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Utilization of Cyclic Amides as Masked Aldehyde Equivalents in Reductive Amination Reactions

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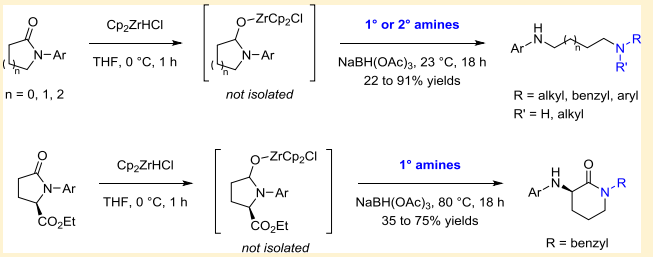
Supporting Information

ABSTRACT: An operationally simple protocol has been discovered that couples primary or secondary amines with *N*-aryl-substituted lactams to deliver differentiated diamines in moderate to high yields. The process allows for the partial reduction of a lactam in the presence of Cp_2ZrHCl (Schwartz's reagent), followed by a reductive amination between the resulting hemiaminal and primary or secondary amine. These reactions can be telescoped in a one-pot fashion to significantly simplify the operation. The scope of amines and substituted lactams of various ring sizes was demonstrated through the formation of a range of differentiated diamine products. Furthermore, this methodology was expanded to include *N*-aryl pyrrolidinone substrates with an enantiopure ester group at the 5-position, and α-amino piperidinones were prepared with complete retention of stereochemical information. The development of this chemistry has enabled the consideration of lactams as useful synthons.



INTRODUCTION

The propensity of amide groups to participate in resonance stabilization is the fundamental attribute which affords them uncharacteristic durability, as compared to other members of the carboxylic acid family.[1] As such, amide bonds are incredibly robust and require forcing conditions to facilitate their hydrolysis.[2] The implementation and commercialization within the pharmaceutical industry[3] of this resilient chemotype and their applications in the synthesis of high strength materials[4] serve as testaments to the strength and utility of these bonds.

Due to their sturdiness, utilization of amides as enabling precursors for functional group manipulation in synthetic organic chemistry has been limited in scope, focusing primarily on complete reductions to afford amines.[5] Recent advances in the use of increasingly mild reducing conditions, and even chemoselective reducing conditions, have expanded the application of reductions of amides.[6] Additionally, imines, enamines, alcohols, and aldehydes compose a significant minority of amide reduction products.[7] Even though the aforementioned array of functionalities could be accessed via amide reduction reactions, these transformations require specialized reagents that lack compatibility with a wide range of other functional groups.[8] Due to this limitation, alternative synthetic strategies are often more desirable for the synthesis of these functional groups over direct amide reductions. Furthermore, syntheses of diamines directly from amides are under-represented in the literature and in all examples, multistep sequences are necessary (vide infra).

However, if a partial reduction product of an amide, for instance, an aminol or other masked aldehyde equivalent, could be readily further functionalized in a coupling reaction, such a protocol would be synthetically attractive, effectively rendering the amide group a useful synthon for further manipulations. Indeed, lactams have been reported to be utilized as starting materials to build molecular complexity.[9] Substituted *N*-Boc pyrrolidinones (functionally imides) have been treated with a variety of reducing agents (generally DIBAL-H, LAH, or $LiEt_3BH$) to afford isolable aminol intermediates, which have been used effectively in a variety of subsequent transformations (Scheme 1, top).[10,11]

Due to the lack of generality of reaction conditions and the sensitive or incompatible reducing agents employed in prior works, the utilization of an in situ-prepared reactive intermediate of a lactam reduction for further functionalization has not been a widely adopted synthetic strategy, specifically to access differentiated diamines. Herein, we report an investigation of lactams as masked aldehyde equivalents, generated by the treatment of an *N*-aryl lactam with a chemoselective reducing agent (Cp_2ZrHCl, Schwartz's reagent[12]) under mild conditions (0 °C) and its subsequent in situ functionalization through a reductive amination sequence. We have telescoped the reaction conditions to enable an operationally simple, one-pot procedure to produce a set of differentiated diamines (Scheme 1, bottom). The rationale behind the choice of *N*-arylated lactams as substrates in this study is 2-fold. First, these

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Scheme 1. Original Scope of Research Project

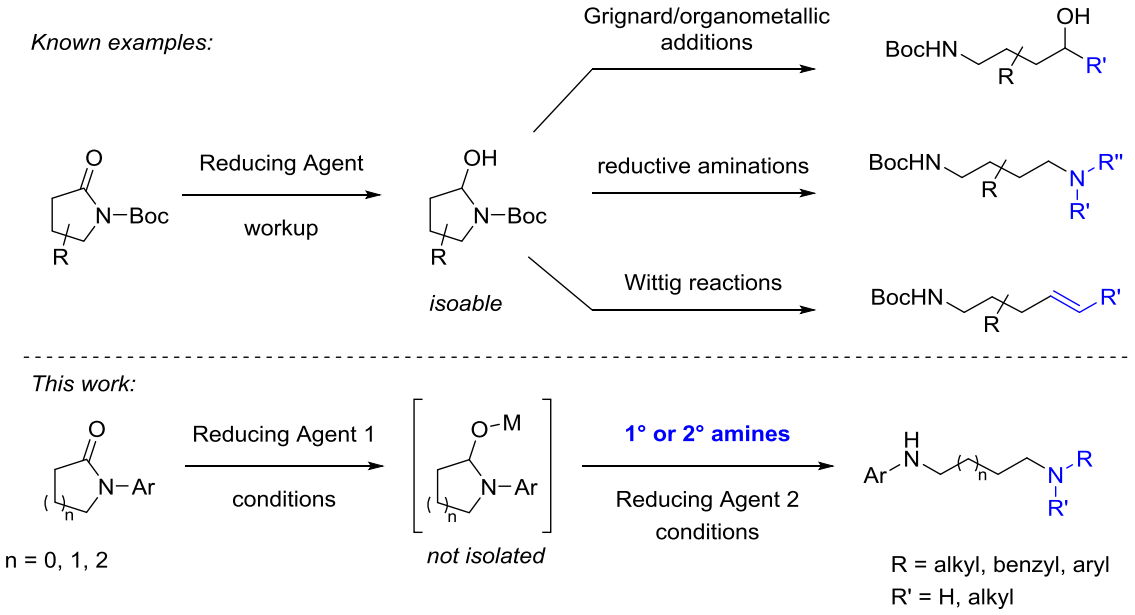
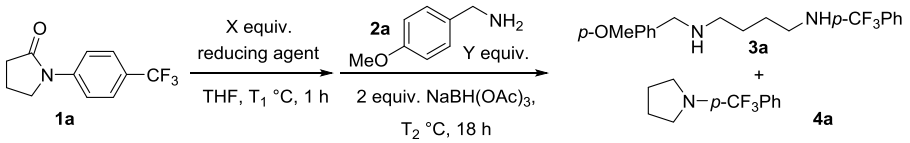


Table 1. Screen of Conditions in Optimizing the One-Pot Coupling Reaction[a]



entry	reducing agent (X)	amine (Y)	T_1 (°C)	T_2 (°C)	Conv. (%)[b]	Yield: **3a**; **4a**[c]
1	DIBAL-H; 1.0 equiv	1.0 equiv	23	23	73	<5%; 30%
2	Cp_2ZrHCl; 1.0 equiv	1.0 equiv	23	23	67	15%; 30%
3	Cp_2ZrHCl; 2.0 equiv	1.0 equiv	23	23	>98	15%; 30%
4	Cp_2ZrHCl; 2.0 equiv	2.0 equiv	23	23	>98	45%; 30%
5	Cp_2ZrHCl; 2.0 equiv	3.0 equiv	23	23	>98	43%; 24%
6	Cp_2ZrHCl; 2.0 equiv	4.0 equiv	23	23	>98	55%; 15%
7	Cp_2ZrHCl; 2.0 equiv	4.0 equiv	23	60	>98	60%; 18%
8	Cp_2ZrHCl; 1.5 equiv	4.0 equiv	0	23	>98	63%[d]; <5%

[a]Average of two runs for each entry. [b]Conversion refers to the disappearance of lactam starting material. [c]Determined by liquid chromatography mass spectroscopy (LCMS). [d]Yield by silica gel chromatography.

lactams can be readily accessed via copper-catalyzed Ullmann couplings between commercially available cyclic carboxamides and various aryl iodides. Second, reactions with these *N*-aryl lactams afford differentiated diamines featuring a versatile aryl amine functionality. Other synthetic strategies for nonvicinal diamines (specifically 1,3-,[13] 1,4-,[14] and 1,5-diamines) involved multiple steps to selectively functionalize one amine at a time. Additionally, these diamine products could not be selectively formed from the previously disclosed Boc-protected amines through palladium-catalyzed C−N coupling chemistry because of the competing secondary amine present in those molecules.[15]

RESULTS AND DISCUSSION

We began our investigation by identifying conditions which would allow both the reduction of the lactam and the reduction of the imine to be carried out in one pot. Our optimization results are summarized in Table 1. We initially evaluated a variety of reducing agents but only saw productive reactions when using DIBAL-H or Schwartz's reagent.[16] Combinations of DIBAL-H or Schwartz's reagent with aluminum or zirconium Lewis acid additives[17] to activate the lactam carbonyl for a more facile reduction afforded no improvement in reactivity or product distribution. When the reducing reagent was omitted in either step of the sequence, the corresponding reactions did not lead to any desired diamine product. Our initial solvent screen showed that tetrahydrofuran (THF) was the most effective solvent[18] for both the partial reduction of **1a** and the following utilization of the resulting aldehyde equivalent in a reductive amination reaction with **2a**. Therefore, *N*-aryl-substituted lactam **1a** was treated with DIBAL-H in THF and a minimal amount of desired diamine **3a** was formed, with mostly over-reduced pyrrolidine **4a** identified in the crude mixture (entry 1, Table 1). Switching from DIBAL-H to Schwartz's reagent (Cp_2ZrHCl) in this reductive coupling reaction delivered 15% yield of **3a** and 30% **4a** with 33% of the remaining lactam **1a** (entry 2, Table 1). Subsequently, we observed full consumption of **1a** when 2.0 equiv of Cp_2ZrHCl was used but did not note an improvement in yield of desired product **3a** (entry 3, Table 1). We surmised that the amine might be

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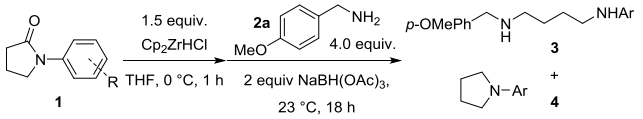
coordinating to the metal center which would render it unavailable to participate in the reductive amination reaction to produce **3a**. Hence, we increased the equivalents of amine to 2.0 equiv and obtained 45% yield of diamine **3a** with 30% of pyrrolidine **4a** (entry 4, Table 1). A comparable yield of diamine **3a** and a slight reduction in yield of pyrrolidine **4a** were observed when the 3.0 equiv. of amine was investigated (entry 5, Table 1). Further increase to 4.0 equiv. of **2a** led to 55% yield of **3a** in the reaction mixture and a decreased amount of pyrrolidine **4a** (15%, entry 6, Table 1). However, no boost in yield of **3a** was noted when more than four equivalents of amine were utilized. Later optimization of reaction temperatures for both sequential steps identified that performing the partial reduction of lactam **1a** at 0 °C followed by the standard reductive amination at ambient temperature completely consumed lactam **1a**, affording diamine **3a** in 63% yield and <5% byproduct **4a** (entry 8, Table 1).

With the optimized conditions in hand, we set out to explore the scope of *N*-aryl-substituted lactam substrates (Table 2). As shown from entries 1−4, para-substituted electron-deficient aromatic substituents on the lactams were capable substrates for this chemistry, giving desired diamines in 35−82% yield with a minimal amount of pyrrolidine byproducts. Electron-withdrawing functional groups on the aryl ring, such as cyano, nitro, and carboxylic ester, were tolerated in this reaction; diamines **3e**, **3f**, and **3g** were obtained in 34−49% yield. However, pyrrolidines **4f** and **4g** were afforded in 40 and 35%, respectively (entries 6 and 7, Table 2). Moreover, as demonstrated in entry 8 of Table 2, the reductive coupling reaction of disubstituted arene containing lactam **1h** resulted in the formation of diamine **3h** in 42% yield and 37% pyrrolidine **4h**. An electron neutral phenyl substituent was also tolerated on the pyrrolidinone substrate. Diamine **3i** was obtained in 36% yield along with 32% fully reduced pyrrolidine **4i**, as shown in entry 9 of Table 2. On the contrary, electron-donating *para*-methoxy substituent containing substrate **1j** decomposed to complex reaction mixtures with <5% desired diamines detected by LCMS (entry 10, Table 2). *ortho*-Methoxyphenyl-substituted lactam **1k**, which was presumably less electron donating due to the inductive effect, was examined in hopes of restoring a certain extent of reaction efficiency; however, **1k** was proven to be an ineffective coupling partner as well, the reaction with which only led to the formation of pyrrolidine **4k** in 35% yield (entry 11).

