JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

Palladium-Catalyzed, Multicomponent Approach to β-Lactams via Aryl Halide Carbonylation

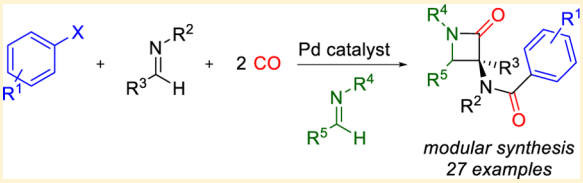
Gerardo M. Torres,[†] Maximiliano De La Higuera Macias,[†] Jeffrey S. Quesnel,[†] Oliver P. Williams,[†] Veeranna Yempally,[†,‡] Ashfaq A. Bengali,*[,‡] and Bruce A. Arndtsen*[,†]

[†]Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 0B8, Canada

[‡]Department of Chemistry, Texas A&M University at Qatar, Doha, Qatar

Supporting Information

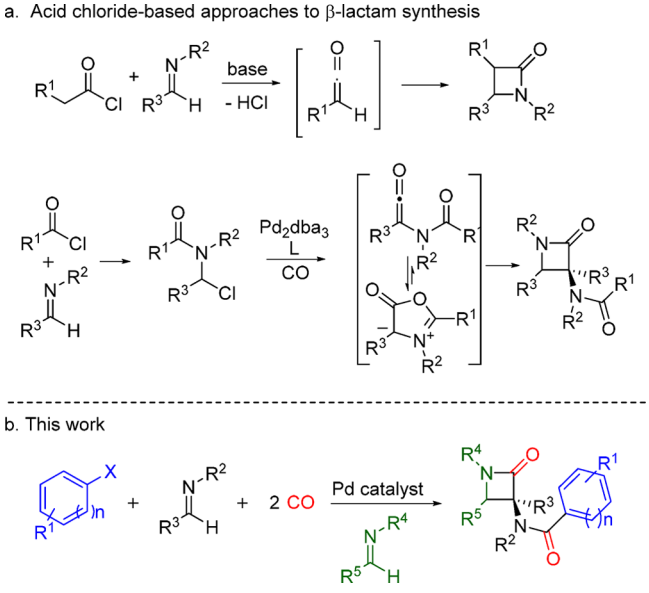
ABSTRACT: A palladium-catalyzed multicomponent method for the synthesis of β-lactams from imines, aryl halides, and CO has been developed. This transformation proceeds via two tandem catalytic carbonylation reactions mediated by $Pd(P^tBu_3)_2$ and provides a route to prepare these products from five separate reagents. A diverse range of polysubstituted β-lactams can be generated by systematic variation of the substrates. This methodology can also be extended to the use of iodo-substituted imines to produce novel spirocyclic β-lactams in good yields and selectivity.



INTRODUCTION

β-Lactams are an important structural core in a diverse range of products, including natural products (e.g., β-lactam-based antibiotics),[1] related biologically active compounds,[2] monomers for polyamide synthesis,[3] and as synthetic precursors in organic chemistry.[4] The utility of β-lactams, as well as the recent rise of antibiotic resistance,[5] has driven interest in the design of efficient methods to access new variants of these structures. A common approach to β-lactam synthesis is through the formal [2 + 2] cycloaddition of imine and ketenes, known as the Staudinger reaction.[6] This typically relies upon the initial generation of a carboxylic acid precursor to ketenes (e.g., acid chlorides, Scheme 1a). A number of alternative approaches to β-lactam synthesis have been devised, including many that employ transition metal catalysis or multicomponent reactions.[7−12] Examples of these include catalytic ketene cycloadditions,[7] carbonylations,[8] alkyne−nitrone cycloaddition (Kinugasa reaction),[10] imine-α-haloketone condensation (Gilman−Speeter reaction),[11] and the use of the Petasis−Ugi reaction.[12] Our own research group has developed a variant of this reaction involving the palladium-catalyzed carbonylation of α-chloroamides.[13] This reaction generates mesoionic 1,3-oxazolium-5-olates (Münchnones), which are in equilibrium with their tautomeric ketene structure.[14] Similar to early reports by Huisgen with presynthesized Münchnones,[15] a Staundinger reaction with this in situ generated ketene yields access to the amide-substituted β-lactam core. One drawback of this chemistry is its required use of acid chlorides, which is common to many approaches to β-lactams. Acid chlorides are highly electrophilic blocks, require themselves a synthesis with high energy and toxic halogenating agents (e.g., $SOCl_2$, PCl_3, oxalyl chloride), and can be challenging to handle or generate in the presence of reactive functional groups. The high reactivity of acid chlorides has also made elaborating this platform to more synthetically complex β-lactam structures problematic.

