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Graphical Abstract

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Stereocontrolled synthesis of bicyclic ureas and sulfamides via Pd-catalyzed alkene carboamination reactions

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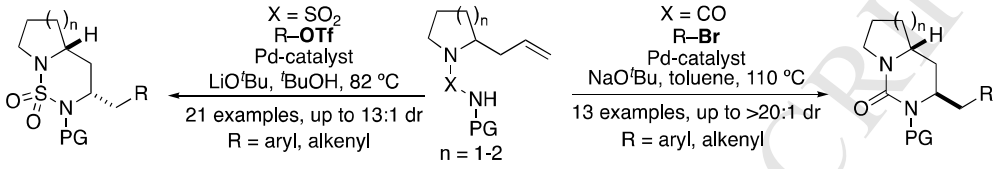

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ABSTRACT

The synthesis of bicyclic ureas and sulfamides via palladium-catalyzed alkene carboamination reactions between aryl/alkenyl halides/triflates and alkenes bearing pendant cyclic sulfamides and ureas is described. The substrates for these reactions are generated in 3–5 steps from commercially available materials, and products are obtained in good yield with up to >20:1 diastereoselectivity. The stereochemical outcome of the sulfamide alkene addition is consistent with a mechanism involving *anti*-aminopalladation of the alkene, whereas the stereochemical outcome of the urea alkene addition is consistent with a *syn*-aminopalladation mechanism.

1. Introduction

A number of interesting biologically active natural products feature substituted polycyclic nitrogen heterocycle motifs.[1] These include tricyclic guanidines such as the batzelladine[2] and merobatzelladine alkaloids (e.g., merobatzelladine B)[3] (Figure 1) and the tetraponerine T1-T8 alkaloids.[4] In many instances these families of natural products contain members with differing relative stereochemistry. For example, merobatzelladine B possesses a *cis*-relationship between the C^{4a} hydrogen atom and the C^{3} alkyl chain,[3] whereas batzelladine K displays a *trans*-relationship between these groups.[2c] Similarly, the odd numbered tetraponerines (T-1, 3, 5, and 7) exhibit *cis* stereochemistry between the C^{4a} and C^{3} groups, whereas the even numbered members of the family have *trans* C^{4a}/C^{3} stereochemistry.

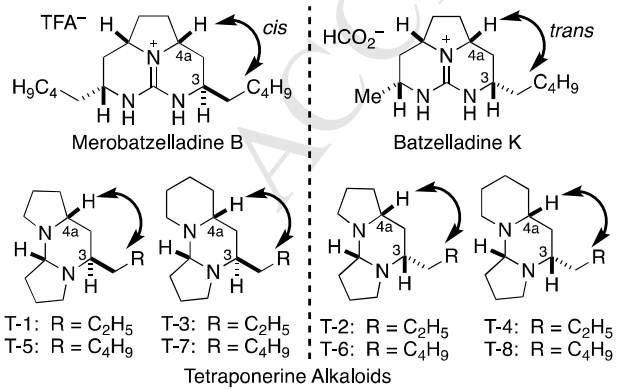

Fig 1. Polycyclic alkaloid natural products

Many routes for the synthesis of polycyclic guanidines, including the batzelladines and merobatzelladines, involve construction of a bicyclic urea, which is then further elaborated to the guanidine.[5] Moreover, a 2-(alkylamino)pyrrolidine derivative, that in principle could be accessed via reduction of a bicyclic urea or sulfamide, was a key intermediate in a prior synthesis of the tetraponerines.[6] In addition to serving as useful synthetic intermediates, substituted cyclic ureas and sulfamides act as peptidomimetics[7] that display a wide spectrum of biological activity, such as antivirals[8], HIV protease inhibitors[9], and hydroxysteroid dehydrogenase inhibitors[10]. As such, there has been considerable interest in the development of methods for the stereocontrolled synthesis of these structures.[11]

We have previously reported a new approach to the construction of cyclic ureas and sulfamides via Pd-catalyzed alkene carboamination reactions[12] between aryl/alkenyl halide/triflate electrophiles and alkenes bearing pendant ureas[13] or sulfamides (Scheme 1, eq 1).[14] These transformations proceed in generally good yields with high diastereoselectivities, as illustrated by the Pd-catalyzed carboamination of urea **1** to afford bicyclic urea **2** in 91% yield with >20:1 dr; this reaction was a key step in the asymmetric synthesis of (–)-merobatzelladine B (Scheme 1, eq 2).[15] We have also described asymmetric desymmetrization reactions of ureas derived from *cis*-2,5-

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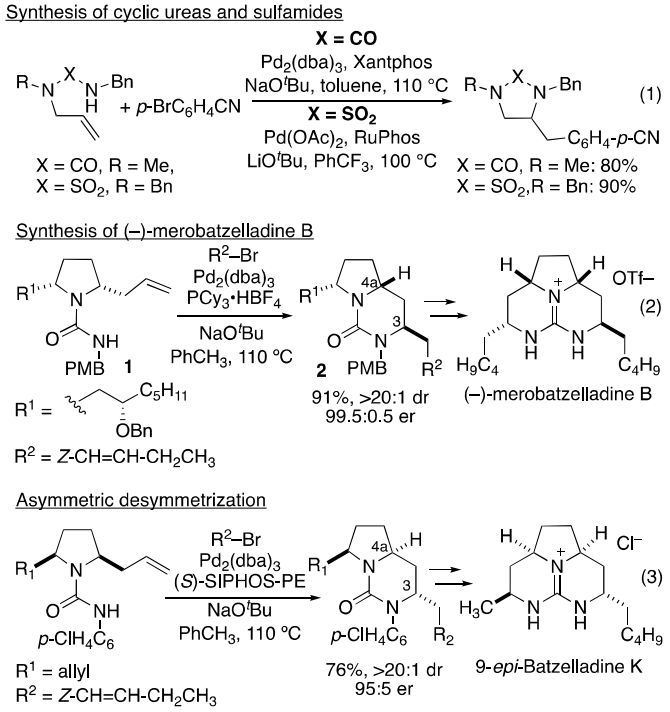
diallylpyrrolidine that afford products with high levels of enantioselectivity; this latter method was applied to the synthesis of an epimer of batzelladine K (Scheme 1, eq 3).[16]



Scheme 1. Synthesis of cyclic ureas and sulfamides via Pd-catalyzed alkene carboamination reactions

Although these transformations have demonstrated utility, as illustrated through the syntheses shown in Scheme 1, the scope of this approach to the construction of bicyclic ureas remains largely unexplored.[15] For example, no cases of formation of bicyclo [4.4.0] ring systems have previously been described. Moreover, the synthesis of 9-*epi*-batzelladine K also illustrates a significant limitation of this method. We would have preferred to make the naturally occurring isomer of batzelladine K, but we have consistently observed complete substrate control in these reactions; in all cases the products contain a *cis*-relationship between the C^3 alkyl group and the C^{4a} hydrogen atom. These transformations do not provide access to the diastereomeric product with a *trans* relationship between the C^3 alkyl/ C^{4a} hydrogen substituents, which would be needed to access batzelladine K rather than its epimer.

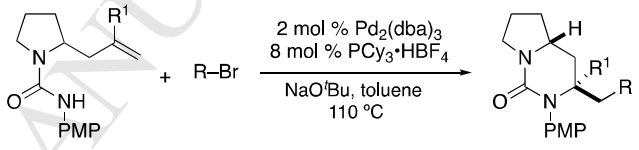
In this article we describe our studies on expanding the scope of our previously reported strategy for the synthesis of bicyclic ureas via Pd-catalyzed alkene carboamination reactions.[15] This includes studies on the reactivity of a variety of aryl and alkenyl halide coupling partners, as well as preparation of both bicyclo[4.3.0] and bicyclo[4.4.0] ring systems. We also describe a method for the construction of bicyclic sulfamides analogous to **2**,[17] along with the corresponding bicyclo[4.4.0] congeners, but that possess the opposite stereochemical relationship between the C^3 alkyl group and the C^{4a} H atom as compared to the ureas. Finally, we illustrate the conversion of these bicyclic products to 2-(alkylamino)pyrrolidine derivatives.

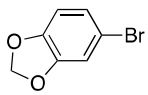
2. Results and discussion.

2.1. Synthesis of bicyclic ureas via Pd-catalyzed alkene carboamination reactions

During the course of model studies directed towards the synthesis of (–)-merobatzelladine B, we briefly examined Pd-catalyzed coupling reactions between **3a** and either *p*-tolylbromide or *E*-1-decenylbromide.[15] As shown in Table 1, entries 1-2, these transformations afforded desired products **4a** and **4b** in good yield with high diastereoselectivity. In order to examine the scope of Pd-catalyzed coupling reactions of ureas derived from cyclic amines, we treated **3a-b** with a range of different aryl halide electrophiles. Transformations of substrates bearing electron-donating groups proceeded in high yield (entries 3-4 and 7), although lower yields were obtained with electron-poor and/or ortho-substituted aryl bromides (entries 5-6). To further illustrate the scope of this transformation, substrate **3b** bearing a methyl group at the internal alkene carbon was coupled with 4-bromobiphenyl to afford **4g** in excellent yield and dr, although a higher reaction temperature (125 °C) was required (entry 7). In contrast, substrates bearing 1,2-disubstituted alkenes were unreactive. We also carried out the coupling of *p*-methoxybenzyl protected substrate **3c** with *Z*-1-bromobutene, which we used as a model system in our studies leading up to the synthesis of merobatzelladine B.[15] As shown in eq 4, this transformation provided the desired product **4i** in 67% yield with >20:1 dr. The coupling of PMP-protected substrate **3a** with *Z*-1-bromobutene led to a similar outcome, affording **4h** in 58% yield with >20:1 dr.

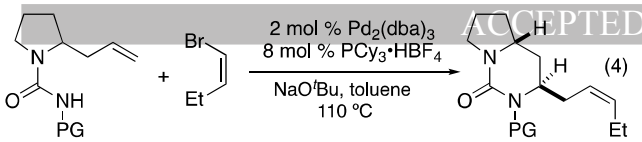
Table 1
Pd-Catalyzed carboamination reactions of 2-allylpyrrolidinyl ureas[a]

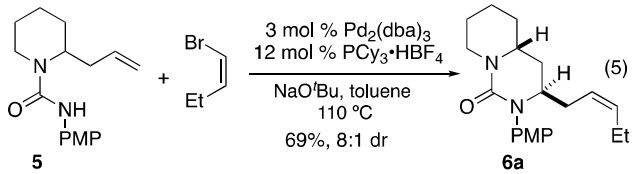


entry	urea	R	product	yield[b] (%)	dr[c]
1	**3a**	*p*-MeC_6H_4	**4a**	70	14:1
2	**3a**	*E*-1-decenyl	**4b**	77	18:1
3	**3a**	*p*-PhC_6H_4	**4c**	87	16:1
4	**3a**		**4d**	86	10:1
5	**3a**	*o*-$F_3CC_6H_4$	**4e**	68	10:1
6	**3a**	*p*-$O_2NC_6H_4$	**4f**	46	>20:1
7	**3b**	*p*-PhC_6H_4	**4g**	97	15:1[d]

[a]Conditions: 1.0 equiv **3a** or **3b**, 2 equiv NaO^tBu, 2 mol% $Pd_2(dba)_3$, 8 mol% PCy_3•HBF_4, 2 equiv, ArBr, toluene (0.2 M), 110 °C, 4–16 h. [b]Isolated yields (average of two or more experiments). [c]Diastereomeric ratio of the pure isolated product. Diastereomeric ratios of isolated materials were identical to those of crude products. [d]The reaction was conducted in xylenes solvent (0.2 M) at 125 °C.

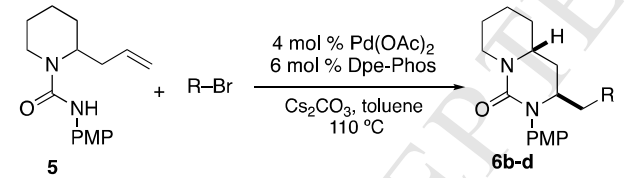
In order to further explore the scope of the urea carboamination reactions we prepared 2-allylpiperidinyl urea **5** and coupled it with *Z*-1-bromobutene using our standard reaction conditions. This transformation provided the desired product **6a** in 69% yield, and 8:1 dr (eq 5), although the use of 5 equiv of both the alkenyl bromide and the base, plus a slightly higher catalyst loading, was necessary to obtain satisfactory results. However, we were surprised to find these standard reaction conditions were not effective for the coupling of PMP-protected substrate **5** with aryl bromides.





Consequently, we examined the use of other bases and ligands for coupling reactions of **5** with aryl bromides, and after some optimization we found that use of Cs_2CO_3 as base, $Pd(OAc)_2$ as the palladium source, and Dpe-Phos as the ligand provided the desired products in moderate yield (Table 2).[18] The stereochemical outcome of these reactions was analogous to that for transformations of pyrrolidinyl ureas **3a-c**. However, chemical yields were generally lower than those obtained in reactions of **3a-c** due to incomplete consumption of starting material. The origin of this difference in reactivity is not clear, but could conceivably be due to differences in the conformational flexibility of 5-membered vs. 6-membered rings. In both systems, there is likely a ground state energy preference for pseudoaxial orientation of the allyl group to minimize allylic strain interactions with the urea moiety,[19] which would position the alkene fairly distant from the metal center in the key palladium amido intermediate that undergoes *syn*-aminopalladation (Scheme 2). However, due to the greater conformational flexibility of 5-membered rings, the presumably reactive conformation in which the allyl group is pseudoequatorial may be more energetically accessible, leading to faster reaction rates relative to the rate of catalyst deactivation.

Table 2
Pd-Catalyzed carboamination reactions of 2-allylpiperidinyl ureas[a]

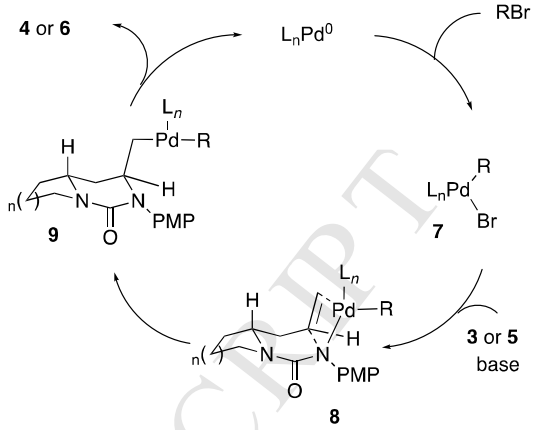


entry	R	product	yield[b] (%)	dr[c]
1	*p*-$MeOC_6H_4$	**6b**	35	15:1
2	*m*-$F_3CC_6H_4$	**6c**	47	15:1
3	*p*-$PhC(O)C_6H_4$	**6d**	59	10:1

[a]Conditions: 1.0 equiv substrate, 2 equiv Cs_2CO_3, 4 mol% $Pd(OAc)_2$, 6 mol% Dpe-Phos 2 equiv, RBr, toluene (0.2 M), 110 °C, 4–16 h. [b]Isolated yields (average of two or more experiments). [c]Diastereomeric ratio of the pure isolated product. Diastereomeric ratios of isolated materials were identical to those of crude products.

