JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

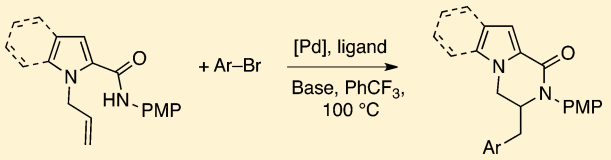
Synthesis of Substituted γ- and δ-Lactams via Pd-Catalyzed Alkene Carboamination Reactions

Jordan R. Boothe, Yifan Shen, and John P. Wolfe*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109-1055, United States

Supporting Information

ABSTRACT: The synthesis of substituted γ- and δ-lactams via palladium-catalyzed alkene carboamination reactions between aryl halides and alkenes bearing pendant amides is described. The substrates for these reactions are generated in 1−3 steps from commercially available materials, and products are obtained in good yield with up to >20:1 diastereoselectivity. The stereochemical outcome of the alkene addition is consistent with a mechanism involving *anti*-aminopalladation of the alkene.



γ-Lactams (pyrrolidin-2-ones) are a common motif present in a variety of biologically active compounds and natural products including Clausenamide (**1**, nootropic agent)[1,2] and streptopyrrolidine (**2**, angiogenesis inhibitor)[3] (Figure 1). Given the

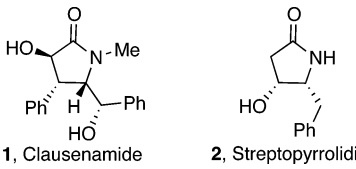
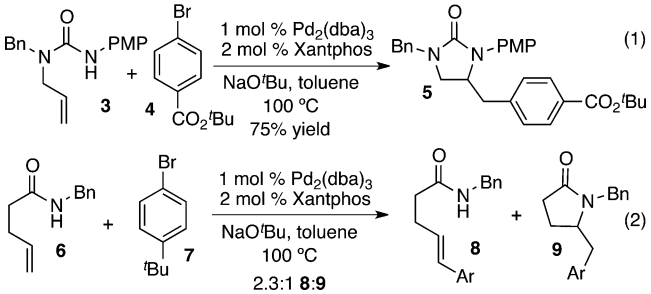


Figure 1. Biologically active 4-benzylpyrrolidin-2-one derivatives.

significance of these molecules, a variety of synthetic techniques have been employed for their construction[4] including alkene hydroamination,[5,6] intramolecular N-arylation of amides,[7] N-centered radical cyclizations of 4-pentenamides,[8,9] four-component coupling reactions,[10] and reductive amination strategies.[11]

Over the past 12 years our group has developed a series of palladium-catalyzed alkene carboamination reactions between alkenes bearing pendant nitrogen nucleophiles and aryl/alkenyl halides/triflates.[12,13] These transformations generate both a C−N and a C−C bond during the ring-forming step and afford the heterocyclic products in generally good chemical yield, typically with high diastereoselectivity. For example, treatment of *N*-allyl urea **3** with **4** in the presence of a Pd/Xantphos catalyst afforded **5** in 75% yield (Scheme 1, eq 1).[14−16] We felt that this approach could be employed for the construction of γ-lactams from *N*-protected 4-pentenamides (Scheme 1, eq 2). However, although we have successfully employed a number of different nitrogen nucleophiles in these reactions, including anilines,[17] guanidines,[18] carbamates,[19] and *N*-acylated amines,[19] our early efforts to extend this method to 4-pentenamides were largely unsuccessful as products were formed in very low yields due to competing Heck arylation of the alkene. For example attempts to couple amide **6** with **7** under conditions that proved optimal with urea substrate **3** afforded a mixture of Heck arylation

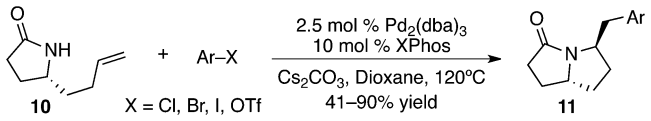
Scheme 1. Pd-Catalyzed Alkene Carboamination of Urea vs Amide



product **8** and desired product **9** in an unfavorable 2.3:1 ratio.[20,21]

Given our unsatisfactory results for the conversion of **6** to **9**, we were quite surprised when Cacchi reported a series of Pd-catalyzed carboamination reactions of **10** that afford substituted (5*R*,7a*R*)-5-aryl hexahydropyrrolizidin-3-ones **11** (Scheme 2).[22]

Scheme 2. Cacchi's Pd-Catalyzed Alkene Carboamination of Lactam 10



Although only a single alkene substrate was examined in these transformations, the coupling of **10** with a range of different aryl halides provided the bicyclic lactam products **11** in generally good yield (41−90%). Given Cacchi's success with this system, coupled with the fact that the scope of the amide carboamination reactions (with respect to amide substrate structure) was not fully explored, we elected to re-examine Pd-

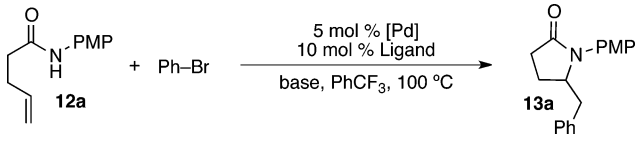
Received: January 6, 2017
Published: February 23, 2017

DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777−2786

catalyzed alkene carboamination reactions of pentenamide-derived substrates related to **6**.

In order to develop satisfactory conditions for Pd-catalyzed alkene carboamination reactions of pentenamide derivatives we explored the coupling of *N*-PMP-substituted pentenamide substrate **12a** with bromobenzene (Table 1).[23] We first examined the conditions reported by Cacchi; however, these conditions failed to produce the desired lactam product; unreacted starting material was observed along with Heck arylation of the alkene (entry 1). We subsequently varied the palladium source, base, solvent, and phosphine ligand, to ultimately arrive at optimized conditions that employed $PdBr_2$/XPhos as the catalyst, LiO^tBu as the base, and $PhCF_3$ as the solvent (entry 7). These conditions afforded a 79% yield of the desired product **13a**.

Table 1. Optimization Studies



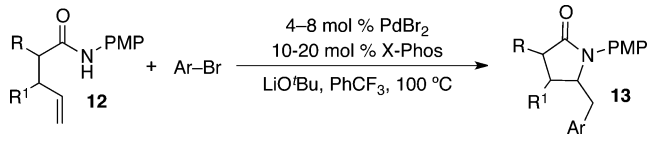
entry	[Pd]	ligand	base	yield[b]
1	$Pd_2(dba)_3$	XPhos	Cs_2CO_3	<5%[c,d]
2	$PdCl_2(MeCN)_2$	CPhos	LiO^tBu	34%
3	$Pd(OAc)_2$	XPhos	LiO^tBu	15%
4	$PdBr_2$	XPhos	LiO^tBu	69%
5	$Pd(OAc)_2$	XPhos	LiO^tBu	<5%[c]
6	$Pd(OAc)_2$	RuPhos	LiO^tBu	58%
7	**$PdBr_2$**	**XPhos**	**LiO^tBu**	**79%**

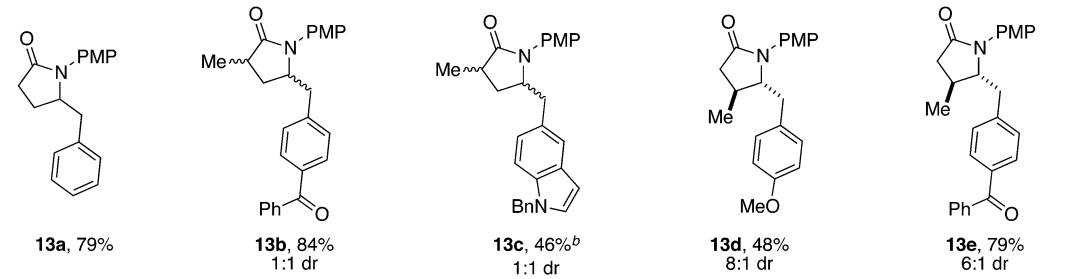
[a]Conditions: 1 equiv of **12a**, 2.0 equiv of PhBr, 2.0 equiv of base, 2.5 mol % $Pd_2(dba)_3$ or 5 mol % $Pd(OAc)_2$ or 5 mol %$PdBr_2$, 10 mol % ligand, solvent (0.1 M), 100 °C, 4–16 h. [b]Yields were determined by ^{1}H NMR using phenanthrene as an internal standard. [c]Yields reported as <5% indicate the desired product was not observed by ^{1}H NMR analysis of the crude reaction mixture. [d]The reaction was conducted in 1,4 dioxane solvent.

Once we had discovered conditions that provided satisfactory results for the coupling of **12a** with bromobenzene we began to explore the scope of the amide carboamination reactions. As shown in Table 2, both aryl chlorides and aryl bromides could be employed as coupling partners, and the reaction was effective with electron-rich, electron-neutral, and electron-poor electrophiles. The coupling of heteroaryl halides was also accomplished, albeit in modest yields. Substrates **12c** (R = H, R^1 = Me) and **12d** (R = H, R^1 = Ph) bearing a substituent at the allylic position were transformed to *trans*-disubstituted lactams **13d–j** in good yield with good to excellent diastereoselectivity. Not surprisingly, increasing the size of the allylic group from methyl to phenyl led to increased diastereoselectivities. In contrast, diastereoselectivities were poor in reactions of **12b** (R = Me, R^1 = H) due to base-mediated scrambling of the α-stereocenter in the lactam products **13b–c**.[24] Unfortunately efforts to employ weaker bases were unsuccessful. Although substitution on the backbone of the substrate was tolerated, efforts to transform substrates bearing a substituent at the internal or terminal alkene carbon atom failed to generate the desired products.

To further explore the scope of these transformations, we elected to investigate the synthesis of six-membered lactams from substituted hex-5-eneamide derivatives. As such, we prepared substrate **14** and investigated its reactivity in the Pd-catalyzed alkene carboamination reactions. Unfortunately, despite extensive studies with a number of different catalyst systems and reaction conditions, efforts to couple **14** with bromobenzene provided little or none of the desired product **15** (Scheme 3).

Table 2. Pd-Catalyzed Synthesis of γ-Lactams[a]

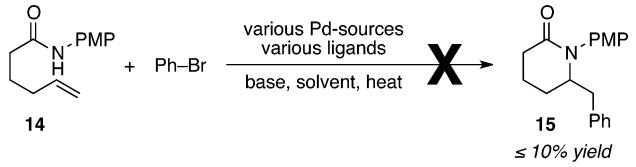




[a]Conditions: 1 equiv of **12**, 2.0 equiv of ArBr, 2.0 equiv of base, 4–10 mol % [Pd], 8–20 mol % ligand, solvent (0.1 M), 100 °C, 4–16 h. Yields are isolated yields (average of two or more experiments). [b]The reaction was conducted using an aryl chloride rather than an aryl bromide.