Next, we investigated steric effects surrounding the lactam functionality. As illustrated in entries 1 and 2 in Table 3, when a methyl group was placed at the 3- or 5-position on the lactam ring, reductive coupling reactions of lactams **1l** and **1m** delivered methyl-substituted diamines **3l** and **3m** in 43 and 34% yields, respectively. Unlike the result observed in entry 1 (Table 2), pyrrolidines **4l** and **4m** were also afforded in high yield (35−45%). In addition to pyrrolidinones, six- and four-membered *N*-arylated lactams were examined as well. Upon treatment with the standard reaction conditions, piperidinone **1n** was transformed into diamine **3n** with a five-carbon linker in between the two nitrogen centers in 72% yield (entry 3, Table 3). Strained azetidinones were more capable coupling partners than either the pyrrolidinones or piperidinones in this sequence of reactions. As shown in entry 4, diamine **3o** was obtained in 92% yield. Interestingly, azetidinones with electron-rich aromatic substituents, entries 5 and 6 (Table 3), were effectively converted into diamines **3p** and **3q** in 30 and 48% yield, respectively. Although some azetidines **4p** and **4q** accompanied the desired products in these reactions, the results were still very encouraging given that electron-rich arene containing pyrrolidinones were ineffective substrates.

Table 2. Scope of Aryl-substituted Lactams in One-Pot Reductive Coupling[a]



Entry	Ar (**1**)	Diamines (**3**)[f] + Pyrrolidine (**4**)[g]
1	*p*-$CF_3C_6H_5$ **1a**	63% **3a** + 3% **4a**
2[b]	4-pyridyl **1b**	59% **3b** + 5% **4b**
3	*p*-BrC_6H_4 **1c**	82% **3c** + 7% **4c**
4[c]	*p*-ClC_6H_4 **1d**	35% **3d** + 3% **4d**
5[d]	*p*-CNC_6H_4 **1e**	49% **3e** + <2% **4e**
6	*p*-$NO_2C_6H_4$ **1f**	39% **3f** + 40% **4f**
7	*p*-$CO_2EtC_6H_4$ **1g**	34% **3g** + 35% **4g**
8	3-Cl, 5-FC_6H_3 **1h**	42% **3h** + 37% **4h**
9	*p*-$OMeC_6H_4$ **1i**	36% **3i** + 32% **4i**
10[e]	*p*-$OMeC_6H_4$ **1j**	<2% **3j** + 10% **4j**
11[e]	*o*-$OMeC_6H_4$ **1k**	<2% **3k** + 35% **4k**

[a]Average of at least two runs for each entry. >98% conversion in all cases unless noted otherwise. [b]95% conversion. [c]90% conversion. [d]85% conversion. [e]Complicated reaction mixtures observed. [f]Yield by silica gel chromatography. [g]Determined by liquid chromatography mass spectroscopy (LCMS).

Having examined the scope of the *N*-aryl-substituted lactams, we set forth to investigate the range of amines that were able to participate in this class of reductive coupling reactions. As illustrated in Table 4, a variety of primary amines were tested in combination with the substrate **1a**. Cyclohexylmethylamine reacted with **1a** to furnish diamine **5a** in 69% yield with <5% of pyrrolidine **4a** present in the crude mixture. Similarly, reductive coupling reactions with cyclohexylamine and nonylamine afforded **5b** and **5c** in 58 and 63% yield, respectively. Amines with an α-stereogenic center were also tolerated in these reactions, as represented by the formation of diamines **5d** and **5e** (61 and 50% yield, Table 4). Reductive coupling of **1a** with *p*-CF_3 benzylamine **2f** resulted in a lower yield of diamine **5f**; pyrrolidine **4a**, in this

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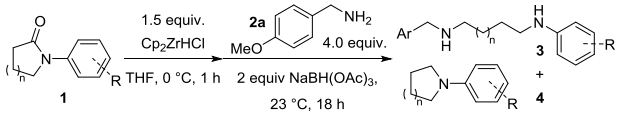
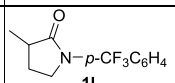
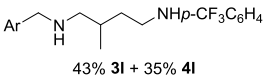
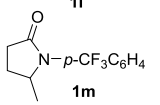
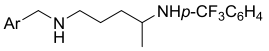
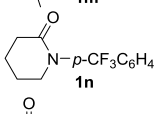
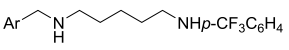
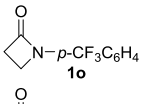
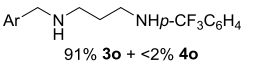
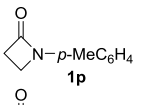
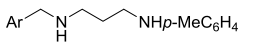
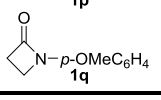
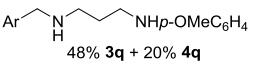
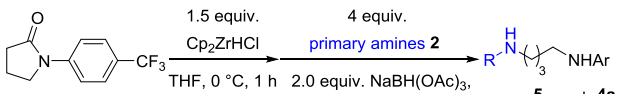
Table 3. Additional Scope of Aryl-substituted Lactams in One-Pot Reductive Coupling[a]

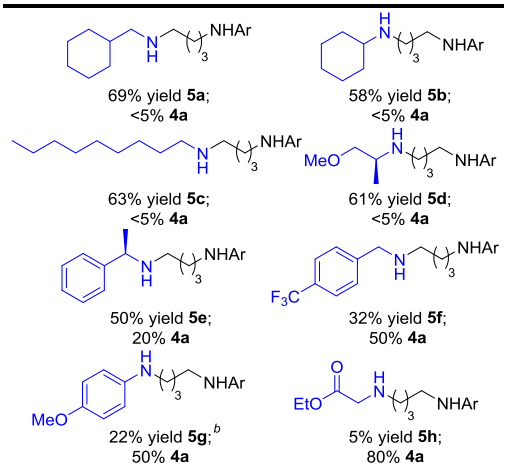


Entry	Lactams (**1**)	Diamines (**3**)[d] + Pyrrolidine (**4**)[e]
1	 **1l**	 43% **3l** + 35% **4l**
2	 **1m**	 34% **3m** + 45% **4m**
3	 **1n**	 72% **3n** + <2% **4n**
4	 **1o**	 91% **3o** + <2% **4o**
5[b]	 **1p**	 30% **3p** + 15% **4p**
6[c]	 **1q**	 48% **3q** + 20% **4q**

[a]Average of at least two runs for each entry; Ar = *p*-OMePh; >98% conversion in all cases unless otherwise noted. [b]70% conversion. [c]87% conversion. [d]Yield by silica gel chromatography. [e]Determined by liquid chromatography mass spectroscopy (LCMS).

Table 4. Scope of Primary Amines in One-Pot Reductive Coupling Reactions[a]



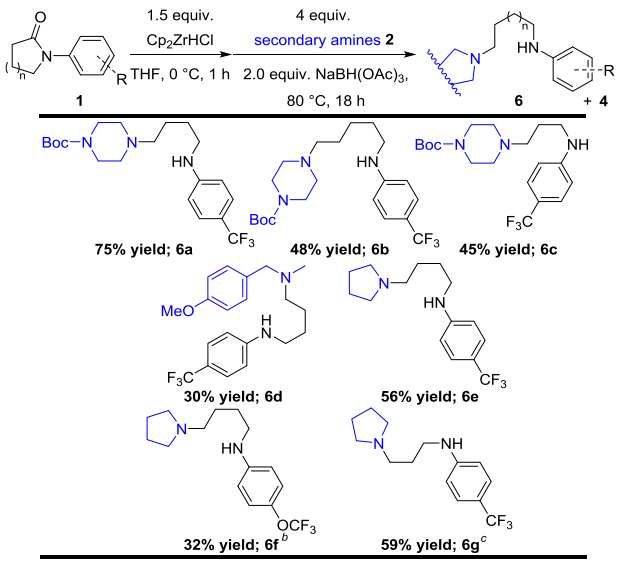


[a]Average of at least two runs for each entry; >98% conversion in all cases unless indicated otherwise; yields for **5** are of isolated diamine products, Ar = *p*-$CF_3C_6H_4$. [b]90% conversion of **1a**.

case, was afforded in 50% yield. The data from reactions with benzyl amines **2a** and **2f** identified the trend of decreased diamine formation as the nucleophilicity of underlying amines decreased; meanwhile, the competing lactam over-reduction process increased. Similarly, the reductive coupling reaction with less nucleophilic aniline **2g** furnished only 22% yield of diamine **5g**. Furthermore, when a primary alkylamine with a carboxylic ester substituent one carbon away was utilized, only 5% yield of product **5h** was obtained along with 80% pyrrolidine **4a**, presumably due to the reduced nucleophilicity of the amine group caused by the electron-withdrawing inductive effect from the ester carbonyl.

In addition to reactions with primary amines, we have also investigated the reductive coupling of lactams with secondary amines, which would give a distinct set of diamine products. The results are summarized in Table 5. Treatment of **1a** with

Table 5. Scope of Secondary Amines in One-Pot Reductive Coupling Reactions[a]



[a]Average of at least two runs for each entry; >98% conversion and <5% **4** observed in all cases unless Indicated otherwise; yields for **6** are of isolated diamine products. [b]72% conversion of **1r**. [c]The second portion of this reaction was carried out at 22 °C; >98% conversion of **1o**.

N-Boc-piperazine under the standard coupling conditions resulted in diamine **6a** in 42% yield. Further optimization of this reaction sequence led to the production of **6a** in 75% yield, when the temperature of the reductive amination step was raised to 80 °C. With the new conditions in hand, we examined several other substrates with *N*-Boc-piperazine. Product **6b**, derived from the reductive coupling of an *N*-arylated piperidinone, was afforded in 48% yield, and desired diamine **6c**, which was generated from an *N*-arylated azetidinone, was furnished in comparable yield. Similarly, reductive coupling reactions using pyrrolidine as the amine nucleophile resulted in diamines **6e**, **6f**, and **6g** in 56%, 32%, and 59% yield, respectively. Notably, pyrrolidinone **1r**, which contains an OCF_3 substituent, was also proven to be a capable coupling partner (i.e., **6f**). Additionally, the secondary amine does not need to be cyclic; as exemplified by diamine **6d**, such a reaction between *N*-methyl-*p*-methoxybenzylamine and lactam **1a** delivered the desired product in 30% yield. To further showcase the practicality of this chemistry, we have performed the reductive coupling reaction on gram scale. As illustrated in eq 1, upon treatment of 1.83 g (8.0 mmol) of **1a** under standard conditions, the coupling with **2a** furnished

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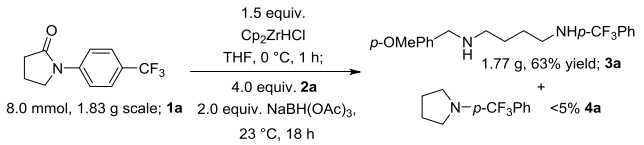


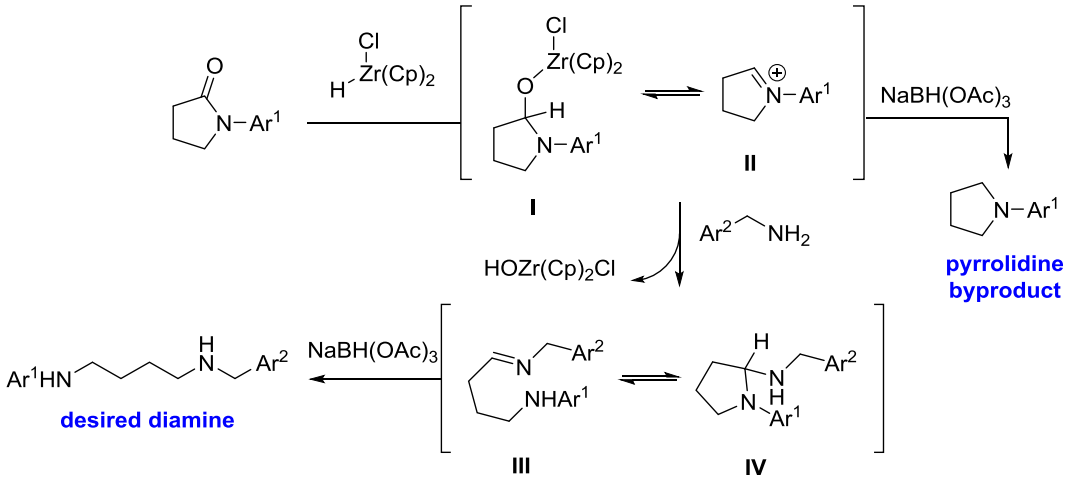
diamine **3a** in 63% yield (1.77 g; 5.0 mmol) with minimal formation of pyrrolidine **4a**. The result demonstrated the amiability to scale up of the current semireduction/reductive amination sequence.

Extensive mechanistic discussions of Schwartz's reagent reductions of amides have suggested that secondary amide reductions proceed through imine intermediates,[19,20] whereas tertiary amide reductions proceed through metal-stabilized complexes.[8a] Based on the precedent, the mechanism for this transformation, as proposed in Scheme 2, invokes a zirconium complex **I** to serve as the masked aldehyde equivalent, as opposed to an iminium intermediate **II**. Nucleophilic primary amines attack the tetrahedral intermediate, which subsequently collapses to form the imine **III** or aminal **IV**. Upon treatment with sodium triacetoxyborohydride (STAB), this imine/aminal is reduced to the corresponding amine, thereby generating an overall diamine product. This mechanism is also invoked when utilizing secondary nucleophilic amines as coupling partners (i.e., the substrates of Table 5).

