Ni-Catalyzed Asymmetric Reductive Arylation of α-Substituted Imides

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ABSTRACT: An asymmetric Ni-catalyzed reductive cross-coupling of α-substituted imides and (hetero)aryl halides has been developed to synthesize enantioenriched α-aryl imides, a commonly found structural motif in bioactive molecules and proteolysis-targeting chimeras (PROTACs) designed for targeted protein degradation (TPD). Employing a two-strategy approach with judiciously designed functional group pairings of the electrophiles allows for the coupling of either electron-rich or electron-deficient aromatics and heteroaromatics in good yields and enantioselectivities.

INTRODUCTION

Stereogenic α-aryl imides are found in a variety of bioactive compounds, and have recently garnered interest owing to their promising potencies as selective inhibitors for various diseases.[1,2] In the early 21st century, Tilley and coworker disclosed the efficacy of imide-derived antagonists in blocking VLA-4 binding to VCAM, guiding research for asthma and rheumatoid arthritis.[3] In 2018, Rossello and coworkers enhanced MMP-12 inhibition by installing a cyclic imide onto a known analog, offering promising prospects for treatment of cardiovascular diseases and lung inflammation (Figure 1a).[4]

Specifically, α-aryl glutarimides have garnered significant attention in the field of targeted protein degradation (TPD) as more chemically stable analogs for immunomodulatory drugs (IMiDs) such as thalidomide, pomalidomide, lenalidomide, and avadomide (Figure 1b).[5–7] These molecules are commonly integrated into the designs of proteolysis-targeting chimeras (PROTACs), which are heterobifunctional small molecules consisting of two covalently linked protein-binding moieties (Figure 1c).[8–10] The electron-withdrawing phthalimide moieties of glutarimides such as thalidomide result in configurational instability of these molecules, leading to issues such as racemization and hydrolysis of the glutarimide moieties within the body, thereby impacting their cell efficacies.[11,12] To address this issue, α-aryl and heteroaryl imides were pursued as potential alternatives, with the aim of broadening the chemical space of the analogs while improving stability.[13,14]

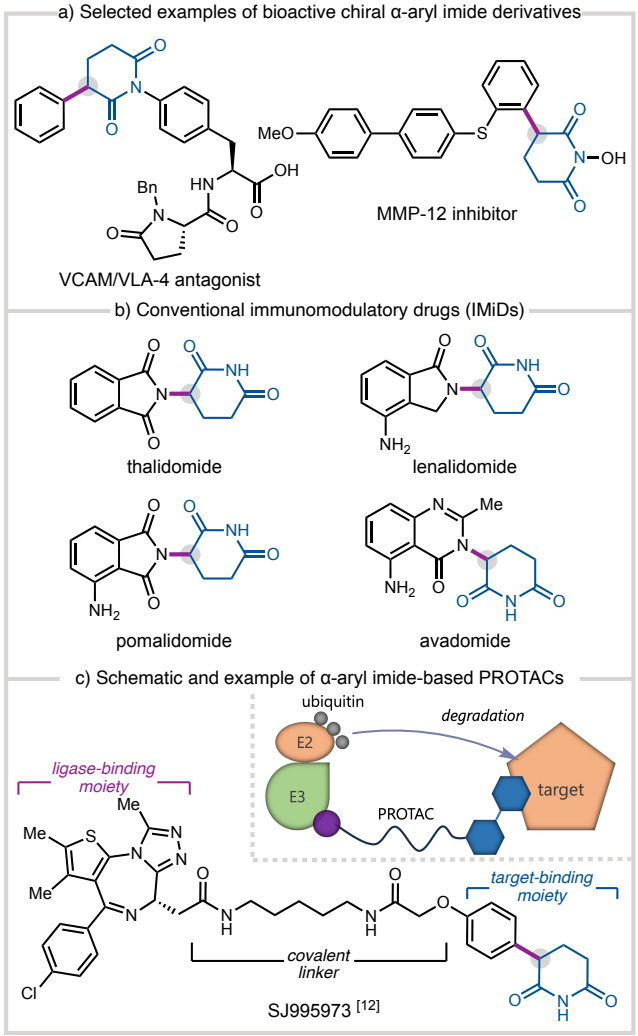
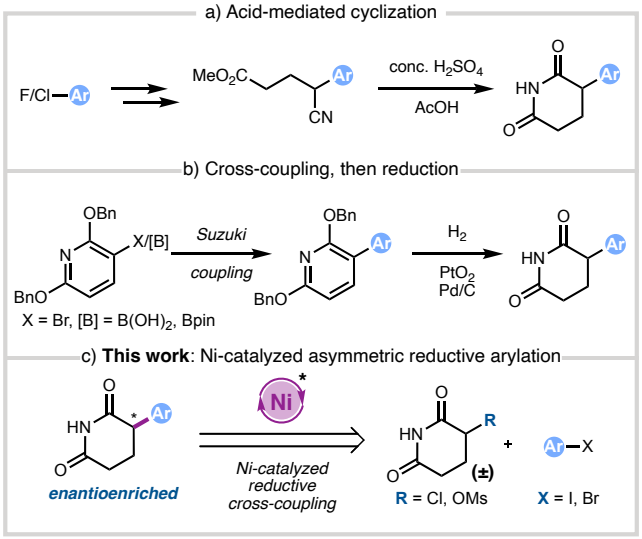