Scheme 1. Substituted β-Lactams and Synthetic Approaches via Münchnones



We have recently reported an alternative route to construct Münchnones via the carbonylative coupling of aryl iodides with imines.[16] A feature of this transformation is its high atom economy (HI as the sole byproduct) and the stability of the reagents, each of which is inexpensive, available in large scale, and, in the case of aryl iodides and imines, easily generated in many different forms. We therefore questioned if this chemistry might provide a more flexible approach to construct diversely

Received: October 3, 2016
Published: November 14, 2016

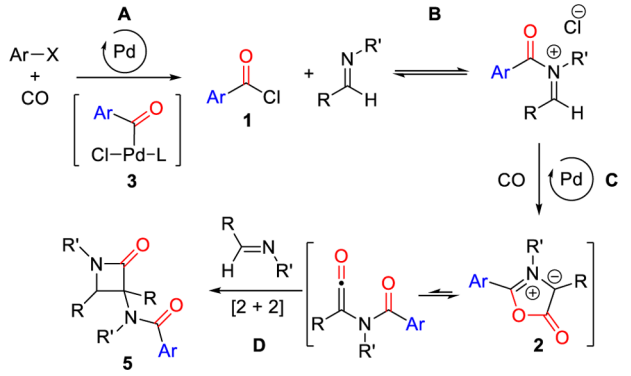
DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115

substituted lactams (Scheme 1b). We describe below our studies toward this goal. These demonstrate that β-lactams can be readily generated from the multicomponent coupling of stable reagents, in a modular fashion, and with broad substrate scope. In addition, the stability of aryl halides can allow the facile incorporation of further structural complexity into these reactions. This includes a multicomponent route to access families of spirocyclic β-lactams.

RESULTS AND DISCUSSION

Catalyst Development for β-Lactam Synthesis. The postulated mechanism for this catalytic β-lactam synthesis is shown in Scheme 2. This involves coupling two palladium-catalyzed carbonylation reactions, the first to generate in situ acid chloride **1** and the second a cyclocarbonylation of an in situ generated *N*-acyl iminium salt to generate Münchnone **2**, with imine nucleophilic attack, and ultimately ketene trapping by imine to form β-lactam. We anticipated that the nature of the palladium catalyst will prove critical in balancing these operations. For example, our initial studies involving the palladium-catalyzed carbonylation of *p*-iodotoluene in the presence of imine shows no β-lactam formation with simple alkyl- or arylphosphines nor with bidentate ligands (Table 1, entries 1−4). However, with more sterically encumbered ligands, we do see β-lactam formation (entries 5−8), and with P^tBu_3, there is a significant spike in catalytic activity (entry 9). Further experiments demonstrated that $Pd(P^tBu_3)_2$ can also serve as a catalyst for this reaction (entry 10) but requires the presence of a chloride source to proceed in reasonable yields (e.g., Bu_4NCl, entry 11).