One benefit of using Schwartz's reagent to reduce the lactam into a masked aldehyde equivalent is the compatibility of these conditions with esters. To take advantage of this tolerability, we investigated the installation of a pendant ester in close proximity to the amide, as indicated in Scheme 3. When treated with Schwartz's reagent, we expected the formation of the masked aldehyde equivalent and upon addition of the amine nucleophile, an ester bearing intermediate diamine was anticipated.[21] We surmised that this intermediate, when treated with heat, would lead to intramolecular lactam formation between the pendant ester and the newly formed amine, a transformation which would not have been feasible with traditional amide reducing reagents. Standard reagents, such as LAH, $LiEt_3BH$, lithium borohydride, DIBAL-H, and lithium aminoborohydrides, directly reduced the pendant ester or over-reduced the starting lactam. Moreover, if such a transformation were to retain the stereochemical configuration of the starting material, a class of enantioenriched α-amino piperidinones could become readily accessible. In Table 6, we summarized the results of reductive coupling reactions with pyrrolidinones that contain a 5-ester substituent, which were prepared in enantiopure form via Ullmann couplings between commercially available ethyl (*R*)-5-oxopyrrolidine-2-carboxylate and a range of aryl iodides.

As shown in entry 1, Table 6, upon treatment of **7a** with benzylamine **2a** under slightly varied conditions, *N*-arylated piperidinone **8a** was identified to be the major product from the reaction mixture, which was isolated in 75% yield and more importantly was obtained with full retention of the stereochemical information. An elevated temperature (80 °C) was needed to induce the cyclization of the benzylic amine center onto the ester after the diamine formation. As established in Tables 2 and 3, a similar trend was observed: electron-withdrawing substrates were generally more capable coupling partners. Piperidinones **8b**−**g** were afforded in good yields, with minimal formation of over-reduced pyrrolidine byproducts (65−77% yield, <5−13% pyrrolidines). Interestingly, electron-rich substrates, which were previously incapable of participation in the coupling reactions (Table 2), were now effective in the formation of piperidinones. For examples, **8h** and **8i** were furnished in 51 and 55% yield, respectively, albeit a higher production of pyrrolidines was observed (7−20%). Reductive coupling of more hindered and electron-rich **7j** did not proceed to completion within 18 h, resulting in 35% yield of **8j**. Additionally, 88−100% ee was obtained for *N*-arylated piperidinones. The complete retention of stereochemistry in this transformation was purported to be derived from two complementary factors: (1) the lack of a basic reducing agent interacting directly with the α-stereocenter and (2) a proposed zirconacycle masked aldehyde equivalent **V**, as depicted in Scheme 4, which would reinforce the retention of the α-stereocenter. Additionally, intermediate **V** disfavors the collapsed iminium ion **VI**, which would lead to the pyrrolidine byproduct. This explains our observation of relatively insignificant yields of pyrrolidines in various examples in Table 6 as compared to the amounts of pyrrolidines formed as side products from the diamine formation reactions described in previous sections (see Tables 2−5).

Scheme 2. Proposed Mechanism



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Scheme 3. Expanded Scope of Research to Synthesize Enantioenriched Piperidinones

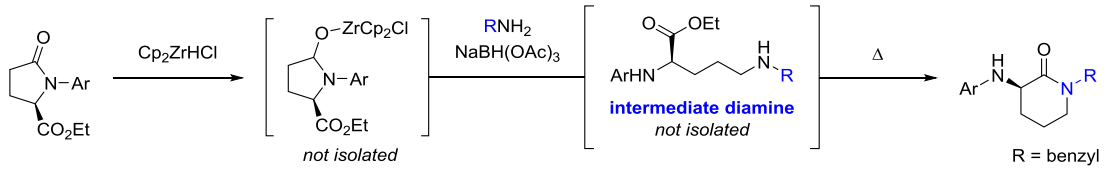
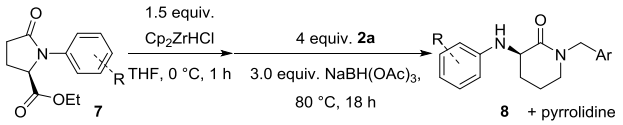


Table 6. Examples of Reductive Coupling/Cyclization Sequence of α-Ester Containing *N*-Arylated Pyrrolidinones[a]



Entry	R (7)	Piperidinone (8) + pyrrolidine
1	4-CF_3	75% yield; 100% ee; **8a**
2	3-CF_3	70% yield; 100% ee; **8b**
3	3-F, 5-CF_3	66% yield; 100% ee; **8c**
4	3-Cl, 5-F	73% yield; 94% ee; **8d** 8% pyrrolidine
5	4-pyridyl	73% yield; 100% ee; **8e** 5% pyrrolidine
6	3-pyridyl	77% yield; 98% ee; **8f** 7% pyrrolidine
7	2-pyridyl	65% yield; 88% ee; **8g** 13% pyrrolidine
8	H	51% yield; 100% ee; **8h** 20% pyrrolidine
9[b]	3-OMe	55% yield; 100% ee; **8i** 7% pyrrolidine
10[c]	2-OMe	35% yield; 100% ee; **8j** 7% pyrrolidine

[a]Average of at least two runs for each entry; >98% conversion in all cases unless indicated otherwise; ee = enantiomer excess as determined by chiral supercritical fluid chromatography (SFC) analysis in comparison with an authentic racemic sample; yield by silica gel chromatography; Ar = *p*-OMePh; pyrrolidine refers to ester containing over-reduction byproducts similar to **4**. [b]90% conversion of **7i**. [c]60% conversion of **7j**.

CONCLUSIONS

In summary, we have established an operationally simple protocol that couples a primary or secondary amine with an *N*-aryl-substituted lactam, delivering a differentiated diamine in 22−91% yield. We have successfully optimized conditions to allow semireduction/reductive amination sequence to be telescoped in a one-pot fashion. Nucleophilic amines and electron-deficient arylated lactams were generally more capable coupling partners in these reactions. Azetidinones, pyrrolidinones, and piperidinones were shown to participate in reductive coupling reactions effectively. This was significant as it allowed for a singular synthetic strategy to access 1,3-, 1,4-, and 1,5-diamines (which, if targeted individually, would require differing synthetic approaches based on the length of the carbon chain). A range of primary and secondary amines were included in the study to diversify the scope of diamine products. This work was further strengthened with a class of α-carboxylic ester containing pyrrolidinones and their efficient conversion to enantiomerically pure α-amino piperidinones in 35−77% yield and complete retention of stereochemical information. Through an operationally simple, one-pot procedure to convert *N*-aryl lactams into masked aldehyde equivalents for use in reductive amination reactions, we have shown that lactams can be considered viable functional group handles potentially for a wider array of further transformations. Additional exploration in the use of lactams in this fashion is currently underway and will be disclosed in due course.

EXPERIMENTAL SECTION

Unless otherwise noted, all reactions were carried out with anhydrous solvents (dichloromethane, toluene, tetrahydrofuran, 1,4-dioxane, acetonitrile) purchased from Fisher Scientific and in standard glass vials and round-bottom flasks. All reagents were purchased from Sigma-Aldrich or Combi-Blocks and used as received, unless noted otherwise. A nitrogen atmosphere was maintained using standard vacuum line technique. The final compounds were analyzed or purified according to one of the analytical or purification methods referred to below unless otherwise described and characterized by ^{1}H, ^{13}C NMR, and high-resolution mass spectrometry. For LC/MS analysis, a sample is dissolved in a suitable solvent such as MeCN, dimethyl sulfoxide (DMSO), or MeOH and is injected directly into the column using an automated sample handler. The analysis used one of the following methods: (1) acidic method (1.5, 2, 3.5, 4, or 7 min runs, see Supporting Information (SI) for additional details): conducted on a Shimadzu 2010 Series, Shimadzu 2020 Series, or Waters Acquity UPLC BEH. (MS ionization: ESI) instrument equipped with a C18 column (2.1 mm × 30 mm, 3.0 mm or 2.1 mm × 50 mm, C18, 1.7 μm), eluting with 1.5 mL/4 L of trifluoroacetic acid (TFA) in water (solvent A) and 0.75 mL/4 L of TFA in acetonitrile (solvent B) or (2) basic method (3, 3.5, 7 min runs, see SI for additional details): conducted on a Shimadzu 2020 Series or Waters Acquity UPLC BEH (MS ionization: ESI) instrument equipped with XBridge Shield RP18, 5um column (2.1 mm × 30 mm, 3.0 mm i.d.) or 2.1 mm × 50 mm, C18, 1.7 μm column, eluting with 2 mL/4 L $NH_3{\cdot}H_2O$ in water (solvent A) and acetonitrile (solvent B). Silica gel column chromatography was performed using 20−40 μM (particle size), 250−400 mesh, or 400−

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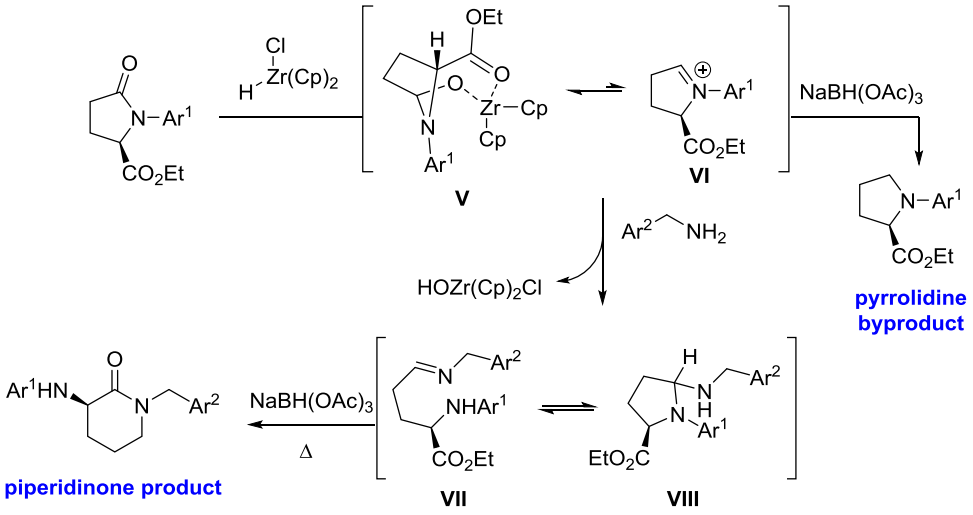
Scheme 4. Proposed Mechanism for the Synthesis of Enantioenriched α-amino Piperidinones



632 mesh silica gel using either a Teledyne ISCO Combiflash RF or a Grace Reveleris X2 with ELSD purification systems. SFC chiral separation was performed using a Waters UPC2 analytical SFC (SFC-H). Column: ChiralCel OJ, 150 mm × 4.6 mm i.d., 3 μm. Mobile phase: A for CO_2 and B for ethanol (0.05% DEA). Gradient: B 40%. Flow rate: 2.5 mL/min. Back pressure: 100 bar. Column temperature: 35° C. Wavelength: 220 nm. Preparative HPLC purifications were performed on a Gilson UV/VIS-156 with UV detection at 220/254 nm, Gilson 281 automatic collection, utilizing acidic, basic and neutral methods (see SI for additional details). The ^{1}H NMR spectra were recorded on a Bruker Avance III HD 500 MHz, Bruker Avance III 500 MHz, Bruker Avance III 400 MHz, Varian-400 VNMRS, or Varian-400 MR. Chemical shifts are expressed in parts per million (ppm) units and referenced to the residual solvent resonance as noted in the spectra (i.e., $CDCl_3$; 7.27 ppm). Coupling constants (J) are in units of Hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dd (doubled doublet), dt (doubled triplet), dq (doubled quartet), m (multiplet), or br (broad). The $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker Avance III HD 500 MHz, Bruker Avance III 500 MHz, Bruker Avance III 400 MHz, Varian-400 VNMRS, or Varian-400 MR. Chemical shifts are expressed in parts per million (ppm) units and referenced to the residual solvent resonance as noted in the spectra (i.e., $CDCl_3$; 77.0 ppm). Coupling constants (J) are in units of Hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as: s (singlet), d (doublet), t (triplet), dd (doubled doublet), dt (doubled triplet), dq (doubled quartet), m (multiplet), or br (broad). High-resolution mass spectrometry data were recorded using Sciex Triple TOF 6600 mass spectrometer (column: Waters UPLC Acquity HSS T3 C18 1.8 μm, 2.1 mm × 50 mm; mobile phase: A = 0.1% formic acid in H_2O; B = 0.1% formic acid in acetonitrile; method: 7 min, A to B gradient 5−65%, positive ionization mode). All masses were reported as the exact masses in the format of $[M + H]^+$, unless noted otherwise.

