Area % of **7** relative to 4,4'-dimethyl-1,1'-biphenyl as an internal standard. B) Adaptation of HTE-derived conditions to less reactive heteroarenes. *1*H-NMR yields were taken using 1,3,5-trimethoxybenzene as an internal standard.

generality for nearly all ligands explored in this screen. commonly observed with protic alcoholic solvents were not detected with t-amylOH, likely due to the bulky steric of the conjugate alkoxide base. Finally, NaO*t*Bu showed excellent reactivity, while no desired product was observed in any BTMG/NaOTf reactions. From our HTE campaign, we identified (tBuBrettPhos)Pd as a highly active catalyst system, furnishing the desired product in >98 RAP in only 1 hr. When translated to preparative scale, these conditions afforded **7** in 77% isolated yield using *t*BuBrettPhos-Pd-G3 as a pre-catalyst.

In the next stage of our optimization campaign, we transitioned from microscale experimentation to milli-scale vial reactions leveraging a more complex aryl halide, **8** (Figure 2). With operational ease for the end user in mind, we utilized the commercially available, single-component pre-catalyst tBuBrettPhosPdG3, which resulted in a 77% NMR yield of **4**. Surprisingly, we found a critical solvent dependence on the success of this coupling with less activated bromopyridine derivative **8**. While THF was generally an effective solvent in the HTE screen, it did not yield appreciable product formation for this less reactive aryl halide. However, changing the amine from aminoglutarimide to a primary alkyl amine restored reactivity in both solvent systems (see SI). A selection of other top-performing ligands was evaluated with this less activated arene, and while all afforded the product in synthetically useful yields, tBuBrettPhosPdG3 remained the most effective pre-catalyst. The back and forth between HTE screening and pressure testing against more complex systems is an important exercise to ensure the generality of hits as well as revealing unique features of the investigated transformation with respect to condition selection.

Scope and Applications

With an optimized set of conditions in hand, the generality of the reaction was probed against a targeted selection of heteroarenes. Given the potential utility of such glutarimide-containing compounds in degrader drug discovery, our scope was deliberately targeted to known and exemplified N-(hetero)aryl glutarimides in the patent literature. The selected examples were previously accessed in either multistep C-N cross-coupling followed by exhaustive hydrogenation or aniline alkylation (vide supra), thus providing a strategic comparison of this method.[8, 11] Furthermore, we elected to test the reaction against different halides (chloride, bromide, and iodide) to show versatility in various synthetic settings, where one halogenated arene may be easier to access than others.

The reaction tolerated a wide range of electronically diverse functionality on halobenzene coupling partners. Fluoro-methoxy benzene-containing coupling partners afforded the N-aryl glutarimide (**9**) in modest yield (44% from the iodide and 62% from the bromide). Cyanotoluene coupling partners were tolerated (**10**), with no nitrile hydrolysis observed (58% from the iodide and 37% from the bromide). Electron-deficient benzenes bearing *para*-fluoro (**11**) and *para*-trifluoromethyl (**12**) provided the *N*-aryl glutarimides in moderate to good yields across bromide and iodide coupling partners. *N*-alkyl indoles were tolerated in the reaction, affording **13** in