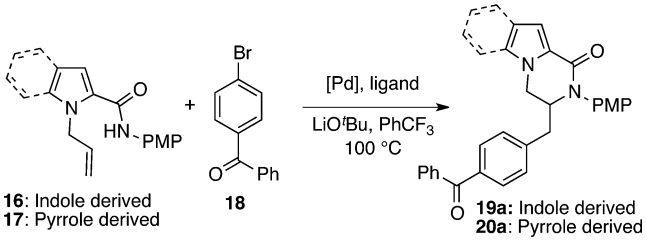
DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777–2786

Scheme 3. Unsuccessful Pd-Catalyzed Carboamination of 14



We reasoned that the failure of substrate **14** to undergo the desired transformation may be due to entropic factors associated with generating the larger sized ring. It seemed that substrates with less conformational flexibility would therefore be more likely to undergo the Pd-catalyzed carboamination, so our attention turned to substrates **16** and **17** derived from *N*-allylindole-2-carboxylic acid and the analogous pyrrole derivative. As shown in Table 3, the conditions that proved optimal for the generation of γ-lactams provided unsatisfactory results in the coupling of **16** or **17** with 4-bromobenzophenone **18** (entry 1). However, use of $Pd(OAc)_2$ in place of $PdBr_2$ led to improved results, and after examining a few biarylphosphine derivatives we found that the S-Phos ligand provided excellent results for the formation of both **19a** (94% NMR yield) and **20a** (91% NMR yield).

Table 3. Optimization Studies[a]



entry	[Pd]	ligand	**19a** yield[b]	**20a** yield[b]
1	$PdBr_2$	XPhos	10%	<5%
2	$Pd(OAc)_2$	XPhos	<5%[c]	24%
3	$Pd(OAc)_2$	CPhos	<5%[c]	60%
4	$Pd(OAc)_2$	RuPhos	17%	29%
5	$Pd(OAc)_2$	BrettPhos	42%	87%
6	$PdBr_2$	SPhos	<5%[c]	39%
7	**$Pd(OAc)_2$**	**SPhos**	**94%(98%)**[d]	**91%(96%)**[d]

[a]Conditions: 1 equiv of **16** or **17**, 2.0 equiv of 4-bromobenzophenone, 2.0 equiv of base, 2 mol % [Pd], 8 mol % ligand, solvent (0.1 M), 100 °C, 4–16 h. [b]Yields were determined by ^{1}H NMR using phenanthrene as an internal standard. [c]Yields reported as <5% indicate the desired product was not observed by ^{1}H NMR analysis of the crude reaction mixture. [d]Isolated yield. The differences between NMR yields and isolated yields reflect experimental error in the measurement of NMR yields.

Having successfully optimized conditions, we proceeded to explore the coupling of **16** and **17** with a range of different aryl bromides. As shown in Table 4, these reactions were effective with electron-rich, electron-poor, *o*-substituted, and heteroaromatic electrophiles. The substituted lactam products were generally formed in good to excellent yields under our standard conditions, although use of *tert*-butanol as solvent provided optimal results for the reaction of **16** with 2-brombenzotrifluoride to afford **19e**, and toluene was superior to $PhCF_3$ as a solvent for the coupling of **17** with *N*,*N*-dimethyl-4-bromoaniline to afford **20c**.

Having successfully prepared a range of PMP-protected lactams, we sought to illustrate the feasibility of removing the PMP protecting group. Fortunately this proved to be fairly straightforward (Scheme 4), as treatment of product **13a** with cerium(IV) ammonium nitrate in acetonitrile/water led to clean deprotection after 1 h, affording product **28** in 96% isolated yield (76% overall yield from **12a** over the two step carboamination/deprotection sequence).

Finally, we sought to obtain information about the mechanism of the carboamination reaction and the key C–N bond forming step, which in principle may occur via either *syn*- or *anti*-aminopalladation of the alkene.[25,26] As such, deuterated 4-pentenamide substrate **21** was synthesized and subjected to our optimized reaction conditions (Scheme 5). This transformation afforded deuterated lactam **22**, which results from *anti*-addition to the alkene, in 63% yield with >20:1 dr.[27,28]

The result of this stereochemical probe indicates the products of these reactions are generated via *anti*-aminopalladation of the alkene,[25,26] rather than *syn*-aminopalladation.[29−33] As such, the mechanism of the amide-forming reactions appears to be similar to related transformations of other electron-deficient nitrogen nucleophiles such as sulfamides[26,34] and sulfonamides[35] and likely proceeds as illustrated in Scheme 6. The catalytic cycle is initiated by oxidative addition of the aryl bromide to Pd(0) to afford **23**. Coordination of the alkene to the metal activates the alkene for attack by the pendant amide nucleophile, and *anti*-aminopalladation of resulting intermediate **24** ensues to provide **25**. Finally, C–C bond-forming reductive elimination of **25** yields the lactam product and regenerates the Pd(0) catalyst.

■ CONCLUSION

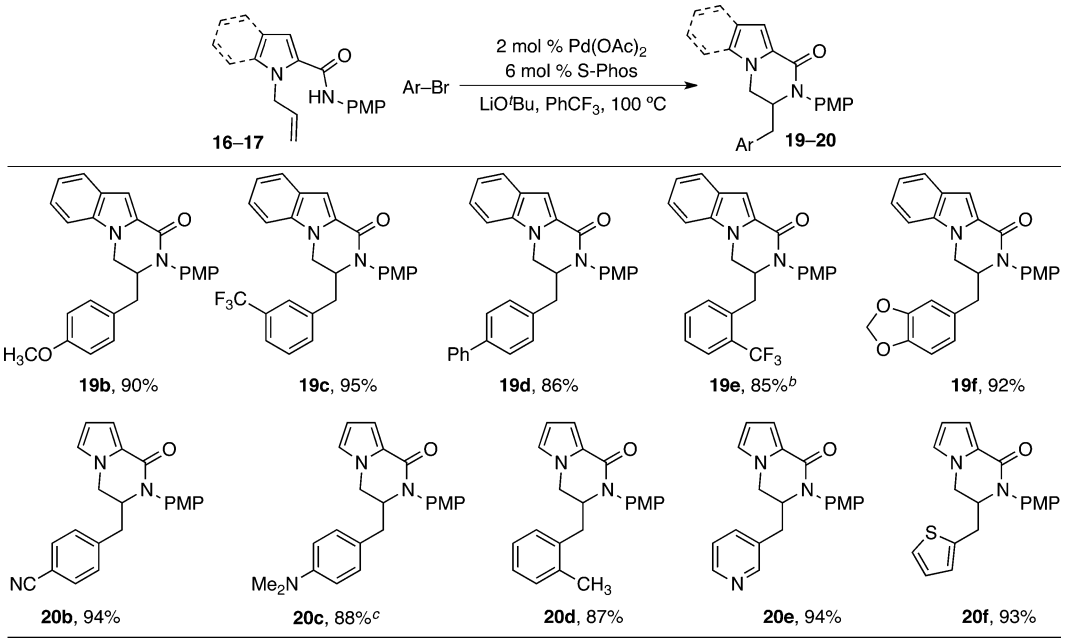
In conclusion, we have explored and significantly expanded the scope of Pd-catalyzed alkene carboamination reactions of amide nucleophiles. These transformations afford substituted γ- and δ-lactam derivatives in good yield with moderate diastereoselectivity. The reactions are effective with a range of different aryl bromide electrophiles, and deuterium labeling studies indicate the mechanism of C–N bond formation involves *anti*-aminopalladation of the alkene.

■ EXPERIMENTAL SECTION

General. All reactions were carried out under a nitrogen atmosphere in flame- or oven-dried glassware. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. Palladium(II) bromide and palladium(II) acetate were purchased from Strem Chemical Co. and used without further purification. SPhos and XPhos were purchased from Sigma-Aldrich Chemical Co. and used without further purification. Dichloromethane, toluene, and tetrahydrofuran were purified using a GlassContour solvent purification system. Pent-4-eneamide,[19] *N*-methylpent-4-eneamide,[17] *tert*-butyl pent-4-enoyl carbamate,[36] and (*E*)-*tert*-butyl-5-d-pent-4-enylcarbamate[37] were synthesized according to published procedures. Benzotrifluoride was 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 2 and 4 and Schemes 4–5 are averages of two or more experiments. Thus, the yields reported in the Experimental Section may differ from those shown in Tables 2 and 4 and Schemes 4–5.

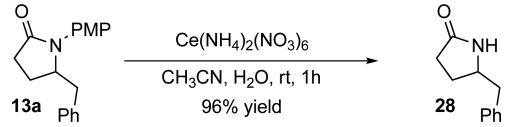
DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777–2786

Table 4. Pd-Catalyzed Synthesis of δ-Lactams[a]

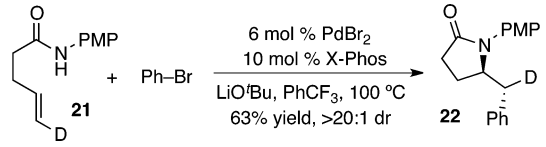


[a]Conditions: 1 equiv of **16** or **17**, 2.0 equiv of ArBr, 2.0 equiv of base, 2 mol % $Pd(OAc)_2$, 6 mol % S-Phos, $PhCF_3$ (0.2 M), 100 °C, 4–16 h. Yields are isolated yields (average of two or more experiments). [b]The reaction was conducted using *tert*-butyl alcohol as solvent. [c]The reaction was conducted using toluene as solvent.

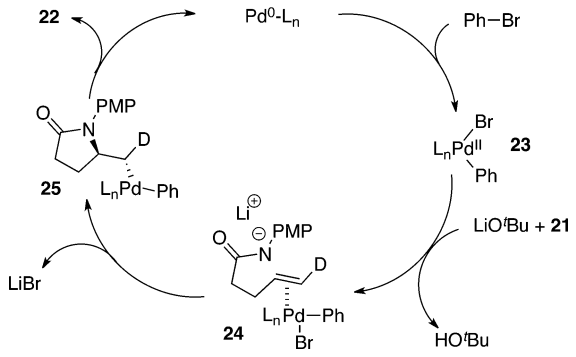
Scheme 4. Removal of PMP Protecting Group from 13a



Scheme 5. Stereochemistry of Alkene Addition



Scheme 6. Catalytic Cycle



Experimental Procedures and Compound Characterization Data for Substrates. *General Procedure 1.*[2] A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with the appropriate carboxylic acid (1.0 equiv), 1,1′-carbonyldiimidazole (1.0 equiv), and tetrahydrofuran (0.95 M). The resulting mixture was stirred at rt for 2 h, then the appropriate aniline (1.0 equiv) was added slowly, and the mixture was stirred at rt for 16 h. Water was then added, and the mixture was transferred to a separatory funnel. The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with 1 M HCl (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), then were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel using 30–40% ethyl acetate/hexanes as the eluent, unless otherwise noted.