Figure 1. Selected examples of bioactive chiral α-substituted imide derivatives.

Prior routes to α-arylglutarimides typically require multistep sequences that incorporate the arene prior to imide formation. A common approach involves the synthesis of α-aryl cyanoesters, which are then hydrolyzed and cyclized under acidic conditions to form the glutarimide moiety (Scheme 1a).[13,15] A second approach functionalizes a 2,6-dibenzyloxypyridine by Suzuki cross-coupling followed by simultaneous debenzylation and hydrogenation to produce the glutarimide (Scheme 1b).[12] Although these approaches provide access to the α-arylglutarimides, the incorporation of functional groups early in the synthesis can limit the diversity of pendant structures, making rapid analog generation more cumbersome. Additionally, if the functional groups are sensitive to acid or prone to reduction, retaining the desired functionality through imide formation steps becomes significantly more challenging. Moreover, neither strategy allows for direct access to enantioenriched products, rendering the investigation of the pivotal role of chirality in their biological properties challenging.[16]

To address these issues, we have developed a modular Ni-catalyzed reductive cross-coupling reaction to prepare α-arylglutarimides (Scheme 1c). This approach enables modular incorporation of a wide array of aryl motifs, thereby aiding investigations into the structure activity relationship (SAR) for IMiD modifications.

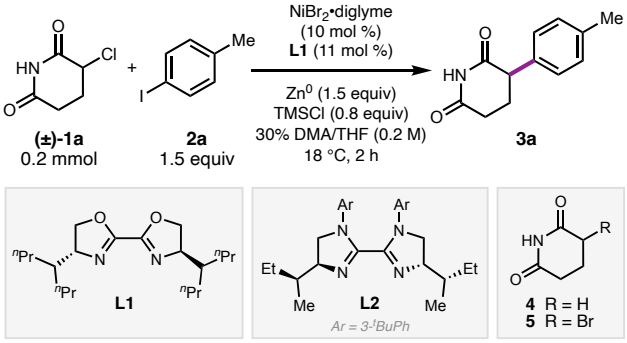
Scheme 1. Previously reported strategies and our proposed strategy and synthetic utility.



RESULTS AND DISCUSSION

We initiated studies on the cross-coupling between 3-chloropiperidine-2,6-dione and 4-iodotoluene (**1a** and **2a**, respectively, Table 1). By screening several ligand scaffolds commonly used for asymmetric Ni-catalysis, such as BiOX, BOX, and PyOX,[17] we determined that 4-heptylBiOX (**L1**) provided the highest enantioselectivity (see SI). With $NiBr_2$·diglyme as the Ni pre-catalyst, Zn^0 as the terminal reductant, and 30% DMA/THF as the solvent, the desired cross-coupled product can be obtained in 85% yield and 94% ee (Table 1, entry 1). This co-solvent system provided an optimal balance between reactivity and enantioselectivity, outperforming either DMA (entry 2) or THF (entry 3) as the sole solvent. With BiIM ligand **L2**, which was recently reported as a more effective ligand than BiOX ligands in related reactions,[18] **3a** was formed in 61% yield and 61% ee (entry 4). The Ni loading can be further reduced to 7.5 mol % with only a modest decrease in ee (entry 5). However, further reducing the loading to 5 mol % resulted in a decrease in yield (entry 6). Use of the soluble organic reductant, tetrakis(dimethylamine)ethylene (TDAE), failed to provide any of the desired product (entry 7).[19]

Table 1. Optimization of reaction conditions for the reductive cross-coupling between α-chloroimides and aryl iodides.