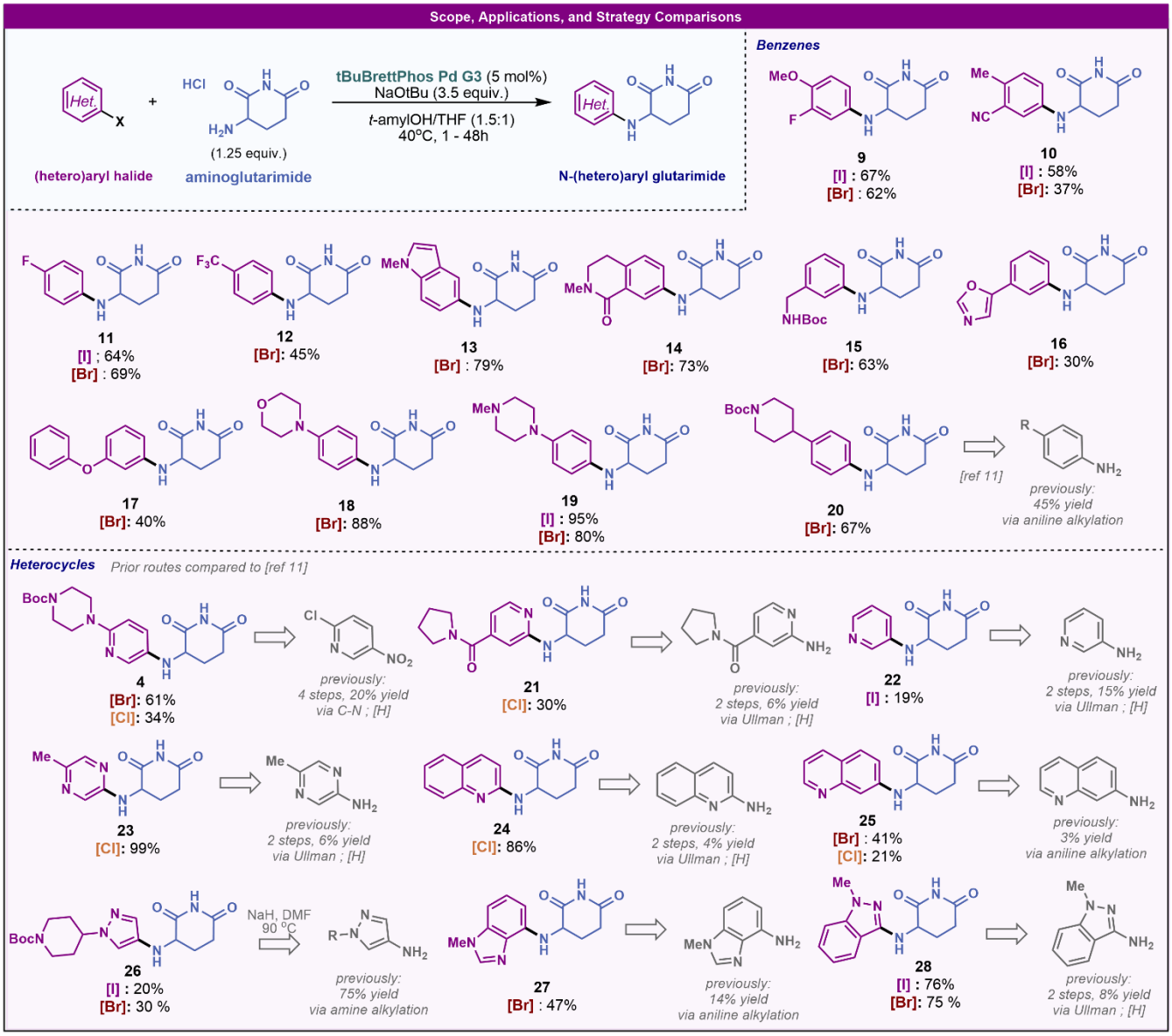

Figure 3: Scope of the Buchwald-Hartwig cross-coupling. Reactions were performed on a 0.5 mmol scale of the limiting (hetero)aryl halide. Isolated yields are reported.

79% yield from the corresponding bromoindole. Fused lactams in the form of a tetrahydroisoquinolone were also tolerated, affording **14** in 73% yield. Pendant *Boc*-protected amines (**15**), oxazoles (**16**), phenyl ethers (**17**), morpholines (**18**), and piperazines with basic amines (**19**) afford a diverse range of N-aryl glutarimides in moderate to high yields. Boc-piperidine containing **20** was prepared in 67% from the corresponding bromide. In comparison, previous patent synthesis leveraging aniline alkylation only afforded the desired compound in 45% yield.