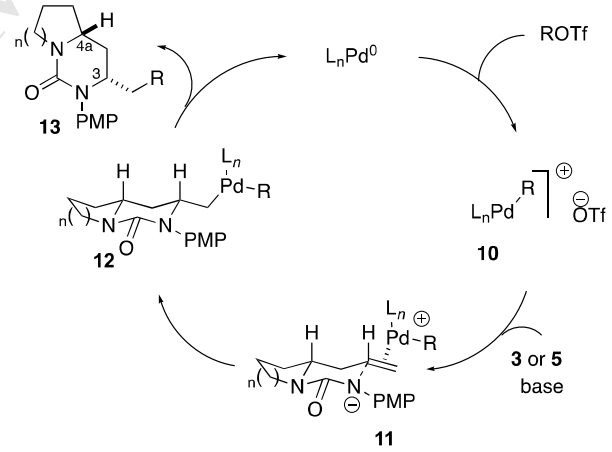
2.2. Mechanism and stereochemistry

Our prior studies on urea carboamination reactions suggest the transformations described above likely proceed through the mechanism illustrated in Scheme 2.[12] The reactions are initiated by oxidative addition of the aryl/alkenyl halide to Pd(0) to afford intermediate **7**, which reacts with the urea substrate **3** or **5** and base to afford amido complex **8**. The Pd-amido complex undergoes *syn*-aminopalladation to provide **9**,[20] which undergoes C–C bond-forming reductive elimination to afford the bicyclic urea product **4** or **6**. The observed *cis*-relationship between the angular hydrogen atom and the arylmethyl group in the products derives from aminopalladation via a boat-like transition state during the *syn*-aminopalladation of **8** to **9**.[15]



Scheme 2. Catalytic cycle – *syn*-aminopalladation

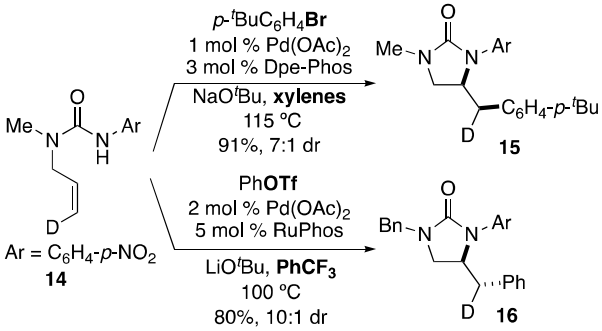
While this method is useful for the stereocontrolled construction of bicyclic ureas, the stereoselectivity is substrate controlled. The conversion of **3** or **5** to bicyclic ureas with a *cis*-relationship between the angular C^{4a} hydrogen atom and the C^3 arylmethyl group proceeds with generally high levels of stereocontrol, but the *syn*-aminopalladation mechanism allows for the selective formation of only the *cis* stereoisomer; diastereomeric molecules bearing a *trans*-relationship between the C^{4a} angular hydrogen atom and the C^3 arylmethyl group are not accessible through this manifold.



Scheme 3. Catalytic cycle – *anti*-aminopalladation

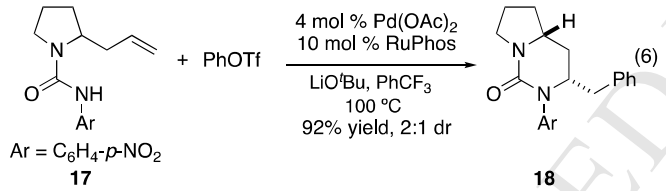
Although the *syn*-aminopalladation mechanism illustrated in Scheme 2 provides selective access to only the *cis* stereoisomer, we reasoned that it may be possible to access the *trans* stereoisomer by inducing the transformations to proceed via an alternative mechanistic pathway. As shown in Scheme 3, we hypothesized that if the transformations could be made to proceed via *anti*-aminopalladation of the alkene (following oxidative addition and alkene coordination to Pd), the *anti*-aminopalladation of Pd-alkene complex **11** would likely proceed via a chair-like transition state to afford **12**. Reductive elimination from **12** would then provide bicyclic urea product **13**, which contains a *trans*-relationship between the C^{4a} hydrogen atom and C^3 arylmethyl group. In addition, although most of our previously reported Pd-catalyzed alkene carboamination reactions proceed via *syn*-aminopalladation,[12] we have observed that urea and sulfamide substrates can be induced to undergo

carboamination via *anti*-aminopalladation under appropriate conditions. Specifically, factors that facilitate the formation of cationic intermediate palladium complexes (such as use of aryl triflates in place of aryl bromides, use of relatively polar solvents, etc.) promote the *anti*-addition pathway.[14] For example, treatment of urea **14** with an aryl bromide in toluene afforded *syn*-addition product **15** in 91 % yield and 7:1 dr using a Pd/Dpe-Phos catalyst. In contrast, the Pd/RuPhos catalyzed coupling of **14** with phenyl triflate in benzotrifluoride solvent afforded *anti*-addition product **16** in 80% yield and 10:1 dr (Scheme 4).[14]



Scheme 4. *Syn- vs. anti*-addition

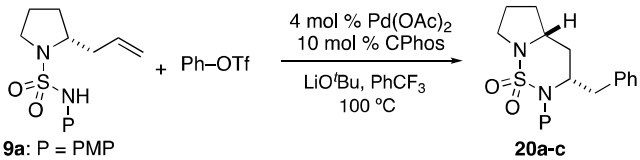
To test this hypothesis, we examined the coupling of *p*-nitrophenyl protected urea **17** with phenyl triflate using the conditions optimized for *anti*-aminopalladation. As shown in eq 6, this transformation did lead to a change in product stereochemistry, as **18** was produced as the major stereoisomer. However, the diastereoselectivity of this transformation was low (2:1 dr), and no increase in selectivity was observed despite numerous changes to the reaction conditions, catalyst/ligand system, and protecting group.



2.3. Synthesis of bicyclic sulfamides via Pd-catalyzed alkene carboamination reactions

We postulated that two factors might be the cause of the modest diastereoselectivity observed for the coupling of **17** with phenyl triflate: (1) the rates of *syn*- and *anti*-aminopalladation may be comparable; and/or (2) the transition states/intermediates leading to the two possible stereoisomers may be close in energy. Both of these factors can be heavily influenced by the structural and electronic features of the substrate. Many reports have illustrated that slight changes to substrate structure can dramatically influence the mechanism of aminopalladation reactions and in turn, the ratio of products resulting from *syn*- or *anti*-addition.[14,21] We reasoned that employing a less nucleophilic substrate, such as a sulfamide, might favor *anti*-aminopalladation by decreasing the likelihood that the substrate would form the Pd-N bond required to undergo *syn*-migratory insertion.[20] We also thought that changing the geometry of the substrate from the trigonal planar carbonyl group to the tetrahedral sulfonyl group may influence the stereodetermining transition states/intermediates leading to the two possible stereoisomers, and consequently the selectivity of the desired transformation could potentially be improved. Additionally, in prior studies on Pd-catalyzed asymmetric desymmetrization reactions of ureas derived from 2,5-diallylpyrrolidine, we observed that the nature of the protecting group on the cyclizing nitrogen atom had a significant influence on diastereoselectivity,[16] and we reasoned this might also be the case for sulfamide substrates.

Table 3
Influence of protecting group on diastereoselectivity[a]



entry	sulfamide	product	yield[b] (%)	dr[c]
1	**19a**	**20a**	80[d]	6:1
2	**19b**	**20b**	86	3:1
3	**19c**	**20c**	82	3:1

[a]Conditions: 1.0 equiv substrate, 2 equiv LiO^{t}Bu, 4 mol% $Pd(OAc)_2$, 10 mol% C-Phos 2 equiv Ph–OTf, $PhCF_3$ (0.2 M), 100 °C, 16 h. [b]Isolated yields (average of two or more experiments). [c]Diastereomeric ratio of the pure isolated product. Diastereomeric ratios of isolated materials were identical to those of crude products. [d]NMR yield with phenanthrene as an internal standard.

In order to test this hypothesis, 2-allylpyrrolidinyl sulfamide substrates **19a-c** were synthesized and coupled with phenyl triflate using conditions we have previously shown to facilitate *anti*-aminopalladation pathways (Table 3).[14] We were gratified to discover that substrate **19a**, which contains an *N*-PMP group, did react with significantly higher diastereoselectivity (6:1 dr) than urea **17**.[22] In contrast, *N*-alkyl protecting groups provided the desired products **20b-c** in comparable yield, but with lower (3:1) dr. Thus, the *N*-PMP group was selected for subsequent studies.

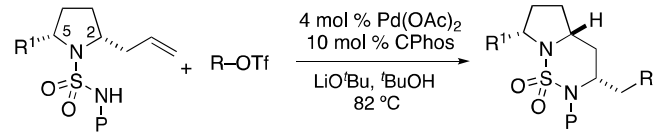
During the course of these studies, we observed inconsistent results for the coupling of **19a** with phenyl triflate, including highly variable yields and impurity profiles. It was noted that using anhydrous LiO^{t}Bu directly from the glove box led to significant amounts of side products resulting from Heck arylation and/or oxidative amination of the alkene, whereas using LiO^{t}Bu stored on the bench under nitrogen led to an improved reaction profile. We reasoned that the difference in reactivity may be due to the bench-stored sample picking up small amounts of water from the air, which would generate lithium hydroxide and *tert*-butanol. After some experimentation, we found that changing the solvent from benzotrifluoride to *tert*-butanol led to significantly improved and reproducible yields, and greatly diminished the formation of side products resulting from Heck arylation or oxidative amination of the alkene.[23] Under these conditions, LiO^{t}Bu obtained directly from the glovebox and LiO^{t}Bu stored on the bench gave comparable results.

With suitable reaction conditions in hand, we proceeded to explore the scope of the bicyclic sulfamide-forming reactions. As shown in Table 4, the transformations of **19a** are effective with both aryl and alkenyl triflate electrophiles, and provide products **20a** and **20d-i** in moderate to good yield with diastereoselectivities in the range of 5–10:1 dr. Yields and diastereoselectivities were comparable with both electron-rich and electron-poor aryl triflates. However, reactions of alkenyl triflates proceeded in slightly lower yield (entries 6–7). Reactions of substrate **19d**, which contains an allyl group at C5, proceeded with slightly higher diastereoselectivities than were observed with **19a** (entries 8–9). Use of short reaction times (2 h) with substrate **19d** was necessary in order to avoid undesired isomerization of the product's allyl group to an internal alkene.

The coupling of **19b** with the alkenyl bromide *Z*-1-bromobutene (entry 10) was achieved in modest yield and 5:1 diastereoselectivity when 2 equiv of LiOTf was added to the reaction mixture, with slightly modified conditions ($PhCF_3$ as solvent and NaO^{t}Bu as base).[24]

Table 4

Pd-Catalyzed carboamination reactions of 2-allylpyrrolidinyl sulfamides[a]



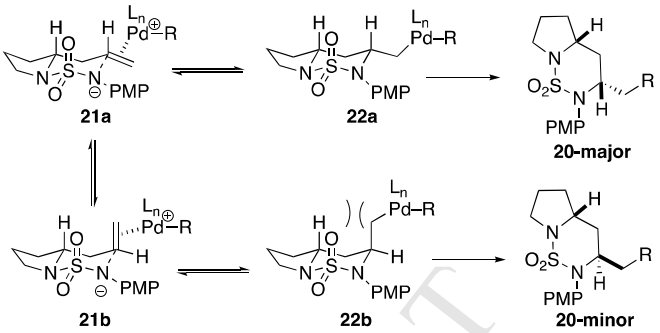
19a: R^1 = H, P = PMP
19b: R^1 = H, P = Bn
19d: R^1 = Allyl, P = PMP

20a, 20d-l

entry	sulfamide	R	product	yield[b] (%)	dr[c]
1	**19a**	Ph	**20a**	89	7:1
2	**19a**	*p*-^{t}BuC$_6$H$_4$	**20d**	78	6:1
3	**19a**	*p*-MeOC$_6$H$_4$	**20e**	70	7:1
4	**19a**	*p*-PhC(O)C$_6$H$_4$	**20f**	61[d]	8:1 (5:1)
5	**19a**	*o*-MeC$_6$H$_4$	**20g**	87	5:1
6	**19a**	1-cyclohexenyl	**20h**	63[d]	6:1
7	**19a**	*E*-1-decenyl	**20i**	45[d]	10:1[f,g]
8	**19d**	Ph	**20j**	65[e]	20:1 (12:1)
9	**19d**	*p*-MeOC$_6$H$_4$	**20k**	63[e]	>20:1 (13:1)
10	**19b**	*Z*-1-bromobutene	**20l**	30[h]	5:1

[a]Conditions: 1.0 equiv substrate, 2 equiv LiO^{t}Bu, 4 mol% Pd(OAc)$_2$, 10 mol% C-Phos 2 equiv, R–OTf, ^{t}BuOH (0.2 M), 82 ºC, 16 h. [b]Isolated yields (average of two or more experiments). [c]Diastereomeric ratio of the pure isolated product. Diastereomeric ratios of isolated materials were identical to those of crude products unless otherwise noted in parentheses. [d]The reaction was conducted with 3.0 equiv of LiO^{t}Bu and 3.0 equiv R-OTf. [e]The reaction time was 2 h. [f]1-Decenyl triflate was employed as 5:1 mixture of *E*:*Z* isomers. [g]The dr was determined following hydrogenation of **20j**. The crude dr of **20j** could not be determined directly due to the presence of *E*/*Z* alkene stereoisomers. However, we estimate the crude dr to be ca. 5-10:1. [h]The reaction was conducted in $PhCF_3$ as solvent using NaO^{t}Bu as the base, with 2.0 equiv added LiOTf, and a reaction temperature of 100 °C.

The relatively high diastereoselectivities observed (5–13:1) are both interesting and surprising, as other related alkene carboamination reactions that proceed via *anti*-aminopalladation typically provide low (ca 1-3:1) diastereoselectivity unless there is a substituent at the allylic position of the alkene.[24] The relatively high selectivity observed in reactions of **19a-d** may be due to either thermodynamic or kinetic control. As shown in Scheme 5, the aminopalladation step in the catalytic cycle is likely reversible, especially since the cyclizing nitrogen atom is relatively electron-poor.[25] The reductive elimination step is most likely not reversible, and there appear to be significant unfavorable 1,3-diaxial interactions present in intermediates **21b** and **22b** where the alkene or arylmethyl group is positioned in a pseudoaxial position that are not present in intermediates **21a** and **22a**.[26] So, if the rates of reductive elimination from **22a** or **22b** are comparable, the relative equilibrium populations of **22a** or **22b** would dictate the outcome. Alternatively, the activation energy for reductive elimination from **22b** may be higher than that for reductive elimination from **22a** if strain in the transition state for reductive elimination from **22** is significant.