Entry	Deviation from standard conditions	yield **3a** (%)[a]	ee **3a** (%)	yield **4** (%)[a]
1	none	**85**	**94**	9
2	DMA as solvent [c]	75	91	21
3	THF as solvent [c]	25	92	40
4	**L2** instead of **L1**	61	61	16
5	Ni/**L1** 7.5/8.25 mol %	85	93	9
6	Ni/**L1** 5/5.5 mol %	76	93	11
7	TDAE instead of Zn^0	0	--	0
8	no Ni/**L1**	0	--	97
9	**5** instead of **1a**	0	--	51
10	4-BrPhMe (**7a**) instead of **2a**	<10	--	33

[a] Determined by ^{1}H NMR versus 1,3,5-trimethoxybenzene as internal standard. [b] Determined by SFC using chiral stationary phase. [c] 3.0 equiv of Zn^0 powder used.

A control experiment performed in the absence of Ni/**L1** afforded no cross-coupled product, suggesting that the C(sp^2)–C(sp^3) bond formation is mediated by nickel. However, under the same conditions, the protodehalogenation product **4** was observed in 97% yield, likely by direct reduction of **1a** by Zn^0 (entry 8). These studies suggest that **1a** can be directly reduced by Zn^0, although they do not reveal if this process interfaces with productive C–C bond formation.[20,21,22] Use of α-bromoimide **5** instead of **1a** failed to give any of the desired product and was converted to substantial amounts of **4** (entry 9) and only minimal yield of **3a** was observed when 4-bromotoluene (**7a**) was employed instead of **2a** (entry 10).

To evaluate the scope of the reaction, a variety of aryl iodides were coupled with **1a** under standard conditions (Figure 2, Method A). The yields of the cross-coupled products were found to be sensitive towards the electronics of the arene coupling partners. For electron-rich aryl iodides (**2a**, **2c**, and **2d**), the coupled products **3a**, **3b**, and **3c** were formed in yields >80%. *Ortho*- (**2l**) and *meta*-tolyl (**2m**)

substrates were coupled with good yields and comparable levels of ee. The reaction tolerates functional groups such as boronic pinacol ester (**2j**) and triflate (**2k**), which can serve as handles for further derivatization of the arene. Electron-rich heterocycles (**2z** and **2aa**) also coupled smoothly in excellent yields, whereas 7-azaindole derivative **3ab** was formed in lower, but serviceable yield.

Through these scope studies, we observed that the yields of **3** decreased correspondingly with the increase in electron-withdrawing strength of the functional groups at the *para* position (**2g-2i**) or *meta* position (**2n-2p**). 4-Iodopyridine derivatives, such as **2v** and **2w**, also underwent coupling in relatively low yields. In these cases, increased amount of biaryl homocoupling were generally observed, which we attribute to their faster rates of oxidative addition relative to the activation rate of the C(sp^3) electrophile **1a**. We also evaluated the cross-coupling of **1a** with 4-bromobenzotrifluoride (**7h**) under otherwise exact conditions. This reaction also furnished low yield of coupled product (19% yield **3h**); however, in this case with full conversion of α-chloroimide **1a** and unreacted **7h** was recovered. In this instance, we hypothesized that **1a** is activated too quickly relative to the aryl bromide, leading to increased amount of **4**.

Given the increased commercial availability and generally lower prices of aryl bromides,[23,24] we became interested in developing conditions that would couple these substrates. We recognized that the rates oxidative addition of aryl bromides are generally slower than their aryl iodide counterparts,[25] and would require an imide coupling partner with a well-matched rate of activation. Drawing from prior literature, we hypothesized that imides with α-sulfonates could be converted *in situ* to the α-haloimide;[26–29] this would serve to keep the concentration of the α-haloimide low, thus effectively decreasing the overall rate of activation.