Next, a series of heteroaryl halides were sampled to access diverse N-heteroaryl glutarimides, which were previously accessed in low-yielding synthetic sequences. Hence, strategic comparisons between the disclosed Buchwald-Hartwig approach and the prior patent synthesis demonstrate a compelling use case for medicinal and process chemists to easily access these compounds. First, **4**, was previously accessed in 4 steps following a C-N cross-coupling, hydrogenation approach in 20% overall yield. Leveraging our Buchwald-Hartwig approach with aminoglutarimide provided **4** in 61% yield from the commercially available bromide and 34% from the corresponding chloride. Aminopyridines are excellent isosteres for the often metabolically fragile aniline motif found in the above benzene examples. As such, there is a pressing medicinal chemistry need to access such heterocyclic matched pairs. 2-pyridyl containing (**21**) was accessed in 30% yield while prior approaches leveraging an Ullman of a dibenzoyl pyridine followed by hydrogenation only gave the target compound in 6% yield. While 2-pyridyl worked efficiently in this reaction, 3-iodopyridine was poor, yielding **22** in 19%. While low yielding, this result is an improvement over the prior two-step Ullman followed by hydrogenation approach, which only resulted in a 15% overall yield. A 2-chloropyrazine derivative afforded **23** in nearly quantitative yield, while previous approaches from the corresponding aminopyrazine only provided **23** in 6% yield over two steps. Similarly, 2-chloroquinoline efficiently afforded **24** in 86% yield, while prior approaches only gave 4% over two steps. Importantly, these substrates were left unreacted in the absence of palladium, thus ruling out a hypothetical S_NAr

mechanism for such electrophilic coupling partners (See SI). Moving the halogen over to the 7-position of the quinoline reduced the reactivity of the substrate affording **25** in 41% yield (Br) and 21% (Cl). While a drop in yield, prior alkylation of 7-aminoquinoline only resulted in 3% yield. An N-alkyl-3-halopyrazole derivate gave **26** in modest yield (20% from the iodide, 30% from the bromide). Such 5-membered heterocycles are challenging substrates for many C-N couplings. While aminopyrazole alkylation gave **26** in 75% in the patent literature, this approach required hazardous alkylation conditions, which preclude large-scale preparations (NaH, DMF). Benzimidazole containing glutarimide **27** was accessed in 47% yield from the corresponding bromide, while prior approaches leveraging aniline alkylation only gave **27** in 14% yield. Finally, *N*-methyl indazole containing **28** was efficiently accessed in 76% yield (I) and 75% yield (Br), while the prior two-step Ullman then hydrogenation approach only gave **28** in 8% overall yield. Collectively, these targeted case studies demonstrated the contextual superiority of the Buchwald-Hartwig approach for the synthesis of medicinally relevant N-(hetero)aryl glutarimides.

While the C-N cross-coupling reaction demonstrated a broad scope under this newly developed method, it is not without some limitations. In this respect, electrophilic partners bearing flanking ortho-substituents failed to engage in the cross-coupling possible due to steric hindrance. Similarly, hetero(aryl) or aryl bromides and chlorides with a strongly deactivating electron-donating group performed poorly in the reaction. Sometimes, the reactivity could be turned on by switching to the corresponding hetero(aryl) or aryl iodide. For instance, while 3-bromopyridine and 3-chloropyridine failed to engage in cross-coupling with **6**, 3-iodopyridine cross-coupled to provide the desired product, **22** in 19% yield. Additionally, employing stereodefined glutarimides resulted in complete racemization under the reaction conditions (See SI). Further optimization of the catalyst and additional reaction components is expected to assist in overcoming these limitations in subsequent HTE studies.

Conclusion

This general protocol for the synthesis of N-(hetero) aryl-linked glutarimides is expected to expedite the rate at which novel CBMs and, thus, degrader molecules are discovered and evaluated. While this transformation benefits from and is primarily the result of nearly three decades of research and precedence in C-N cross-coupling, the strategic simplification it offers enroute to potential therapeutics is noteworthy. It is anticipated that this single-step procedure that links commercially available starting materials to valuable chemical matter will have utility in TPD drug discovery and subsequent medicinal chemistry efforts. This work further highlights the enabling power of high-throughput experimentation in chemical synthesis and catalysis.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website and contains the experimental procedures, compound characterization and NMR data.

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Author Contributions

M. D. P. and J. M. G. conceived the work. M. D. P. and J. M. G. designed the experiments and optimized the reaction. H. L. and F. R. conducted solubility studies. M. S. O performed initial scope studies. J. W. G. completed the scope and collected all the data. J. W. G., M. S. O., J. M. G. and M. D. P. wrote the manuscript.

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