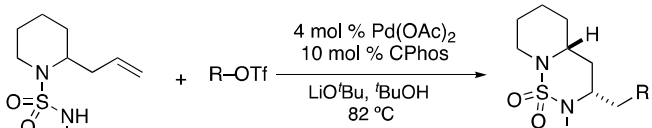


Scheme 5. Control of stereoselectivity

We subsequently elected to explore the reactivity of 2-allylpiperidine-derived sulfamides for the synthesis of bicyclo[4.4.0] heterocyclic ring systems (Table 5). In contrast to the reactions of urea derivatives, in which the pyrrolidinyl and piperidinyl derived substrates had considerably different reactivity, and required different reaction conditions, our standard parameters were effective with both pyrrolidinyl (**19a-d**) and piperidinyl sulfamides (**23**). The coupling of **23** with a range of different aryl and alkenyl triflates provided products in comparable yields, but slightly lower diastereoselectivities, than were observed in reactions of **19a**. The origin of the lower diastereoselectivities is not clear, but the differences are also relatively small (5–10:1 vs. 3–6:1). A range of electronic properties of the aryl triflate were tolerated, and the transformation was also effective with the heteroaryl bromide 2-bromothiophene and the alkenyl bromide *Z*-1-bromobutene when 2 equiv of LiOTf was added to the reaction mixture (eq 7-8). These latter two substrates are noteworthy, as the butenyl group and the 2-thiophenyl group[27] could conceivably be reduced to the alkyl side chain present in batzelladine K and the tetraponerine alkaloids.

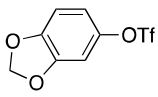
Table 5

Pd-Catalyzed carboamination reactions of 2-allylpiperidinyl sulfamides [a]



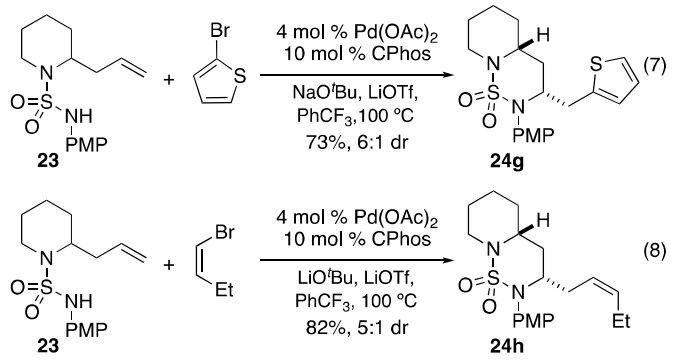
23

24a-g

entry	R	product	yield[b] (%)	dr[c]
1	Ph	**24a**	80	5:1
2	1-cyclohexenyl	**24b**	85	5:1
3	*p*-^{t}BuC$_6$H$_4$	**24c**	71	4:1
4	*o*-MeC$_6$H$_4$	**24d**	83	4:1
5		**24e**	87	5:1
6	*p*-MeOC$_6$H$_4$	**24f**	76	3:1

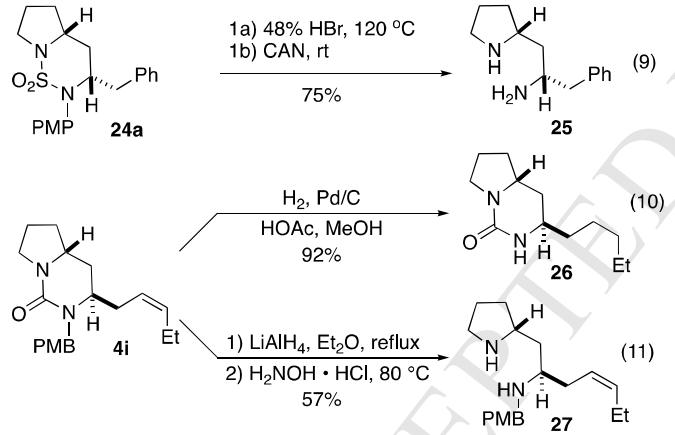
[a]Conditions: 1.0 equiv substrate, 2 equiv LiO^{t}Bu, 4 mol% Pd(OAc)$_2$, 10 mol% C-Phos 2 equiv, R–OTf, ^{t}BuOH (0.2 M), 82 ºC, 16 h. [b]Isolated yields (average of two or more experiments). [c]Diastereomeric ratio of the pure

isolated product. Diastereomeric ratios of isolated materials were identical to those of crude products.



2.4. Elaboration of products

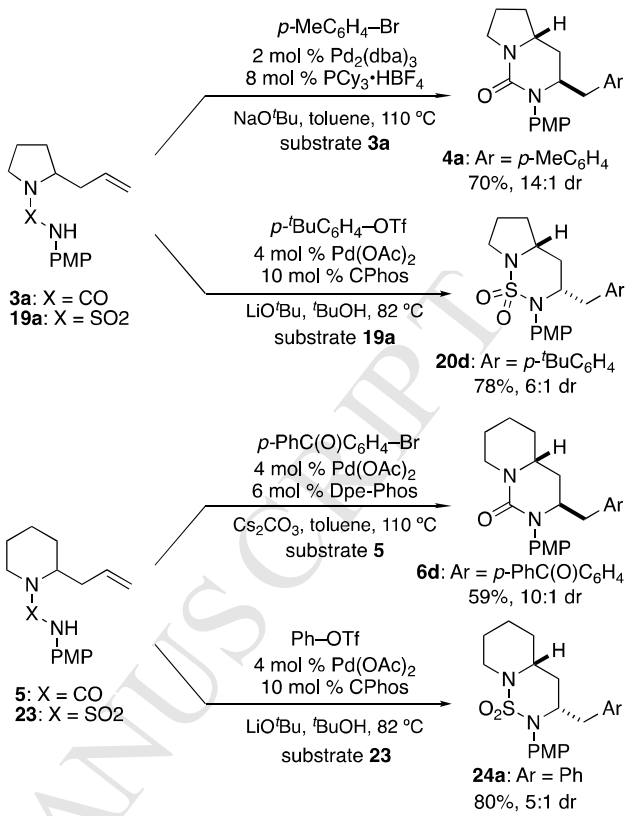
To further demonstrate the potential synthetic utility of the transformations described above, we elected to examine deprotection of products **24a** and **4i** (Scheme 6). After some experimentation, we found that treatment of **24a** with concentrated HBr led to cleavage of the SO_2 group, with concomitant demethylation of the *p*-methoxyphenyl group. Oxidation of the resulting product, in a one-pot process, with ceric ammonium nitrate then removed the nascent *p*-hydroxyphenyl group to provide diamine **25** in 75% yield (eq 9). The PMB protecting group was cleaved from **4i** by hydrogenation, with concomitant reduction of the alkene, to afford **26** in 92% yield (eq 10). The urea carbonyl was removed to provide diamine **26** in 57% yield through reduction with $LiAlH_4$ and subsequent treatment with hydroxylamine (eq 11).



Scheme 6. Elaboration of products

3. Conclusion

In conclusion, Pd-catalyzed alkene carboamination reactions between ureas or sulfamides derived from 2-allylpyrrolidine or 2-allylpiperidine are coupled with a range of aryl or alkenyl halides or triflates to afford bicyclic ureas or sulfamides. As shown in Scheme 7, the coupling of sulfamides with aryl/alkenyl triflates affords bicyclic products with *trans* relative stereochemistry between the C^3 arylmethyl group and the angular C^{4a} hydrogen atom in good yield with moderate, but synthetically useful, levels of diastereoselectivity. In contrast, the reactions of analogous urea derivatives with aryl/alkenyl bromides affords bicyclic products with *cis* relative stereochemistry, in moderate to good yield, and with good diastereoselectivity. The change in the stereochemical outcome of these transformations is due to a change in reaction mechanism. Circumstances (conditions, substrate structure) that lead to a *syn*-aminopalladation pathway provide the *cis*-disubstituted products, whereas reactions that proceed via *anti*-aminopalladation afford the *trans*-disubstituted products.



Scheme 7. Summary

4. Experimental section

4.1. General

All reactions were carried out under nitrogen atmosphere in flame- or oven-dried glassware. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. *Bis*-(dibenzylidineacetone) dipalladium(0), palladium (II) acetate, tricyclohexylphosphonium tetrafluoroborate, CPhos, and Dpe-phos were purchased from Strem Chemical Co. and used without further purification. Dichloromethane, toluene, and tetrahydrofuran were purified using a GlassContour solvent purification system. *N*-Boc-2-allylpyrrolidine,[28] *N*-Boc-2-(2-methallyl)pyrrolidine,[29] *N*-Boc-2-allylpiperidine,[28] *E*-1-bromodecene,[30] *Z*-1-bromobut-1-ene,[31] **19d**,[16] the oxooxazolidin sulfonamides used to prepare **19a-c**,[14a] and 1-decenyl triflate,[14a] were synthesized according to published procedures. Aryl triflates were either purchased from commercial sources, or prepared according to the procedure of Frantz *et. al.*[32] Benzotrifluoride was purified by distillation from P_2O_5, and xylenes were purified by distillation from CaH_2 prior to use. Structural and stereochemical assignments were based on 2-D COSY and NOESY experiments. Ratios of diastereomers were determined by ^{1}H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in Tables 1–2, and 4–5 are averages of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Tables 1–2 and 4–5.

4.2. Preparation of starting materials

4.2.1. General procedure 1:synthesis of urea substrates

A clean, flame-dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with *N*-Boc-2-allylpyrrolidine,[28] *N*-Boc-2-(2-methallyl)pyrrolidine,[29] or *N*-Boc-2-allylpiperidine[28] (1.0 equiv) and dichloromethane (0.2 M). The resulting solution was cooled to 0 ºC and trifluoroacetic acid (10.0 equiv) was added. The reaction mixture was stirred until judged as complete by thin layer chromatography (c.a. 4 hours), then diluted with water and quenched with ammonium hydroxide until pH reached 12. The organic layer was reserved, and the aqueous layer extracted with dichloromethane. The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting crude intermediate was then carried on to the next step without any additional purification.

The crude intermediate was re-dissolved in dichloromethane (0.2M) and charged to a new clean, dry round bottom flask with a stir bar. The appropriately substituted isocyanate (1.2 equiv) was added slowly, and the resulting reaction stirred at 20 ºC until judged as complete by TLC (ca. 4–14 hours). After concentration *in vacuo*, the resulting residue was purified via flash column chromatography on silica gel (20–40% ethyl acetate/hexanes gradient).

*4.2.1.1. (±)-2-Allyl-N-(4-methoxyphenyl)pyrrolidine-1-carboxamide **3a***

The title compound was prepared from *N*-Boc-2-allylpyrrolidine (1.3 g, 6.1 mmol) following General Procedure 1. This procedure afforded 997 mg (81% yield) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 9.5 Hz, 2 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 6.07 (s, 1 H), 5.82 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1 H), 5.13-5.07 (m, 2 H), 4.07–4.04 (m, 1 H), 3.78 (s, 3 H), 3.45–3.42 (m, 2 H), 2.60–2.55 (m, 1 H), 2.22–2.16 (m, 1 H), 2.04–1.93 (m, 3 H), 1.83–1.79 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 154.3, 135.2, 132.2, 121.7, 117.4, 114.1, 57.2, 55.5, 46.3, 38.7, 29.5, 23.8; IR (film) 3306, 1639 cm^{-1}. HRMS (ESI$^+$ TOF) m/z [M + H]$^+$: $C_{15}H_{20}N_2O_2$ 261.1598; found 261.1599.

*4.2.1.2. (±)-N-(4-Methoxyphenyl)-2-(2-methylallyl)pyrrolidine-1-carboxamide **3b***

The title compound was prepared from *N*-Boc-2-(2-methallyl)pyrrolidine (663 mg, 2.9 mmol) following General Procedure 1. This procedure afforded 186 mg (23% yield) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H), 6.84–6.83 (m, 2 H), 6.11 (s, 1 H), 5.63–5.60 (m, 1 H), 5.46–5.44 (m, 1 H), 4.03–4.01 (m, 1 H), 3.78 (s, 3 H), 3.47–3.44 (m, 2 H), 2.55 (dd, *J* = 4.1, 13.6 Hz, 1 H), 2.23–2.03 (m, 1 H), 2.01–1.94 (m, 3 H), 1.79–1.67 (m, 1 H), 1.82 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 154.4, 132.3, 126.6, 121.8, 121.7, 114.0, 57.6, 55.5, 46.3, 31.6, 29.9, 23.8, 13.1; IR (film) 2966.8, 1638.0, 1638.0, 1510.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{22}N_2O_2$ 275.1754; found 275.1760.

*4.2.1.3. (±)-2-Allyl-N-(4-methoxybenzyl)pyrrolidine-1-carboxamide **3c***

The title compound was prepared from 4-methoxybenzyl isocyanate (1.8 mL, 12.6 mmol) and *N*-Boc-2-allylpyrrolidine (1.77 g, 8.4 mmol) via General Procedure 1. This procedure afforded 862 mg (37%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 2 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 5.78 (dddd, *J* = 6.6, 7.8, 10.2, 16.9 Hz, 1 H), 5.10–5.00 (m, 2 H), 4.43–4.30 (m, 3 H), 3.97 (m, 1 H), 3.80 (s, 3 H), 3.34–3.23 (m, 2 H), 2.54–2.49 (m, 1 H), 2.18–2.08 (m, 1 H), 2.02–1.82 (m, 3 H), 1.78–1.73 (m, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.8, 156.6, 135.3, 131.9, 129.1, 117.1, 113.9, 56.8, 55.3, 46.0, 44.1, 38.8, 29.4, 23.6; IR (film) 3324, 1626 cm^{-1}. HRMS (ESI$^+$ TOF) m/z [M + H]$^+$: calcd for $C_{16}H_{22}N_2O_2$ 275.1754; found 275.1747

*4.2.1.4. (±)-2-Allyl-N-(4-methoxyphenyl)piperidine-1-carboxamide **5***

The title compound was prepared from N-Boc-2-allylpiperidine (762 mg, 3.4 mmol) following General Procedure 1. This resulted in 355 mg (38% yield) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.17 (m, 2 H), 6.85–6.75 (m, 2 H), 6.32 (s, 1 H), 5.79 (ddt, J = 7.2, 10.1, 17.2 Hz, 1 H), 5.18–5.02 (m, 2 H), 4.29–4.21 (m, 1 H), 3.91 (dt, J = 3.1, 13.4 Hz, 1 H), 3.76 (s, 3 H), 2.93 (td, J = 2.8, 13.1 Hz, 1 H), 2.52–2.47 (m, 1 H), 2.32–2.27 (m, 1 H), 1.71–1.52 (m, 5 H), 1.54–1.40 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 135.4, 132.6, 122.2, 122.1, 117.3, 114.0, 55.5, 51.1, 39.3, 34.3, 27.9, 25.5, 18.8; IR (film) 2934.8, 1628.9, 1509.5, 1416.8 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{22}N_2O_2$ 275.1761; found 275.1761.