Representative Experimental Procedure for Ullmann Couplings. *Compounds **1a**−**r** were Prepared by ChemPartner, Except Where Noted Otherwise. Nonetheless, Many are Commercially Available.* A round-bottom flask was charged with aryl iodide or aryl bromide (1 equiv), 2-pyrrolidinone OR 2-piperidinone OR 2-azetidinone (1.4 equiv), copper iodide (0.25 equiv), cesium carbonate (2 equiv), and *p*-dioxane (0.5 M reaction concentration) under an atmosphere of nitrogen. Then, tetramethylethylenediamine (TMEDA) or 1,2-dimethylethylenediamine (DMEDA) (0.5 equiv) was added, and the resulting mixture was heated to 40 °C and stirred at that temperature for 5 h. Additional portions of copper iodide (0.12 equiv) and TMEDA or DMEDA (0.25 equiv) were added (as needed). The reaction mixture continued to stir at 40 °C overnight. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was concentrated, and the crude material was purified by silica gel column chromatography (EtOAc/heptanes, 1:1) to give the desired *N*-aryl azetidinones, *N*-aryl pyrrolidinones, or *N*-aryl piperidinones.

*1-(4-(Trifluoromethyl)phenyl)pyrrolidin-2-one (**1a**, White Solid, 2.6 g, Yield: 96%).*[22] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.89 (2H, br d, J = 9.2 Hz), 7.73 (2H, d, J = 8.5 Hz), 3.88 (2H, t, J = 7.0 Hz), 2.57−2.52 (2H, m), 2.08 (2H, br t, J = 7.6 Hz). LRMS (ESI)$^+$: 192.2.

*1-(Pyridin-4-yl)pyrrolidin-2-one (**1b**, White Solid, 2.7 g, Yield: 72%).* ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.52−8.45 (2H, m), 7.71−7.63 (2H, m), 3.88−3.80 (2H, m), 2.58−2.52 (2H, m), 2.12−2.03 (2H, m). LRMS (ESI)$^+$: 163.1.

*1-(4-Bromophenyl)pyrrolidin-2-one (**1c**, White Solid, 2.2 g, yield: 78%).*[23] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.68−7.61 (2H, m), 7.58−7.52 (2H, m), 3.84−3.78 (2H, m), 2.49−2.44 (2H, m), 2.10−2.01 (2H, m). LRMS (ESI)$^+$: 240.1.

*1-(4-Chlorophenyl)pyrrolidin-2-one (**1d**, White Solid, 2.4 g, Yield: 53%).*[24] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.74−7.64 (2H, m), 7.47−7.39 (2H, m), 3.85−3.78 (2H, m), 2.48 (2H, s), 2.11−2.00 (2H, m). LRMS (ESI)$^+$: 196.1.

*4-(2-Oxopyrrolidin-1-yl)benzonitrile (**1e**, White Solid, 2.3 g, Yield: 71%).*[25] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.92−7.80 (4H, m), 3.91−3.84 (2H, m), 2.58−2.53 (2H, m), 2.13−2.04 (2H, m). LRMS (ESI)$^+$: 187.1.

*1-(4-Nitrophenyl)pyrrolidin-2-one (**1f**, Yellow Solid, 3.2 g, Yield: 67%).*[26] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.29−8.24 (2H, m), 7.97−7.91 (2H, m), 3.91 (2H, t, J = 7.3 Hz), 2.58 (2H, t, J = 8.2 Hz), 2.13−2.05 (2H, m). LRMS (ESI)$^+$: 207.1.

*Ethyl 4-(2-Oxopyrrolidin-1-yl)benzoate (**1g**, White Solid, 3.6 g, Yield: 67%).*[27] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.00−7.93 (2H, m), 7.85−7.80 (2H, m), 4.29 (2H, q, J = 7.1 Hz), 3.87 (2H, t, J = 7.3 Hz), 2.54 (2H, t, J = 8.2 Hz), 2.12−2.03 (2H, m), 1.31 (3H, t, J = 7.0 Hz). LRMS (ESI)$^+$: 234.2.

*1-(3-Chloro-5-fluorophenyl)pyrrolidin-2-one (**1h**, Yellow Solid, 3.5 g, Yield: 70%).* ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.71−7.63 (1H, m), 7.58 (1H, td, J = 11.6 Hz, 2.1 Hz), 7.18 (1H, td, J = 8.5 Hz, 2.2 Hz), 3.83 (2H, t, J = 7.3 Hz), 2.55−2.52 (2H, m), 2.10−2.01 (2H, m). LRMS (ESI)$^+$: 214.1.

*1-Phenylpyrrolidin-2-one (**1i**, White Solid).* This material was purchased from Sigma-Aldrich and used as received. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65−7.59 (2H, m), 7.42−7.34 (2H, m), 7.19−7.12 (1H, m), 3.88 (2H, t, J = 7.0 Hz), 2.63 (2H, t, J = 8.0 Hz), 2.23−2.12 (2H, m). LRMS (ESI)$^+$: 162.1.

*1-(4-Methoxyphenyl)pyrrolidin-2-one (**1j**, White Solid, 3.2 g, Yield: 72%).*[28] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.59−7.49 (2H, m), 6.99−6.90 (2H, m), 3.78 (2H, t, J = 7.0 Hz), 3.74 (3H, s), 2.45 (2H, t, J = 8.2 Hz), 2.04 (2H, quin, J = 7.5 Hz). LRMS (ESI)$^+$: 192.2.

*1-(2-Methoxyphenyl)pyrrolidin-2-one (**1k**, Clear Oil, 2.1 g, Yield: 64%).*[29] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31−7.24 (2H, m), 7.02−

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6.94 (2H, m), 3.84 (3H, s), 3.79−3.74 (2H, m), 2.60−2.53 (2H, m), 2.24−2.15 (2H, m). LRMS (ESI)$^+$: 192.0.

*3-Methyl-1-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one (**1l**, White Solid, 900 mg, Yield: 78%).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (2H, d, J = 8.5 Hz), 7.62 (2H, d, J = 8.5 Hz), 3.85−3.78 (2H, m), 2.78−2.64 (1H, m), 2.42 (1H, tdd, J = 13.0 Hz, 8.1 Hz, 5.0 Hz), 1.90−1.75 (1H, m), 1.33 (3H, d, J = 7.0 Hz). LRMS (ESI)$^+$: 244.1.

*5-Methyl-1-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one (**1m**, White Solid, 854 mg, Yield: 87%).*[30] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67−7.63 (2H, m), 7.61−7.57 (2H, m), 4.45−4.36 (1H, m), 2.75−2.65 (1H, m), 2.63−2.53 (1H, m), 2.46−2.36 (1H, m), 1.86−1.75 (1H, m), 1.27 (3H, d, J = 6.1 Hz). LRMS (ESI)$^+$: 244.0.

*1-(4-(Trifluoromethyl)phenyl)piperidin-2-one (**1n**, White Solid, 2.1 g, Yield: 78%).*[31] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.74 (2H, d, J = 8.5 Hz), 7.53 (2H, d, J = 8.5 Hz), 3.66 (2H, t, J = 5.5 Hz), 2.43 (2H, t, J = 6.4 Hz), 1.93−1.80 (4H, m). LRMS (ESI)$^+$: 244.1.

*1-(4-(Trifluoromethyl)phenyl)azetidin-2-one (**1o**, White Solid).* This material was purchased from Sigma-Aldrich and used as received. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.74 (2H, d, J = 8.5 Hz), 7.51 (2H, d, J = 8.5 Hz), 3.70 (2H, t, J = 4.9 Hz), 3.14 (2H, t, J = 4.9 Hz). LRMS (ESI)$^+$: 216.1.

*1-(p-Tolyl)azetidin-2-one (**1p**, White Solid, 1.0 g, Yield: 44%).*[32] ^{1}H NMR (CD_3OD, 500 MHz): δ 7.30−7.24 (2H, m), 7.16 (2H, d, J = 7.9 Hz), 3.65 (2H, t, J = 4.3 Hz), 3.08 (2H, t, J = 4.6 Hz), 2.30 (3H, s). LRMS (ESI)$^+$: 162.1.

*1-(4-Methoxyphenyl)azetidin-2-one (**1q**, White Solid, 830 mg, Yield: 34%).*[32] ^{1}H NMR (CD_3OD, 500 MHz): δ 7.35−7.30 (2H, m), 6.94−6.89 (2H, m), 3.77 (3H, s), 3.64 (2H, t, J = 4.3 Hz), 3.07 (2H, t, J = 4.6 Hz). LRMS (ESI)$^+$: 178.1.

*1-(4-(Trifluoromethoxy)phenyl)pyrrolidin-2-one (**1r**, White Solid, 2.2 g, Yield: 78%).* ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.83−7.73 (2H, m), 7.38 (2H, d, J = 9.2 Hz), 3.84 (2H, t, J = 7.0 Hz), 2.54−2.51 (2H, m), 2.13−2.00 (2H, m). LRMS (ESI)$^+$: 246.1.

Representative Experimental Procedure for Reductive Coupling of Nonester Containing Aryl Lactams with Primary and Secondary Amines (for Tables 1−5). To a 2-dram vial equipped with a magnetic stir bar was added Schwartz's reagent (155 mg, 0.6 mmol, 1.5 equiv; preferably less than 1 month old) as a solid in the air. The vial was then sealed with a red open top cap (with a solvent-resistant Teflon cover), and a N_2 flow ran through the sealed vial for 5 min. The N_2 line was then removed, and THF (2 mL) was added through a syringe under positive pressure. The reaction mixture was cooled to 0 °C in an ice-water cooling bath and subjected to vigorous stirring, followed by the injection of a solution of the substrate (0.4 mmol in 1 mL of THF). After 1 h at 0 °C, to the milky white suspension was added neat amine coupling partner (1.6 mmol, 4 equiv). The vial was then removed from the ice-water bath, and STAB (170 mg, 0.8 mmol, 2 equiv) was added in one portion as a solid to the reaction mixture. The vial was capped and stirred at 23 °C for 18 h. A sample was taken from the vial to be analyzed by LCMS. Upon reaction completion, water (1 mL) was added to the vial. The mixture was stirred for 10 min before the addition of EtOAc (2 mL). The mixture was filtered through a plug of Celite into a 30 mL vial. The filtrate was dried by a V10 rotovap. The residue was purified by silica gel column chromatography (4g of silica gel column) with an automatic purification system (grading from 0% MeOH/EtOAc to 50% MeOH/EtOAc over 13 min). The fractions were collected and dried to give the desired diamine products as clear films.

*N^1-(4-Methoxybenzyl)-N^4-(4-(trifluoromethyl)phenyl)butane-1,4-diamine (**3a**; 88.7 mg, 63% Yield).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.33 (1H, br s), 7.38 (2H, br d, J = 8.1 Hz), 7.25 (2H, d, J = 8.0 Hz), 6.83 (2H, br d, J = 7.8 Hz), 6.61 (2H, br d, J = 8.3 Hz), 4.56 (1H, br s), 3.86 (2H, br s), 3.70 (3H, s), 3.06 (2H, br t, J = 5.6 Hz), 2.85 (2H, br s), 1.73 (2H, br s), 1.61 (2H, br s). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.4, 150.0, 131.4, 126.6 (q, J = 4 Hz), 124.9 (q, J = 271 Hz), 122.0, 119.3 (q, J = 32 Hz), 114.4, 112.2, 55.2, 50.7, 46.0, 42.8, 25.6, 23.4. HRMS (ESI$^+$): calcd for $C_{19}H_{23}F_3N_2O$ [M + H]$^+$: 353.1835; found: 353.1828.

*N^1-(4-Methoxybenzyl)-N^4-(pyridin-4-yl)butane-1,4-diamine (**3b**; 67.3 mg, 59% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.97 (1H, br s), 8.70 (1H, br s), 8.24 (1H, br d, J = 6.8 Hz), 8.08 (1H, br d, J = 6.8 Hz), 7.40 (2H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.6 Hz), 6.87 (2H, br t, J = 5.7 Hz), 4.07 (2H, br s), 3.76 (3H, s), 3.28 (2H, q, J = 6.3 Hz), 2.92 (2H, br s), 1.74-1.54 (4H, m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 159.7, 157.9, 140.8, 138.5, 131.5, 123.7, 114.0, 109.8, 104.7, 55.2, 49.5, 45.8, 41.5, 25.0, 22.8. HRMS (ESI$^+$): calcd for $C_{17}H_{24}N_3O$ [M + H]$^+$: 286.1914; found: 286.1908.

*N^1-(4-Bromophenyl)-N^4-(4-methoxybenzyl)butane-1,4-diamine (**3c**; 118.7 mg, 82% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.81 (2H, br s), 7.40 (2H, d, J = 8.6 Hz), 7.21 (2H, d, J = 8.6 Hz), 6.98 (2H, d, J = 8.6 Hz), 6.57−6.50 (2H, m), 4.07 (2H, br t, J = 5.4 Hz), 3.76 (3H, s), 2.99 (2H, t, J = 6.7 Hz), 2.94−2.85 (2H, m), 1.68 (2H, quin, J = 7.5 Hz), 1.61−1.49 (2H, m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 159.7, 147.7, 131.5, 131.4, 123.7, 117.5, 114.2, 114.0, 55.2, 49.5, 46.0, 42.3, 25.4, 23.1. HRMS (ESI$^+$): calcd for $C_{18}H_{23}BrN_2O$ [M + H]$^+$: 363.1067; found: 363.1066.