*N-(4-Methoxyphenyl)-pent-4-enamide (**12a**).*[38] The title compound was prepared from 4-pentenoic acid (0.98 g, 9.7 mmol) and *p*-anisidine (1.20 g, 9.7 mmol) according to General Procedure 1. This procedure afforded 1.62 g (87%) of the title compound as a light brown solid, mp 91–92 °C (lit.[38] mp 86–88 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 2.7, 9.7 Hz, 2 H), 7.07 (s, 1 H), 6.87–6.82 (m, 2 H), 5.92–5.85 (m, 1 H), 5.19–5.09 (m, 2 H), 3.78 (s, 3 H), 2.51–2.45 (m, 2 H), 2.43 (dd, *J* = 6.3, 7.8 Hz, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.2, 156.4, 136.9, 121.7, 115.9, 114.1, 55.5, 36.7, 29.5.

*N-(4-Methoxyphenyl)-2-methylpent-4-enamide (**12b**).*[38] The title compound was prepared from 2-methyl 4-pentenoic acid (2.22 g, 19.4 mmol), and *p*-anisidine (2.40 g, 19.4 mmol) according to General Procedure 1. This procedure afforded 2.06 g (95%) of the title compound as a light brown solid, mp 82–83 °C (lit.[38] mp 65–68 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42–7.35 (m, 2 H), 7.14 (s, br, 1 H), 6.86–6.82 (m, 2 H), 5.87–5.76 (m, 1 H), 5.16–5.09 (m, 2 H), 3.73 (s, 3 H), 2.53–2.43 (m, 1 H), 2.42–2.33 (m, 1 H), 2.22 (dt, *J* = 7.0, 14.1 Hz, 1 H), 1.23 (s, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.8, 135.7, 130.9, 121.7, 117.2, 114.1, 55.5, 42.1, 38.5, 17.5.

*N-(4-Methoxyphenyl)-3-methylpent-4-enamide (**12c**).*[38] The title compound was prepared from 3-methyl-4-pentenoic acid (1.11 g, 9.7 mmol) and *p*-anisidine (1.20 g, 9.7 mmol) according to General Procedure 1. This procedure afforded 0.87 g (78%) of the title compound as a pale brown solid, mp 91–92 °C (lit.[38] mp 57–60 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2 H), 7.05 (s, br, 1 H), 6.91–6.82 (m, 2 H), 5.88–5.80 (m, 1 H), 5.12–4.99 (m, 2 H), 3.77 (s, 3 H), 2.83–2.74 (m, 1 H), 2.38–2.33 (m, 1 H), 2.31–2.22 (m, 1 H), 1.11 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (176 MHz, CDCl3) δ 142.7, 121.8, 114.1, 113.9, 55.5, 44.6, 34.9, 19.7.

*N-(4-Methoxyphenyl)-3-phenylpent-4-enamide (**12d**).*[17] The title compound was prepared from 3-phenyl-4-pentenoic acid (1.71 g, 9.7

DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777–2786

mmol) and *p*-anisidine (1.20 g, 9.7 mmol) according to General Procedure 1. This procedure afforded 0.95 g (35%) of the title compound as a pale brown solid, mp 109−110 °C (lit.[17] mp not reported). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 (d, J = 7.6 Hz, 2 H), 7.28−7.18 (m, 5 H), 6.80 (d, 2 H), 6.11−5.99 (m, 1 H), 5.15−5.10 (m, 2 H), 3.95 (q, J = 7.3 Hz, 1 H), 3.76 (s, 3 H), 2.77 (dd, J = 7.2, 14.1 Hz, 1 H), 2.67 (dd, J = 7.8, 14.1 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.2, 140.2, 130.6, 128.8, 127.6, 126.9, 122.0, 115.2, 114.0, 55.4, 46.1, 43.8.

*N-(4-Methoxyphenyl)hex-5-enamide (**14**).*[38] A flame-dried round-bottom flask and stir bar was charged with 5-hexenoic acid (0.7 mL, 5.9 mmol), benzene (15 mL), and triethylamine (3 mL, 21.5 mmol). Oxalyl chloride (0.8 mL, 9.3 mmol) was slowly added, and the reaction was stirred overnight at rt (12 h). Neat *p*-anisidine (3.0 g, 24.4 mmol) was then added, and the reaction mixture was stirred at rt for 2 h. The reaction was slowly quenched through addition of water (10 mL). The resulting mixture was extracted with ethyl acetate (3 × 50 mL), and the organic layers were combined, dried over anhydrous sodium sulfate, and concenterated *in vacuo* to afford 524 mg (41%) of the title compound as an off-yellow solid, mp 69−71 °C (lit.[38] mp 61−63 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.38 (m, 2 H), 7.05 (s, 1 H), 6.93−6.91−6.82 (m, 2 H), 5.82 (ddt, J = 6.7, 10.2, 17.0 Hz, 1 H), 5.12−4.99 (m, 2 H), 3.80 (s, 3 H), 2.35 (t, J = 7.5 Hz, 2 H), 2.22−2.15 (m, 2 H), 1.85 (p, J = 7.4 Hz, 2 H).

*1-Allyl-N-(4-methoxyphenyl)-1H-indole-2-carboxamide (**16**).*[39] Ethyl indole-2-carboxylate (1.91 g, 10.1 mmol) was dissolved in *N*,*N*-dimethylformamide (10 mL), and the resulting solution was added dropwise to a suspension of sodium hydride (470 mg, 11.8 mmol) in *N*,*N*-dimethylformamide (10 mL) at 0 °C. The mixture was stirred for 30 min at rt, and then a solution of allyl bromide (1.3 mL, 15.0 mmol) was added dropwise. The mixture was stirred at 50 °C overnight, then was cooled to rt, and poured into a mixture of ice and water (20 mL). Diethyl ether (20 mL) was added, and the mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was then extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with water (5 × 25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a mixture of ethyl 1-allyl-indole-2-carboxylate and *N*,*N*-dimethylformamide, which was not further purified. Ethanol (15 mL) and 5 M sodium hydroxide (15 mL) were added to the mixture, which was then heated to reflux overnight. The mixture was then cooled to rt, ethanol was evaporated under reduced pressure, and the aqueous layer was acidified with 5 M hydrochloric acid until pH 1 was achieved. The resulting mixture was extracted with ethyl acetate (3 × 30 mL), and the organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 1-allyl-indole-2-carboxylic acid which was used without further purification.

1,1′-Carbonyldiimidazole (1.65 g, 10.1 mmol) was added to a solution of 1-allyl-indole-2-carboxylic acid in tetrahydrofuran (20 mL), and the resulting mixture was stirred at rt for 2 h. Neat *p*-anisidine (1.42 g, 11.5 mmol) was added, and the resulting mixture was stirred at rt overnight. The mixture was then transferred to a separatory funnel and washed with saturated aqueous $NaHCO_3$ (20 mL), ethyl acetate (3 × 25 mL), and brine (20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford the title compound (2.02 g, 66% yield over three steps) as a white solid, mp 177−178 °C (lit.[39] mp not reported). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.59−7.49 (m, 2 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.35 (ddd, J = 1.2, 6.9, 8.2 Hz, 1 H), 7.25−7.13 (m, 1 H), 7.02 (s, 1 H), 6.95−6.89 (m, 2 H), 6.06 (ddt, J = 5.1, 10.2, 17.0 Hz, 1 H), 5.24 (dt, J = 1.8, 5.2 Hz, 2 H), 5.13 (dq, J = 1.6, 10.3 Hz, 1 H), 4.98 (dq, J = 1.6, 17.1 Hz, 1H), 3.83 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 156.6, 138.7, 134.1, 131.7, 130.7, 126.2, 124.4, 122.0, 120.8, 116.2, 114.3, 114.2, 110.7, 104.6, 55.5, 46.9, 14.6.

*1-Allyl-N-(4-methoxyphenyl)-1H-pyrrole-2-carboxamide (**17**).* The title compound was prepared using a procedure analogous to that employed for the preparation of **16** except methyl pyrrole-2-carboxylate (1.40 g, 10.1 mmol) was used as the starting material. This procedure afforded the title compound (1.92 g, 75% over three steps) as a yellow solid, mp 117−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 7.48−7.39 (m, 2 H), 7.24 (s, 1 H), 6.93−6.79 (m, 3 H), 6.67 (dt, J = 1.8, 3.8 Hz, 1 H), 6.16 (dt, J = 2.1, 4.1 Hz, 1 H), 6.08−5.93 (m, 1 H), 5.13 (dt, J = 1.6, 10.3 Hz, 1 H), 5.01 (ddq, J = 1.7, 5.3, 8.8 Hz, 2 H), 3.78 (d, J = 1.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 156.3, 134.9, 131.0, 127.4, 125.3, 122.0, 116.5, 114.2, 112.1, 107.8, 77.2, 55.5, 51.0; IR (film) 3320, 1638 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calculated for $C_{15}H_{16}N_2O_2$ 257.1285; found 257.1288.

Experimental Procedures and Compound Characterization Data for Lactam Products. *General Procedure 2: Synthesis of Five-Membered Lactams.* A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the amide substrate (1.0 equiv), the aryl halide (2.0 equiv), LiO^tBu (2.0 equiv), $PdBr_2$ (4−10 mol %), and XPhos (8−20 mol %). The tube was purged with nitrogen, and benzotrifluoride (5 mL/mmol substrate) was added via syringe. The mixture was heated to 100 °C with stirring until the reaction was complete as determined by TLC analysis. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (3 mL), and extracted with dichloromethane (3 × 2 mL). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and subsequently purified by flash chromatography on silica gel using 30−60% ethyl acetate/hexanes as the eluent unless otherwise noted.

*(±)-5-Benzyl-1-(4-methoxyphenyl)pyrrolidine-2-one (**13a**).* The title compound was prepared from substrate **12a** (40 mg, 0.20 mmol), bromobenzene (42 μL, 0.40 mmol), LiO^tBu (32 mg, 0.40 mmol), $PdBr_2$ (1.5 mg, 0.006 mmol), and XPhos (8.4 mg, 0.018 mmol) according to General Procedure 2. This procedure afforded 39 mg (69%) of the title compound as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37 (dd, J = 2.5, 9.0 Hz, 2 H), 7.28 (td, J = 2.3, 7.6 Hz, 2 H), 7.26−7.19 (m, 1 H), 7.10 (dd, J = 2.3, 7.8 Hz, 2 H), 7.00−6.92 (m, 2 H), 4.41−4.31 (m, 1 H), 3.82 (s, 3 H), 3.02−2.93 (m, 1 H), 2.64−2.55 (m, 1 H), 2.45−2.34 (m, 2 H), 2.17−2.05 (m, 1 H), 1.94−1.84 (m, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 136.9, 130.4, 129.2, 128.5, 126.7, 125.7, 114.5, 61.2, 55.5, 39.4, 30.8, 23.4; IR (film) 1682.8, 1506.4, 1239.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calculated for $C_{18}H_{19}NO_2$ 282.1489; found 282.1488.