*4.2.1.5. (±)-2-Allyl-N-(4-nitrophenyl)pyrrolidine-1-carboxamide **17***

The title compound was prepared from *N*-Boc-2-allylpyrrolidine (887 mg, 4.2 mmol) following General Procedure 1. The chromatographed product material was diluted with dichloromethane (35 mL) and washed with 1M HCl (2 x 15 mL) to remove any remaining 4-nitroanniline. This procedure afforded 290 mg (25%) of the title compound as a yellow solid: mp = 104–106 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.1 Hz, 2 H), 7.58 (d, *J* = 9.1 Hz, 2 H), 6.64 (s, 1 H), 5.84–5.78 (m, 1 H), 5.17–5.09 (m, 2 H), 4.09 (s, br, 1 H), 3.53–3.46 (m, 2 H), 2.56 (dt, *J* = 5.3, 12.4 Hz, 1 H), 2.25–2.18 (m, 1 H), 2.09–2.02 (m, 1 H), 2.04–1.94 (m, 2 H), 1.86–1.82 (m, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 152.7, 145.4, 142.3, 134.7, 125.1, 118.0, 117.9, 57.5, 46.5, 38.5, 29.6, 23.7; IR (film) 3314, 1652, 1501, 1329 cm^{-1}. HRMS (ESI$^+$ TOF) m/z [M + H]$^+$: calcd for $C_{14}H_{17}N_3O_3$ 276.1343; found 276.1344.

4.2.2. General procedure 2: synthesis of sulfamide substrates

A clean, flame-dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with *N*-Boc-2-allylpyrrolidine or *N*-Boc-2-allylpiperidine[28] (1.0 equiv), dichloromethane (0.2 M), and trifluoroacetic acid (1.0 M). The reaction mixture was stirred until judged as complete by thin layer chromatography (c.a. 4 hours), then diluted with water and quenched with ammonium hydroxide until pH reached 12. The organic layer was reserved, and the aqueous layer extracted with dichloromethane . Organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting crude intermediates were then carried on to the next step without any additional purification.

A separate clean, flame-dried round bottom flask was cooled under a stream of nitrogen, and charged with the appropriate *N*-protected-2-oxo-oxazolidanone-3-sulfonamide[14a] (1.2 equiv), 4-dimethylaminopyridine (0.2 equiv), and a stir bar, and then was evacuated and backfilled with nitrogen. Acetonitrile (0.12 M based on added amine) was added, followed by triethylamine (3.0 equiv), and then the reaction vessel was heated in an oil bath to 75 ºC. After one hour at 75 ºC, the crude 2-allylpyrrolidine or 2-allylpiperidine from above was added, and the reaction mixture stirred at 75 ºC overnight (approximately 16 hours). The mixture was cooled to 20 ºC, solvent was removed *in vacuo*, and the

residue was partitioned between dichloromethane and 3M hydrochloric acid (aq). The organic layer was reserved, and the aqueous layer extracted with dichloromethane. Organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo*, and the resulting residue purified via flash column chromatography on silica gel (20–40% ethyl acetate/hexanes gradient).

4.2.2.1. (±)-2-Allyl-N-(4-methoxyphenyl)pyrrolidine-1-sulfonamide ***19a***

The title compound was prepared from *N*-Boc-2-allylpyrrolidine (1.06 g, 5.0 mmol) following General Procedure 2. This procedure afforded 808 mg (68%) of the title compound as a pale yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18 (d, *J* = 9.1 Hz, 2 H), 6.85 (d, *J* = 9.1 Hz, 2 H), 6.30 (s, br, 1 H), 5.70–5.61 (m, 1 H), 5.05–4.99 (m, 2 H), 3.79 (s, 3 H), 3.79–3.77 (m, 1 H), 3.36–3.27 (m, 2 H), 2.46–2.41 (m, 1 H), 2.12 (dt, *J* = 13.9, 8.5 Hz, 1 H), 1.86–1.73 (m, 3 H), 1.70–1.66 (m, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.2, 134.5, 130.1, 123.7, 117.5, 114.4, 60.3, 55.5, 49.1, 39.9, 30.1, 24.2; IR (film) 3267, 1327, 1245, 1146 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{20}N_2O_3S$ 297.1267; found 297.1274.

4.2.2.2. (±)-2-Allyl-N-benzylpyrrolidine-1-sulfonamide ***19b***

The title compound was prepared from *N*-benzyl-2-oxooxazolidine-3-sulfonamide (2.1 g, 8.3 mmol) and *N*-Boc-2-allylpyrrolidine (2.1 g, 10.0 mmol) in two steps following General Procedure 2. This procedure afforded 1.22 g (52%) of the title compound as a pale-yellow solid: mp = 38–41 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30–7.20 (m, 5 H), 5.72–5.64 (m, 1 H), 5.03–4.96 (m, 2 H), 4.68 (s, br, 1 H), 4.15 (s, 2 H), 3.76 (ddt, *J* = 3.9, 7.8, 9.0 Hz, 1 H), 3.31–3.24 (m, 1 H), 3.16 (ddd, *J* = 4.9, 6.6, 9.5 Hz, 1 H), 2.46 (dddt, *J* = 1.4, 4.0, 6.8, 13.7 Hz, 1 H), 2.18–2.10 (m, 1 H), 1.84–1.69 (m, 3 H), 1.68–1.61 (m, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 137.0, 134.6, 128.7, 127.9, 127.9, 117.5, 59.6, 49.0, 47.4, 40.1, 30.3, 24.3; IR (film) 3282, 1312, 1143 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{20}N_2O_2S$ 281.1318; found 281.1325.

4.2.2.3. (±)-2-Allyl-N-(4-methoxybenzyl)pyrrolidine-1-sulfonamide ***19c***

The title compound was prepared from *N*-(4-methoxybenzyl)-2-oxooxazolidine-3-sulfonamide (2.4 g, 8.3 mmol) and *N*-Boc-2-allylpyrrolidine (2.1 g, 10.0 mmol) following General Procedure 2. This procedure afforded 1.10 g (43%) of the title compound as a yellow solid: mp = 39–42 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.1 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 5.77 (ddt, *J* = 7.1, 10.2, 17.2 Hz, 1 H), 5.12–5.04 (m, 2 H), 4.16 (s, 2 H), 3.88–3.79 (m, 1 H), 3.80 (s, 3 H), 3.37 (dt, *J* = 7.3, 9.9, Hz, 1 H), 3.25 (ddd, *J* = 5.1, 6.7, 9.7 Hz, 1 H), 2.56–2.53 (m, 1 H), 2.27–2.19 (m, 1 H), 1.95–1.79 (m, 3 H), 1.75–1.69 (m, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.3, 134.7, 129.3, 129.0, 117.5, 114.1, 59.6, 55.3, 49.1, 47.0, 40.1, 30.3, 24.3; IR (film) 3289, 1302, 1247, 1144 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{22}N_2O_3S$ 311.1424; Found 311.1416.

4.2.2.4. (±)-(2S,5R*)-2,5-Diallyl-N-(4-methoxyphenyl)pyrrolidine-1-sulfonamide* ***19d***

The title compound was prepared from *N*-(4-methoxyphenyl)-2-oxooxazolidine-3-sulfonamide (1.6 g, 5.9 mmol) and (±)-(*E*,2*R**,5*S**)-*tert*-butyl 2-allyl-5-[3-(trimethylsilyl)allyl]pyrrolidine-1-carboxylate (2.3 g, 7.1 mmol) following General Procedure 2. This procedure afforded 1.46 g (73%) of the title compound as an off-white solid: mp = 57–60 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 5.75–5.67 (m, 2 H), 5.07–5.02 (m, 4 H), 3.79 (s, 3 H), 3.79–3.74 (m, 2 H), 2.50 (dt, *J* = 5.5, 12.0 Hz, 2 H), 2.16 (dt, *J* = 8.3, 14.8 Hz, 2 H), 1.77–1.71 (m, 2 H), 1.68–1.62 (m, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.2, 134.6, 130.0, 123.7, 117.5, 114.4, 61.6, 55.4, 40.4, 29.0; IR (film) 3268, 1508, 1247, 1151 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{24}N_2O_3S$, 337.1580; found 337.1580.

4.2.2.5. (±)-2-Allyl-N-(4-methoxyphenyl)piperidine-1-sulfonamide ***23***

The title compound was prepared from *N*-Boc-2-allylpiperidine (2.0 g, 8.9 mmol) following General Procedure 2. This afforded 1.25 g (45% yield) of the title compound as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.12–7.07 (m, 2 H), 6.86–6.81 (m, 2 H), 6.15 (s, 1 H), 5.72–5.64 (m, 1 H), 5.06–4.99 (m, 2 H), 3.98–3.92 (m, 1 H), 3.78 (s, 3 H), 3.59 (dd, *J* = 4.5, 14.0 Hz, 1 H), 2.97 (td, *J* = 2.8, 13.3 Hz, 1 H), 2.41–2.30 (m, 2 H), 1.59–1.49 (m, 2 H), 1.50–1.37 (m, 2 H), 1.33–1.22 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.1, 135.0, 130.1, 123.3, 117.3, 114.4, 55.5, 53.5, 41.4, 34.1, 26.7, 24.9, 18.0; IR (film) 3271.5, 1509.0, 1246.2, 1142.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{22}N_2O_3S$ 311.1424; found 311.1422.

4.3. Preparation of products

4.3.1. General procedure 3: Synthesis of bicyclic pyrrolidinyl ureas

A clean, flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the urea substrate, $Pd_2(dba)_3$, tricyclohexylphosphonium tetrafluoroborate, sodium *tert*-butoxide, and aryl or alkenyl bromide. The tube was purged with nitrogen and 2.5 mL toluene per 1 mmol substrate was added via syringe. The reaction mixture was heated to 110 °C with stirring until judged complete as determined by TLC analysis. Subsequently, the crude reaction mixture was diluted with ethyl acetate (2 mL) and quenched with saturated aqueous ammonium chloride (3 mL). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (2 mL x 2). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and purified by flash chromatography on silica gel using 20–60% ethyl acetate/hexanes as the eluent unless otherwise noted.

4.3.1.1. (±)-(3R,4aR*)-2-(4-Methoxyphenyl)-3-(4-methylbenzyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one* ***4a***

A flame-dried Schlenk tube was cooled under a stream of N_2 and charged with $Pd_2(dba)_3$ (6.4 mg, 0.007 mmol), PCy_3•HBF_4 (10.3 mg, 0.028 mmol) and NaO^tBu (50 mg, 0.52 mmol). The flask was purged with N_2, then a solution of **3a** (83 mg, 0.35 mmol) in toluene (3.5 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. 4-Bromotoluene (89 µL, 0.52 mmol) was added and the flask was heated to 110 °C and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH_4Cl (3 mL) and ethyl acetate (3 mL) were added. The organic layer was filtered through a plug of silica gel and the silica gel was washed with ethyl acetate (10 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Analysis of the crude material by ^{1}H NMR revealed the product had been formed as a 14:1 mixture of diastereomers. The crude material was purified by flash chromatography on silica gel to afford 78 mg (70%) of the title compound as a pale yellow oil with 14:1 dr. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 9.0 Hz, 2 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 6.92–6.90 (m,

4 H), 3.96 (dt, *J* = 4.5, 11.5 Hz, 1 H), 3.82 (s, 3 H), 3.82–3.76 (m, 1 H), 3.60 (dt, *J* = 7.5, 11.5 Hz, 1 H), 3.55–3.51 (m, 1 H), 3.02 (dd, *J* = 3.8, 13.8 Hz, 1 H), 2.64 (dd, *J* = 11.0, 13.5 Hz, 1 H), 2.30 (s, 3 H), 2.13 (dt, *J* = 5.5, 12.0 Hz, 1 H), 2.05–1.95 (m, 2 H), 1.88–1.82 (m, 1 H), 1.54 (dt, *J* = 2.5, 12.5 Hz, 1 H) 1.50–1.44 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 154.4, 135.9, 135.5, 134.8, 130.1, 129.2, 128.8, 114.2, 60.4, 55.4, 52.5, 46.1, 38.1, 33.8, 29.5, 23.4, 20.9; IR (film) 1640 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}N_2O_2$, 351.2071; found 351.2071

4.3.1.2. (±)-(E,3R,4aR*)-2-(4-Methoxyphenyl)-3-(undec-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one* ***4b***

The title compound was prepared in a manner analogous to **4a** except using $Pd_2(dba)_3$ (6.4 mg, 0.007 mmol), PCy_3•HBF_4 (10.3 mg, 0.028 mmol) and NaO^{t}Bu (67 mg, 0.70 mmol), a solution of **3a** (83 mg, 0.35 mmol) in toluene (3.5 mL), and a solution of (*E*)-1-bromodec-1-ene (153 mg, 0.70 mmol) in toluene (1 mL). Analysis of the crude material by ^{1}H NMR revealed the product had been formed as a 18:1 mixture of diastereomers. The crude material was purified by flash chromatography on silica gel to afford 98 mg (77%) of the title compound as a pale yellow oil with 18:1 dr. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 9.0 Hz, 2 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 5.42 (dt, *J* = 7.5, 15.5 Hz, 1 H), 5.16 (dt, *J* = 7.0, 15.0 Hz, 1 H), 3.79 (s, 3 H), 3.76–3.73 (m, 1 H), 3.68–3.62 (m, 1 H), 3.58 (dt, *J* = 7.5, 11.5 Hz, 1 H), 3.50–3.46 (m, 1 H), 2.39 (dt, *J* = 5.0, 13.5 Hz, 1 H), 2.24 (ddt, *J* = 1.5, 2.0, 13.0 Hz, 1 H), 2.20–2.11 (m, 2 H), 2.00–1.91 (m, 3 H), 1.85–1.78 (m, 1 H), 1.62 (dt, *J* = 5.0, 12.3 Hz, 1 H), 1.49 (ddt, *J* = 7.5, 10.0, 12.0 Hz, 1 H), 1.30–1.23 (m, 12 H), 0.87 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 154.4, 135.7, 134.2, 129.3, 125.4, 114.1, 58.7, 55.4, 52.5, 46.0, 35.9, 33.9, 32.5, 31.8, 30.3, 29.4, 29.2, 29.1, 23.4, 22.6, 14.1 (one carbon signal is absent due to incidental equivalence); IR (film) 1640 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{38}N_2O_2$ 399.3006; found 399.3009

4.3.1.3. (±)-(3R,4aR*)-3-[(1,1'-biphenyl)-4-ylmethyl]-2-(4-methoxyphenyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one* ***4c***

The title compound was prepared from substrate **3a** (53 mg, 0.20 mmol), 4-bromobiphenyl (95 mg, 0.41 mmol), NaO^{t}Bu (40 mg, 0.42 mmol), $Pd_2(dba)_3$ (3.4 mg, 0.007 mmol), and PCy_3•HBF_4 (6.8 mg, 0.018 mmol) according to General Procedure 3. This procedure afforded 64 mg (77%) of the title compound as a brown foamy solid. The compound was obtained as a 16:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 2 H), 7.48 (d, *J* = 7.8 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.33 (t, *J* = 7.4 Hz, 1 H), 7.23 (d, *J* = 13.3 Hz, 2 H), 7.09 (d, *J* = 7.8 Hz, 2 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 4.09–4.00 (m, 1 H), 3.81 (s, 3 H), 3.80–3.76 (m, 1H) 3.65–3.59 (m, 1 H), 3.59–3.49 (m, 1 H), 3.10 (dd, *J* = 4.2, 13.6 Hz, 1 H), 2.74 (dd, *J* = 11.0, 13.6 Hz, 1 H), 2.17–1.84 (m, 4 H), 1.63–1.45 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.7, 154.5, 140.7, 139.4, 137.1, 135.6, 129.4, 129.2, 128.8, 127.3, 127.0, 114.2, 60.5, 55.4, 52.7, 46.2, 38.4, 33.9, 29.8, 23.5 (one carbon signal is absent due to incidental equivalence); IR (film) 2931.6, 2228.0, 1627.9, 1447.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{28}N_2O_2$ 413.2224; found 413.2220.