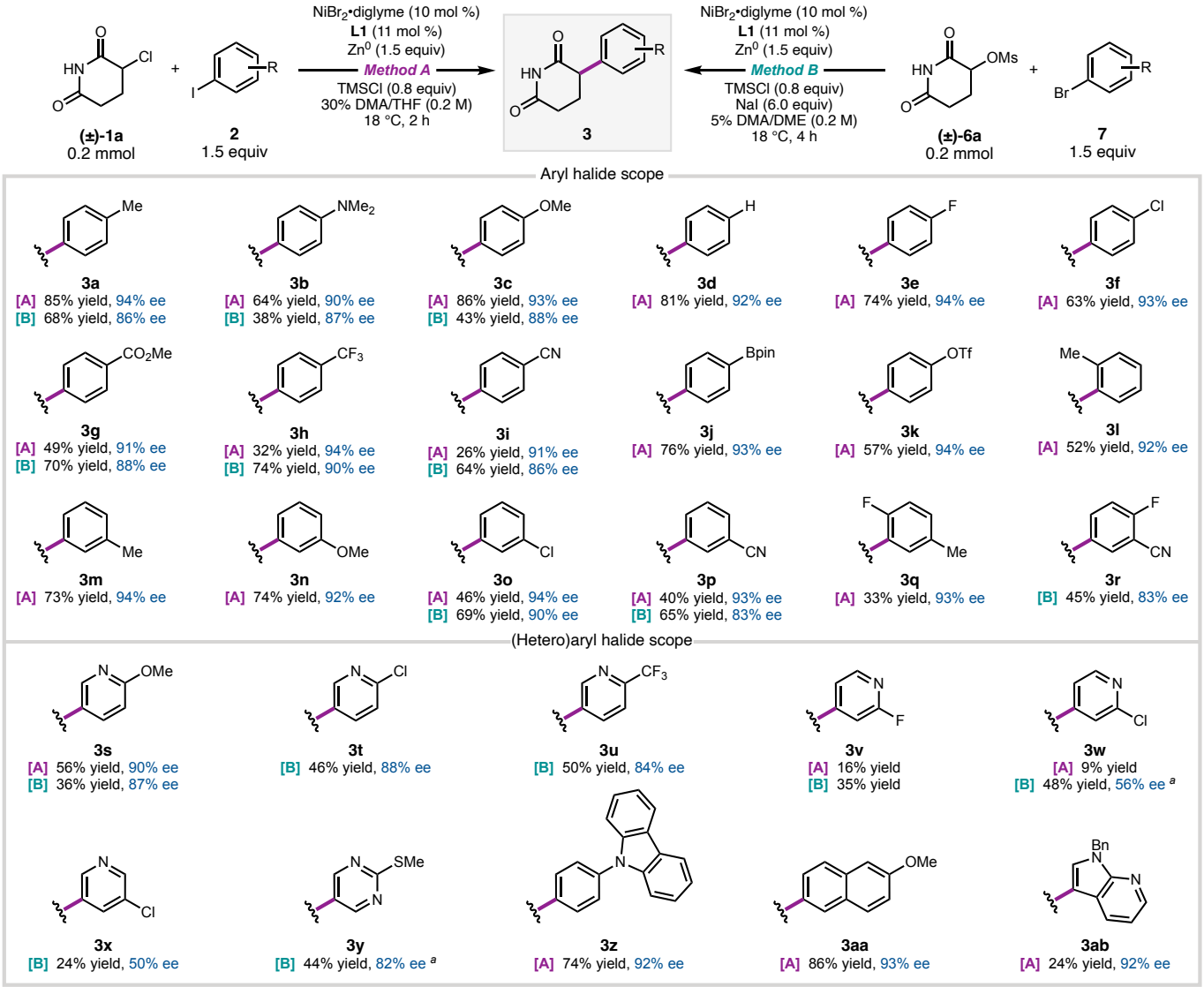
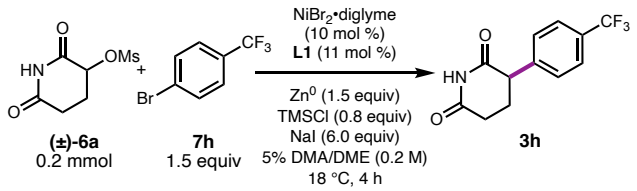


Figure 2. Substrate scope of (hetero)aryl halides. qNMR yields are provided versus 1,3,5-trimethoxybenzene as internal standard. ee was determined by SFC using a chiral stationary phase. [a] 3.0 equiv of Zn^0 used.

Table 2. Optimization of reaction conditions for the reductive cross-coupling between imide α-mesylates and aryl bromides.



Entry	Deviation from standard conditions	yield **3h** (%)[a]	ee **3h** (%)	recovered **6a** (%)[a]
1	30% DMA/THF, no NaI, 21 h	0	--	57
2	30% DMA/THF, 1 equiv NaI, 21 h	13	76	45
3	5% DMA/THF, 2 h [c]	69	87	11
4	5% DMA/THF, 3 h	73	80	5
5	none	**74**	**90**	8
6	24 h	72	86	0
7	no Ni/**L1**, 5% DMA/THF, 3 h [c]	0	--	12

[a] Determined by ^{1}H NMR versus 1,3,5-trimethoxybenzene as internal standard. [b] Determined by SFC using chiral stationary phase. [c] 1.0 equiv **5h** was used.