*(±)-5-(4-Benzoylbenzyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (**13b**).* The title compound was prepared from substrate **12b** (35 mg, 0.16 mmol), 4-bromobenzophenone (110 mg, 0.42 mmol), LiO^tBu (38 mg, 0.45 mmol), $PdBr_2$ (1.9 mg, 0.007 mmol), and XPhos (8.8 mg, 0.018 mmol) according to General Procedure 2. This procedure afforded 50 mg (79%) of the title compound as a pale yellow foam. The compound was obtained as a 1:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78−7.68 (m, 4 H), 7.57 (dd, J = 5.3, 9.0 Hz, 2 H), 7.48 (d, J = 2.7 Hz, 2 H), 7.47 (s, 2 H), 7.48−7.41 (m, 2 H), 7.44−7.36 (m, 2 H), 7.27−7.13 (m, 8 H), 6.96−6.91 (m, 4 H), 4.42−4.35 (m, 1 H), 4.30−4.24 (m, 1 H), 3.80 (s, 6 H), 3.15−3.10 (m, 1 H), 3.03−2.98 (m, 1 H), 2.76−2.69 (m, 1 H), 2.59−2.52 (m, 1 H), 2.52−2.45 (m, 1 H), 2.42−2.30 (m, 1 H), 2.18−2.12 (m, 1 H), 1.87−1.76 (m, 3 H), 1.71 (s, 1 H), 1.47−1.41 (m, 1 H), 1.30−1.21 (m, 3 H), 1.24−1.17 (m, 3 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.2, 176.9, 176.4, 157.3, 142.2, 142.0, 137.6, 136.0, 136.0, 132.4, 130.6, 130.4, 130.3, 129.9, 129.2, 129.1, 128.3, 126.4, 125.0, 114.4, 58.9, 58.7, 55.5, 40.8, 38.9, 36.8, 35.9, 33.9, 31.9, 25.9, 16.7, 16.2; IR (film) 1659.1, 1510.2, 1249.2 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ calculated for $C_{26}H_{25}NO_3$ 400.1907; found 400.1917.

*(±)-5-[(1-Benzyl-1H-indol-5-yl)methyl]-1-(4-methoxyphenyl)-3-methyl-pyrrolidin-2-one (**13c**).* The title compound was prepared from substrate **12b** (43 mg, 0.20 mmol), *N*-benzyl-5-chloroindole (122 mg, 0.50 mmol), LiO^tBu (39 mg, 0.49 mmol), $PdBr_2$ (1.9 mg, 0.007 mmol), and XPhos (8.8 mg, 0.018 mmol) according to General Procedure 2. This procedure afforded 50 mg (43%) of the title compound as an orange oil. The compound was obtained as a 1:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51−7.47 (m, 2 H), 7.37 (dd, J = 1.6, 18.0 Hz, 2 H), 7.34−7.23 (m, 8 H), 7.18 (dd, J = 5.1, 8.4 Hz, 2 H), 7.13−7.05 (m, 6 H), 6.99−6.93 (m, 4 H), 6.89 (ddd, J = 1.6, 8.3, 10.8 Hz, 2 H), 6.52 (s, 2 H), 5.29 (s, 4 H), 4.38−4.30 (m, 1 H),

DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777−2786

4.26–4.19 (m, 1 H), 3.82 (d, J = 2.4 Hz, 6 H), 3.19 (dd, J = 3.7, 13.5 Hz, 1 H), 3.03 (dd, J = 3.4, 13.7 Hz, 1 H), 2.67 (dd, J = 9.3, 13.7 Hz, 1 H), 2.55–2.43 (m, 3 H), 2.32–2.19 (m, 2 H), 1.76–1.68 (m, 1 H), 1.54–1.47 (m, 1 H), 1.33–1.21 (m, 3 H), 1.16 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 137.4, 135.3, 128.8, 128.75, 128.69, 127.6, 126.79, 126.77, 126.3, 124.8, 123.1, 121.3, 121.2, 114.4, 114.3, 109.7, 109.6, 101.3, 59.7, 59.6, 55.5, 50.2, 40.8, 38.6, 35.9, 34.0, 31.8, 16.7, 16.3; IR (film) 1688.4, 1509.1, 1244.9, 1178.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{28}H_{28}N_2O_2$ 425.2224; found 425.2234.

(±)-(4S,5R*)-5-(4-Methoxybenzyl)-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (**13d**).* The title compound was prepared from substrate **12c** (54 mg, 0.25 mmol), 4-bromoanisole (60 μL, 0.48 mmol), LiO^{t}Bu (31 mg, 0.39 mmol), $PdBr_2$ (2.4 mg, 0.009 mmol), and XPhos (14.2 mg, 0.029 mmol) according to General Procedure 2. This procedure afforded 52 mg (66%) of the title compound as an orange oil. The compound was obtained as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 (dd, J = 2.7, 9.5 Hz, 2 H), 7.02–6.92 (m, 4 H), 6.86–6.77 (m, 2 H), 3.88 (dt, J = 3.6, 7.8 Hz, 1 H), 3.83–3.72 (m, 6 H), 2.86 (dd, J = 3.7, 13.9 Hz, 1 H), 2.64–2.56 (m, 1 H), 2.53 (dd, J = 8.6, 17.0 Hz, 1 H), 2.23 (t, J = 9.3 Hz, 1 H), 2.07–2.01 (m, 1 H), 1.01 (t, J = 5.2 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.5, 158.4, 157.4, 130.6, 130.2, 129.8, 128.8, 126.3, 125.5, 114.4, 114.3, 113.9, 113.8, 68.7, 64.4, 55.5, 55.2, 39.7, 39.2, 37.7, 37.7, 33.5, 30.2, 29.7, 20.7, 15.1; IR (film) 1681.4, 1509.3, 1242.3, 1177.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{20}H_{23}NO_3$ 326.1751; found 326.1748.

(±)-(4S,5R*)-5-(4-Benzoylbenzyl)-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (**13e**).* The title compound was prepared from substrate **12c** (54 mg, 0.25 mmol), 4-bromobenzophenone (113 mg, 0.43 mmol), LiO^{t}Bu (36 mg, 0.45 mmol), $PdBr_2$ (5.2 mg, 0.02 mmol), and XPhos (12.4 mg, 0.026 mmol) according to General Procedure 2. This procedure afforded 59 mg (60%) of the title compound as a yellow 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 7.77–7.68 (m, 4 H), 7.63–7.54 (m, 1 H), 7.49–7.43 (m, 2 H), 7.35–7.29 (m, 2 H), 7.20–7.14 (m, 2 H), 6.96–6.90 (m, 2 H), 4.00–3.97 (m, 1 H), 3.79 (s, 3 H), 3.00 (dd, J = 4.2, 13.8 Hz, 1 H), 2.78 (dd, J = 8.0, 13.8 Hz, 1 H), 2.71–2.59 (m, 1 H), 2.31–2.21 (m, 1 H), 2.10 (dd, J = 4.9, 17.1 Hz, 1 H), 1.05 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.2, 173.4, 157.7, 142.1, 137.6, 136.0, 132.4, 130.3, 130.2, 129.9, 129.2, 128.8, 128.3, 126.4, 125.7, 114.5, 114.2, 68.4, 64.3, 55.5, 39.0, 38.9, 30.6, 20.5; IR (film) 1675.6, 1510.7, 1249.0, 909.6 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{26}H_{25}NO_3$ 422.1727; found 422.1739.

(±)-(2R,3S*)-3-{[1-(4-Methoxyphenyl)-3-methyl-5-oxopyrrolidin-2-yl]methyl}benzonitrile (**13f**).* The title compound was prepared from substrate **12c** (41 mg, 0.19 mmol), 3-bromobenzonitrile (70 mg, 0.39 mmol), LiO^{t}Bu (42 mg, 0.52 mmol), $PdBr_2$ (4.2 mg, 0.016 mmol), and XPhos (15.1 mg, 0.032 mmol) according to General Procedure 2. This procedure afforded 35 mg (52%) of the title compound as a colorless oil. The compound was obtained as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51–7.47 (m, 1 H), 7.41–7.32 (m, 1 H), 7.31–7.24 (m, 4 H), 6.92 (dd, J = 2.7, 9.5 Hz, 2 H), 3.96–3.91 (m, 1 H), 3.80 (s, 3 H), 2.93 (dd, J = 4.3, 14.0 Hz, 1 H), 2.76 (dd, J = 7.7, 14.0 Hz, 1 H), 2.69–2.56 (m, 1 H), 2.23–2.18 (m, 1 H), 2.18–2.07 (m, 2 H), 1.09–1.05 (m, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 168.2, 138.5, 133.7, 132.8, 131.0, 130.4, 130.1, 129.3, 125.8, 121.9, 118.5, 114.5, 114.1, 112.6, 68.2, 55.49, 55.45, 38.9, 38.5, 30.7, 24.3, 20.3; IR (film) 2226.8, 1682.0, 1509.8, 1244.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{20}H_{20}N_2O_2$ 321.1598; found 321.1595.

(±)-(4R,5R*)-5-(4-Methoxyphenyl)-1-(4-methoxyphenyl)-4-phenylpyrrolidin-2-one (**13g**).* The title compound was prepared from substrate **12d** (54 mg, 0.19 mmol), 4-bromoanisole (50 μL, 0.40 mmol), LiO^{t}Bu (35 mg, 0.43 mmol), $PdBr_2$ (4.1 mg, 0.015 mmol), and XPhos (13.5 mg, 0.028 mmol) according to General Procedure 2. This procedure afforded 51 mg (75%) of the title compound as a 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 (700 MHz, $CDCl_3$) δ 7.38 (dd, J = 2.5, 9.1 Hz, 2 H), 7.32–7.24 (m, 2 H), 7.24–7.19 (m, 1 H), 7.08 (dd, J = 2.2, 7.9 Hz, 2 H), 7.03–6.94 (m, 4 H), 6.80 (dd, J = 2.4, 8.7 Hz, 2 H), 4.37–4.31 (m, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.32–3.27 (m, 1 H), 2.94–2.88 (m, 1 H), 2.83–2.76 (m, 2 H), 2.58–2.51 (m, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.5, 130.5, 128.9, 126.9, 126.6, 125.3, 114.4, 114.0, 69.1, 55.5, 55.2, 40.5, 38.9, 37.4; IR (film) 1688.0, 1510.4, 1246.8, 1032.2 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{25}H_{25}NO_3$ 388.1907; found 388.1905.