4.3.1.4. (±)-(3R,4aR*)-3-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(4-methoxyphenyl) hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one* ***4d***

The title compound was prepared from substrate **3a** (41 mg, 0.16 mmol), 1-bromo-3,4-methylenedioxybenzene (48 µL, 0.40 mmol), NaO^{t}Bu (40 mg, 0.42 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.008 mmol), and PCy_3•HBF_4 (6.7 mg, 0.018 mmol) according to General Procedure 3. This procedure afforded 48 mg (79%) of the title compound as a pale brown foam. The compound was obtained as a 10:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.14 (m, 2 H), 6.93–6.86 (m, 2 H), 6.69 (d, *J* = 8.3 Hz, 1 H), 6.48 (dt, *J* = 2.0, 4.0 Hz, 2 H), 5.90 (s, 2 H), 3.97–3.89 (m, 1 H), 3.81 (s, 3 H), 3.79–3.71 (m, 1 H), 3.65–3.48 (m, 2 H), 2.96 (dd, *J* = 4.2, 13.7 Hz, 1 H), 2.59 (dd, *J* = 11.1, 13.7 Hz, 1 H), 2.20–1.75 (m, 4 H), 1.61–1.42 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 154.8, 148.1, 146.5, 135.9, 132.1, 129.6, 122.4, 114.6, 109.6, 108.7, 101.3, 60.9, 55.8, 53.0, 46.6, 38.8, 34.3, 30.0, 23.9; IR (film) 2936.5, 1626.3, 1445.6, 1240.4 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{24}N_2O_4$ 381.1809; found 381.1805.

4.3.1.5. (±)-(3R,4aR*)-2-(4-Methoxyphenyl)-3-[2-(trifluoromethyl)benzyl]hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one* ***4e***

The title compound was prepared from substrate **3a** (41 mg, 0.16 mmol), 2-bromobenzotrifluoride (55 µL, 0.40 mmol), NaO^{t}Bu (41 mg, 0.42 mmol), $Pd_2(dba)_3$ (3.4 mg, 0.007 mmol), and PCy_3•HBF_4 (5.6 mg, 0.015 mmol) according to General Procedure 3. This procedure afforded 49 mg (78%) of the title compound as a brown foam. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 1 H), 7.42–7.38 (m, 1 H), 7.28–7.21 (m, 1 H), 7.15–7.05 (m, 3 H), 6.85 (d, *J* = 8.3 Hz, 2 H), 4.15 (dd, *J* = 5.4, 10.6 Hz, 1 H), 3.82–3.78 (m, 1 H), 3.78 (s, 3 H), 3.62–3.51 (m, 2 H), 3.18–3.12 (m, 1 H), 3.04–2.96 (m, 1 H), 2.17–1.82 (m, 4 H), 1.62–1.57 (m, 1 H), 1.50–1.43 (m, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.7 154.3, 136.6, 135.2, 131.7, 130.5, 129.2, 129.1 (q, *J* = 220 Hz), 126.6, 126.3, 114.5, 60.0, 55.3, 52.5, 46.1, 35.2, 33.8, 30.2, 23.4 (one carbon signal is absent due to incidental equivalence); ^{19}F NMR (377 MHz, $CDCl_3$) δ –58.8; IR (film) 2934.5, 1628.7, 1510.6, 1450.1, 1342.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{23}F_3N_2O_2$ 405.1784; Found 405.1781.

4.3.1.6. (±)-(3R,4aR*)-2-(4-Methoxyphenyl)-3-(4-nitrobenzyl)hexahydropyrrolo[1,2-c] pyrimidin-1(2H)-one* ***4f***

The title compound was prepared from substrate **3a** (40 mg, 0.15 mmol), 1-bromo-4-nitrobenzene (83 mg, 0.41 mmol), NaO^{t}Bu (40 mg, 0.42 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.008 mmol), and PCy_3•HBF_4 (5.6 mg, 0.015 mmol) according to General Procedure 3. This procedure afforded 23 mg (39%) of the title compound as a sticky brown solid. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 2 H), 7.29–7.16 (m, 4 H), 6.91–6.89 (m, 2 H), 4.10–4.07 (m, 1 H), 3.82 (s, 3 H), 3.81–3.75 (m, 1 H), 3.65–3.49 (m, 2 H), 3.17 (dd, *J* = 4.5, 13.6 Hz, 1 H), 2.85 (dd, *J* = 10.5, 13.7 Hz, 1 H), 2.18–2.15 (m, 1 H), 2.06–1.94 (m, 2 H), 1.93–1.83 (m, 1 H), 1.67–1.64 (m, 1 H), 1.51–1.44 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 154.2 146.8, 145.7, 130.1 129.8, 129.1, 123.8, 114.3, 60.0, 55.5, 52.6, 46.2, 38.9, 33.9, 30.1, 23.4; IR (film) 2931.3, 1604.9, 1509.5, 1446.0 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{23}N_3O_4$ 382.1761; found 382.1758.

4.3.1.7. (±)-(3R,4aR*)-3-[(1,1'-Biphenyl)-4-ylmethyl]-2-(4-methoxyphenyl)-3-methylhexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one* ***4g***

The title compound was prepared from substrate **3b** (42 mg, 0.15 mmol), 4-bromobiphenyl (89 mg, 0.38 mmol), NaO^{t}Bu (38 mg, 0.40 mmol), $Pd_2(dba)_3$ (3.1 mg, 0.006 mmol), and PCy_3•HBF_4 (5.6 mg, 0.015 mmol) according to General Procedure 3. This procedure afforded 64 mg (97%) of the title compound as a brown solid, mp 73–74 ºC. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 2 H), 7.48–7.42 (m, 2 H), 7.41–7.37 (m, 2 H), 7.31–7.27 (m, 1 H), 7.20–7.11 (m, 4 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 3.95–3.91 (m, 1 H), 3.79 (s, 3 H), 3.64–3.58 (m, 1 H), 3.51 (t, *J* = 10.2 Hz, 1 H), 3.17 (d, *J* = 13.3 Hz, 1 H), 3.00 (d, *J* = 13.3 Hz, 1 H), 2.20–2.00 (m, 2 H), 1.99–1.97 (m, 1 H), 1.92–1.81 (m, 1 H), 1.50–1.43 (m, 1 H), 1.41–1.34 (m, 1 H), 1.00 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 155.3, 140.6, 139.5, 136.4, 132.2, 131.0, 128.8, 127.3, 126.93, 126.88, 114.0, 59.3, 55.4, 52.6, 46.3, 43.8, 37.9, 34.0, 27.7, 23.2; IR (film) 2930.4, 1603.5, 1509.9, 1435.6 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{28}H_{30}N_2O_2$ 427.2380; found 427.2376.

*4.3.1.8. (±)-(*Z*,3*R**,4a*R**)-2-(4-methoxybenzyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2*H*)-one* ***4h***

The title compound was prepared from substrate **3a** (274 mg, 1.0 mmol) and (*Z*)-1-bromobutene (2.0 mL, 4.0 mmol, 2.0 M solution in toluene), NaO^{t}Bu (384 mg, 4.0 mmol), $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol), and PCy_3•HBF_4 (29.5 mg, 0.08 mmol) according to a modification of General Procedure 3. This procedure afforded 219 mg (67%) of the title compound as a brown oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 5.50–5.44 (m, 1 H), 5.23 – 5.17 (m, 1 H), 5.13 (d, *J* = 15.1 Hz, 1 H), 4.03 (d, *J* = 15.1 Hz, 1 H), 3.79 (s, 3 H), 3.60 (dt, *J* = 10.5, 6.0 Hz, 1 H), 3.58–3.54 (m, 1 H), 3.49 (dt, *J* = 9.1, 1.8 Hz, 1 H), 3.25–3.21 (m, 1 H), 2.38 (dd, *J* = 13.5, 6.7 Hz, 1 H), 2.19 (dt, *J* = 14.4, 9.4 Hz, 1 H), 2.09–1.94 (m, 5 H), 1.80 (ttd, *J* = 12.5, 9.6, 6.6 Hz, 1 H), 1.43 (qd, *J* = 11.9, 7.1 Hz, 1 H), 1.25 (td, *J* = 12.3, 5.0 Hz, 1 H), 0.95 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.6, 155.0, 134.5, 131.3, 129.1, 124.5, 113.8, 55.2, 53.4, 52.6, 47.9, 46.1, 33.9, 30.6, 30.1, 23.5, 20.8, 14.2; IR (film) 1626 cm^{-1}. (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{28}N_2O_2$ 329.2224; found 329.2221.

*4.3.1.9. (±)-(*Z*,3*R**,4a*R**)-2-(4-methoxyphenyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2*H*)-one* ***4i***

The title compound was prepared from substrate **3a** (52 mg, 0.2 mmol) and (*Z*)-1-bromobutene (200 µL, 0.4 mmol, 2.0 M solution in toluene), NaO^{t}Bu (38 mg, 0.40 mmol), $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol), and PCy_3•HBF_4 (6.0 mg, 0.016 mmol) according to General Procedure 3. This procedure afforded 36 mg (58%) of the title compound as a brown oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 9.1 Hz, 2 H), 5.47–5.40 (m, 1 H), 5.14–5.10 (m, 1 H), 3.80 (s, 3 H), 3.80–3.74 (m, 1 H), 3.69–3.61 (m, 1 H), 3.58 (td, *J* = 10.6, 7.4 Hz, 1 H), 3.50 (ddd, *J* = 10.9, 8.8, 2.0 Hz, 1 H), 2.36–2.30 (m, 1 H), 2.30–2.26 (m, 1 H), 2.19 (ddd, *J* = 13.3, 3.5,1.4 Hz, 1 H), 2.16–2.10 (m, 1 H), 2.01–1.92 (m, 3 H), 1.87–1.77 (m, 1 H), 1.64 (td, *J* = 12.3, 5.2 Hz, 1 H), 1.51 (tdd, *J* = 12.1, 10.0, 7.1 Hz, 1 H), 0.90 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.5, 154.4, 135.7, 134.5, 129.2, 124.2, 114.1, 58.7, 55.4, 52.6, 46.0, 33.9, 30.5, 30.4, 23.4, 20.7, 14.0; IR (film) 1638 cm^{-1}. (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{26}N_2O_2$ 315.2067; found 315.2070.

*4.3.1.10. (±)-(*Z*,3*R**,4a*R**)-2-(4-methoxyphenyl)-3-(pent-2-en-1-yl)octahydro-1*H*-pyrido[1,2-c]pyrimidin-1-one* ***6a***

The title compound was prepared from substrate **5** (55 mg, 0.2 mmol) and (*Z*)-1-bromobutene (500 µL, 1.0 mmol, 2.0 M solution in toluene), NaO^{t}Bu (96 mg, 1.0 mmol), $Pd_2(dba)_3$ (5.5 mg, 0.006 mmol), and PCy_3•HBF_4 (9.0 mg, 0.024 mmol) according to a modification of General Procedure 3. This procedure afforded 45 mg (69%) of the title compound as a brown oil. The compound was obtained as an 8:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.14 (d, *J* = 9.1 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 5.47–5.41 (m, 1 H), 5.17–5.14 (m, 1 H), 4.58 (d, *J* = 13.3 Hz, 1 H), 3.79 (s, 3 H), 3.59–3.55 (m, 1 H), 3.30 (dddd, *J* = 13.7, 11.0, 6.1, 3.6 Hz, 1 H), 2.57 (td, *J* = 12.7, 2.9 Hz, 1 H), 2.42–2.39 (m, 1 H), 2.27 (dt, *J* = 14.2, 9.4 Hz, 1 H), 2.04–1.93 (m, 3 H), 1.84 (d, *J* = 12.6 Hz, 1 H), 1.74–1.68 (m, 2 H), 1.50–1.35 (m, 2 H), 1.31–1.24 (m, 2 H), 0.93 (t, *J* = 7.7 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.6, 155.0, 136.4, 134.5, 129.0, 124.1, 114.0, 57.1, 55.4, 50.8, 43.5, 33.6, 32.8, 30.9, 25.3, 24.0, 20.8, 14.1; IR (film) 1637 cm^{-1}. (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{28}N_2O_2$ 329.2224; found 329.2228.

4.3.2. General procedure 4: synthesis of bicyclic piperidinyl ureas

A clean, flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the urea substrate, $Pd(OAc)_2$, Dpe-Phos, Cs_2CO_3, and aryl bromide. The tube was purged with nitrogen and 2.5 mL toluene per 1 mmol substrate was added via syringe. The reaction mixture was heated to 110 ºC with stirring until judged complete as determined by TLC analysis. Subsequently, the crude reaction mixture was diluted with ethyl acetate and quenched with saturated aqueous ammonium chloride. The organic layer was separated, and the aqueous layer extracted with ethyl acetate. The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and purified by flash chromatography on silica gel using 20–60% ethyl acetate/hexanes as the eluent unless otherwise noted.

4.3.2.1. (±)-(3R,4aR*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)octahydro-1H-pyrido[1,2-c]pyrimidin-1-one* ***6b***

The title compound was prepared from substrate **5** (45 mg, 0.16 mmol), 4-bromoanisole (50 µl, 0.40 mmol), Cs_2CO_3 (126 mg, 0.39 mmol), $Pd(OAc)_2$ (1.7 mg, 0.008 mmol), and Dpe-Phos (7.5 mg, 0.014 mmol) according to General Procedure 4. This procedure afforded 23 mg (37%) of the title compound as a light brown oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.7 Hz, 2 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 6.92–6.84 (m, 2 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 4.66–4.57 (m, 1 H), 3.80 (s, 3 H), 3.80–3.77 (m, 1H), 3.77 (s, 3 H), 3.43–3.34 (m, 1 H), 3.08–2.99 (m, 1 H), 2.68–2.56 (m, 2 H), 1.90–1.82 (m, 3 H), 1.73–1.69 (m, 2 H), 1.52–1.35 (m, 2 H), 1.25–1.16 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 157.6, 154.9, 136.5, 130.1, 130.0, 129.0, 114.1, 114.0, 59.0, 55.4, 55.2, 50.7, 43.5, 38.4, 33.6, 32.1, 25.4, 24.0; IR (film) 1635.6, 1510.9, 1457.2, 1245.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{23}H_{28}N_2O_3$ 381.2173; found 381.2170.