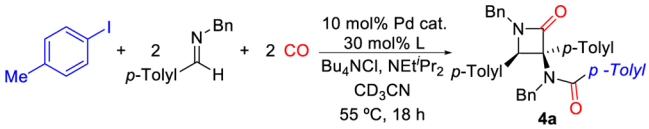
Scheme 2. Mechanistic Postulate for a Palladium-Catalyzed Synthesis of β-Lactams from Aryl Halides, Imines, and CO

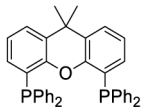
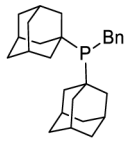
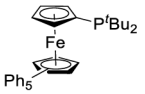


The observation of catalysis with P^tBu_3 and a chloride source is consistent with the in situ generation of acid chloride (step A, Scheme 2), where chloride is a required reagent and the sterically encumbered P^tBu_3 ligand can favor reductive elimination of this intermediate from **3** as a mechanism to relieve steric strain.[17] Increasing the temperature with this catalyst system, which can help drive imine trapping of an *in situ* generated Münchnone, can allow the formation of β-lactam in high yield (entry 12). Notably, under these conditions, the catalyst loading can be lowered to 1 mol % without a significant loss in yield (entry 13).

Aryl Bromide Substrates. Relative to aryl iodides, aryl bromides are less expensive, and, with the advent of palladium-catalyzed cross-coupling reactions, much more broadly available reagents. Unfortunately, the stronger Ar−Br bond typically requires more pressing conditions to activate it toward carbonylations, and these substrates have not been previously shown to be viable building blocks for catalytic Münchnone formation.[16] The latter is potentially due to the lability of this product and the *N*-acyl iminium salt intermediate at elevated temperatures.[18] However, the rapid trapping of these intermediates in the tandem catalytic β-lactam synthesis above suggests this platform might be expanded to use aryl bromide reagents. Indeed, as shown in Table 2, the carbonylative coupling

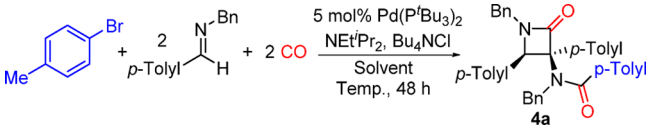
Table 1. β-Lactam Synthesis via Aryl Iodide Carbonylation[a]



Entry	Pd cat.	Ligand	% 4a[b]
1	$[Pd(allyl)Cl]_2$	PPh_3	0
2	$[Pd(allyl)Cl]_2$	PCy_3	0
3	$[Pd(allyl)Cl]_2$	dppe	0
4	$[Pd(allyl)Cl]_2$		0
5	$[Pd(allyl)Cl]_2$	P(*o*-tolyl)$_3$	9
6	$[Pd(allyl)Cl]_2$	(2-biphenyl)P^tBu_2	8
7	$[Pd(allyl)Cl]_2$		28
8	$[Pd(allyl)Cl]_2$		34
9	$[Pd(allyl)Cl]_2$	P^tBu_3	69
10	$Pd(P^tBu_3)_2$	-	64
11[c]	$Pd(P^tBu_3)_2$	-	18
12[d]	$Pd(P^tBu_3)_2$	-	91
13[e]	1% $Pd(P^tBu_3)_2$	-	88

[a]4-Iodotoluene (6.5 mg, 0.03 mmol), imine (25 mg, 0.12 mmol), NEt^iPr_2 (5.8 mg, 0.045 mmol), Bu_4NCl (8.3 mg, 0.03 mmol), Pd (1.5 μmol), L (0.009 mmol), 5 atm CO, CD_3CN (0.75 mL), 55 °C, 18 h. [b]NMR yield. [c]No Bu_4NCl. [d]70 °C. [e]1% $Pd(P^tBu_3)_2$, 70 °C.

Table 2. Synthesis of β-Lactams via Aryl Bromide Carbonylation[a]



entry	temp (°C)	solvent	% 4a[b]
1	55	MeCN	0
2	70	MeCN	0
3	80	MeCN	0
4[c]	90	MeCN	10
5	80	PhH	18
6[d]	80	PhH	37
7[e]	80	PhH	73

[a]4-Bromotoluene (26 mg, 0.15 mmol), imine (126 mg, 0.6 mmol), NEt^iPr_2 (29 mg, 0.23 mmol), Bu_4NCl (42 mg, 0.15 mmol), $Pd(P^tBu_3)_2$ (3.8 mg, 7.5 μmol), 5 atm CO, 1 mL of solvent. [b]NMR yield. [c]20 atm CO. [d]0.015 mmol P^tBu_3. [e]0.045 mmol P^tBu_3.

DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115

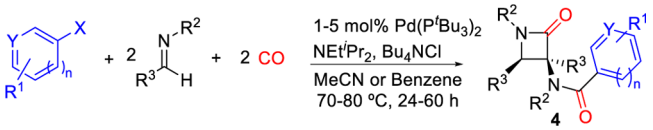
of 4-bromotoluene and imine can also allow the generation of β-lactams. This reaction does not proceed to an appreciable extent at temperatures below 80 °C (entries 1 and 2) and in only low yields at elevated temperatures and CO pressure (entries 4 and 5). However, we note the formation of palladium black under each of these conditions, which presumably reflects the slow oxidative addition of aryl bromide in the presence of CO and ultimate loss of the P^tBu_3 ligand from palladium. The addition of P^tBu_3 and use of a less coordinating solvent helps minimize these effects and leads to the formation of β-lactam in yields similar to those observed with aryl iodides (entries 6 and 7).

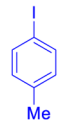
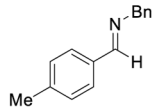
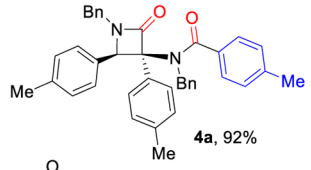
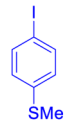
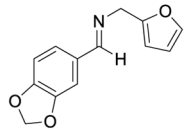
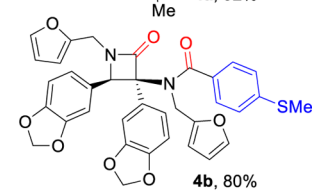
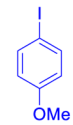
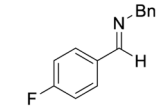
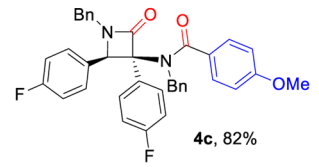
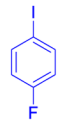
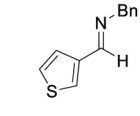
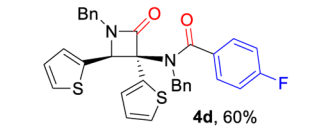
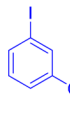
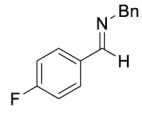
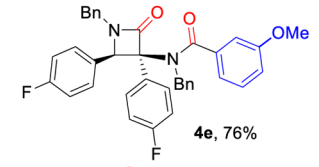
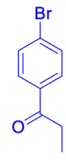
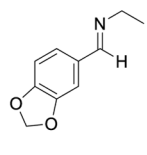
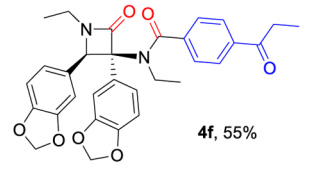
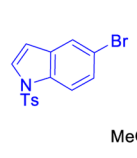
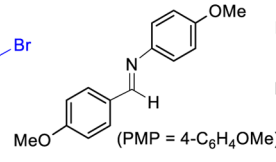
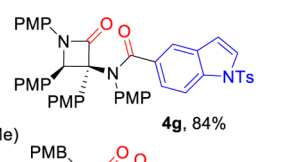
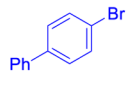
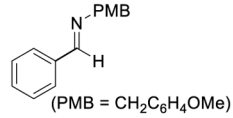
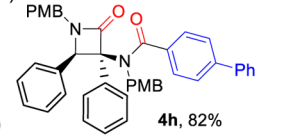
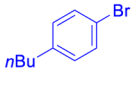
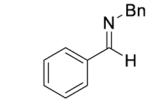
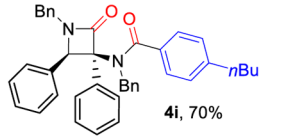
Scope of β-Lactam Synthesis. With a method for the efficient synthesis of β-lactams in hand, we next probed the scope of this reaction (Table 3). A useful feature in this regard is the broad availability of the imine and aryl halide reagents. As such, the reaction can be performed with a diverse array of aryl iodides, including those with electron-donating (**4b**,**c**) and electron-withdrawing (**4d**) groups. Meta-substitution on the aryl iodide is also tolerated (**4e**). We see similar diversity employing aryl bromide substrates, where this reagent can be modulated to incorporate alkyl (**4i**), ketone (**4f**), aryl (**4h**), and even indoles (**4g**). As noted above, these reactions require more elevated temperatures but proceed in yields comparable to that noted with aryl iodides. The imine can also be systematically modulated to include substrates derived from various aromatic aldehydes. Of note, alkyl (**4a**), halide (**4c**), and methoxy (**4g**) substituents are all compatible with the transformation. Heteroaryl imines also afford β-lactams (**4d**). Conversely, imines derived from enolizable aldehydes are not compatible with the reaction conditions due to the formation of enamides.[19] In each of these reactions, **4** is generated as a single diastereomer with a *trans*-orientation of the aromatic units.[20] The latter is presumably to minimize steric interactions between these substituents on cyclization.[21]