(±)-(4R,5R*)-5-(4-Methoxybenzyl)-1-(4-methoxyphenyl)-4-phenylpyrrolidin-2-one (**13h**).* The title compound was prepared from substrate **12d** (54 mg, 0.19 mmol), bromobenzene (42 μL, 0.40 mmol), LiO^{t}Bu (38 mg, 0.47 mmol), $PdBr_2$ (2.1 mg, 0.078 mmol), and XPhos (13.5 mg, 0.028 mmol) according to General Procedure 2. This procedure afforded 48 mg (65%) of the title compound as a 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 (700 MHz, $CDCl_3$) δ 7.46–7.36 (m, 2 H), 7.29–7.25 (m, 4 H), 7.27–7.15 (m, 2 H), 7.09–7.02 (m, 4 H), 6.99–6.93 (m, 2 H), 4.40–4.33 (m, 1 H), 3.82 (s, 3 H), 3.33–3.26 (m, 1 H), 3.01–2.96 (m, 1 H), 2.87–2.80 (m, 2 H), 2.56 (dd, J = 6.9, 17.4 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.9, 157.8, 141.5, 136.0, 132.4, 130.3, 130.1, 130.0, 129.3, 129.0, 128.5, 127.1, 126.6, 125.7, 114.5, 68.6, 55.5, 41.5, 39.2, 39.0; IR (film) 1684.2, 1509.8, 1246.3, 1176.0 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{24}H_{23}NO_2$ 358.1802; found 358.1801.

(±)-(4R,5R*)-1-(4-Methoxyphenyl)-4-phenyl-5-(thiophen-2-ylmethyl)pyrrolidin-2-one (**13i**).* The title compound was prepared from substrate **12d** (41 mg, 0.15 mmol), 2-bromothiophene (30 μL, 0.31 mmol), LiO^{t}Bu (31 mg, 0.39 mmol), $PdBr_2$ (3.9 mg, 0.015 mmol), and XPhos (15.2 mg, 0.032 mmol) according to General Procedure 2. This procedure afforded 35 mg (49%) of the title compound as a pale 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 (400 MHz, $CDCl_3$) δ 7.47–7.34 (m, 2H), 7.36–7.21 (m, 3H), 7.25–7.14 (m, 3H), 6.99–6.89 (m, 3H), 6.76 (dd, J = 3.6, 1.2 Hz, 1H), 4.40–4.31 (m, 1H), 3.81 (s, 3H), 3.36 (dt, J = 4.5, 9.1 Hz, 1H), 3.11 (d, J = 5.1 Hz, 2H), 2.80 (dd, J = 9.4, 17.5 Hz, 1H), 2.57 (dd, J = 5.0, 17.5 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.2, 143.6, 137.6, 130.0, 129.0, 127.1, 127.0, 126.9, 126.7, 125.5, 124.8, 114.5, 68.4, 55.5, 40.6, 39.1, 32.0; IR (film) 2926.4, 1690.7, 1510.4, 1248.9 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{22}H_{21}NO_2S$ 364.1368; found 364.1368.

(±)-(4R,5R*)-5-(2-Methoxybenzyl)-1-(4-methoxyphenyl)-4-phenylpyrrolidin-2-one (**13j**).* The title compound was prepared from substrate **12d** (42 mg, 0.15 mmol), 2-chloroanisole (45 μL, 0.35 mmol), LiO^{t}Bu (42 mg, 0.52 mmol), $PdBr_2$ (3.5 mg, 0.013 mmol), and XPhos (15.1 mg, 0.031 mmol) according to General Procedure 2. This procedure afforded 48 mg (81%) of the title compound as a 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 (700 MHz, $CDCl_3$) δ 7.46 (dd, J = 2.4, 9.3 Hz, 2 H), 7.22–7.12 (m, 4 H), 7.03 (dd, J = 1.7, 7.4 Hz, 1 H), 6.99–6.94 (m, 2 H), 6.96–6.90 (m, 2 H), 6.87–6.83 (m, 1 H), 6.74 (dd, J = 1.0, 8.2 Hz, 1 H), 4.48–4.41 (m, 1 H), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.36–3.28 (m, 1 H), 3.21 (dd, J = 4.1, 13.4 Hz, 1 H), 3.05 (dd, J = 9.3, 17.4 Hz, 1 H), 2.67 (dd, J = 9.4, 13.4 Hz, 1 H), 2.60 (dd, J = 3.9, 17.4 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.1, 157.5, 157.3, 144.4, 131.1, 130.7, 128.7, 128.2, 126.59, 126.56, 126.5, 125.3, 125.0, 120.5, 114.2, 110.3, 67.7, 55.5, 55.1, 40.8, 39.0, 34.5; IR (film) 1680.2, 1601.1, 1492.4, 1242.8 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{25}H_{25}NO_3$ 388.1907; found 388.1910.

General Procedure 3: Synthesis of Six-Membered Lactams. A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the amide substrate (1.0 equiv), the aryl halide (2.0 equiv), LiO^{t}Bu (2.0 equiv), $Pd(OAc)_2$ (2 mol %), and SPhos (6 mol %). The tube was purged with nitrogen, and

DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777–2786

benzotrifluoride (5 mL/mmol substrate) was added via syringe. The mixture was heated to 100 °C with stirring until the reaction was complete as determined by TLC analysis. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (3 mL), and extracted with dichloromethane (3 × 2 mL). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and subsequently purified by flash chromatography on silica gel using 30−60% ethyl acetate/hexanes as the eluent unless otherwise noted.

*(±)-3-(4-Benzoylbenzyl)-2-(4-methoxyphenyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**19a**).* The title compound was prepared from substrate **16** (61 mg, 0.20 mmol), 4-bromobenzophenone (109 mg, 0.42 mmol), LiO^{t}Bu (35 mg, 0.44 mmol), $Pd(OAc)_2$ (1.0 mg, 0.004 mmol), and SPhos (5.1 mg, 0.012 mmol) according to General Procedure 3. This procedure afforded 95 mg (98%) of the title compound as a viscous yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82−7.75 (m, 3 H), 7.69 (d, J = 8.0 Hz, 2 H), 7.64−7.55 (m, 1H), 7.49 (t, J = 7.7 Hz, 2 H), 7.42−7.30 (m, 4 H), 7.21 (d, J = 7.9 Hz, 2 H), 7.04 (d, J = 7.9 Hz, 2 H), 7.02−6.95 (m, 2 H), 4.34−4.28 (m, 1 H), 4.23 (qd, J = 2.9, 12.7 Hz, 2 H), 3.83 (s, 3 H), 3.20 (dd, J = 4.5, 13.4 Hz, 1 H), 2.83 (dd, J = 10.5, 13.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 158.8, 158.6, 141.5, 137.4, 136.7, 136.4, 133.5, 132.5, 130.6, 130.0, 129.3, 128.9, 128.6, 128.3, 127.6, 124.9, 122.8, 120.9, 114.6, 109.5, 107.0, 62.0, 55.5, 41.9, 37.5; IR (film) 1648.5, 1605.3 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{32}H_{26}N_2O_3$ 487.2016; found 487.2018.

*(±)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**19b**).* The title compound was prepared from substrate **16** (61 mg, 0.20 mmol), 4-bromoanisole (50 μL, 0.40 mmol), LiO^{t}Bu (37 mg, 0.46 mmol), $Pd(OAc)_2$ (1.0 mg, 0.004 mmol), and SPhos (5.2 mg, 0.013 mmol) according to General Procedure 3. This procedure afforded 71 mg (90%) of the title compound as a yellow solid, mp 140−142 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 1 H), 7.41−7.31 (m, 4 H), 7.25−7.17 (m, 2 H), 7.03−6.97 (m, 2 H), 6.86−6.77 (m, 4 H), 4.27 (s, 1 H), 4.22−4.12 (m, 2 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.11 (dd, J = 4.1, 13.4 Hz, 1 H), 2.64 (dd, J = 10.9, 13.6 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.9, 158.7, 158.5, 136.8, 133.7, 130.3, 129.1, 128.8, 128.6, 127.6, 124.7, 122.8, 120.7, 114.6, 114.2, 109.5, 106.9, 62.7, 55.5, 55.3, 41.5, 36.4; IR (film) 1649 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{26}H_{24}N_2O_3$ 413.1860; found 413.1862.

*(±)-2-(4-Methoxyphenyl)-3-[3-(trifluoromethyl)benzyl]-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**19c**).* The title compound was prepared from substrate **16** (72 mg, 0.24 mmol), 3-bromobenzotrifluoride (60 μL, 0.43 mmol), LiO^{t}Bu (35 mg, 0.44 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and SPhos (5.7 mg, 0.014 mmol) according to General Procedure 3. This procedure afforded 95 mg (95%) of the title compound as a brown solid, mp 164−165 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 1 H), 7.51 (d, J = 7.8 Hz, 1 H), 7.42−7.34 (m, 3 H), 7.34−7.29 (m, 2 H), 7.24−7.14 (m, 3 H), 7.09 (d, J = 7.7 Hz, 1 H), 7.02−6.92 (m, 2 H), 4.24 (ddd, J = 2.5, 5.0, 10.5 Hz, 1 H), 4.19 (d, J = 2.8 Hz, 2 H), 3.83 (d, J = 1.9 Hz, 3 H), 3.19 (dd, J = 4.5, 13.6 Hz, 1 H), 2.79 (dd, J = 10.6, 13.5 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 158.6, 137.7, 136.7, 133.4, 132.8, 131.3 (q, J = 31.5 Hz), 129.4, 128.9, 128.6, 127.6, 126.0, 125.9 (q, 3.78 Hz), 125.0, 124.9, 124.0 (q, J = 3.8 Hz), 123.9 (q, J = 272 Hz), 122.8, 120.9, 114.7, 114.0, 109.4, 107.2, 62.1, 55.5, 41.7, 37.2, 29.7; IR (film) 1649 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{26}H_{21}F_3N_2O_2$ 451.1628; found 451.1631.