4.3.2.2. (±)-(3R,4aR*)-2-(4-Methoxyphenyl)-3-[3-(trifluoromethyl)benzyl]octahydro-1H-pyrido[1,2-c]pyrimidin-1-one* ***6c***

The title compound was prepared from substrate **5** (48 mg, 0.17 mmol), 3-bromobenzotrifluoride (60 µl, 0.40 mmol), Cs_2CO_3 (117 mg, 0.36 mmol), $Pd(OAc)_2$ (1.4 mg, 0.006 mmol), and Dpe-Phos (5.8 mg, 0.011 mmol) according to General Procedure 4. This procedure afforded 36 mg (56%) of the title compound as a viscous brown oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.49–7.47 (m, 1 H), 7.40–7.38 (m, 1 H), 7.29–7.22 (m, 2 H), 7.18–7.10 (m, 2 H), 6.95–6.84 (m, 2 H), 4.63 (dd, *J* = 1.9, 13.2 Hz, 1 H), 3.87 (dd, *J* = 3.3, 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.42–3.40 (m, 1 H), 3.16 (dd, *J* = 4.8, 13.6 Hz, 1 H), 2.81–2.76 (m, 1 H), 2.64–2.61 (m, 1 H), 1.98–1.81 (m, 3 H), 1.77–1.69 (m, 2 H), 1.49–1.45 (m, 2 H), 1.32–1.22 (m, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.8, 154.7, 139.0, 136.2, 132.5, 130.8 (q, 234 Hz), 129.1, 129.0, 125.5, 124.8, 123.5, 114.2, 58.6, 55.4, 50.7, 43.5, 39.2, 33.6, 32.4, 25.3, 24.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.6; IR (film) 1635.7, 1511.3, 1444.6, 1331.5, 1233.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{25}C_3N_2O_3$ 419.1941; found 419.1938.

4.3.2.3. (±)-(3R,4aR*)-3-(4-Benzoylbenzyl)-2-(4-methoxyphenyl)octahydro-1H-pyrido[1,2-c]pyrimidin-1-one* ***6d***

The title compound was prepared from substrate **5** (42 mg, 0.15 mmol), 4-bromobenzophenone (103.1 mg, 0.39 mmol), Cs_2CO_3 (122 mg, 0.37 mmol), $Pd(OAc)_2$ (1.4 mg, 0.006 mmol), and Dpe-Phos (6.6 mg, 0.012 mmol) according to General Procedure 4. This procedure afforded 43 mg (54%) of the title compound as a viscous yellow oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 2 H), 7.72–7.65 (m, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.48–7.39 (m, 2 H), 7.22–7.08 (m, 4 H), 6.93–6.83 (m, 2 H), 4.67–4.56 (m, 1 H), 3.91–3.83 (m, 1 H), 3.79 (s, 3 H), 3.42–3.39 (m, 1 H), 3.16 (dd, *J* = 4.7, 13.6 Hz, 1 H), 2.79 (dd, *J* = 10.3, 13.4 Hz, 1 H), 2.65–2.59 (m, 1 H), 1.93–1.81 (m, 3 H), 1.74–1.68 (m, 2 H), 1.52–1.37 (m, 2 H), 1.29–1.21 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.2, 157.7, 154.8, 143.0, 137.5, 136.3, 135.9, 132.4, 130.5, 129.9, 129.0, 128.9, 128.3, 114.2, 58.7, 55.4, 50.8, 43.5, 39.5, 33.6, 32.4, 25.3, 24.0; IR (film) 1633.8, 1603.6, 1510.0, 1443.5, 1276.0 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{29}H_{30}N_2O_3$ 455.2329; found 455.2324.

4.3.3. General procedure 5: synthesis of bicyclic ureas and sulfamides from aryl triflates (for reactions carried out in benzotrifluoride)

A test tube was charged with $Pd(OAc)_2$ (0.04 equiv), a phosphine ligand (0.1 equiv), and Li*O*t*Bu (2.0 equiv). The test tube was purged with N_2 then the appropriate aryl triflate (2.0 equiv) was added, followed by the appropriate substrate (1.0 equiv) in benzotrifluoride (0.2 M). The tube was heated to 100 °C and stirred overnight or until the starting material was completely consumed as judged by ^{1}H NMR analysis. The mixture was cooled to room temperature and saturated aqueous NH_4Cl (5 mL/mmol substrate) and dichloromethane (5 mL/mmol substrate) were added. The layers were separated and the organic layer was concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

4.3.3.1. (±)-(3S,4aR*)-3-Benzyl-2-(4-nitrophenyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one* ***18***

General procedure 5 was employed for the coupling of **7** (55 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and RuPhos (9.3 mg, 0.02 mmol). This procedure afforded 66 mg (94%) of the title compound as a yellow solid and as a 2:1 mixture of diastereomers as determined by ^{1}H NMR analysis: mp = 51–55 °C. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.1 Hz, 2 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.29–7.23 (m, 3 H), 7.04 (d, *J* = 7.0 Hz, 2 H), 4.14 (tt, *J* = 3.9, 10.6 Hz, 1 H), 3.58–3.47 (m, 3 H), 2.85 (dd, *J* = 3.8, 13.5 Hz, 1 H), 2.32 (dd, *J* = 10.1, 13.4 Hz, 1 H), 2.26–1.46 (m, 6 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.5, 147.5, 145.2, 137.0, 129.0, 128.7, 128.6, 126.7, 124.0, 58.2, 54.7, 46.0, 41.6, 35.0, 33.5, 23.0; IR (film) 1639, 1515, 1339 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}N_3O_3$ 352.1656; found 352.1656.

4.3.3.2. (±)-(3S,4aR*)-3-Benzyl-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20a***

General procedure 5 was employed for the coupling of **19a** (59 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure provided an 80% NMR yield (using phenanthrene as an internal standard) of the title compound that was a 6:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Data for this compound are provided below in entry 4.3.4.1.

4.3.3.3. (±)-(3S,4aR*)-2,3-Dibenzylhexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20b***

General procedure 5 was employed for the coupling of **19b** (56 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 61 mg (86%) of the title compound as a white solid and as a 3:1 mixture of diastereomers as determined by ^{1}H NMR analysis: mp = 113–116 °C. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.0 Hz, 2 H), 7.34–7.18 (m, 6 H), 7.07 (d, *J* = 7.0 Hz, 2 H), 4.59 (d, *J* = 16.2 Hz, 1 H), 4.15 (d, *J* = 16.1 Hz, 1 H), 4.15–4.09 (m, 1 H), 3.50–3.46 (m, 1 H), 3.26–3.21 (m, 2 H), 2.92 (dd, *J* = 4.6, 13.4 Hz, 1 H), 2.54 (dd, *J* = 10.5, 13.4 Hz, 1 H), 2.07–2.01 (m, 1 H), 1.98–1.90 (m, 1 H), 1.83–1.75 (m, 1 H), 1.71–1.49 (m, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.5, 137.4, 129.2, 128.5, 128.4, 127.7, 127.2, 126.7, 61.6, 60.8, 49.6, 45.8, 40.6, 31.6, 30.7, 21.1; IR (film) 1333, 1155 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}N_2O_2S$ 357.1631; found 357.1632.

4.3.3.4. (±)-(3S,4aR*)-3-Benzyl-2-(4-methoxybenzyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20c***

General procedure 5 was employed for the coupling of **19c** (62 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 63 mg (82%) of the title compound as a red-brown oil and as a 3:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2 H), 7.26–7.15 (m, 3 H), 7.08 (d, *J* = 7.0 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 4.51 (d, *J* = 15.9 Hz, 1 H), 4.08 (d, *J* = 16.1 Hz, 1 H), 4.11–4.03 (m, 1 H), 3.80 (s, 3 H), 3.48–3.42 (m, 1 H), 3.27–3.21 (m, 2 H), 2.92 (dd, *J* = 13.3, 4.9 Hz, 1 H), 2.55 (dd, *J* = 13.4, 10.3 Hz, 1 H), 2.06–1.98 (m, 1 H), 1.96–1.85 (m, 1 H), 1.82–1.76 (m, 1 H), 1.70–1.46 (m, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.8, 137.5, 130.4, 129.1, 129.1, 128.5,

126.6, 113.7, 61.3, 60.7, 55.2, 49.3, 45.9, 40.7, 31.6, 30.9, 21.3; IR (film) 1332, 1245, 1155 cm^{-1}. MS (ESI) 387.1725 (387.1737 calcd for $C_{21}H_{26}N_2O_3S$, M + H^+).

4.3.4. General procedure 6: synthesis of bicyclic sufamides (for reactions carried out in tert-butanol)

A test tube was charged with $Pd(OAc)_2$ (0.04 equiv), a phosphine ligand (0.1 equiv), and Li*O*t*B*u (2.0–3.0 equiv). The test tube was purged with N_2 then the appropriate aryl or alkenyl triflate (2.0–3.0 equiv) was added, followed by the appropriate substrate (1.0 equiv) in *tert*-butanol (0.1 M). The tube was heated to 82 °C and stirred overnight or until the starting material was completely consumed as judged by ^{1}H NMR analysis. The mixture was cooled to room temperature and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

4.3.4.1. (±)-(3S,4aR*)-3-Benzyl-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20a***

General procedure 6 was employed for the coupling of **19a** (59 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 67 mg (90%) of the title compound as a white solid and as a 7:1 mixture of diastereomers as determined by ^{1}H NMR analysis: mp = 45–48 °C. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2 H), 7.29–7.20 (m, 3 H), 7.06 (d, *J* = 7.7 Hz, 2 H), 6.91 (d, *J* = 9.1 Hz, 2 H), 4.26–4.19 (m, 1 H), 3.80 (s, 3 H), 3.53 (td, *J* = 5.7, 9.5 Hz, 1 H), 3.38 (td, *J* = 5.8, 9.5 Hz, 1 H), 2.81 (dd, *J* = 4.4, 13.6 Hz, 1 H), 2.21–2.08 (m, 2 H), 2.07–1.91 (m, 3 H), 1.68–1.53 (m, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.4, 137.4, 130.9, 130.4, 129.1, 128.6, 126.6, 114.3, 61.8, 60.2, 55.4, 46.5, 40.4, 32.6, 31.3, 21.3; IR (film) 1506, 1337, 1248, 1158 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{24}N_2O_3S$ 373.1580; found 373.1589.

4.3.4.2. (±)-(3S,4aR*)-3-[4-(tert-Butyl)benzyl]-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20d***

General procedure 6 was employed for the coupling of **19a** (59 mg, 0.2 mmol) and 4-(*tert*-butyl)phenyl triflate (113 mg, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 62 mg (72%) of the title compound as a white solid and as a 7:1 mixture of diastereomers as determined by ^{1}H NMR analysis: mp = 61–63 °C. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 (d, *J* = 9.1 Hz, 2 H), 7.27 (d, *J* = 7.7 Hz, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 6.90 (d, *J* = 9.1 Hz, 2 H), 4.25–4.19 (m, 1 H), 3.81 (s, 3 H), 3.80–3.76 (m, 1 H), 3.54–3.49 (m, 1 H), 3.41–3.34 (m, 1 H), 2.77 (dd, *J* = 4.3, 13.7 Hz, 1 H), 2.14–2.09 (m, 2 H), 2.07–1.87 (m, 2 H), 1.70–1.52 (m, 3 H), 1.29 (s, 9 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.4, 149.5, 134.2, 130.9, 130.4, 128.7, 125.4, 114.3, 61.8, 60.2, 55.4, 46.5, 39.9, 37.4, 34.4, 32.6, 31.3, 21.3; IR (film) 1506, 1338, 1247, 1158 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{32}N_2O_3S$ 429.2215; found 429.2215.

4.3.4.3. (±)-(3S,4aR*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20e***

General procedure 6 was employed for the coupling of **19a** (59 mg, 0.2 mmol) and 4-methoxyphenyl triflate (72 µL, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 52 mg (65%) of the title compound as a white solid and as a 7:1 mixture of diastereomers as determined by ^{1}H NMR analysis: mp = 48–51 °C. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2 H), 6.97 (d, *J* = 8.4 Hz, 2 H), 6.91 (d, *J* = 9.1 Hz, 2 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 4.20–4.14 (m, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.80–3.73 (m, 1 H), 3.56–3.46 (m, 1 H), 3.37 (td, *J* = 5.7, 9.4 Hz, 1 H), 2.74 (dd, *J* = 4.4, 13.7 Hz, 1 H), 2.15–2.08 (m, 2 H), 2.04–1.91 (m, 2 H), 1.64–1.50 (m, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.4, 158.3, 130.9, 130.4, 130.0, 129.3, 114.3, 113.9, 61.9, 60.3, 55.4, 55.2, 46.5, 39.5, 32.5, 31.3, 21.3; IR (film) 1507, 1338, 1247, 1158 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{26}N_2O_4S$ 403.1686; found 403.1679.

4.3.4.4. (±)-(3S,4aR*)-{4-{[2-(4-Methoxyphenyl)-1,1-dioxidohexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazin-3-yl]methyl}phenyl}(phenyl)methanone* ***20f***

General procedure 6 was employed for the coupling of **19a** (59 mg, 0.2 mmol) and 4-benzoylphenyl triflate (132 mg, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). The diastereoselectivity of the reaction was judged to be 5:1 dr as determined by ^{1}H NMR analysis prior to flash chromatography. This procedure afforded 62 mg (65%) of the title compound as a white solid and as a 8:1 mixture of diastereomers as determined by ^{1}H NMR analysis: mp = 58–61 °C. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.38 (d, *J* = 8.8 Hz, 2 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 4.33–4.28 (m, 1 H), 3.79 (s, 3 H), 3.79–3.77 (m, 1 H), 3.54 (td, *J* = 5.7, 9.4 Hz, 1 H), 3.39 (td, *J* = 5.8, 9.3 Hz, 1 H), 2.87 (dd, *J* = 4.8, 13.7 Hz, 1 H), 2.33 (dd, *J* = 9.8, 13.7 Hz, 1 H), 2.19–2.12 (m, 1 H), 2.01–1.95 (m, 2 H), 1.68–1.62 (m, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 196.2, 159.5, 142.4, 137.5, 136.1, 132.5, 130.9, 130.4, 130.2, 130.0, 129.0, 128.3, 114.4, 61.5, 60.1, 55.4, 46.5, 40.4, 32.9, 31.4, 21.3; IR (film) 1654, 1605, 1506, 1339, 1278, 1249, 1157 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]$^+$ calcd for $C_{27}H_{28}N_2O_4S$ 477.1843; found 477.1847.