Thus, we investigated the cross-coupling between α-mesylate **6a** and aryl bromide **7h**. Under identical conditions to those used for the α-chloroimide–aryl iodide coupling, no product was formed (Table 2, entry 1), suggesting that neither the Ni catalyst nor zinc could directly activate α-mesylate **6a**. However, addition of 1 equivalent of NaI turned on reactivity for the system, forming the desired cross-coupled product in 13% yield and 76% ee (entry 2). Increasing the NaI loading to 6 equivalents and reducing the DMA/THF ratio from 30% to 5% was found to be critical in improving reactivity (entry 3, see SI for optimization details). However, extending the reaction time from 2 h to 3 h did not result in substantial further conversion of starting material to product (entry 4), and it was found that product **3h** was slowly epimerized under reaction conditions leading to formation of **3h** with decreased ee. Additional screening of solvents determined that DME suppresses racemization, resulting in 74% yield of **3h** with 90% ee after 4 h reaction time (entry 5). The effect of this solvent change can be further corroborated by extending the reaction time to 24 h, where only a slight decrease in ee was observed (entry 6). In the absence of Ni/**L1**, no cross-coupled product was observed, but again protodehalogenation product **4** was observed in 53% yield.

The scope of aryl bromides was then evaluated using this new set of conditions (Figure 2, Method B), enabling the direct comparison and assessment of the complementarity of this approach for accessing electron-deficient substrates. Substrates bearing electron-withdrawing groups such as ester and cyano groups at either the *para* (**7g-7i**) or *meta* position (**7o**, **7p**, **7r**) underwent coupling with higher yields than in Method A, albeit with a slightly reduced ee. Mildly electron-donating groups such as *para*-methyl (**7a**) resulted in comparable yields, yet further increase in the donating strength of the substituents led to decrease in yield (**7b** and **7c**). This observation highlights how the judicious matching of C(sp^3) and C(sp^2) electrophile activation can be used to obtain good yield of a broad array of α-arylimide products.

In the case of heteroaryl bromides, 3-pyridyl (**7s-7u, 7x**) or 4-pyridyl (**7v** and **7w**) substrates were well tolerated in the reaction and afforded in good yields. We note that the enantioselectivity of several of the products was observed to be substantially lower, likely due to their increased propensity to epimerization under the reaction conditions. Pyrimidine substrates such as **7y** can also be coupled in 44% yield and 82% ee. The reductive cross-coupling between imide α-mesylates and heteroaryl bromides thus serves as a promising complementary strategy to access electron-deficient arene substrates, greatly expanding the chemical space for SAR studies of α-heteroaryl glutarimide derivatives.

In many Ni-catalyzed cross-couplings, the C(sp^3) coupling partner undergoes oxidative addition through a radical mechanism involving halogen atom transfer.[30] In the case of α-haloimides, Zn^0 can also activate the imide, which may undergo further reduction to the Zn-enolate. To probe the intermediacy of a radical species, the reaction was conducted in the presence of TEMPO under the standard reaction conditions. No cross-coupled product was observed; instead, the TEMPO adduct of the glutarimide (**8**) was detected by LC-MS, which is consistent with a radical pathway. We also note that this reaction tolerates the unprotected imide; it is likely that the acidic N-H would quench any zinc enolate. Although this might be a process that gives rise to **4**, it seems unlikely that it is catalytically relevant.

Based on previous reports of BiOX·Ni-catalyzed reductive cross-coupling reactions,[22,31,32] we propose the following mechanism for the reaction. For the α-chloroimide–aryl iodide system, upon the reduction of the **L1**·$NiBr_2$ precatalyst, the resulting **L1**·Ni^IX complex is partitioned between two cycles. Oxidative addition of the aryl halide by **L1**·Ni^I followed by reduction can give an **L1**·Ni^{II}ArX species.[33] This process can occur either through the reduction of a transient Ni^{III} species by Zn^0 or **L1**·Ni^IX.[22,32,34] Simultaneously, the α-chloroimide can be activated either *via* XAT by the **L1**·Ni^IX complex,[20,35] or through Zn-mediated reduction,[21] resulting in the generation of a cage-escaped radical α-imidoyl radical. This radical can be captured by the **L1**·Ni^{II}ArX species, followed by reductive elimination to yield the final product.

For the α-imide mesylate–aryl bromide system, a time course analysis was conducted monitor the recovery of starting materials and the formation of byproducts across different time points. Initially, there was an accumulation of aryl iodide, which decreased at later time points. This conversion of aryl bromide to the corresponding iodide is ascribed to a halogen exchange reaction mediated by the Ni complex.[36] We also determined that independent treatment of imide α-mesylate **6a** with 1 equiv of NaI in 5% DMA/DME afforded the