*(±)-3-([1,1′-Biphenyl]-4-ylmethyl)-2-(4-methoxyphenyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**19d**).* The title compound was prepared from substrate **16** (66 mg, 0.22 mmol), 4-bromobiphenyl (95 mg, 0.41 mmol), LiO^{t}Bu (34 mg, 0.42 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and SPhos (6.0 mg, 0.015 mmol) according to General Procedure 3. This procedure afforded 84 mg (86%) of the title compound as an off-yellow solid, mp 176−178 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.59 (d, J = 7.9 Hz, 1 H), 7.39 (d, J = 7.6 Hz, 2 H), 7.31 (d, J = 7.7 Hz, 2 H), 7.28−7.22 (m, 3 H), 7.21−7.14 (m, 4 H), 7.07−7.00 (m, 3 H), 6.83−6.77 (m, 4 H), 4.10 (d, J = 12.4 Hz, 1 H), 4.07−4.02 (m, 1 H), 3.97 (dd, J = 3.3, 12.3 Hz, 1 H), 3.65 (d, J = 2.3 Hz, 3 H), 3.56 (t, J = 3.1 Hz, 1 H), 3.02−2.96 (m, 1 H), 2.55 (s, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.8, 158.5, 140.3, 139.9, 136.7, 135.7, 133.5, 129.7, 129.6, 129.0, 128.73, 128.70, 128.50, 128.47, 127.50, 127.47, 127.37, 127.35, 127.31, 127.28, 126.85, 126.82, 124.71, 124.68, 122.68, 122.65, 120.7, 114.53, 114.51, 109.5, 106.84, 106.82, 77.2, 77.0, 76.8, 62.4, 62.3, 55.39, 55.36, 41.6, 36.9; IR (film) 1648 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{31}H_{26}N_2O_2$ 459.2067; found 459.2068.

*2-(4-Methoxyphenyl)-3-(2-(trifluoromethyl)benzyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**19e**).* The title compound was prepared from substrate **16** (61 mg, 0.20 mmol), 2-bromobenzotrifluoride (60 μL, 0.44 mmol), LiO^{t}Bu (34 mg, 0.42 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and SPhos (5.7 mg, 0.014 mmol) according to General Procedure 3, using *tert*-butyl alcohol as the solvent instead of benzotrifluoride. This procedure afforded 76 mg (85%) of the title compound as a yellow solid, mp 181−183 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 7.8 Hz, 1 H), 7.48−7.34 (m, 4 H), 7.28−7.20 (m, 3 H), 7.01−6.92 (m, 2 H), 6.89 (d, J = 7.6 Hz, 1 H), 4.40 (dt, J = 10.1, 4.3 Hz, 1 H), 4.33−4.20 (m, 2 H), 3.84 (s, 3 H), 3.43 (dd, J = 4.7, 14.0 Hz, 1 H), 2.91 (dd, J = 10.7, 13.8 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 158.5, 136.7, 135.0, 133.3, 133.2, 132.1, 129.2, 129.1, 129.1 (q, J = 13.9 Hz), 128.5, 127.7, 127.5, 126.6 (q, J = 6.3 Hz), 124.9, 124.1 (q, J = 273 Hz), 123.0, 122.9, 120.8, 114.5, 109.5, 107.2, 61.2, 55.5, 41.9, 34.7; IR (film) 1651 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{26}H_{21}F_3N_2O_2$ 451.1628; found 451.1637.

*(±)-3-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(4-methoxyphenyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**19f**).* The title compound was prepared from substrate **16** (62 mg, 0.20 mmol), 5-bromobenzo[*d*][1,3]dioxole (80 μL, 0.66 mmol), LiO^{t}Bu (37 mg, 0.46 mmol), $Pd(OAc)_2$ (1.0 mg, 0.004 mmol), and SPhos (5.2 mg, 0.013 mmol) according to General Procedure 3. This procedure afforded 80 mg (92%) of the title compound as a yellow solid, mp 145−146 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 1 H), 7.43−7.29 (m, 4 H), 7.29−7.16 (m, 2 H), 6.99 (d, J = 8.3 Hz, 2 H), 6.69 (d, J = 7.7 Hz, 1 H), 6.40 (d, J = 1.7 Hz, 1 H), 6.34 (dd, J = 1.8, 7.8 Hz, 1 H), 5.92 (dt, J = 1.3, 9.8 Hz, 2 H), 4.29 (d, J = 12.2 Hz, 1 H), 4.23−4.11 (m, 2 H), 3.90−3.80 (m, 3 H), 3.06 (dd, J = 4.1, 13.6 Hz, 1 H), 2.61 (dd, J = 10.8, 13.6 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 158.6, 148.0, 146.7, 136.8, 133.6, 130.4, 129.1, 128.6, 127.6, 124.8, 122.8, 122.5, 120.8, 114.6, 109.5, 109.3, 108.5, 107.0, 101.1, 62.6, 55.5, 41.6, 37.0; IR (film) 1652 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{26}H_{22}N_2O_4$ 427.1652; found 427.1656.

*(±)-3-(4-Benzoylbenzyl)-2-(4-methoxyphenyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (**20a**).* The title compound was prepared from substrate **17** (68 mg, 0.27 mmol), 4-bromobenzophenone (133 mg, 0.51 mmol), LiO^{t}Bu (41 mg, 0.52 mmol), $Pd(OAc)_2$ (1.5 mg, 0.006 mmol), and SPhos (6.0 mg, 0.014 mmol) according to General Procedure 3. This procedure afforded 113 mg (96%) of the title compound as a viscous yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83−7.63 (m, 4 H), 7.63−7.50 (m, 1 H), 7.50−7.40 (m, 2 H), 7.34−7.23 (m, 2 H), 7.14−7.06 (m, 2 H), 7.06−7.00 (m, 1 H), 6.98−6.91 (m, 2 H), 6.76−6.67 (m, 1 H), 6.29 (p, J = 2.3 Hz, 1 H), 4.29 (dd, J = 4.0, 12.9 Hz, 1 H), 4.16 (dt, J = 4.0, 9.1 Hz, 1 H), 3.92 (d, J = 12.8 Hz, 1 H), 3.82 (d, J = 2.1 Hz, 3 H), 3.24−3.13 (m, 1 H), 2.89−2.74 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.1, 158.4, 158.2, 141.7, 137.4, 136.4, 133.7, 132.5, 130.6, 129.9, 129.1, 128.7, 128.3, 124.4, 123.2, 114.5, 114.4, 110.3, 61.6, 55.5, 45.5, 37.2, 28.4, 14.1; IR (film) 1646 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{28}H_{24}N_2O_3$ 437.1860; found 437.1859.

*(±)-4-{[2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrazin-3-yl]methyl}benzo-nitrile (**20b**).* The title compound was prepared from substrate **17** (50 mg, 0.20 mmol), 4-bromobenzonitrile (72 mg, 0.40 mmol), LiO^{t}Bu (32 mg, 0.40 mmol), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), and SPhos (5.7 mg, 0.014 mmol) according to General Procedure 3. This procedure afforded 65 mg (94%) of the title compound as a yellow solid, mp 174−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.9 Hz, 2 H), 7.20 (s, 1 H), 7.06 (d, J = 7.9 Hz, 2 H), 6.99−6.93 (m, 1 H), 6.88 (d, J = 8.6 Hz, 2 H), 6.68 (t, J = 2.0 Hz, 1 H), 6.29−6.22 (m, 1 H), 4.24 (dd, J = 4.1,

DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777−2786

13.0 Hz, 1 H), 4.12 (dd, J = 4.9, 10.1 Hz, 1 H), 3.82 (dd, J = 1.7, 12.9 Hz, 1 H), 3.78 (s, 3 H), 3.09 (dd, J = 4.8, 13.6 Hz, 1 H), 2.75 (dd, J = 10.4, 13.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 158.1, 142.4, 133.5, 132.5, 130.0, 128.6, 124.2, 123.2, 118.5, 114.5, 114.4, 111.0, 110.3, 77.4, 61.3, 55.5, 45.6, 37.3; IR (film) 2227.3, 1641 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{22}H_{19}N_3O_2$ 358.1550; found 358.1555.

(±)-3-[4-(Dimethylamino)benzyl]-2-(4-methoxyphenyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (**20c**). The title compound was prepared from substrate **17** (49 mg, 0.19 mmol), 4-bromo-*N*,*N*-dimethylaniline (82 mg, 0.41 mmol), LiO^{t}Bu (33 mg, 0.41 mmol), $Pd(OAc)_2$ (0.9 mg, 0.004 mmol), and SPhos (5.2 mg, 0.013 mmol) according to General Procedure 3, using toluene as the solvent rather than benzotrifluoride. This procedure afforded 63 mg (88%) of the title compound as a green liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.26 (m, 1 H), 7.03 (dd, J = 1.5, 3.9 Hz, 1 H), 6.96 (d, J = 8.8 Hz, 1 H), 6.86 (d, J = 8.3 Hz, 1 H), 6.72 (t, J = 2.0 Hz, 1 H), 6.67 (d, J = 7.3 Hz, 1 H), 6.29 (dd, J = 2.5, 3.9 Hz, 1 H), 4.19 (dd, J = 4.0, 12.6 Hz, 1 H), 4.05−3.93 (m, 1 H), 3.84 (s, 2 H), 3.03 (dd, J = 4.3, 13.7 Hz, 1 H), 2.92 (s, 6 H), 2.58 (dd, J = 11.3, 13.7 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 158.2, 149.5, 134.0, 129.9, 128.7, 124.52, 123.2, 114.5, 114.2, 114.0, 113.0, 109.9, 62.2, 55.5, 45.1, 40.7, 36.0, 29.7; IR (film) 1641 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{23}H_{25}N_3O_2$ 376.2020; found 376.2028.

(±)-2-(4-Methoxyphenyl)-3-(2-methylbenzyl)-3,4-dihydropyrrolo-[1,2-a]pyrazin-1(2H)-one (**20d**). The title compound was prepared from substrate **17** (54 mg, 0.21 mmol), 2-bromotoluene (50 μL, 0.42 mmol), LiO^{t}Bu (32 mg, 0.40 mmol), $Pd(OAc)_2$ (0.9 mg, 0.004 mmol), and SPhos (5.4 mg, 0.013 mmol) according to General Procedure 3. This procedure afforded 63 mg (87%) of the title compound as a white solid, mp 130−131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 3 H), 7.13 (ddd, J = 1.8, 6.1, 12.6 Hz, 2 H), 7.12−7.02 (m, 1 H), 7.02−6.86 (m, 2 H), 6.85−6.70 (m, 1 H), 6.31 (dd, J = 2.5, 3.9 Hz, 1 H), 4.24 (dd, J = 4.2, 12.8 Hz, 1 H), 4.16−4.03 (m, 1 H), 3.96 (dd, J = 1.8, 12.7 Hz, 1 H), 3.84 (s, 2 H), 3.10 (dd, J = 4.0, 13.7 Hz, 1 H), 2.76 (dd, J = 11.3, 13.7 Hz, 1 H), 1.96 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.34, 158.27, 136.4, 135.1, 133.7, 130.8, 130.3, 128.8, 127.2, 126.3, 124.5, 123.2, 114.49, 114.48, 114.2, 110.1, 60.7, 55.5, 45.2, 34.1, 18.9; IR (film) 1641 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{22}H_{22}N_2O_2$ 347.1754; found 347.1757.