4.3.4.5. (±)-(3S,4aR*)-2-(4-Methoxyphenyl)-3-(2-methylbenzyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20g***

General procedure 6 was employed for the coupling of **19a** (59 mg, 0.2 mmol) and 2-tolyl triflate (96 mg, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 65 mg (84%) of the title compound as a white solid and as a 5:1 mixture of diastereomers as determined by ^{1}H NMR analysis: mp = 39–43 °C. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 (d, *J* = 9.1 Hz, 2 H), 7.12–7.10 (m, 3 H), 7.05–7.02 (m, 1 H), 6.91 (d, *J* = 9.1 Hz, 2 H), 4.24–4.17 (m, 1 H), 3.82 (s, 3 H), 3.81–3.74 (m, 1 H), 3.55 (td, *J* = 5.7, 9.4 Hz, 1 H), 3.43–3.36 (m, 1 H), 2.75 (dd, *J* = 4.4, 13.8 Hz, 1 H), 2.22 (dd, *J* = 10.5, 13.8 Hz, 1 H), 2.18 (s, 3 H), 2.13 (ddt, *J* = 6.5, 9.6, 12.6 Hz, 1 H), 2.09–1.95 (m, 2 H), 1.67–1.60 (m, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.4, 136.3, 135.5, 130.9, 130.5, 130.4, 130.1, 126.8, 125.9, 114.3, 60.4, 60.2, 55.4, 46.5, 37.9, 32.7, 31.3, 21.3, 19.6; IR (film) 1506, 1338, 1248, 1157 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{26}N_2O_3S$ 387.1737; found 387.1745.

4.3.4.6. (±)-(3S,4aR*)-3-(Cyclohex-1-en-1-ylmethyl)-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20h***

General procedure 6 was employed for the coupling of **19a** (59 mg, 0.2 mmol) and 1-cyclohexenyl triflate (63 µL, 0.6

mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 55 mg (73%) of the title compound as a pale yellow oil and as a 6:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 9.1 Hz, 2 H), 5.33 (s, 1 H), 4.13–4.07 (m, 1 H), 3.87–3.82 (m, 1 H), 3.79 (s, 3 H), 3.51 (td, *J* = 5.6, 9.4 Hz, 1 H), 3.36 (td, *J* = 5.8, 9.4 Hz, 1 H), 2.20 (ddt, *J* = 6.5, 9.7, 12.7 Hz, 1 H), 2.08–1.42 (m, 15 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.2, 133.1, 131.0, 130.4, 124.9, 114.0, 60.4, 58.5, 55.4, 46.4, 42.8, 33.0, 31.4, 28.2, 25.2, 22.8, 22.2, 21.3; IR (film) 1506, 1337, 1248, 1156 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{28}N_2O_3S$, 377.1893; found 377.1903.

4.3.5. (±)-(E,3S,4aR*)-2-(4-Methoxyphenyl)-3-(undec-2-en-1-yl)-hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20i***

General procedure 6 was employed for the coupling of **19a** (15 mg, 0.05 mmol) and 1-decenyl triflate (29 µL, 0.15 mmol, 5:1 mixture of *E*/*Z* isomers), using a catalyst composed of $Pd(OAc)_2$ (0.45 mg, 0.002 mmol), and CPhos (2.2 mg, 0.005 mmol). The crude diastereoselectivity of the reaction could not be precisely determined directly due to the formation of a complex mixture of diastereomers and *E*/*Z* isomers. However, the crude diastereoselectivity was estimated to be between 5:1 and 10:1 dr as determined by ^{1}H NMR analysis prior to flash chromatography. Following flash chromatography, this procedure afforded 10 mg (46%) of the title compound as a pale yellow oil and as a 10:1 mixture of diastereomers as determined by ^{1}H NMR analysis following hydrogenation of the olefin (see below for details). Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 9.0 Hz, 2 H), 6.88 (d, *J* = 9.1 Hz, 2 H), 5.46–5.41 (m, 1 H), 5.26–5.20 (m, 1 H), 4.01–3.90 (m, 2 H), 3.80 (s, 3 H), 3.52 (td, *J* = 6.0, 9.4 Hz, 1 H), 3.40 (td, *J* = 5.8, 9.4 Hz, 1 H), 2.20 (ddt, *J* = 6.7, 9.8, 12.8 Hz, 1 H), 2.10–1.91 (m, 3 H), 1.88–1.78 (m, 3 H), 1.73–1.54 (m, 2 H), 1.33–1.26 (m, 13 H), 0.88 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.3, 133.3, 130.9, 130.2, 123.8, 114.2, 60.4, 60.0, 55.4, 46.6, 32.8, 31.9, 31.5, 31.4, 29.7, 29.4, 29.4, 29.3, 27.4, 22.7, 21.4, 14.1; IR (film) 2922, 1507, 1349, 1248, 1161 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{38}N_2O_3S$ 435.2676; found 435.2678.

4.3.5.1. (±)-(3S,4aR*)-2-(4-Methoxyphenyl)-3-undecylhexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (reduction of* ***20i****).*

A flask equipped with a stirbar was charged with **20i** (10 mg, 0.023 mmol) and methanol (2 mL). Pd/C (10 mg) was added to the solution and the flask was capped with a rubber septum. The flask was briefly flushed with hydrogen and then a hydrogen-filled balloon attached to a needle (via an adaptor) was connected to the flask through the septum. The mixture was stirred at rt until the starting material had been consumed as judged by ESI$^+$ MS analysis (ca. 1 hr). The crude product was then filtered through a plug of celite to remove the Pd/C and washed with methanol (5 mL). The crude material was concentrated *in vacuo* and required no further purification. This procedure afforded 9 mg (90%) of the title compound as a clear colorless oil and as a 10:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 9.1 Hz, 2 H), 4.00–3.94 (m, 1 H), 3.88–3.78 (m, 1 H), 3.80 (s, 3 H), 3.50 (td, *J* = 9.4, 5.6 Hz, 1 H), 3.35 (td, *J* = 9.4, 5.9 Hz, 1 H), 2.21 (ddt, *J* = 6.3, 9.6, 12.5 Hz, 1 H), 2.07–1.92 (m, 2 H), 1.81 (dt, *J* = 3.2, 13.9, Hz, 1 H), 1.73–1.57 (m, 2 H), 1.35–1.04 (m, 20 H), 0.88 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.2, 131.0, 130.4, 114.1, 60.7, 60.4, 55.4, 46.4, 33.4, 33.1, 31.9, 31.5, 29.6, 29.6, 29.4, 29.4, 29.3, 29.3, 25.4, 22.7, 21.2, 14.1; IR (film) 1507, 1345, 1248, 1161 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{40}N_2O_3S$ 437.2832; found 437.2836.

4.3.5.2. (±)-(3S,4aR*,7S*)-7-Allyl-3-benzyl-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20j***

General procedure 6 was employed for the coupling of **19d** (67 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). The diastereoselectivity of the reaction was judged to be 12:1 dr as determined by ^{1}H NMR analysis prior to flash chromatography. This procedure afforded 51 mg (62%) of the title compound as a pale yellow oil and as a 20:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2 H), 7.26–7.19 (m, 3 H), 7.09 (d, *J* = 7.0 Hz, 2 H), 6.88 (d, *J* = 9.1 Hz, 2 H), 5.78 (ddt, *J* = 7.1, 11.2, 15.8 Hz, 1 H), 5.10–5.04 (m, 2 H), 4.41 (tdd, *J* = 2.6, 5.3, 9.9 Hz, 1 H), 3.82 (s, 3 H), 3.77–3.72 (m, 1 H), 3.44 (tdd, *J* = 3.0, 5.0, 11.3 Hz, 1 H), 2.82 (dd, *J* = 5.3, 13.8 Hz, 1 H), 2.64–2.58 (m, 1 H), 2.37 (dt, *J* = 7.8, 14.0 Hz, 1 H), 2.11 (dd, *J* = 10.0, 13.8 Hz, 1 H), 2.01–1.94 (m, 1 H), 1.90 (ddt, *J* = 8.9, 10.2, 13.0 Hz, 1 H), 1.78–1.68 (m, 2 H), 1.68–1.53 (m, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.4, 137.3, 134.4, 131.4, 130.5, 129.1, 128.5, 126.7, 117.7, 114.0, 62.8, 61.7, 57.8, 55.4, 40.0, 39.8, 32.9, 30.5, 26.8; IR (film) 1506, 1344, 1249, 1155 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}N_2O_3S$ 413.1893; found 413.1895.

4.3.5.3. (±)-(3S,4aR*,7S*)-7-Allyl-3-(4-methoxybenzyl)-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20k***

General procedure 6 was employed for the coupling of **19d** (67 mg, 0.2 mmol) and 4-methoxyphenyl triflate (72 µL, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). The diastereoselectivity of the reaction was judged to be 13:1 dr as determined by ^{1}H NMR analysis prior to flash chromatography. This procedure afforded 57 mg (64%) of the title compound as a white solid and as a >20:1 mixture of diastereomers as determined by ^{1}H NMR analysis: mp = 44–46 °C. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.6 Hz, 2 H), 7.00 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 9.1 Hz, 2 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 5.82–7.73 (m, 1 H), 5.10–5.04 (m, 2 H), 4.39–4.35 (m, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.77–3.72 (m, 1 H), 3.46–3.39 (m, 1 H), 2.76 (dd, *J* = 5.3, 13.9 Hz, 1 H), 2.61 (dd, *J* = 6.0, 14.4 Hz, 1 H), 2.37 (dt, *J* = 7.9, 15.0 Hz, 1 H), 2.04 (dd, *J* = 10.0, 13.9 Hz, 1 H), 2.01–1.88 (m, 2 H), 1.78–1.68 (m, 2 H), 1.62–1.53 (m, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.5, 158.4, 134.4, 131.5, 130.6, 130.0, 129.3, 117.7, 114.0, 113.9, 62.9, 61.9, 57.9, 55.4, 55.2, 39.8, 39.1, 32.9, 30.5, 26.8; IR (film) 1507, 1345, 1247, 1156 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{30}N_2O_4S$ 443.1999; found 443.1993.

4.3.5.4. (±)-(Z,3S,4aR*)-2-Benzyl-3-(pent-2-en-1-yl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***20l***

A modified version of General Procedure 6 was employed for the coupling of **19b** (56 mg, 0.2 mmol) and (*Z*)-1-bromobutene (400 µL, 0.8 mmol, 2.0 M solution in $PhCF_3$), using NaO*t*Bu (96 mg, 1.0 mmol), LiOTf (156 mg, 1.0 mmol), and a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). The reaction was heated to 100 °C and stirred overnight or until the starting material was completely consumed as judged by ^{1}H NMR analysis. The mixture was cooled to room

temperature and saturated aqueous NH_4Cl (5 mL/mmol substrate) and dichloromethane (5 mL/mmol substrate) were added. The layers were separated and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel. This procedure afforded 20 mg (30%) of the title compound as a pale yellow brown oil and as a 5:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.44–7.29 (m, 4 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 5.41–5.37 (m, 1 H), 5.19–5.13 (m, 1 H), 4.50 (d, *J* = 16.2 Hz, 1 H), 4.11 (d, *J* = 16.2 Hz, 1 H), 3.90–3.85 (m, 1 H), 3.47 (td, *J* = 5.4, 9.0 Hz, 1 H), 3.40–3.31 (m, 1 H), 3.24 (td, *J* = 6.1, 9.3 Hz, 1 H), 2.25–2.08 (m, 3 H), 1.95–1.80 (m, 5 H), 1.59–1.45 (m, 2 H), 0.88 (t, *J* = 7.7 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.7, 134.7, 128.4, 127.6, 127.1, 123.9, 60.9, 60.6, 49.2, 45.9, 31.7, 31.6, 31.3, 21.0, 20.7, 13.9; IR (film) 1334, 1156 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{26}N_2O_2S$ 335.1788; found 335.1793.

4.3.5.5. (±)-(3S,4aR*)-3-Benzyl-2-(4-methoxyphenyl)octahydropyrido[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***24a***

General procedure 6 was employed for the coupling of **23** (62 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 65 mg (84%) of the title compound as a white solid and as a 5:1 mixture of diastereomers as determined by ^{1}H NMR analysis: mp = 46–49 °C. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2 H), 7.28–7.20 (m, 3 H), 7.07 (d, *J* = 7.5 Hz, 2 H), 6.91 (d, *J* = 9.0 Hz, 2 H), 4.41–4.37 (m, 1 H), 3.82 (s, 3 H), 3.59–3.43 (m, 2 H), 2.97–2.88 (m, 1 H), 2.79 (dd, *J* = 4.8, 13.6 Hz, 1 H), 2.13 (dd, *J* = 10.1, 13.7 Hz, 1 H), 1.89–1.65 (m, 4 H), 1.58–1.36 (m, 4 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.4, 137.2, 131.2, 130.0, 129.1, 128.5, 126.7, 114.2, 60.4, 57.1, 55.4, 44.3, 40.3, 32.1, 31.9, 24.9, 21.9; IR (film) 1507, 1338, 1250, 1156 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{26}N_2O_3S$ 387.1737; found 387.1737.

4.3.5.6. (±)-(3S,4aR*)-3-(Cyclohex-1-en-1-ylmethyl)-2-(4-methoxyphenyl)octahydropyrido[1,2-b][1,2,6]thiadiazine 1,1-dioxide* ***24b***

The title compound was prepared from substrate **23** (62 mg, 0.20 mmol), cyclohex-1-en-1-yl trifluoromethanesulfonate (70 µl, 0.40 mmol), LiO^{t}Bu (35 mg, 0.44 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), and CPhos (11.9 mg, 0.027 mmol) according to General Procedure 6. This procedure afforded 60 mg (77%) of the title compound as a sticky off-white foam. The compound was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 5.32 (s, 1 H), 4.29–4.21 (m, 1 H), 3.79 (s, 3 H), 3.62–3.46 (m, 2 H), 2.91–2.85 (m, 1 H), 2.32–2.28 (m, 1 H), 2.20–2.16 (m, 1 H), 2.00–1.45 (m, 16 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.3, 132.9, 131.2, 130.0, 124.7, 114.0, 57.3, 57.1, 55.4, 44.4, 42.5, 32.9, 32.1, 28.3, 25.2, 25.0, 22.8, 22.3, 21.6; IR (film) 1505.6, 1441.8, 1337.8, 1246.8 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{30}N_2O_3S$ 391.2050; found 391.2049.

4.3.5.7. (±)-(3S,4aR*)-3-[4-(tert-Butyl)benzyl]-2-(4-methoxyphenyl)octahydropyrido[1,2-b][1,2,6]thiadiazine 1,1-dioxide* ***24c***

The title compound was prepared from substrate **23** (65 mg, 0.21 mmol), 4-(*tert*-butyl)phenyl trifluoromethanesulfonate (112 µl, 0.40 mmol), LiO^{t}Bu (40 mg, 0.50 mmol), $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (7.4 mg, 0.017 mmol) according to General Procedure 6. This procedure afforded 80 mg (86%) of the title compound as a sticky light brown foam. The compound was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2 H), 7.31–7.26 (m, 2 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 6.90 (d, *J* = 9.0 Hz, 2 H), 4.44–4.32 (m, 1 H), 3.81 (s, 3 H), 3.58–3.50 (m, 1 H), 3.48–3.44 (m, 1 H), 2.93–2.89 (m, 1 H), 2.75 (dd, *J* = 4.7, 13.7 Hz, 1 H), 2.08 (dd, *J* = 10.2, 13.7 Hz, 1 H), 1.84–1.64 (m, 6 H), 1.51–1.40 (m, 2 H), 1.29 (s, 9 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.4, 149.5, 134.0, 131.2, 129.1, 128.7, 125.4, 114.3, 66.2, 60.5, 57.1, 55.4, 44.3, 39.8, 34.4, 32.2, 31.9, 31.4, 25.0, 21.9 (one carbon signal is absent due to incidental equivalence); IR (film) 1507.6, 1336.4, 1247.1, 1157.0 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ Calculated for $C_{25}H_{34}N_2O_3S$ 443.2363; found 443.2364.