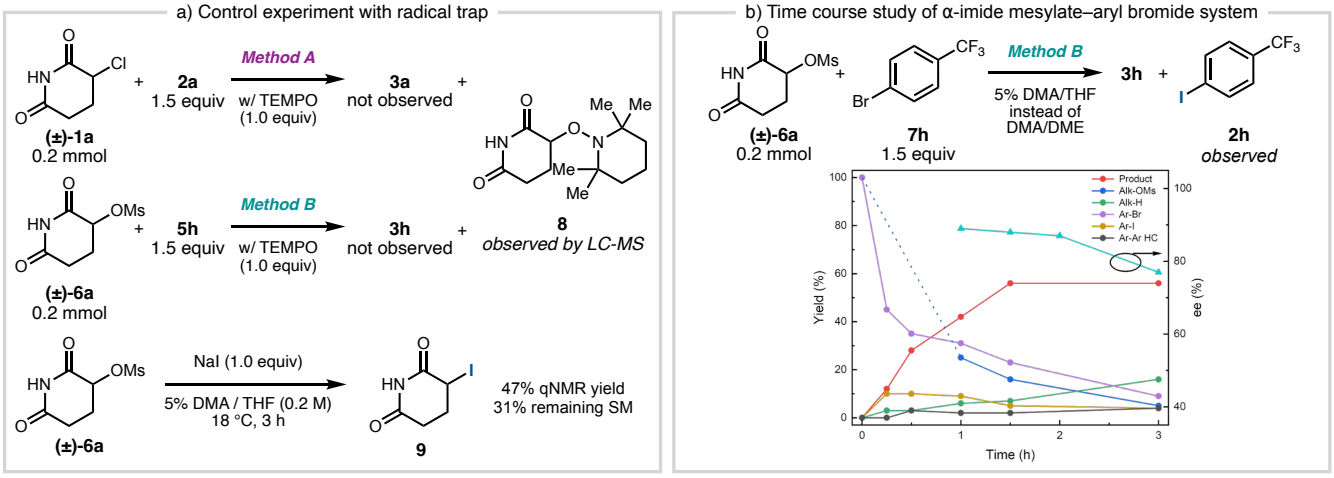


Figure 3. (a) Radical trap experiments and investigation of in situ halide exchange. (b) time course study.

corresponding α-iodoimide in a 47% yield at 3 h; however, this species was not observed at different time points in the Ni-catalyzed reaction, indicating the rapid consumption of such highly reactive species. We therefore propose that activation of the mesylate is not directly mediated by the Ni complex; instead, it is slowly converted to the α-haloimide *in situ*, which is then further activated by the Ni complex or Zn^0 to generate the cage-escaped radical. Analogously, capture of the cage-escaped radical by the **L1**·Ni^{II}ArX species and subsequent reductive elimination affords the final product.

CONCLUSION

In conclusion, we have developed a Ni-catalyzed asymmetric reductive cross-coupling between α-substituted imides and aryl halides. This transformation enables the facile assembly of highly enantioenriched α-arylimide motifs, which can serve as a powerful tool for elaboration towards PROTACs and other bioactive molecules. The reaction was found to be highly sensitive towards activation rates of either $C(sp^2)$ or $C(sp^3)$ coupling partners, where pairing of well-matched electrophiles was crucial for high cross-selectivity. Collectively, these conditions enable the cross-coupling of both electron-rich and electron-deficient arenes and heterocycles, and we anticipate that it will find applications in further medicinal chemistry studies.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Kim, Y.-C.; Karton, Y.; Ji, X.; Melman, N.; Linden, J.; Jacobson, K. A. Acyl-hydrazide derivatives of a xanthine carboxylic congener (XCC) as selective antagonists at human A2B adenosine receptors. *Drug Dev. Res.* **1999**, *47*, 178–188.

(2) Bojarski, A. J.; Mokrosz, M. J.; Duszyńska, B.; Kozioł, A.; Bugno, R. New Imide 5-HT1A Receptor Ligands – Modification of Terminal Fragment Geometry. *Molecules* **2004**, *9*, 170–177.

(3) Tilley, J. W.; Kaplan, G.; Rowan, K.; Schwinge, V.; Wolitzky, B. Imide and Lactam Derivatives of N-Benzylpyroglutamyl-l-Phenylalanine as VCAM/VLA-4 Antagonists. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1–4.

(4) Nuti, E.; Cuffaro, D.; Bernardini, E.; Camodeca, C.; Panelli, L.; Chaves, S.; Ciccone, L.; Tepshi, L.; Vera, L.; Orlandini, E.; Nencetti, S.; Stura, E. A.; Santos, M. A.; Dive, V.; Rossello, A. Development of Thioaryl-Based Matrix Metalloproteinase-12 Inhibitors with Alternative Zinc-Binding Groups: Synthesis, Potentiometric, NMR, and Crystallographic Studies. *J. Med. Chem.* **2018**, *61*, 4421–4435.