*N^1-(4-Chlorophenyl)-N^4-(4-methoxybenzyl)butane-1,4-diamine (**3d**; 44.5 mg, 35% Yield).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (1H, br s), 7.30 (2H, br d, J = 8.1 Hz), 7.07 (2H, d, J = 8.6 Hz), 6.84 (2H, br d, J = 7.8 Hz), 6.46 (2H, d, J = 8.6 Hz), 5.42 (1H, br s), 3.83 (2H, br s), 3.72 (3H, s), 2.98 (2H, br t, J = 6.0 Hz), 2.77 (2H, t, J = 5.9 Hz), 1.77 (2H, br s), 1.64−1.52 (2H, m). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.0, 146.8, 131.3, 128.9, 123.4, 121.5, 114.2, 113.6, 55.2, 50.3, 45.8, 43.0, 26.1, 23.8. HRMS (ESI$^+$): calcd for $C_{18}H_{23}ClN_2O$ [M + H]$^+$: 319.1572; found: 319.1569.

*4-((4-((4-Methoxybenzyl)amino)butyl)amino)benzonitrile (**3e**; 60.5 mg, 49% Yield).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.30 (1H, br s), 7.35 (2H, br d, J = 8.6 Hz), 7.25 (2H, br d, J = 8.1 Hz), 6.83 (2H, br d, J = 8.1 Hz), 6.48 (2H, br d, J = 8.3 Hz), 4.59 (1H, br s), 3.85 (2H, br s), 3.69 (3H, s), 3.05 (2H, br t, J = 6.2 Hz), 2.85 (2H, br s), 1.71 (2H, m), 1.64−1.52 (2H, m). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.4, 151.2, 133.6, 131.3, 121.9, 120.4, 114.4, 112.0, 98.3, 55.2, 50.7, 46.0, 42.0, 25.5, 23.3. HRMS (ESI$^+$): calcd for $C_{19}H_{23}N_3O$ [M + H]$^+$: 310.1914; found: 310.1908.

*N^1-(4-Methoxybenzyl)-N^4-(4-nitrophenyl)butane-1,4-diamine (**3f**; 51.3 mg, 39% Yield).* ^{1}H NMR (CD_3OD, 400 MHz): δ 8.02 (2H, d, J = 8.0 Hz), 7.27 (2H, d, J = 8.0 Hz), 6.90 (2H, d, J = 8.0 Hz), 6.59 (2H, d, J = 8.0 Hz), 3.80 (2H, s), 3.78 (3H, s), 3.24−3.19 (2H, m), 2.75−2.70 (2H, m), 1.71−1.65 (4H, m). ^{13}C{^{1}H} NMR (CD_3OD, 125 MHz): δ 161.0, 156.2, 138.0, 131.4, 130.7, 127.5, 115.1, 111.8, 55.9, 53.5, 43.8, 27.7, 27.2. One carbon signal under solvent multiplet. HRMS (ESI$^+$): calcd for $C_{18}H_{23}N_3O_3$ [M + H]$^+$: 330.1812; found: 330.1806.

*Ethyl 4-((4-((4-Methoxybenzyl)amino)butyl)amino)benzoate (**3g**; 48.4 mg, 34% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.67 (2H, d, J = 8.8 Hz), 7.42 (2H, d, J = 8.6 Hz), 6.93 (2H, d, J = 8.6 Hz), 6.64−6.60 (1H, m), 6.57 (2H, d, J = 8.6 Hz), 4.19 (2H, q, J = 7.1 Hz), 3.92 (2H, s), 3.75 (3H, s), 3.11−3.02 (2H, m), 2.75 (2H, br t, J = 7.3 Hz), 1.76−1.63 (2H, m), 1.62−1.51 (2H, m), 1.26 (4H, t, J = 7.1 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 165.9, 159.2, 152.8, 131.0, 130.9, 126.2, 115.8, 113.8, 110.8, 59.5, 55.1, 50.1, 46.4, 41.8, 25.7, 24.0, 14.4. HRMS (ESI$^+$): calcd for $C_{21}H_{28}N_2O_3$ [M + H]$^+$: 357.2173; found: 357.2168.

*N^1-(3-Chloro-5-fluorophenyl)-N^4-(4-methoxybenzyl)butane-1,4-diamine (**3h**; 56.4 mg, 42% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.93 (2H, br s), 7.42 (2H, br d, J = 8.1 Hz), 6.99 (2H, br d, J = 7.8 Hz), 6.43 (1H, s), 6.42−6.37 (1H, m), 6.35−6.28 (1H, m), 4.08 (2H, br t, J = 5.4 Hz), 3.77 (3H, s), 3.02 (2H, t, J = 6.8 Hz), 2.92 (2H, br s), 1.69 (2H, br s), 1.60−1.50 (2H, m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 163.4 (d, J = 242 Hz), 159.7, 151.4 (d, J = 13 Hz), 134.2 (d, J = 14 Hz), 131.5, 123.8, 114.0, 107.7, 101.9 (d, J = 26 Hz), 96.8 (d, J = 25 Hz), 55.2, 49.5, 46.0, 41.9, 25.4, 23.1. HRMS (ESI$^+$): calcd for $C_{18}H_{22}ClFN_2O$ [M + H]$^+$: 337.1477; found: 337.1474.

*N^1-(4-Methoxybenzyl)-N^4-phenylbutane-1,4-diamine (**3i**; 40.9 mg, 36% Yield).* ^{1}H NMR (CD_3OD, 500 MHz): δ 7.60−7.52 (2H, m), 7.52−7.46 (3H, m), 7.43−7.38 (2H, m), 7.01−6.95 (2H, m), 4.12 (2H, s), 3.80 (3H, s), 3.49−3.39 (2H, m), 3.10−3.02 (2H, m), 1.88−1.74 (4H, m). ^{13}C{^{1}H} NMR (CD_3OD, 125 MHz): δ 162.3, 137.5, 132.7, 131.6, 130.5, 124.4, 123.5, 115.7, 56.0, 52.0, 47.6, 24.4, 24.3. One carbon signal under solvent multiplet. HRMS (ESI$^+$): calcd for $C_{18}H_{24}N_2O$ [M + H]$^+$: 285.1961; found: 285.1967.

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*N^1-(4-Methoxybenzyl)-2-methyl-N^4-(4-(trifluoromethyl)phenyl)-butane-1,4-diamine (**3l**; 62.9 mg, 43% Yield).* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (2H, d, J = 8.5 Hz), 7.25 (2H, d, J = 8.5 Hz), 6.88 (2H, d, J = 8.5 Hz), 6.54 (2H, d, J = 8.5 Hz), 4.53 (1H, br s), 3.83−3.79 (3H, m), 3.74 (2H, s), 3.24−3.16 (1H, m), 3.15−3.07 (1H, m), 2.55 (2H, d, J = 6.1 Hz), 1.84−1.70 (2H, m), 1.61−1.49 (2H, m), 0.99 (3H, d, J = 6.7 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 158.7, 150.9, 132.3, 129.3, 126.5 (q, J = 4 Hz), 125.1 (d, J = 270 Hz), 118.2 (q, J = 33 Hz), 113.8, 111.5, 55.3, 55.3, 53.5, 41.3, 34.2, 31.6, 18.6. HRMS (ESI$^+$): calcd for $C_{20}H_{25}F_3N_2O$ [M + H]$^+$: 367.1992; found: 367.1985.

*N^1-(4-Methoxybenzyl)-N^4-(4-(trifluoromethyl)phenyl)pentane-1,4-diamine (**3m**; 49.2 mg, 34% Yield).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (2H, br s), 7.39 (2H, d, J = 8.8 Hz), 7.34 (2H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.6 Hz), 6.65 (2H, d, J = 8.6 Hz), 4.06 (2H, br t, J = 5.6 Hz), 3.76 (3H, s), 3.54−3.40 (1H, m), 2.94−2.81 (2H, m), 1.77−1.60 (2H, m), 1.57−1.41 (2H, m), 1.11 (3H, d, J = 6.4 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 159.0, 151.2, 130.8, 126.7, 126.2 (q, J = 3 Hz), 125.4 (q, J = 270 Hz), 114.5 (q, J = 32 Hz), 113.7, 111.4, 55.1, 50.2, 46.8, 46.7, 33.1, 23.4, 20.1. HRMS (ESI$^+$): calcd for $C_{20}H_{25}F_3N_2O$ [M + H]$^+$: 367.1992; found: 367.1985.

*N^1-(4-Methoxybenzyl)-N^5-(4-(trifluoromethyl)phenyl)pentane-1,5-diamine (**3n**; 105.4 mg, 72% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.81 (2H, br s), 7.41 (2H, d, J = 7.5 Hz), 7.35 (2H, d, J = 8.5 Hz), 6.99 (2H, d, J = 7.7 Hz), 6.64 (2H, d, J = 8.6 Hz), 4.08 (2H, t, J = 5.6 Hz), 3.76 (3H, s), 3.04 (2H, t, J = 6.8 Hz), 2.93−2.83 (2H, m), 1.64 (2H, br quin, J = 7.7 Hz), 1.55 (2H, br quin, J = 7.1 Hz), 1.38 (2H, br quin, J = 7.6 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 159.7, 151.8, 131.5, 126.2 (q, J = 4 Hz), 125.4 (q, J = 270 Hz), 123.8, 114.9 (q, J = 32 Hz), 114.0, 111.1, 55.2, 49.5, 46.1, 42.0, 27.8, 25.1, 23.5. HRMS (ESI$^+$): calcd for $C_{20}H_{25}F_3N_2O$ [M + H]$^+$: 367.1992; found: 367.1985.

*N^1-(4-Methoxybenzyl)-N^3-(4-(trifluoromethyl)phenyl)propane-1,3-diamine (**3o**; 123.0 mg, 91% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.87 (2H, br s), 7.40 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz), 6.98 (2H, d, J = 7.7 Hz), 6.66 (2H, d, J = 8.6 Hz), 4.09 (2H, t, J = 5.5 Hz), 3.76 (3H, s), 3.15 (2H, t, J = 6.8 Hz), 3.05−2.94 (2H, m), 1.88 (2H, quint, J = 7.1 Hz). ^{13}C{^{1}H} NMR (CD_3OD, 125 MHz): δ 160.8, 151.2, 131.1, 126.0 (q, J = 4 Hz), 125.2 (q, J = 268 Hz), 122.8, 117.7 (q, J = 32 Hz), 114.2, 111.4, 54.4, 50.5, 44.9, 39.7, 26.2. HRMS (ESI$^+$): calcd for $C_{18}H_{22}F_3N_2O$ [M + H]$^+$: 339.1679; found: 339.1673.

*N^1-(4-Methoxybenzyl)-N^3-(p-tolyl)propane-1,3-diamine (**3p**; 34.1 mg, 30% Yield).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31−7.23 (2H, m), 7.05−6.98 (2H, m), 6.94−6.86 (2H, m), 6.60−6.52 (2H, m), 3.82 (3H, s), 3.76 (2H, s), 3.21 (2H, t, J = 6.6 Hz), 2.79 (2H, t, J = 6.6 Hz), 2.27 (3H, s), 1.83 (2H, quin, J = 6.6 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 158.7, 146.4, 132.5, 129.8, 129.3, 126.3, 113.9, 113.0, 55.3, 53.5, 47.7, 43.3, 29.6, 20.4. HRMS (ESI$^+$): calcd for $C_{18}H_{24}N_2O$ [M + H]$^+$: 285.1961; found: 285.1967.

*N^1-(4-Methoxybenzyl)-N^3-(4-methoxyphenyl)propane-1,3-diamine (**3q**; 57.6 mg, 48% Yield).* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20−7.13 (2H, m), 6.79 (2H, br d, J = 7.9 Hz), 6.70 (2H, br d, J = 9.2 Hz), 6.49 (2H, br d, J = 9.2 Hz), 3.73 (3H, s), 3.68−3.64 (5H, m), 3.08 (2H, t, J = 6.4 Hz), 2.68 (2H, t, J = 6.4 Hz), 1.73 (2H, quin, J = 6.6 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 158.6, 151.9, 142.9, 132.5, 129.2, 114.9, 114.0, 113.8, 55.8, 55.3, 53.5, 47.7, 43.8, 29.6. HRMS (ESI$^+$): calcd for $C_{18}H_{24}N_2O_2$ [M + H]$^+$: 301.1911; found: 301.1924.

*N^1-(Cyclohexylmethyl)-N^4-(4-(trifluoromethyl)phenyl)butane-1,4-diamine (**5a**; 90.5 mg, 69% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.35 (2H, br s), 7.36 (2H, d, J = 8.6 Hz), 6.65 (2H, d, J = 8.6 Hz), 3.08 (2H, t, J = 6.6 Hz), 2.99−2.86 (2H, m), 2.81−2.69 (2H, m), 1.81−1.49 (10H, m), 1.34−1.08 (3H, m), 1.03−0.82 (2H, m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 151.7, 126.2 (q, J = 4 Hz), 125.4 (q, J = 270 Hz), 115.0 (q, J = 32 Hz), 111.2, 52.6, 47.2, 41.7, 34.4, 29.9, 25.5, 25.4, 25.0, 23.0. HRMS (ESI$^+$): calcd for $C_{18}H_{27}F_3N_2$ [M + H]$^+$: 329.2199; found: 329.2191.