One limitation of the above reactions is the incorporation of two identical imines into the β-lactam core. In principle, this can be addressed by the initial catalytic formation of Münchnone **3**, followed by the addition of a second imine. In contrast to many ketenes, the stability of the cyclic Münchnone can allow this latent ketene to be built up in solution. This is illustrated in Table 4, where the initial catalytic generation of **2** followed by the addition of a second imine leads to the formation of diversely substituted β-lactams. In order to enforce imine selectivity, an excess of aryl iodide is used in this transformation, which allows the high yield formation of β-lactams **5** with a range of imines. The functional group compatibility of this reaction is similar to that demonstrated in Table 2. Moreover, the second imine employed in cycloaddition can incorporate a broad range of substituents. This includes various heterocyclic substrates (thiophene, furan, indole, **5a**,**b**,**i**) and even coordinating imidazyl imines (**5g**). Overall, this reaction provides a straightforward method to prepare families of β-lactams from simple building blocks, where all five substituents can be individually varied.

Synthesis of Spirocyclic β-Lactams. Finally, we have probed its ability to access new variants of β-lactams. A feature of this reaction is its ability to generate β-lactams from substrates that are all by themselves relatively inert (aryl halides, imines, CO). This suggested the potential of incorporating more structural complexity into this transformation. For example, spirocyclic β-lactams have recently attracted attention as effective β-lactamase inhibitors.[22] This is believed to arise from the strain in the lactam ring, which modulates its reactivity with the enzyme.[22b] While common routes to these products involve the use of reactants with an exocyclic functionality (either exocyclic ketenes or imines), we postulated that the carbonylation of

Table 3. Scope of β-Lactams Synthesis[a,b]