(±)-2-(4-Methoxyphenyl)-3-(pyridin-3-ylmethyl)-3,4-dihydro-pyrrolo[1,2-a]pyrazin-1(2H)-one (**20e**). The title compound was prepared from substrate **17** (51 mg, 0.20 mmol), 3-bromopyridine (40 μL, 0.42 mmol), LiO^{t}Bu (34 mg, 0.42 mmol), $Pd(OAc)_2$ (1.0 mg, 0.004 mmol), and SPhos (5.8 mg, 0.014 mmol) according to General Procedure 3. This procedure afforded 62 mg (94%) of the title compound as a yellow solid, mp 143−145 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, J = 4.7 Hz, 1 H), 8.26 (s, 1 H), 7.32 (dt, J = 1.9, 7.8 Hz, 1 H), 7.27−7.16 (m, 3 H), 6.99 (dd, J = 1.5, 3.9 Hz, 1 H), 6.96−6.88 (m, 2 H), 6.71 (t, J = 2.0 Hz, 1 H), 6.28 (dd, J = 2.5, 3.9 Hz, 1 H), 4.28 (dd, J = 4.1, 12.9 Hz, 1 H), 4.11 (dtd, J = 1.6, 3.1, 3.8, 10.1 Hz, 1 H), 3.88 (dd, J = 1.9, 12.9 Hz, 1 H), 3.80 (s, 3 H), 3.07 (dd, J = 4.6, 13.8 Hz, 1 H), 2.73 (dd, J = 10.6, 13.8 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 158.1, 150.1, 148.2, 136.9, 133.6, 132.6, 128.6, 124.3, 123.7, 123.2, 114.6, 114.5, 110.3, 61.4, 55.5, 45.4, 34.4, 29.7; IR (film) 1638 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{20}H_{19}N_3O_2$ 334.1550; found 334.1556.

(±)-2-(4-Methoxyphenyl)-3-(thiophen-2-ylmethyl)-3,4-dihydro-pyrrolo[1,2-a]pyrazin-1(2H)-one (**20f**). The title compound was prepared from substrate **17** (49 mg, 0.19 mmol), 2-bromothiophene (40 μL, 0.41 mmol), LiO^{t}Bu (35 mg, 0.44 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and SPhos (5.8 mg, 0.014 mmol) according to General Procedure 3. This procedure afforded 60 mg (93%) of the title compound as a yellow solid, mp 161−163 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.24 (m, 2 H), 7.19−7.08 (m, 1H), 7.03 (dd, J = 1.5, 3.8 Hz, 1 H), 7.01−6.94 (m, 1 H), 6.96 (s, 1 H), 6.95 (s, 1 H), 6.95−6.82 (m, 2 H), 6.75−6.68 (m, 3 H), 6.29 (dd, J = 2.5, 3.8 Hz, 2 H), 4.28 (dd, J = 4.1, 12.8 Hz, 1 H), 4.12 (ddd, J = 2.0, 4.3, 8.9 Hz, 1 H), 4.12−3.99 (m, 2 H), 3.83 (s, 3 H), 3.25 (dd, J = 4.3, 14.6 Hz, 1 H), 2.98 (dd, J = 11.0, 14.6 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 158.2, 138.7, 133.7, 130.0, 128.6, 127.3, 126.7, 124.7, 124.3, 123.4, 117.9, 114.6, 114.55, 114.4, 112.1, 110.6, 110.1, 105.8, 61.8, 55.5, 55.48, 45.4, 31.0, 18.2; IR (film) 1640 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calculated for $C_{19}H_{18}N_2O_2S$ 339.1162; found 339.1165.

Deprotection of the N-PMP Group From Product **13a**. *(±)-5-Benzylpyrrolidin-2-one* (**28**). A scintillation vial equipped with a stir bar was charged with **13a** (25 mg, 0.089 mmol), ammonium cerium(IV) nitrate (320 mg, 0.58 mmol), acetonitrile (1.75 mL), and water (0.35 mL). The resulting mixture was stirred at rt until the starting material had been completely consumed as judged by TLC analysis (ca. 1.5 h). Water (5 mL) was added, and the resulting mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, dried over sodium sulfate, and concentrated. The crude product was then purified by flash chromatography on silica gel using 40−60% ethyl acetate/hexanes as the eluent to afford 15 mg (96%) of the title compound as a pale yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (s, 2 H), 7.33 (t, J = 7.3 Hz, 1 H), 7.20 (s, 2 H), 6.73 (s, 1 H), 4.03 (s, 1 H), 2.88 (dd, J = 5.3, 13.7 Hz, 1 H), 2.77 (dd, J = 7.7, 13.6 Hz, 1 H), 2.48−2.43 (m, 2 H), 2.37−2.30 (m, 1 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 136.5, 128.98, 128.95, 127.2, 77.2, 77.0, 76.8, 57.2, 42.4, 29.7, 26.3.

Synthesis and Reactivity of Deuterated Substrate **21**. *(E)-N-(4-Methoxyphenyl)-pent-4-(5-d)-enamide* (**21**). This reaction was conducted with the hood light turned off. A flame-dried three-neck round-bottom flask equipped with a stir bar was cooled under a stream of nitrogen, wrapped in aluminum foil, charged with THF (5 mL), and bisdicyclopentylzirconium(IV) dichloride (1.5 g, 5.13 mmol), and cooled to 0 °C. A solution of lithium triethylborohydride (4.9 mL, 4.9 mmol, × 1.0 M in THF) at 0 °C was added via syringe. The resulting mixture was warmed to rt and stirred for 2 h with the hood light off. The reaction mixture was then cooled to 0 °C, a solution of *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (502 mg, 2.52 mmol) in THF (5 mL) was added dropwise, and the resulting mixture was warmed to rt and stirred for 30 min. Deuterium oxide (2 mL, 93 mmol) was added, and the mixture was stirred at rt for 15 min. Then the mixture was diluted with hexanes (15 mL), filtered through a pad of silica gel, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel using 10% ethyl acetate/hexanes as the eluent to afford 382 mg (75%) of (*E*)-*tert*-butyldimethyl[(pent-4-en-1-yl-5-*d*)oxy]silane as a colorless oil. This material was judged to have undergone 95% d-incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (dt, J = 6.6, 15.4 Hz, 1 H), 5.00 (d, J = 1.6, 17.1 Hz, 1 H), 3.91 (q, J = 7.1 Hz, 2 H), 2.14−2.07 (m, 2 H), 1.63 (qd, J = 4.5, 7.3, 8.1 Hz, 2 H), 1.36−1.12 (m, 9 H), 1.04−0.84 (m, 6 H).

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with (*E*)-*tert*-butyldimethyl[(pent-4-en-1-yl-5-*d*)oxy]silane (382 mg, 1.9 mmol) and THF (2 mL). A solution of tetrabutylammonium fluoride (5 mL, 1 M in THF) was added, and the resulting solution was stirred at rt until the starting material had been completely consumed as judged by TLC analysis (ca. 16 h). The mixture was then diluted with diethyl ether (15 mL), extracted with saturated sodium chloride (5 × 10 mL), and purified via column chromatography on silica gel using 5% ethyl acetate/hexanes as the eluent to afford (*E*)-pent-4-en-5-*d*-1-ol (143 mg, 84%).

Jones Reagent was prepared first by cooling a flame-dried 100 mL round-bottom flask and stir bar under a stream of nitrogen. This vessel was then charged with chromium(VI) trioxide (13.3 g, 133.0 mmol) and water (39 mL). The reaction vessel was cooled to room temperature, and concentrated sulfuric acid (11 mL, 202.4 mmol) was slowly added, bringing the total volume to 50 mL.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with (*E*)-pent-4-en-5-*d*-1-ol (143 mg, 1.6 mmol) and acetone (50 mL). Subsequent dropwise addition of Jones Reagent (4 mL, of prepared stock solution described above) at 0 °C resulted in a murky solution, which was warmed to rt and stirred overnight. The mixture was then diluted with water (60 mL) and extracted with dichloromethane (3 × 15 mL) to afford a solution of (*E*)-pent-4-enoic-5-*d* acid in dichloromethane that was carried on in the next step without further purification.

DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777−2786

The title compound was prepared from the (*E*)-pent-4-en-5-*d*-oic acid solution and *p*-anisidine (0.7 g, 5.68 mmol) according to General Procedure 1. This procedure afforded 69 mg (21% over two steps) of the title compound as a pale brown solid, mp 83−85 °C, with 95% deuterium incorporation. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41−7.35 (m, 2 H), 7.11 (s, 1 H), 6.87−6.81 (m, 2 H), 5.90−5.85 (m, 1 H), 5.12−5.08 (m, 1 H), 3.77 (s, 3 H), 2.50−2.40 (m, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.3, 136.8, 130.9, 121.7, 114.1, 55.5, 36.6, 29.5; IR (film) 3296.5, 1650.0, 1514.5, 1251.1 cm^{-1}. HRMS (ESI$^+$ TOF) *m*/*z*: [M + H]$^+$ calculated for $C_{12}H_{15}DNO_2$ 207.1238; found 207.1238.

(±)-(5R,1′R*)-1-(4-Methoxyphenyl)-5-(phenylmethyl-d)-pyrrolidin-2-one (**22**).* The title compound was prepared from substrate **21**[37] (49 mg, 0.24 mmol), bromobenzene (50 μL, 0.48 mmol), LiO^{t}Bu (31 mg, 0.39 mmol), $PdBr_2$ (4.2 mg, 0.016 mmol), and XPhos (18.2 mg, 0.038 mmol) according to General Procedure 2. This procedure afforded 30 mg (45%) of the title compound as a 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 (700 MHz, $CDCl_3$) δ 7.41−7.34 (m, 2 H), 7.28 (d, *J* = 7.4 Hz, 2 H), 7.28−7.19 (m, 1 H), 7.13−7.08 (m, 2 H), 6.99−6.93 (m, 2 H), 4.40−4.31 (m, 1 H), 3.82 (s, 3 H), 2.56 (d, *J* = 9.1 Hz, 1 H), 2.45−2.34 (m, 2 H), 2.16−2.08 (m, 1 H), 1.91−1.85 (m, 1 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 174.4, 157.6, 136.8, 130.4, 129.2, 128.6, 126.7, 125.7, 121.7, 114.5, 114.0, 77.2, 77.0, 76.9, 61.2, 55.5, 39.2, 39.1, 30.9, 23.4. IR (film) 1679.7, 1508.8, 1242.8, 909.9 cm^{-1}. HRMS (ESI$^+$ TOF) *m*/*z*: [M + H]$^+$ calculated for $C_{18}H_{18}DNO_2$ 283.1551; found 283.1557. The stereochemistry of this compound was assigned by reduction to the corresponding pyrrolidine **26** and then comparison of the NMR spectra of **26** to its diastereomer **27**, which was prepared via Pd-catalyzed carboamination of *tert*-butyl pent-4-enoyl carbamate followed by deprotection and *N*-arylation as described below.