(5) Bartlett, J. B.; Dredge, K.; Dalgleish, A. G. The Evolution of Thalidomide and Its IMiD Derivatives as Anticancer Agents. *Nat. Rev. Cancer* **2004**, *4*, 314–322.

(6) Hanzl, A.; Winter, G. E. Targeted Protein Degradation: Current and Future Challenges. *Curr. Opin. Chem. Biol.* **2020**, *56*, 35–41.

(7) Luh, L. M.; Scheib, U.; Juenemann, K.; Wortmann, L.; Brands, M.; Cromm, P. M. Prey for the Proteasome: Targeted Protein Degradation—A Medicinal Chemist's Perspective. *Angew. Chem. Int. Ed.* **2020**, *59*, 15448–15466.

(8) Ishoey, M.; Chorn, S.; Singh, N.; Jaeger, M. G.; Brand, M.; Paulk, J.; Bauer, S.; Erb, M. A.; Parapatics, K.; Müller, A. C.; Bennett, K. L.; Ecker, G. F.; Bradner, J. E.; Winter, G. E. Translation Termination Factor GSPT1 Is a Phenotypically Relevant Off-Target of Heterobifunctional Phthalimide Degraders. *ACS Chem. Biol.* **2018**, *13*, 553–560.
(9) Fuchs, O. Targeting Cereblon in Hematologic Malignancies. *Blood Rev.* **2023**, *57*, 100994.
(10) Békés, M.; Langley, D. R.; Crews, C. M. PROTAC Targeted Protein Degraders: The Past Is Prologue. *Nat. Rev. Drug Discov.* **2022**, *21*, 181–200.
(11) Schumacher, H.; Smith, R. L.; Williams, R. T. The Metabolism of Thalidomide: The Fate of Thalidomide and Some of Its Hydrolysis Products in Various Species. *Br. J. Pharmacol.* **1965**, *25*, 338–351.
(12) Min, J.; Mayasundari, A.; Keramatnia, F.; Jonchere, B.; Yang, S. W.; Jarusiewicz, J.; Actis, M.; Das, S.; Young, B.; Slavish, J.; Yang, L.; Li, Y.; Fu, X.; Garrett, S. H.; Yun, M.-K.; Li, Z.; Nithianantham, S.; Chai, S.; Chen, T.; Shelat, A.; Lee, R. E.; Nishiguchi, G.; White, S. W.; Roussel, M. F.; Potts, P. R.; Fischer, M.; Rankovic, Z. Phenyl-Glutarimides: Alternative Cereblon Binders for the Design of PROTACs. *Angew. Chem. Int. Ed.* **2021**, *60*, 26663–26670.
(13) Phillips, A. J.; Nasveschuk, C. G.; Henderson, J. A.; Liang, Y.; He, M.; Lazarski, K.; Veits, G. K.; Vora, H. U. Preparation of C3-Carbon Linked Glutarimide Degronimers for Target Protein Degradation. WO2017197046A1, 2017.
(14) Nasveschuk, C. G.; Zeid, R.; Yin, N.; Jackson, K. L.; Veits, G. K.; Moustakim, M.; Yap, J. L. Compounds for Targeted Degradation of BRD9. WO2021178920A1, 2021.
(15) Nowicki, A.; Keldenich, J.; Agbossou-Niedercorn, F. Highly Selective Preparation of a Chiral Quaternary Allyl Aryl Piperidinedione by Palladium-Catalyzed Asymmetric Allylation Under Solid–Liquid Phase-Transfer Catalysis. *Eur. J. Org. Chem.* **2007**, *2007*, 6124–6127.
(16) Tokunaga, E.; Yamamoto, T.; Ito, E.; Shibata, N. Understanding the Thalidomide Chirality in Biological Processes by the Self-Disproportionation of Enantiomers. *Sci. Rep.* **2018**, *8*, 17131.
(17) Poremba, K. E.; Dibrell, S. E.; Reisman, S. E. Nickel-Catalyzed Enantioselective Reductive Cross-Coupling Reactions. *ACS Catal.* **2020**, *10*, 8237–8246.
(18) Zhou, P.; Li, X.; Wang, D.; XU, T. Dual Nickel- and Photoredox-Catalyzed Reductive Cross-Coupling to Access Chiral Trifluoromethylated Alkanes. *Org. Lett.* **2021**, *23*, 4683–4687.
(19) Broggi, J.; Terme, T.; Vanelle, P. Organic Electron Donors as Powerful Single-Electron Reducing Agents in Organic Synthesis. *Angew. Chem. Int. Ed.* **2014**, *53*, 384–413.