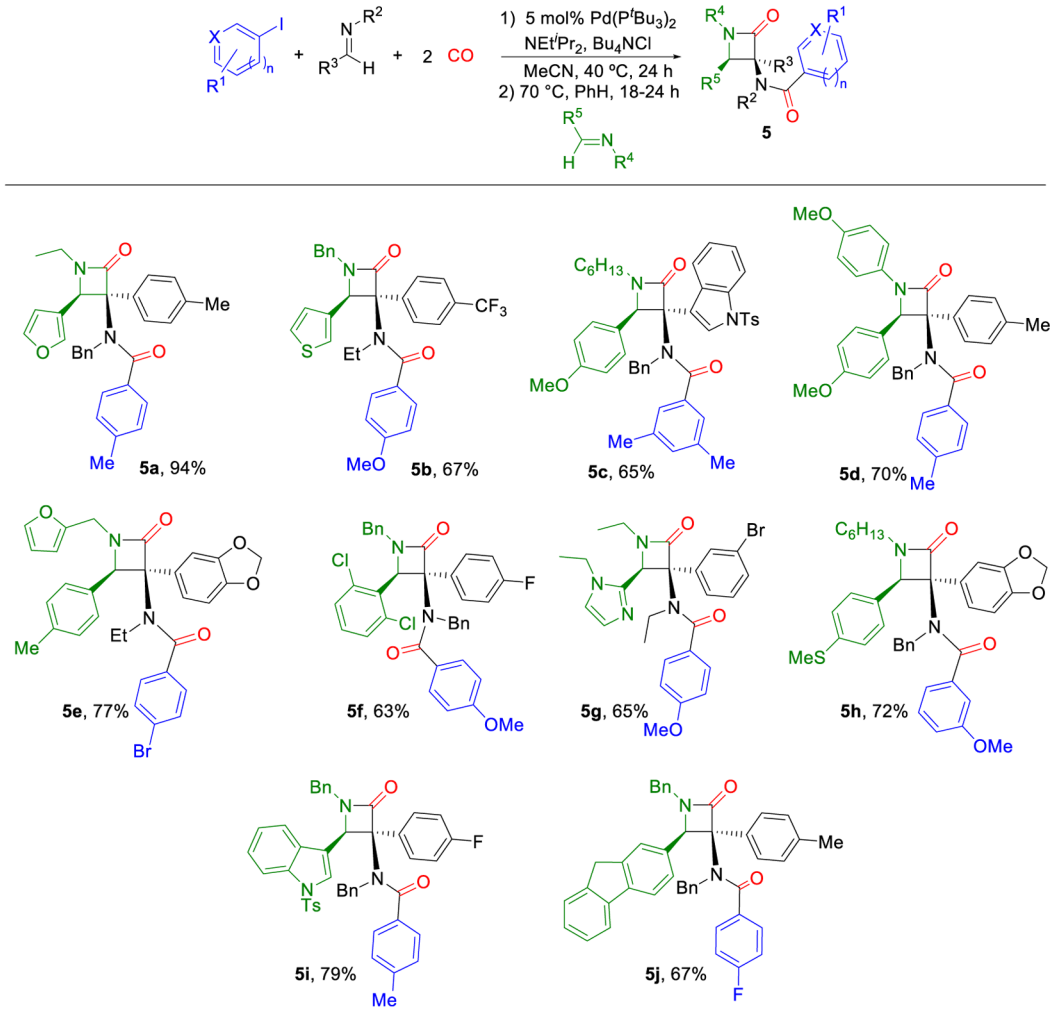


Aryl Halide	Imine	β-Lactam (%)
		 **4a**, 92%
		 **4b**, 80%
		 **4c**, 82%
		 **4d**, 60%
		 **4e**, 76%
		 **4f**, 55%
	 (PMP = 4-C_6H_4OMe)	 **4g**, 84%
	 (PMB = $CH_2C_6H_4OMe$)	 **4h**, 82%
		 **4i**, 70%

[a]Aryl halide (0.5 mmol), imine (2.0 mmol), NEt^iPr_2 (97 mg, 0.75 mmol), $Pd(P^tBu_3)_2$ (2.6 mg, 5.0 μmol), Bu_4NCl (0.5 mmol), 5 atm CO, 3.3 mL of MeCN, 24−36 h, 70 °C. [b]Ar−Br:$Pd(P^tBu_3)_2$ (0.025 mmol), P^tBu_3 (30 mg, 0.15 mmol), 3.3 mL of C_6H_6, 48−60 h, 80 °C.

DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115

Table 4. Synthesis of β-Lactams from Different Imines[a]



[a]Conditions: (1) imine (0.5 mmol), aryl iodide (2.5 mmol), NEt^{i}Pr$_2$ (97 mg, 0.75 mmol), Bu$_4$NCl (139 mg, 0.5 mmol), Pd(P^{t}Bu$_3$)$_2$ (13 mg, 0.025 mmol), CO (10 atm), MeCN (3.3 mL), 40 °C, 24 h; (2) imine (1.0 mmol), 70 °C, 18−24 h.

simply *ortho*-iodo-substituted aryl imines might open a more straightforward route to generate these products (Scheme 3a). This reaction would also create non-Münchnone-stabilized ketenes **7**, as these cannot cyclize, and therefore should display enhanced cycloaddition reactivity. Interestingly, although the palladium-catalyzed carbonylation of *ortho*-haloimines has previously been examined as a way of preparing isoindolinone derivatives,[23] products arising from a second carbonylation event are unknown.