(±)-(2R,1′R*)-1-(4-Methoxyphenyl)-2-(phenylmethyl-d)-pyrrolidine (**26**).* A flame-dried round-bottom flask was cooled with nitrogen and charged with pyrrolidin-2-one **22** (30 mg, 0.11 mmol) and tetrahydrofuran (0.5 mL). A solution of lithium aluminum hydride (0.5 mL, 0.5 mmol, 1 M in THF) was then added, and the resulting mixture was stirred at rt for 3 min followed by heating to 45 °C and stirring until the starting material had been completely consumed as judged by TLC analysis (ca. 3 h). The solution was then was cooled to 0 °C, quenched with H_2O (0.5 mL), and diluted with diethyl ether (5 mL). A solution of aqueous NaOH (0.5 mL, 10 M) was added, and an insoluble white material precipitated. The organic supernatant was decanted, and the precipitate was washed with diethyl ether (5 mL). The combined organic washes were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via column chromatography on silica gel using 5% ethyl acetate/hexanes as the eluent to afford 7 mg (25%) of the title compound as a clear oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.7 Hz, 2 H), 7.29−7.22 (m, 3 H), 6.93−6.79 (m, 2 H), 6.65 (dd, *J* = 3.0, 9.8 Hz, 2 H), 3.91−3.86 (m, 1 H), 3.83 (s, 3 H), 3.43−3.37 (m, 1 H), 3.16−3.10 (m, 1 H), 2.53 (t, *J* = 10.2 Hz, 1 H), 1.93−1.81 (m, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.7, 142.0, 139.6, 129.3, 128.3, 126.1, 115.2, 112.6, 77.2, 77.0, 76.8, 60.2, 56.0, 55.7, 49.0, 29.6, 23.2. IR (film) 1510.6, 1241.8, 1039.6 cm^{-1}. HRMS (ESI$^+$ TOF) *m*/*z*: [M + H]$^+$ calculated for $C_{18}H_{20}DNO$ 269.1759; found 269.1758.

(±)-(2S,1′R*)-1-(4-Methoxyphenyl)-2-(phenylmethyl-d)-pyrrolidine (**27**).* Prepared following previously reported procedures that have been shown to afford *syn*-addition products[37] via Pd-catalyzed carboamination reactions of carbamate substrates. A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with *tert*-butyl pent-4-enoyl carbamate (233 mg, 0.89 mmol), $Pd(OAc)_2$ (5.4 mg, 0.024 mmol), DPEphos (20.1 mg, 0.037 mmol), and NaO^{t}Bu (209 mg, 2.17 mmol). The tube was purged with nitrogen, and toluene (4 mL) and bromobenzene (100 μL, 0.95 mmol) were added via syringe. The mixture was heated to 100 °C with stirring until the reaction was complete as determined by TLC analysis. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (3 mL), and extracted with dichloromethane (3 × 2 mL). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, concentrated *in vacuo*, and subsequently purified by flash chromatography on silica gel to afford 175 mg (53%) of (±)-(2*S**,1′*R**)-*tert*-butyl 2-(phenylmethyl-*d*)pyrrolidine-1-carboxylate as a clear oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.52 (s, 1 H), 7.33−7.26 (m, 3 H), 7.21 (dd, *J* = 8.9, 16.0 Hz, 4 H), 4.06 (s, 1 H), 3.96 (s, 1 H), 3.40−3.35 (m, 2 H), 3.30 (s, 1 H), 3.16 (s, 1 H), 3.06 (d, *J* = 15.3 Hz, 1 H), 1.80−1.67 (m, 4 H), 1.64 (d, *J* = 3.2 Hz, 1 H), 1.61−1.56 (m, 1 H), 1.46 (d, *J* = 4.3 Hz, 1 H), 1.28 (d, *J* = 6.4 Hz, 1 H).

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with (±)-(2*S**,1′*R**)-*tert*-butyl 2-(phenylmethyl-*d*)pyrrolidine-1-carboxylate (75 mg, 0.29 mmol), 2 mL of dichloromethane, and 2 mL of trifluoroacetic acid. The reaction mixture was stirred until the starting material had been completely consumed as judged by TLC analysis (ca. 5 h) and then was quenched with saturated ammonium hydroxide (10 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo*. The resulting crude pyrrolidine was then N-arylated:[40] A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2.0 mg, 0.009 mmol), (2-biphenyl)di-*tert*-butylphosphine (10.2 mg, 0.038 mmol), sodium *tert*-butoxide (90.8 mg, 0.94 mmol), 4-bromoanisole (50 μL, 0.40 mmol), and a solution of the crude pyrrolidine in toluene (1 mL). The mixture was heated to 110 °C until the starting material had been completely consumed as judged by TLC analysis. The reaction mixture was then worked up by addition of saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate (3 × 3 mL). The organic layers were reserved and dried over sodium sulfate, and solvent was removed *in vacuo*. The product was then purified by flash chromatography on silica gel to afford 23 mg (35% yield over two steps) of the title compound as a clear oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5 H), 6.95−6.86 (m, 2 H), 6.68−6.64 (m, 2 H), 3.92−3.87 (m, 1 H), 3.81 (s, 3 H), 3.44−3.36 (m, 1 H), 3.18−3.10 (m, 1 H), 3.09−3.02 (m, 1 H), 1.92−1.82 (m, 2 H), 1.30 (d, *J* = 2.3 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.3, 128.3, 126.1, 125.3, 115.2, 113.8, 112.6, 77.2, 77.0, 76.7, 60.1, 56.0, 55.5, 49.0, 29.6, 28.7, 23.2. IR (film) 1510.6, 1241.8, 1039.6 cm^{-1}. HRMS (ESI$^+$ TOF) *m*/*z*: [M + H]$^+$ calculated for $C_{18}H_{20}DNO$ 269.1759; found 269.1759.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00041.

Descriptions of stereochemical assignments and copies of ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jpwolfe@umich.edu.

ORCID

John P. Wolfe: 0000-0002-7538-6273

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the NIH-NIGMS (GM098314) for financial support of this work.

DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777−2786

REFERENCES

(1) Li, X.; Lai, K.; Wu, K.; Huang, D.; Huang, L. *Eur. J. Med. Chem.* **2014**, *74*, 736−741.
(2) Ming-He, Y.; Yan-Yong, C.; Liang, H. *Phytochemistry* **1988**, *27*, 445−450.
(3) Shin, J. S.; Kim, T. S.; Lee, H. − S.; Park, J. Y.; Choi, I. − K.; Kwon, H. J. *Phytochemistry* **2008**, *69*, 2363−2366.
(4) For a recent review on the synthesis of γ-lactams, see: Martelli, G.; Orena, M.; Rinaldi, S. *Curr. Org. Chem.* **2014**, *18*, 1373−1481.
(5) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471−1474.
(6) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707−2710.
(7) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428.
(8) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625−628.
(9) Lu, H.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 5983−5985.
(10) Wei, J.; Shaw, J. T. *Org. Lett.* **2007**, *9*, 4077−4080.
(11) Qi, J.; Sun, C.; Tian, Y.; Wang, X.; Li, G.; Xiao, Q.; Yin, D. *Org. Lett.* **2014**, *16*, 190−192.
(12) Wolfe, J. P. *Top. Heterocycl. Chem.* **2013**, *32*, 1−38.
(13) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351−361.
(14) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2531−2534.
(15) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838−6852.
(16) Hopkins, B. A.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9886−9890.
(17) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605−3608.
(18) Zavesky, B. P.; Babij, N. R.; Fritz, J. A.; Wolfe, J. P. *Org. Lett.* **2013**, *15*, 5420−5423.
(19) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447−6459.
(20) Giampietro, N. C. Ph.D. Thesis, University of Michigan, 2010.
(21) Use of XPhos as a ligand for the coupling of **6** with **7** otherwise using conditions shown in Scheme 1 eq 2 failed to afford any of the desired product **9**.
(22) Bagnoli, L.; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Scarponi, C.; Tiecco, M. *J. Org. Chem.* **2010**, *75*, 2134−2137.
(23) Substrate **12a**, bearing a *N*-PMP group, was chosen over substrate **6** as our prior studies on Pd-catalyzed carboamination reactions of ureas suggested this protecting group may provide superior results.
(24) Resubjection of a single diastereomer of **13b** to the reaction conditions led to equilibration to a 1:1 mixture of diastereomers.
(25) For reviews, see: (a) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981−3019. (b) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083−4088.
(26) Fornwald, R. M.; Fritz, J. A.; Wolfe, J. P. *Chem. - Eur. J.* **2014**, *20*, 8782−8790.
(27) The stereochemistry of the deuterated product was established through reduction to the corresponding pyrrolidine and then comparison to a related deuterated pyrrolidine of known stereochemistry.
(28) The difference in chemical yields obtained in the coupling of bromobenzene with **12** vs deuterated compound **21** appear to be due to experimental error associated with isolation. Both reactions proceeded to completion in comparable amounts of time.
(29) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 6276−6277.
(30) Hanley, P. S.; Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 6302−6303.
(31) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *Organometallics* **2011**, *30*, 1269−1277.
(32) Hanley, P. S.; Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 15661−15673.
(33) White, P. B.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 18594−18597.
(34) Babij, N. R.; McKenna, G. M.; Fornwald, R. M.; Wolfe, J. P. *Org. Lett.* **2014**, *16*, 3412−3415.
(35) Peterson, L. J.; Wolfe, J. P. *Adv. Synth. Catal.* **2015**, *357*, 2339−2344.
(36) Li, K.; Cheng, X.; Hii, K. K. M. *Eur. J. Org. Chem.* **2004**, *2004*, 959−964.
(37) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851−8860.
(38) Tellitu, I.; Urrejola, A.; Serna, S.; Moreno, I.; Herrero, M. T.; Dominguez, E.; SanMartin, R.; Correa, A. *Eur. J. Org. Chem.* **2007**, *2007*, 437−444.
(39) Abbiati, G.; Beccalli, E.; Broggini, G.; Martinelli, M.; Paladino, G. *Synlett* **2006**, 73−76.
(40) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174.

DOI: 10.1021/acs.joc.7b00041
J. Org. Chem. 2017, 82, 2777−2786