*N^1-Cyclohexyl-N^4-(4-(trifluoromethyl)phenyl)butane-1,4-diamine (**5b**; 72.8 mg, 58% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.65 (1H, br s), 7.36 (2H, br d, J = 8.3 Hz), 6.66 (2H, br d, J = 8.6 Hz), 6.46 (1H, br t, J = 5.4 Hz), 3.08 (2H, q, J = 6.4 Hz), 2.99−2.82 (3H, m), 2.02 (2H, br d, J = 10.3 Hz), 1.79−1.64 (4H, m), 1.62−1.53 (3H, m), 1.34−1.15 (4H, m), 1.15−1.02 (1H, m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 151.8, 126.2 (q, J = 4 Hz), 125.4 (q, J = 270 Hz), 114.8 (q, J = 32 Hz), 111.1, 55.8, 43.2, 41.7, 28.4, 25.5, 24.8, 23.9, 23.3. HRMS (ESI$^+$): calcd for $C_{17}H_{25}F_3N_2$ [M + H]$^+$: 315.2043; found: 315.2037.

*N^1-Nonyl-N^4-(4-(trifluoromethyl)phenyl)butane-1,4-diamine (**5c**; 90.2 mg, 63% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.71 (1H, br s), 7.35 (2H, d, J = 8.6 Hz), 6.66 (2H, d, J = 8.6 Hz), 6.47 (1H, br s), 3.07 (2H, br d, J = 5.4 Hz), 2.90−2.71 (4H, m), 1.69 (2H, quin, J = 7.4 Hz), 1.64−1.52 (4H, m), 1.25 (12H, br s), 0.85 (3H, br t, J = 6.6 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 151.7, 126.1 (d, J = 4 Hz), 125.4 (q, J = 269 Hz), 114.8 (q, J = 32 Hz), 111.1, 46.6, 46.3, 41.6, 31.2, 28.8, 28.6, 28.5, 26.0, 25.4, 25.3, 23.1, 22.1, 13.9. HRMS (ESI$^+$): calcd for $C_{20}H_{33}F_3N_2$ [M + H]$^+$: 359.2669; found: 359.2661.

*(S)-N^1-(1-Methoxypropan-2-yl)-N^4-(4-(trifluoromethyl)phenyl)-butane-1,4-diamine (**5d**; 74.1 mg, 61% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.78 (1H, br s), 8.65 (1H, br s), 7.36 (2H, d, J = 8.6 Hz), 6.66 (2H, m, J = 8.6 Hz), 6.45 (1H, br t, J = 5.4 Hz), 3.58−3.43 (2H, m), 3.31 (3H, s), 3.08 (2H, q, J = 6.3 Hz), 2.99−2.82 (2H, m), 1.77−1.66 (2H, m), 1.66−1.51 (2H, m), 1.21 (3H, d, J = 6.6 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 151.8, 126.2 (q, J = 4 Hz), 125.5 (q, J = 269 Hz), 114.9 (q, J = 32 Hz), 111.2, 71.8, 58.4, 52.4, 44.0, 41.7, 25.5, 23.3, 13.6. HRMS (ESI$^+$): calcd for $C_{15}H_{23}F_3N_2O$ [M + H]$^+$: 305.1835; found: 305.1829.

*(S)-N^1-(1-Phenylethyl)-N^4-(4-(trifluoromethyl)phenyl)butane-1,4-diamine (**5e**; 67.2 mg, 50% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (1H, br s), 8.78 (1H, br s), 7.55-7.39 (5H, m), 7.36 (2H, d, J = 8.6 Hz), 6.63 (2H, d, J = 8.6 Hz), 4.42−4.29 (1H, m), 3.04 (2H, t, J = 6.7 Hz), 2.88 (1H, br s), 2.74−2.59 (1H, m), 1.71−1.59 (2H, m), 1.58−1.46 (5H, m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 151.7, 137.5, 128.8, 128.7, 127.9, 126.2, 125.4 (q, J = 269 Hz), 114.9 (q, J = 32 Hz), 111.1, 57.2, 44.7, 41.7, 25.5, 23.2, 19.8. HRMS (ESI$^+$): calcd for $C_{19}H_{23}F_3N_2$ [M + H]$^+$: 337.1886; found: 337.1878.

*N^1-(4-(Trifluoromethyl)benzyl)-N^4-(4-(trifluoromethyl)phenyl)-butane-1,4-diamine (**5f**; 49.9 mg, 32% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.13 (2H, br s), 7.82 (2H, d, J = 8.1 Hz), 7.72 (2H, d, J = 8.3 Hz), 7.36 (2H, d, J = 8.6 Hz), 6.65 (2H, d, J = 8.6 Hz), 4.26 (2H, br t, J = 5.5 Hz), 3.08 (2H, t, J = 6.7 Hz), 2.98 (2H, br s), 1.78−1.65 (2H, m), 1.65−1.53 (2H, m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 151.8, 136.7, 130.9, 129.6 (q, J = 32 Hz), 126.4 (q, J = 4 Hz), 125.7 (q, J = 4 Hz), 125.5 (q, J = 269 Hz), 124.2 (q, J = 272 Hz), 115.0 (q, J = 32 Hz), 111.4, 49.6, 46.8, 41.8, 25.5, 23.3. HRMS (ESI$^+$): calcd for $C_{19}H_{20}F_6N_2$ [M + H]$^+$: 391.1603; found: 391.1595.

*N^1-(4-Methoxyphenyl)-N^4-(4-(trifluoromethyl)phenyl)butane-1,4-diamine (**5g**; 29.7 mg, 22% Yield).* ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.35 (2H, d, J = 8.6 Hz), 6.70 (2H, d, J = 8.8 Hz), 6.65 (2H, d, J = 8.6 Hz), 6.52 (2H, d, J = 8.8 Hz), 6.36 (1H, br t, J = 5.1 Hz), 5.09 (1H, br s), 3.63 (3H, s), 3.13−3.04 (2H, m), 2.97 (2H, br s), 1.72−1.56 (4H, m). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 151.9, 150.5, 143.4, 126.2 (q, J = 4 Hz), 125.4 (q, J = 270 Hz), 114.8 (q, J = 32 Hz), 114.6, 112.9, 111.1, 55.3, 43.5, 42.2, 26.5, 26.2. HRMS (ESI$^+$): calcd for $C_{18}H_{21}F_3N_2O$ [M + H]$^+$: 339.1679; found: 339.1670.

*tert-Butyl 4-(4-((4-(Trifluoromethyl)phenyl)amino)butyl)-piperazine-1-carboxylate (**6a**; 120.3 mg, 75% Yield).* ^{1}H NMR (CD_3OD, 500 MHz): δ 7.32 (2H, d, J = 9.2 Hz), 6.64 (2H, d, J = 8.5 Hz), 3.42 (4H, br, s), 3.15 (2H, br t, J = 6.4 Hz), 2.47−2.35 (6H, m), 1.71−1.56 (4H, m), 1.45 (9H, s). ^{13}C{^{1}H} NMR (CD_3OD, 125 MHz): δ 156.5, 153.4, 127.4 (q, J = 4 Hz), 126.9 (q, J = 269 Hz), 118.4 (q, J = 32 Hz), 112.6, 81.4, 59.5, 54.1, 44.5 (br d, rotameric quaternary carbon), 44.0, 28.8, 28.1, 25.2. HRMS (ESI$^+$): calcd for $C_{20}H_{30}F_3N_3O_2$ [M + H]$^+$: 402.2363; found: 402.2370.

*tert-Butyl 4-(5-((4-(Trifluoromethyl)phenyl)amino)pentyl)-piperazine-1-carboxylate (**6b**; 79.7 mg, 48% Yield).* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 (2H, d, J = 8.5 Hz), 6.58 (2H, d, J = 8.5 Hz), 3.97 (1H, br s), 3.49−3.38 (4H, m), 3.19−3.11 (2H, m) 2.42−2.31 (6H, m), 1.73−1.61 (2H, m), 1.59−1.51 (2H, m), 1.48−1.41

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(11H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 154.7, 150.7, 126.6 (q, J = 4 Hz), 125.0 (q, J = 271 Hz), 118.5 (q, J = 33 Hz), 111.6, 79.6, 58.5, 53.1, 43.7 (br d, rotameric quaternary carbon), 43.4, 29.2, 28.4, 26.6, 24.9. HRMS (ESI^+): calcd for $C_{21}H_{32}F_3N_3O_2$ $[M + H]^+$: 416.2519; found: 416.2522.

*tert-Butyl 4-(3-((4-(Trifluoromethyl)phenyl)amino)propyl)-piperazine-1-carboxylate (**6c**; 69.7 mg, 45% Yield).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39 (2H, d, J = 8.3 Hz), 6.58 (2H, d, J = 8.3 Hz), 5.13 (1H, br s), 3.52−3.42 (4H, m), 3.24 (2H, q, J = 6.0 Hz), 2.51 (2H, t, J = 6.4 Hz), 2.42 (4H, t, J = 5.0 Hz), 1.82 (2H, quin, J = 6.4 Hz), 1.48 (9H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 154.7, 151.0, 126.6 (q, J = 4 Hz), 125.0 (q, J = 270 Hz), 118.4 (q, J = 32 Hz), 111.6, 79.8, 57.2, 53.1, 43.7 (br d, rotameric quaternary carbon), 43.0, 28.4, 25.3. HRMS (ESI^+): calcd for $C_{19}H_{28}F_3N_3O_2$ $[M + H]^+$: 388.2206; found: 388.2208.

*N^1-(4-Methoxybenzyl)-N^1-methyl-N^4-(4-(trifluoromethyl)phenyl)-butane-1,4-diamine (**6d**; 43.9 mg, 30% Yield).* ^1H NMR (CD_3OD, 400 MHz): δ 7.35−7.31 (2H, m), 7.31−7.26 (2H, m), 6.90 (2H, d, J = 7.8 Hz), 6.64 (2H, d, J = 8.5 Hz), 3.78 (3H, s), 3.75 (2H, s), 3.14 (2H, t, J = 6.7 Hz), 2.72−2.62 (2H, m), 2.40 (3H, s), 1.78−1.68 (2H, m) 1.68−1.59 (2H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.0, 150.8, 130.7, 128.9, 126.5 (q, J = 4 Hz), 125.0 (q, J = 270 Hz), 118.1 (q, J = 32 Hz), 113.7, 111.5, 60.9, 56.0, 55.2, 43.1, 41.2, 26.7, 24.3. HRMS (ESI^+): calcd for $C_{20}H_{25}F_3N_2O$ $[M + H]^+$: 367.1992; found: 367.2008.

*N-(4-(Pyrrolidin-1-yl)butyl)-4-(trifluoromethyl)aniline (**6e**; 64.0 mg, 56% Yield).* ^1H NMR (CD_3OD, 400 MHz): δ 7.34 (2H, d, J = 8.5 Hz), 6.68 (2H, d, J = 8.5 Hz), 3.68−3.59 (2H, m), 3.24−3.17 (4H, m), 3.11−3.00 (2H, m), 2.19−2.07 (2H, m), 2.07−1.95 (2H, m), 1.88−1.79 (2H, m), 1.75−1.66 (2H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 150.2, 126.5 (q, J = 4 Hz), 124.9 (q, J = 268 Hz), 118.7 (q, J = 33 Hz), 112.0, 55.0, 53.8, 42.4, 25.6, 23.2, 23.1. HRMS (ESI^+): calcd for $C_{15}H_{21}F_3N_2$ $[M + H]^+$: 287.1730; found: 287.1732.

*N-(4-(Pyrrolidin-1-yl)butyl)-4-(trifluoromethoxy)aniline (**6f**; 38.7 mg, 32% Yield).* ^1H NMR (CD_3OD, 400 MHz): δ 7.12 (2H, d, J = 8.6 Hz), 6.87 (2H, d, J = 7.8 Hz), 3.64 (2H, br s), 3.26−3.18 (4H, m), 3.14−2.99 (2H, m), 2.20−2.08 (2H, m), 2.08−1.95 (2H, m), 1.88−1.78 (2H, m), 1.78−1.68 (2H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 144.8, 140.8, 122.4, 120.4 (q, J = 257 Hz), 118.7, 54.8, 53.8, 47.2, 24.3, 23.0, 22.9. HRMS (ESI^+): calcd for $C_{15}H_{21}F_3N_2O$ $[M + H]^+$: 303.1679; found: 303.1683.

*N-(3-(Pyrrolidin-1-yl)propyl)-4-(trifluoromethyl)aniline (**6g**; 64.2 mg, 59% Yield).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39 (2H, d, J = 8.3 Hz), 6.57 (2H, d, J = 8.5 Hz), 5.14 (1H, br s), 3.26−3.21 (2H, m), 2.61 (2H, t, J = 6.7 Hz), 2.56−2.49 (4H, m), 1.87−1.78 (6H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 151.2, 126.5 (q, J = 4 Hz), 122.9 (q, J = 271 Hz), 118.1 (q, J = 32 Hz), 111.6, 54.9, 54.2, 43.1, 27.6, 23.5. HRMS (ESI^+): calcd for $C_{14}H_{19}F_3N_2$ $[M + H]^+$: 273.1573; found: 273.1581.