(20) Diccianni, J. B.; Katigbak, J.; Hu, C.; Diao, T. Mechanistic Characterization of (Xantphos)Ni(I)-Mediated Alkyl Bromide Activation: Oxidative Addition, Electron Transfer, or Halogen-Atom Abstraction. *J. Am. Chem. Soc.* **2019**, *141*, 1788–1796.
(21) Noyori, R.; Hayakawa, Y. Reductive Dehalogenation of Polyhalo Ketones with Low-Valent Metals and Related Reducing Agents. In *Organic Reactions*; John Wiley & Sons, Ltd, 2005; pp 163–344.
(22) Turro, R. F.; Wahlman, J. L. H.; Tong, Z. J.; Chen, X.; Yang, M.; Chen, E. P.; Hong, X.; Hadt, R. G.; Houk, K. N.; Yang, Y.-F.; Reisman, S. E. Mechanistic Investigation of Ni-Catalyzed Reductive Cross-Coupling of Alkenyl and Benzyl Electrophiles. *J. Am. Chem. Soc.* **2023**, *145*, 14705–14715.
(23) Mormino, M. G.; Fier, P. S.; Hartwig, J. F. Copper-Mediated Perfluoroalkylation of Heteroaryl Bromides with (Phen)CuRF. *Org. Lett.* **2014**, *16*, 1744–1747.
(24) Klapars, A.; Buchwald, S. L. Copper-Catalyzed Halogen Exchange in Aryl Halides: An Aromatic Finkelstein Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 14844–14845.
(25) Bajo, S.; Laidlaw, G.; Kennedy, A. R.; Sproules, S.; Nelson, D. J. Oxidative Addition of Aryl Electrophiles to a Prototypical Nickel(0) Complex: Mechanism and Structure/Reactivity Relationships. *Organometallics* **2017**, *36*, 1662–1672.
(26) Duan, J.; Du, Y.-F.; Pang, X.; Shu, X.-Z. Ni-Catalyzed Cross-Electrophile Coupling between Vinyl/Aryl and Alkyl Sulfonates: Synthesis of Cycloalkenes and Modification of Peptides. *Chem. Sci.* **2019**, *10*, 8706–8712.
(27) Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. Cobalt Co-Catalysis for Cross-Electrophile Coupling: Diarylmethanes from Benzyl Mesylates and Aryl Halides. *Chem. Sci.* **2015**, *6*, 1115–1119.
(28) Herbert, C. A.; Jarvo, E. R. Nickel-Catalyzed Stereoselective Coupling Reactions of Benzylic and Alkyl Alcohol Derivatives. *Acc. Chem. Res.* **2023**, *56*, 3313–3324.
(29) Do, H.-Q.; Chandrashekar, E. R. R.; Fu, G. C. Nickel/Bis(Oxazoline)-Catalyzed Asymmetric Negishi Arylations of Racemic Secondary Benzylic Electrophiles to Generate Enantioenriched 1,1-Diarylalkanes. *J. Am. Chem. Soc.* **2013**, *135*, 16288–16291.
(30) Fu, G. C. Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to SN1 and SN2 Processes. *ACS Cent. Sci.* **2017**, *3*, 692–700.
(31) Diccianni, J. B.; Diao, T. Mechanisms of Nickel-Catalyzed Cross-Coupling Reactions. *Trends Chem.* **2019**, *1*, 830–844.
(32) Ju, L.; Lin, Q.; LiBretto, N. J.; Wagner, C. L.; Hu, C. T.; Miller, J. T.; Diao, T. Reactivity of (Bi-Oxazoline)Organonickel Complexes and Revision of a Catalytic Mechanism. *J. Am. Chem. Soc.* **2021**, *143*, 14458–14463.
(33) Ting, S. I.; Williams, W. L.; Doyle, A. G. Oxidative Addition of Aryl Halides to a Ni(I)-Bipyridine Complex. *J. Am. Chem. Soc.* **2022**, *144*, 5575–5582.
(34) Lin, Q.; Diao, T. Mechanism of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 17937–17948.
(35) Lin, Q.; Fu, Y.; Liu, P.; Diao, T. Monovalent Nickel-Mediated Radical Formation: A Concerted Halogen-Atom Dissociation Pathway Determined by Electroanalytical Studies. *J. Am. Chem. Soc.* **2021**, *143*, 14196–14206.
(36) Tsou, T. T.; Kochi, J. K. Mechanism of Oxidative Addition. Reaction of Nickel(0) Complexes with Aromatic Halides. *J. Am. Chem. Soc.* **1979**, *101*, 6319–6332.