4.3.5.8. (±)-(3S,4aR*)-2-(4-Methoxyphenyl)-3-(2-methylbenzyl)octahydropyrido[1,2-b][1,2,6]thiadiazine 1,1-dioxide* ***24d***

The title compound was prepared from substrate **23** (57 mg, 0.18 mmol), 2-tolyl trifluoromethanesulfonate (96 µl, 0.40 mmol), LiO^{t}Bu (30 mg, 0.37 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol), and CPhos (7.7 mg, 0.018 mmol) according to General Procedure 6. This procedure afforded 49 mg (67%) of the title compound as a sticky off-white foam. The compound was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 2 H), 7.14–7.06 (m, 4 H), 6.95–6.87 (m, 2 H), 4.41–4.36 (m, 1 H), 3.79 (s, 3 H), 3.59–3.47 (m, 2 H), 2.97–2.92 (m, 1 H), 2.72 (dd, *J* = 4.9, 14.0 Hz, 1 H), 2.19–2.16 (m, 1 H), 2.16 (s, 3 H), 1.90 (dt, *J* = 12.1, 14.4 Hz, 1H), 1.73–1.64 (m, 5 H), 1.55–1.38 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.5, 136.3, 135.4, 131.1, 130.5, 130.0, 128.6, 126.8, 126.0, 114.4, 59.1, 57.0, 55.4, 44.2, 37.6, 32.3, 31.8, 25.0, 21.8, 19.5; IR (film) 1606.1, 1506.1, 1463.5, 1338.8 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{28}N_2O_3S$ 401.1893; found 401.1891.

4.3.5.9. (±)-(3S,4aR*)-3-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(4-methoxyphenyl)octahydropyrido[1,2-b][1,2,6]thiadiazine 1,1-dioxide* ***24e***

The title compound was prepared from substrate **23** (64 mg, 0.21 mmol), benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate (100 µl, 0.40 mmol), LiO^{t}Bu (35 mg, 0.44 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), and CPhos (10.0 mg, 0.023 mmol) according to General Procedure 6. This procedure afforded 70 mg (79%) of the title compound as a sticky white foam. The compound was obtained as a 5:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.34 (m, 2 H), 6.97–6.86 (m, 2 H), 6.71–6.66 (m, 1 H), 6.55 (s, 1 H), 6.53–6.47 (m, 1 H), 5.91 (s, 2 H), 4.31–4.28 (m, 1 H), 3.80 (s, 3 H), 3.52–3.48 (m, 2 H), 2.97–2.91 (m, 1 H), 2.69–2.66 (m, 1 H), 2.04 (dd, *J* = 10.1, 13.7 Hz, 1 H), 1.84–1.65 (m, 5 H), 1.54–1.40 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 147.7, 146.3, 131.1, 130.0, 128.5, 122.1, 114.4, 109.3, 108.3, 101.0, 60.5, 57.0, 55.4, 44.3, 40.0, 32.1, 31.8, 24.8, 21.8; IR (film) 1504.4, 1442.5, 1337.0, 1246.3 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{26}N_2O_5S$ 431.1635; found 431.1634.

4.3.5.10. (±)-(3S,4aR*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)octahydropyrido[1,2-b][1,2,6]thiadiazine 1,1-dioxide* ***24f***

The title compound was prepared from substrate **23** (63 mg, 0.20 mmol), 4-methoxyphenyl trifluoromethanesulfonate (72 µl,

0.40 mmol), LiO^{t}Bu (30 mg, 0.37 mmol), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), and CPhos (10.1 mg, 0.023 mmol) according to General Procedure 6. This procedure afforded 58 mg (72%) of the title compound as a sticky off-white foam. The compound was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2 H), 7.00–6.93 (m, 2 H), 6.93–6.86 (m, 2 H), 6.86–6.75 (m, 2 H), 4.38–4.30 (m, 1 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.56–3.50 (m, 1 H), 3.49–3.42 (m, 1 H), 2.92–2.88 (m, 1 H), 2.71 (dd, *J* = 4.8, 13.8 Hz, 1 H), 2.10–2.03 (m, 1 H), 1.86–1.72 (m, 3 H), 1.72–1.64 (m 2 H), 1.56–1.39 (m, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.4, 158.3, 131.2, 130.5, 130.0, 129.1, 114.3, 113.9, 60.5, 57.1, 55.4, 55.2, 44.3, 39.4, 32.2, 31.9, 25.0, 22.0; IR (film) 1506.8, 1442.4, 1338.2, 1338.2 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{28}N_2O_4S$ 417.1837; found 417.1843.

4.3.5.11. (±)-(3R,4aR*)-2-(4-Methoxyphenyl)-3-(thiophen-2-ylmethyl)octahydropyrido [1,2b][1,2,6]thiadiazine 1,1-dioxide* ***24g***

A modified version of General Procedure 6 was employed for the coupling of substrate **23** (62 mg, 0.20 mmol) and 2-bromothiophene (40 µl, 0.41 mmol), using LiO^{t}Bu (30 mg, 0.37 mmol), lithium trifluoromethanesulfonate (64 mg, 0.41 mmol), and a catalyst composed of $Pd(OAc)_2$ (2.3 mg, 0.010 mmol), and CPhos (8.4 mg, 0.019 mmol).The reaction was heated to 100 °C and stirred overnight or until the starting material was completely consumed as judged by ^{1}H NMR analysis. The mixture was cooled to room temperature and saturated aqueous NH_4Cl (5 mL/mmol substrate) and dichloromethane (5 mL/mmol substrate) were added. The layers were separated and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel. This procedure afforded 58 mg (74%) of the title compound as a sticky light brown foam. The compound was obtained as a 6:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2 H), 7.19–7.13 (m, 1 H), 6.92–6.88 (m, 3 H), 6.76–6.73 (m, 1 H), 4.45–4.33 (m, 1 H), 3.80 (s, 3 H), 3.56–3.46 (m, 2 H), 3.01–2.89 (m, 2 H), 2.45 (dd, *J* = 9.5, 14.9 Hz, 1 H), 1.74–1.64 (m, 8 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.5, 139.1, 131.1, 127.0, 126.9, 126.1, 124.3, 114.3, 60.4, 56.8, 55.4, 44.2, 34.3, 32.0, 31.7, 24.9, 21.6; IR (film) 1505.5, 1441.0, 1338.2, 1248.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{24}N_2O_3S_2$ 393.1301; found 393.1302.

4.3.5.12. (±)-(Z,3S,4aR*)-2-(4-Methoxyphenyl)-3-(pent-2-en-1-yl)octahydropyrido[1,2-b][1,2,6]thiadiazine-1,1-dioxide* ***24h***

A modified version of General Procedure 6 was employed for the coupling of **23** (62 mg, 0.2 mmol) and (*Z*)-1-bromobutene (400 µL, 0.8 mmol, 2.0 M solution in $PhCF_3$), using NaO*t*Bu (96 mg, 1.0 mmol), LiOTf (156 mg, 1.0 mmol) and a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). The reaction was heated to 100 °C and stirred overnight or until the starting material was completely consumed as judged by ^{1}H NMR analysis. The mixture was cooled to room temperature and saturated aqueous NH_4Cl (5 mL/mmol substrate) and dichloromethane (5 mL/mmol substrate) were added. The layers were separated and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel. This procedure afforded 60 mg (82%) of the title compound as a pale yellow oil and as a 5:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 9.1 Hz, 2 H), 5.51–5.40 (m, 1 H), 5.25–5.19 (m, 1 H), 4.13–4.06 (m, 1 H), 3.80 (s, 3 H), 3.67–3.62 (m, 1 H), 3.49 (ddd, *J* = 3.7, 6.6, 10.8 Hz, 1 H), 2.99 (ddd, *J* = 3.5, 8.4, 11.7 Hz, 1 H), 2.04 (dt, *J* = 6.0, 13.8 Hz, 1 H), 1.92–1.66 (m, 8 H), 1.62–1.45 (m, 3 H), 0.88 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.3, 134.7, 131.1, 130.0, 123.5, 114.2, 59.5, 56.7, 55.4, 44.1, 32.1, 31.7, 31.4, 24.9, 21.5, 20.7, 13.9; IR (film) 1506, 1339, 1248, 1159 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{28}N_2O_3S$ 365.1893; found365.1905.

4.3.6. Elaboration of products

4.3.6.1. (±)-(S,R*)-1-Phenyl-3-(pyrrolidin-2-yl)propan-2-amine* ***25***

The title compound was prepared via the following two-step one-pot procedure. The first step was carried out according to the published work by Snyder and Heckert.[33] A flask equipped with a stirbar and reflux condenser was charged with **24a** (66 mg, 0.18 mmol). Hydrobromic acid (48%, 4 mL) was slowly added to the flask and the reaction was heated to 120 °C and stirred until the starting material had been completely consumed (ca. 2 h) as judged by MS ESI+ analysis (297.1 m/z, $M + H^+$). The mixture was cooled to rt, CH_3CN (2 mL) was added, followed by a solution of ceric ammonium nitrate (494 mg, 0.9 mmol) in H_2O (2 mL) and then stirred overnight (ca. 8 hr) at rt. Dichloromethane (8 mL) was added to the solution, the mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was carefully basified with NH_4OH to pH > 12 and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with Na_2SO_3 (1 x 10 mL) and brine (1 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. This procedure afforded 27 mg (75%) of the title compound as a yellow brown oil and as a 7:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 2 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 7.17 (d, *J* = 7.5 Hz, 2 H), 3.37–3.33 (m, 1 H), 3.15–3.12 (m, 1 H), 3.06–2.97 (m, 2 H), 2.86 (s, br, 3 H), 2.79 (dd, *J* = 4.9, 13.3 Hz, 1 H), 2.54 (dd, *J* = 8.2, 13.3 Hz, 1 H), 2.02–1.97 (m, 1 H), 1.83–1.77 (m, 2 H), 1.70–1.66 (m, 1 H), 1.48–1.43 (m, 1 H), 1.37–1.32 (m, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.7, 129.3, 128.5, 126.4, 58.5, 52.4, 45.8, 45.7, 41.7, 32.1, 24.6; IR (film) 3360, 2929 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{20}N_2$ 205.1699; found 205.1700.

4.3.6.2. (±)-(3R,4aR)-3-Pentylhexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one ***26***

A flame-dried flask was cooled under vacuum and charged with 10% Pd/C (120 mg). The flask was capped with a rubber septum, evacuated and backfilled with nitrogen. A solution of **4f** (66 mg, 0.2 mmol) in methanol (8 mL) was added to the flask via a syringe, followed by acetic acid (0.2 mL). The flask was briefly flushed with hydrogen and then a hydrogen-filled balloon attached to a needle (via an adaptor) was connected to the flask through the septum. The mixture was placed in an oil bath at 50 °C and the reaction was stirred overnight (ca. 16 h). The crude material was then filtered through a plug of celite to remove the Pd/C and washed with methanol (5 mL). The crude material was concentrated *in vacuo* and purified by flash chromatography on silica gel to afford 38.5 mg (92%) of the title compound as a pale yellow solid: mp = 63–66 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.79 (s, br, 1 H), 3.54–3.44 (m, 3 H), 3.39–3.32 (m, 1 H), 2.15–2.08 (m, 1 H), 1.97–1.92 (m, 2 H), 1.80–1.74 (m, 2 H), 1.54–1.25 (m, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.3, 52.3, 50.0, 45.3, 36.8, 33.6, 32.2, 31.6, 25.7, 23.0, 22.6, 14.0; IR (film) 3214, 1650 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{22}N_2O$ 211.1805; found 211.1812.

4.3.6.3. (±)-(Z,R,R)-N-(4-Methoxybenzyl)-1-(pyrrolidin-2-yl)hept-4-en-2-amine ***27***

This compound was prepared via a modification of a published procedure by Trost.[34] A flame-dried flask was cooled under vacuum and charged with LAH (190 mg, 5.0 mmol). A reflux condenser was attached to the flask and the apparatus was evacuated and backfilled with nitrogen. Diethyl ether (4 mL) was added, followed by a solution of **4i** (66 mg, 0.2 mmol) in diethyl ether (4 mL). The flask was placed in an oil bath and allowed to reflux overnight (ca. 16 h). The reaction flask was allowed to cool to rt and then the mixture was diluted with ether (10 mL). The reaction flask was placed in an ice bath and quenched slowly with water (2 mL). 1M NaOH (2 mL) was added, followed by more water (2 mL) and the biphasic mixture was stirred vigorously for 15 min. The mixture was decanted, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product appeared to by clean by ^{1}H NMR and taken unto the next step without further purification. A round bottom flask, equipped with a stirbar was charged with the crude product and aqueous 0.01% HCl (10 mL). H_2NOH•HCl (69 mg, 1.0 mmol) was added and the reaction mixture was heated to 60 °C in an oil bath and stirred until the starting material had been consumed as judged by ESI$^+$ MS analysis (ca. 60 min). The reaction was cooled to rt and aqueous 1M HCl (20 mL) was added. The solution was then washed with $CHCl_3$ (2 x 20 mL) and then the aqueous layer was carefully basified with Na_2CO_3 and extracted with $CHCl_3$ (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to afford 35 mg (57%) of the title compound as a pale yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.2 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 5.52–5.46 (m, 1 H), 5.33–5.30 (m, 1 H), 3.79 (s, 3 H), 3.75 (d, *J* = 12.8 Hz, 1 H), 3.69 (d, *J* = 12.8 Hz, 1 H), 3.17 (s, br, 1 H), 2.97–2.94 (m, 1 H), 2.85–2.80 (m, 1 H), 2.75–2.71 (m, 1 H), 2.28 (dt, *J* = 6.7, 13.9 Hz, 1 H), 2.22 (dt, *J* = 6.7, 14.1 Hz, 1 H), 2.1–2.06 (m, 2 H), 1.85 (td, *J* = 7.3, 12.6 Hz, 1 H), 1.73–1.66 (m, 2 H), 1.63–1.51 (m, 2 H), 1.25 (m, 1 H), 0.95 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.6, 134.3, 129.3, 125.2, 113.8, 56.3, 55.3, 54.9, 50.5, 46.2, 39.8, 31.9, 31.8, 25.1, 20.8, 14.3 (one carbon signal is absent due to incidental equivalence); IR (film) 3002, 1611, 1511, 1246 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{30}N_2O$ 303.2431; found 303.2427.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

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