Representative Experimental Procedure for Ullmann Couplings. *Compounds **7a**−**j** were Prepared by ChemDiscover LLC.* A round-bottom flask was charged with aryl iodide or aryl bromide (1 equiv), ethyl (*R*)-5-oxopyrrolidine-2-carboxylate (1.4 equiv), copper iodide (0.25 equiv), cesium carbonate (2 equiv), and *p*-dioxane (0.5 M reaction concentration) under an atmosphere of nitrogen. Then, TMEDA or DMEDA (0.5 equiv) was added, and the resulting mixture was heated to 40 °C and stirred at that temperature for 5 h. Additional portions of copper iodide (0.12 equiv) and TMEDA or DMEDA (0.25 equiv) were added (as needed). The reaction mixture continued to stir at 40 °C overnight. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was concentrated, and the crude material was purified by silica gel column chromatography (EtOAc/petroleum ether, 1:2) to give the desired *N*-aryl pyrrolidinones.

*Ethyl (R)-5-Oxo-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (**7a**, Yellow Oil, 18.2 g, Yield: 86%, 99.5% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.82−7.67 (4H, m), 5.10 (1H, dd, J = 8.9 Hz, 2.7 Hz), 4.21−4.07 (2H, m), 2.66−2.53 (3H, m), 2.17−2.07 (1H, m), 1.15 (3H, t, J = 7.0 Hz). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 175.0, 171.9, 142.5, 126.5 (q, J = 4 Hz), 124.9 (q, J = 32 Hz), 124.7 (q, J = 270 Hz), 120.7, 61.8, 60.6, 31.1, 22.7, 14.4. HRMS (ESI^+): calcd for $C_{14}H_{14}F_3NO_3$ $[M + H]^+$: 302.0999; found: 302.1003.

*Ethyl (R)-5-Oxo-1-(3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (**7b**, Yellow Oil, 10.0 g, Yield: 80%, 97.5% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.98 (1H, s), 7.71−7.65 (1H, m), 7.65−7.60 (1H, m), 7.52 (1H, d, J = 7.9 Hz), 5.15−5.10 (1H, m), 4.17−4.09 (2H, m), 2.66−2.53 (2H, m), 2.49−2.44 (1H, m), 2.17−2.07 (1H, m), 1.13 (3H, t, J = 7.3 Hz). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 174.4, 171.5, 139.2, 130.1, 129.4 (q, J = 32 Hz), 124.3, 124.0 (q, J = 272 Hz), 121.1 (q, J = 4 Hz), 117.1 (q, J = 4 Hz), 61.3, 60.3, 30.5, 22.2, 13.8. HRMS (ESI^+): calcd for $C_{14}H_{14}F_3NO_3$ $[M + H]^+$: 302.0999; found: 302.1005.

*Ethyl (R)-1-(3-Fluoro-5-(trifluoromethyl)phenyl)-5-oxopyrrolidine-2-carboxylate (**7c**, Yellow Oil, 3.2 g, Yield: 58%, 97.0% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.77 (1H, s), 7.73 (1H, dd, J = 11.3 Hz, 2.1 Hz), 7.49 (1H, br d, J = 8.5 Hz), 5.21 (1H, dd, J = 8.9 Hz, 2.7 Hz), 4.14 (2H, q, J = 7.1 Hz), 2.68−2.53 (2H, m), 2.50−2.44 (1H, m), 2.18−2.10 (1H, m), 1.14 (3H, t, J = 7.0 Hz). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 174.7, 171.2, 162.0 (d, J = 245 Hz), 141.1 (d, J = 11 Hz), 131.1 (dq, J = 33 Hz, 10 Hz), 123.2 (dq, J = 272 Hz, 4 Hz), 112.8 (q, J = 4 Hz), 111.1 (d, J = 26 Hz), 108.5 (dq, J = 25 Hz, 4 Hz), 61.4, 60.2, 30.6, 22.1, 13.8. HRMS (ESI^+): calcd for $C_{14}H_{13}F_4NO_3$ $[M + H]^+$: 320.0904; found: 320.0910.

*Ethyl (R)-1-(3-Chloro-5-fluorophenyl)-5-oxopyrrolidine-2-carboxylate (**7d**, Yellow Oil, 3.1 g, Yield: 55%, 95.5% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.48 (1H, s), 7.43 (1H, td, J = 11.1 Hz, 2.1 Hz), 7.24 (1H, td, J = 8.5 Hz, 2.1 Hz), 5.12 (1H, dd, J = 9.2 Hz, 3.1 Hz), 4.15 (2H, q, J = 7.3 Hz), 2.66−2.52 (2H, m), 2.48−2.40 (1H, m), 2.14−2.07 (1H, m), 1.15 (3H, t, J = 7.0 Hz). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 174.5, 171.2, 162.1 (d, J = 245 Hz), 141.0 (d, J = 13 Hz), 134.1 (d, J = 13 Hz), 116.1 (d, J = 4 Hz), 111.8 (d, J = 25 Hz), 106.2 (d, J = 26 Hz), 61.2, 60.2, 30.6, 22.1, 13.9. HRMS (ESI^+): calcd for $C_{13}H_{13}ClF_3NO_3$ $[M + H]^+$: 286.0641; found: 286.0643.

*Ethyl (R)-5-Oxo-1-(pyridin-4-yl)pyrrolidine-2-carboxylate (**7e**, White Solid, 12.5 g, Yield: 76%, 97.4% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.54−8.44 (2H, m), 7.57−7.49 (2H, m), 5.07 (1H, dd, J = 9.2 Hz, 2.4 Hz), 4.21−4.08 (2H, m), 2.70−2.54 (2H, m), 2.49−2.42 (1H, m), 2.17−2.08 (1H, m), 1.18 (3H, t, J = 7.3 Hz). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 175.1, 171.2, 150.4, 145.1, 113.1, 61.5, 59.3, 30.8, 22.2, 13.9. HRMS (ESI^+): calcd for $C_{12}H_{14}N_2O_3$ $[M + H]^+$: 235.1077; found: 235.1080.

*Ethyl (R)-5-Oxo-1-(pyridin-3-yl)pyrrolidine-2-carboxylate (**7f**, Yellow Oil, 10.6 g, Yield: 91%, 99.3% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.69 (1H, d, J = 2.4 Hz), 8.36 (1H, dd, J = 4.6 Hz, 1.5 Hz), 7.96−7.89 (1H, m), 7.45−7.39 (1H, m), 5.12−5.05 (1H, m), 4.18−4.07 (2H, m), 2.63−2.52 (3H, m), 2.19−2.08 (1H, m), 1.14 (3H, t, J = 7.0 Hz). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 174.4, 171.4, 145.6, 142.3, 135.1, 128.2, 123.6, 61.3, 59.9, 30.1, 22.5, 13.9. HRMS (ESI^+): calcd for $C_{12}H_{14}N_2O_3$ $[M + H]^+$: 235.1077; found: 235.1081.

*Ethyl (R)-5-Oxo-1-(pyridin-2-yl)pyrrolidine-2-carboxylate (**7g**, Yellow Oil, 11.1 g, Yield: 95%, 98.6% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.34−8.22 (2H, m), 7.89−7.77 (1H, m), 7.13 (1H, ddd, J = 7.3 Hz, 4.9 Hz, 1.2 Hz), 4.99 (1H, dd, J = 9.8 Hz, 3.1 Hz), 4.18−4.08 (2H, m), 2.71−2.54 (2H, m), 2.43 (1H, qd, J = 13.0 Hz, 9.5 Hz), 2.06−1.97 (1H, m), 1.16 (3H, t, J = 7.0 Hz). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 174.4, 172.0, 150.7, 147.4, 138.0, 119.7, 113.5, 60.7, 59.1, 31.5, 21.2, 13.9. HRMS (ESI^+): calcd for $C_{12}H_{14}N_2O_3$ $[M + H]^+$: 235.1077; found: 235.1079.

*Ethyl (R)-5-Oxo-1-phenylpyrrolidine-2-carboxylate (**7h**, 15.0 g, Yield: 87%, 95.7% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.47 (2H, br d, J = 7.3 Hz), 7.36 (2H, t, J = 7.9 Hz), 7.20-7.11 (1H, m), 4.99−4.93 (1H, m), 4.19−4.06 (2H, m), 2.63−2.52 (2H, m), 2.48−2.42 (1H, m), 2.12−2.01 (1H, m), 1.13 (3H, t, J = 7.3 Hz). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 173.9, 171.8, 138.5, 128.8, 124.8, 120.9, 61.1, 60.6, 30.5, 22.4, 13.9. HRMS (ESI^+): calcd for $C_{13}H_{15}NO_3$ $[M + H]^+$: 234.1125; found: 234.1132.

*Ethyl (R)-1-(3-Methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (**7i**, Yellow Oil, 14.6 g, Yield: 93%, 99.8% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.27 (1H, t, J = 8.2 Hz), 7.20−7.13 (1H, m), 6.98

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(1H, dd, J = 8.2 Hz, 1.5 Hz), 6.75 (1H, dd, J = 8.2 Hz, 2.1 Hz), 4.95 (1H, dd, J = 8.9 Hz, 2.7 Hz), 4.12 (2H, q, J = 6.9 Hz), 3.73 (3H, s), 2.62−2.52 (1H, m), 2.49−2.40 (2H, m), 2.10−2.02 (1H, m), 1.21−1.11 (3H, m). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 174.0, 171.8, 159.4, 139.6, 129.6, 112.8, 110.0, 107.0, 61.2, 60.7, 55.1, 30.7, 22.3, 13.9. HRMS (ESI$^+$): calcd for $C_{14}H_{17}NO_4$ $[M + H]^+$: 264.1230; found: 264.1232.

*Ethyl (R)-1-(2-Methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (**7j**, Yellow Oil, 14.8 g, Yield: 80%, 99.7% ee).* ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.33−7.26 (1H, m), 7.21 (1H, dd, J = 7.6 Hz, 1.5 Hz), 7.09 (1H, d, J = 7.9 Hz), 6.95 (1H, dt, J = 7.6 Hz, 1.2 Hz), 4.68−4.60 (1H, m), 4.04 (2H, qq, J = 10.9 Hz, 7.0 Hz), 3.78 (3H, s), 2.50−2.34 (3H, m), 2.15−2.05 (1H, m), 1.09 (3H, t, J = 7.0 Hz). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ: 174.3, 171.6, 154.3, 129.5, 128.7, 125.6, 120.2, 112.2, 60.9, 55.6, 29.1, 22.9, 13.9. One carbon signal under solvent multiplet. HRMS (ESI$^+$): calcd for $C_{14}H_{17}NO_4$ $[M + H]^+$: 264.1230; found: 264.1234.

Representative Experimental Procedure for Reductive Coupling/Cyclization of Ester Containing Aryl Lactams with Primary Amines (for Table 6). To a 2-dram vial equipped with a magnetic stir bar was added Schwartz's reagent (155 mg, 0.6 mmol, 1.5 equiv; preferably less than 1 month old) as a solid in the air. The vial was then sealed with a red open top cap (with a solvent-resistant Teflon cover), and a N_2 flow ran through the sealed vial for 5 min. The N_2 line was then removed, and THF (2 mL) was added through a syringe under positive pressure. The reaction mixture was cooled to 0 °C in an ice-water cooling bath and subjected to vigorous stirring, followed by the injection of a solution of the substrate (0.4 mmol in 1 mL of THF). After 1 h at 0 °C, to the milky white suspension was added neat amine coupling partner (1.6 mmol, 4 equiv). The vial was then removed from the ice-water bath, and STAB (254 mg, 1.2 mmol, 3 equiv) was added in one portion as a solid to the reaction mixture. The vial was capped and stirred at 80 °C for 18 h. A sample was taken from the vial to be analyzed by LCMS. Upon reaction completion, water (1 mL) was added to the vial. The mixture was stirred for 10 min before the addition of EtOAc (2 mL). The layers were separated, and the aqueous phase was extracted with additional portions of EtOAc (3 mL × 3 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated. The residue was purified by silica gel column chromatography (12g silica gel column) with an automatic purification system (grading from 0% EtOAc/heptanes to 30% EtOAc/heptanes over 18 min). The fractions were collected and dried to give the desired lactam products as white solids.

*(R)-1-(4-Methoxybenzyl)-3-((4-(trifluoromethyl)phenyl)amino)-piperidin-2-one (**8a**; 113.9 mg, 75% Yield).* ^1H NMR (CD_3OD, 400 MHz): δ 7.36 (2H, br d, J = 8.3 Hz), 7.29−7.17 (2H, m), 6.92−6.86 (2H, m), 6.77 (2H, br d, J = 8.5 Hz), 4.53 (2H, s), 4.16 (1H, br dd, J = 10.2 Hz, 5.9 Hz), 3.79−3.76 (3H, m), 3.36−3.33 (2H, m), 2.23 (1H, br dd, J = 12.7 Hz, 5.1 Hz), 1.96−1.85 (2H, m), 1.84−1.68 (1H, m). $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ 172.3, 160.8, 152.3, 130.7, 130.3, 127.4 (q, J = 4 Hz), 126.8 (q, J = 269 Hz), 119.5 (q, J = 32 Hz), 115.2, 113.8, 55.8, 54.8, 51.1, 48.1, 28.7, 21.8. HRMS (ESI$^+$): calcd for $C_{20}H_{22}N_2F_3O_2$ $[M + H]^+$: 379.1628; found: 379.1623. Product enantiomer excess: 100% ee.

*(R)-1-(4-Methoxybenzyl)-3-((3-(trifluoromethyl)phenyl)amino)-piperidin-2-one (**8b**; 105.9 mg, 70% Yield).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27 (1H, t, J = 8.0 Hz), 7.21 (2H, d, J = 8.3 Hz), 6.97 (1H, d, J = 7.6 Hz), 6.90−6.80 (4H, m), 4.64-4.50 (2H, m), 3.89 (1H, dd, J = 11.3 Hz, 5.4 Hz), 3.81 (3H, s), 3.38-3.23 (2H, m), 2.52−2.42 (1H, m), 1.99−1.90 (2H, m), 1.70−1.58 (1H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 170.0, 159.1, 147.7, 131.5 (q, J = 32 Hz), 129.6, 129.5, 128.8, 124.3 (q, J = 273 Hz), 116.7, 114.3 (q, J = 4 Hz), 114.0, 109.3 (q, J = 4 Hz), 55.2, 54.3, 50.2, 46.3, 27.5, 20.5. HRMS (ESI$^+$): calcd for $C_{20}H_{22}N_2F_3O_2$ $[M + H]^+$: 379.1628; found: 379.1623. Product enantiomer excess: 100% ee.

*(R)-3-((3-Fluoro-5-(trifluoromethyl)phenyl)amino)-1-(4-methoxybenzyl)piperidin-2-one (**8c**; 104.5 mg, 66% Yield).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21 (2H, d, J = 8.3 Hz), 6.88 (2H, d, J = 8.6 Hz), 6.68-6.62 (2H, m), 6.48 (1H, d, J = 11.0 Hz), 5.39 (1H, br s), 4.56 (2H, d, J = 14.4 Hz), 3.86 (1H, br dd, J = 11.2 Hz, 5.1 Hz), 3.81 (3H, s), 3.36−3.24 (2H, m), 2.51−2.39 (1H, m), 1.99−1.88 (2H, m), 1.70−1.55 (1H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.5, 164.6 (d, J = 244 Hz), 159.1, 149.6 (d, J = 11 Hz), 132.7 (dq, J = 33 Hz, 11 Hz), 129.4, 128.6, 123.5 (dq, J = 272 Hz, 4 Hz), 114.0, 105.9 (t, J =3 Hz), 102.6 (d, J = 26 Hz), 101.1 (dd, J = 26 Hz, 4 Hz), 55.2, 54.1, 50.1, 46.1, 27.2, 20.4. HRMS (ESI$^+$): calcd for $C_{20}H_{21}N_2F_4O_2$ $[M + H]^+$: 397.1534; found: 397.1528. Product enantiomer excess: 100% ee.

*(R)-3-((3-Chloro-5-fluorophenyl)amino)-1-(4-methoxybenzyl)-piperidin-2-one (**8d**; 105.7 mg, 73% Yield).* ^1H NMR (DMSO-d_6, 400 MHz): δ 7.19 (2H, d, J = 8.3 Hz), 6.89 (2H, d, J = 8.6 Hz), 6.56 (1H, s), 6.46−6.40 (3H, m), 4.49−4.38 (2H, m), 4.15−4.09 (1H, m), 3.73 (3H, s), 3.27−3.15 (2H, m), 2.12−2.06 (1H, m), 1.84−1.77 (2H, m), 1.63−1.57 (1H, m). $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ 172.2, 166.3, 164.4, 160.7, 152.3 (d, J = 13 Hz), 136.4 (d, J = 14 Hz), 130.5 (d, J = 45 Hz), 115.2, 110.1 (d, J = 2 Hz), 104.6 (d, J = 25 Hz), 99.2 (d, J = 25 Hz), 55.8, 54.8, 51.0, 48.0, 28.8, 21.7. HRMS (ESI$^+$): calcd for $C_{19}H_{21}ClFN_2O_2$ $[M + H]^+$: 363.1270; found: 363.1265. Product enantiomer excess: 94% ee.

*(R)-1-(4-Methoxybenzyl)-3-(pyridin-4-ylamino)piperidin-2-one (**8e**; 90.8 mg, 73% Yield).* ^1H NMR (DMSO-d_6, 400 MHz): δ 8.71 (1H, d, J = 8.3 Hz), 8.24 (1H, br d, J = 6.8 Hz), 8.12 (1H, br d, J = 6.8 Hz), 7.20 (2H, d, J = 7.2 Hz), 7.08−6.99 (1H, m), 6.97−6.93 (1H, m), 6.92−6.87 (2H, m), 4.57 (1H, ddd, J = 10.6 Hz, 8.3 Hz, 6.0 Hz), 4.51−4.40 (2H, m, 2H), 3.74 (3H, s), 3.31−3.19 (2H, m), 2.13 (1H, br dd, J = 12.5 Hz, 5.6 Hz), 1.92−1.83 (2H, m), 1.82−1.70 (1H, m). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz): δ 167.5, 158.6, 158.5, 140.3, 138.7, 129.2, 129.0, 113.9, 109.9, 106.2, 55.1, 52.2, 48.9, 46.4, 26.9, 20.4. HRMS (ESI$^+$): calcd for $C_{18}H_{21}N_3O_2$ $[M + H]^+$: 312.1707; found: 312.1700. Product enantiomer excess: 100% ee.

*(R)-1-(4-Methoxybenzyl)-3-(pyridin-3-ylamino)piperidin-2-one (**8f**, 95.8 mg, 77% Yield).* ^1H NMR (DMSO-d_6, 400 MHz): δ 8.04 (1H, d, J = 2.4 Hz), 7.75 (1H, d, J = 4.4 Hz), 7.20 (2H, d, J = 8.3 Hz), 7.08−6.97 (2H, m), 6.90 (2H, d, J = 8.3 Hz), 6.02 (1H, d, J = 7.1 Hz), 4.50−4.39 (2H, m), 4.08 (1H, dt, J = 10.4 Hz, 6.4 Hz), 3.74 (3H, s), 3.30−3.16 (2H, m), 2.11 (1H, br d, J = 12.7 Hz, 5.1 Hz), 1.89−1.80 (2H, m), 1.69−1.58 (1H, m). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz): δ 169.6, 158.4, 144.5, 136.8, 135.8, 129.3, 129.1, 123.3, 118.1, 113.8, 55.0, 52.3, 48.8, 46.3, 27.4, 20.3. HRMS (ESI$^+$): calcd for $C_{18}H_{21}N_3O_2$ $[M + H]^+$: 312.1707; found: 312.1700. Product enantiomer excess: 98% ee.

*(R)-1-(4-Methoxybenzyl)-3-(pyridin-2-ylamino)piperidin-2-one (**8g**; 81.0 mg, 65% Yield).* ^1H NMR (CD_3OD, 500 MHz): δ 7.95−7.92 (1H, m), 7.44 (1H, ddd, J = 8.5 Hz, 6.7 Hz, 1.8 Hz), 7.24 (2H, d, J = 8.6 Hz), 6.91−6.87 (2H, m), 6.61 (1H, d, J = 8.5 Hz), 6.59−6.56 (1H, m), 4.60−4.49 (m, 2H), 4.48 (1H, dd, J = 10.4 Hz, 6.1 Hz), 3.78 (3H, s), 3.35−3.32 (2H, m), 2.29−2.21 (1H, m), 1.96−1.89 (2H, m), 1.86−1.76 (1H, m). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz): δ 169.8, 158.4, 158.3, 147.1, 136.5, 129.4, 129.0, 113.8, 111.8, 109.0, 55.0, 51.1, 48.9, 46.5, 27.8, 20.8. HRMS (ESI$^+$): calcd for $C_{18}H_{21}N_3O_2$ $[M + H]^+$: 312.1707; found: 312.1701. Product enantiomer excess: 88% ee.

*(R)-1-(4-Methoxybenzyl)-3-(phenylamino)piperidin-2-one (**8h**; 63.2 mg, 51% Yield).* ^1H NMR (CD_3OD, 400 MHz): δ 7.20 (2H, d, J = 8.6 Hz), 7.07 (2H, t, J = 7.7 Hz), 6.90 (2H, d, J = 8.3 Hz), 6.66 (2H, d, J = 8.1 Hz), 6.55 (1H, t, J = 7.2 Hz), 5.70 (1H, d, J = 6.6 Hz), 4.53−4.40 (2H, m), 4.04−3.94 (1H, m), 3.74 (3H, s), 3.27−3.16 (2H, m), 2.17−2.10 (1H, m), 1.86−1.79 (2H, m), 1.65−1.57 (1H, m). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz): δ 169.8, 158.4, 148.2, 129.4, 129.1, 128.7, 115.9, 113.8, 112.6, 55.0, 52.9, 48.9, 46.2, 27.5, 20.2. HRMS (ESI$^+$): calcd for $C_{19}H_{22}N_2O_2$ $[M + H]^+$: 311.1754; found: 311.1747. Product enantiomer excess: 100% ee.

*(R)-1-(4-Methoxybenzyl)-3-((3-methoxyphenyl)amino)piperidin-2-one (**8i**; 74.8 mg, 55% Yield).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21 (2H, d, J = 8.6 Hz), 7.11 (1H, t, J = 8.2 Hz), 6.87 (2H, d, J = 8.3 Hz), 6.33−6.31 (2H, m), 6.24 (1H, s), 4.60−4.52 (2H, m), 3.85 (1H, dd, J = 11.3 Hz, 5.6 Hz), 3.81 (3H, s), 3.78 (3H, s), 3.33−3.22 (2H, m), 2.53−2.46 (1H, m), 1.95−1.88 (2H, m), 1.65−1.59 (1H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 170.4, 160.7, 159.1, 148.9, 129.9, 129.5, 128.9, 114.0, 106.8, 102.9, 99.7, 55.3, 55.1, 54.7, 50.2,

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46.3, 27.8, 20.5. HRMS (ESI$^+$): calcd for $C_{20}H_{25}N_2O_3$ [M + H]$^+$: 341.1860; found: 341.1853. Product enantiomer excess: 100% ee.

*(R)-1-(4-Methoxybenzyl)-3-((2-methoxyphenyl)amino)piperidin-2-one (**8j**; 47.6 mg, 35% Yield).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (2H, d, J = 8.6 Hz), 6.90−6.86 (3H, m), 6.80 (1H, d, J = 7.6 Hz), 6.73 (1H, t, J = 7.6 Hz), 6.62 (1H, d, J = 7.8 Hz), 4.61−4.53 (2H, m), 3.88 (3H, s), 3.87−3.83 (1H, m), 3.81 (3H, s), 3.34−3.23 (2H, m), 2.52−2.43 (1H, m), 1.98−1.89 (2H, m), 1.78−1.66 (1H, m). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 170.3, 159.0, 147.6, 137.4, 129.6, 129.0, 120.9, 117.4, 114.0, 110.2, 109.5, 55.4, 55.3, 54.7, 50.1, 46.5, 28.0, 20.6. HRMS (ESI$^+$): calcd for $C_{20}H_{25}N_2O_3$ [M + H]$^+$: 341.1860; found: 341.1853. Product enantiomer excess: 100% ee.

*Preparation and Isolation of Compound **9**.* The compound was prepared following the same general procedure that was used for the preparation of compound **8a** except that the reaction mixture was stirred at 22 °C instead of 80 °C after the addition of STAB. After keeping the reaction mixture at 22 °C overnight, **9** was present in the reaction mixture as a major component. The reaction was worked-up following the same protocol, and the crude was purified by mass-directed prep-HPLC (SunFire C18 column, 60 mL/min flow rate, 10% acetonitrile in water to 70% acetonitrile in water, with 0.1% TFA modifier) to give ethyl (*R*)-5-((4-methoxybenzyl)amino)-2-((4-(trifluoromethyl)phenyl)-amino)pentanoate as a colorless oil. Yield was not determined since it was isolated just for characterization.

*Ethyl (R)-5-((4-Methoxybenzyl)amino)-2-((4-(trifluoromethyl)-phenyl)amino)pentanoate (**9**).* ^{1}H NMR (CD_3OD, 400 MHz): δ 7.41−7.36 (4H, m), 6.98−6.94 (2H, m), 6.71 (2H, br d, J = 12.0 Hz), 4.20−4.08 (5H, m), 3.79 (3H, s), 3.07−3.03 (2H, m), 2.02−1.82 (4H, m), 1.22 (3H, t, J = 8.0 Hz). ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz): δ 174.9, 162.3, 152.1, 132.6, 127.6 (q, J = 3 Hz), 126.6 (q, J = 267 Hz), 124.3, 120.2 (q, J = 36 Hz), 115.7, 113.6, 62.6, 56.9, 55.9, 52.0, 47.8, 30.4, 24.0, 14.6. HRMS (ESI$^+$): calcd for $C_{22}H_{27}N_2F_3O_3$ [M + H]$^+$: 425.2047; found: 425.2051.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00816.

Descriptions of LCMS and HPLC methods; chiral SFC traces of the chiral piperidinone products in Table 6; and ^{1}H and ^{13}C NMR spectra of the products (PDF)

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Notes

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(18) Different solvents were tested to identity the best reaction medium. While dichloromethane and acetonitrile were largely ineffective to promote the reductive coupling reaction, tetrahydrofuran and toluene were capable solvents. However, in toluene, diamine **3a** was formed in 43% yield, presumably due to the lower solubility of reactants in comparison to reactions with THF. Therefore, THF was chosen to be the optimal solvent going forward.

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