The feasibility of this multicomponent strategy is shown in Scheme 3b. Employing the conditions developed for aryl iodides with 2-iodo-substituted imine **8a** gives the spiro product **9a** in a modest 40% yield. A second imine can also be used as the cycloaddition partner. As with the results using only **8a**, this reaction proceeds in only low yields at 40 °C (entry 1) and even less efficiently at more elevated temperatures (entry 2). We postulated that this may arise from the lack of stabilization of the ketene intermediate **7** in this reaction since it cannot cyclize to form a Münchnone. Lower reaction temperatures did lead to an increase in yield (entry 3). In addition, there is a marked influence of base on the reaction, and increasing the amount of NEt^{i}Pr$_2$ (entry 4) or employing an inorganic base (entry 5) allows the formation of **9b** in good yield (85%). This may arise from the greater difficulty associated with deprotonation to form **7**, as it does not lead to a stabilized ketene.

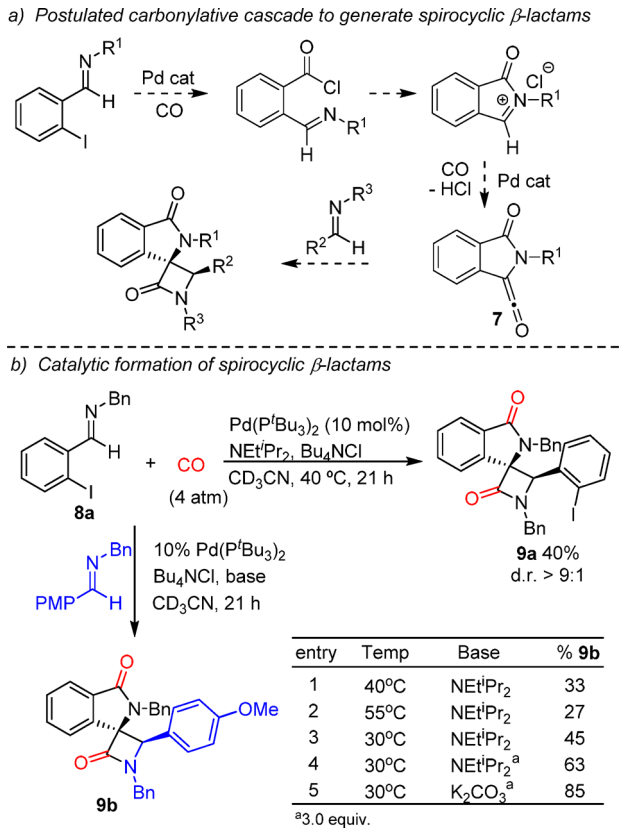
As with the results in Tables 3 and 4, this reaction can also be diversified to form various spirocyclic β-lactams (Table 5). Of note, *N*-alkyl or -benzyl substituents can be incorporated only in the aryl iodide reagent (**9c−e**). Alternatively, the imine employed in cycloaddition can include not only substituted donor or acceptor aryl substituents (**9e−g**) but also heterocyclic (**9c**) and even vinyl units (**9h**). These products are also generated with a *trans* orientation of the aromatic units, as confirmed by NOE analysis and the crystal structure of **9g** (see Supporting Information for details). As far as we are aware, this represents the first carbonylative method to synthesize spirocyclic β-lactam products.

CONCLUSIONS

In conclusion, a versatile platform for the multicomponent synthesis of β-lactams has been developed. This reaction employs a single palladium catalyst in a tandem sequence of two separate carbonylations and provides a route to generate amido-substituted β-lactams in a single operation from substrates that are all available, stable, and easily diversified: aryl halides, imines, and carbon monoxide. The availability and stability of

DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115

Scheme 3. Spirocyclic β-Lactams from Iodoaryl-Substituted Imines and CO



entry	Temp	Base	% 9b
1	40°C	NEt^iPr_2	33
2	55°C	NEt^iPr_2	27
3	30°C	NEt^iPr_2	45
4	30°C	NEt^iPr_2[a]	63
5	30°C	K_2CO_3[a]	85

[a]3.0 equiv.

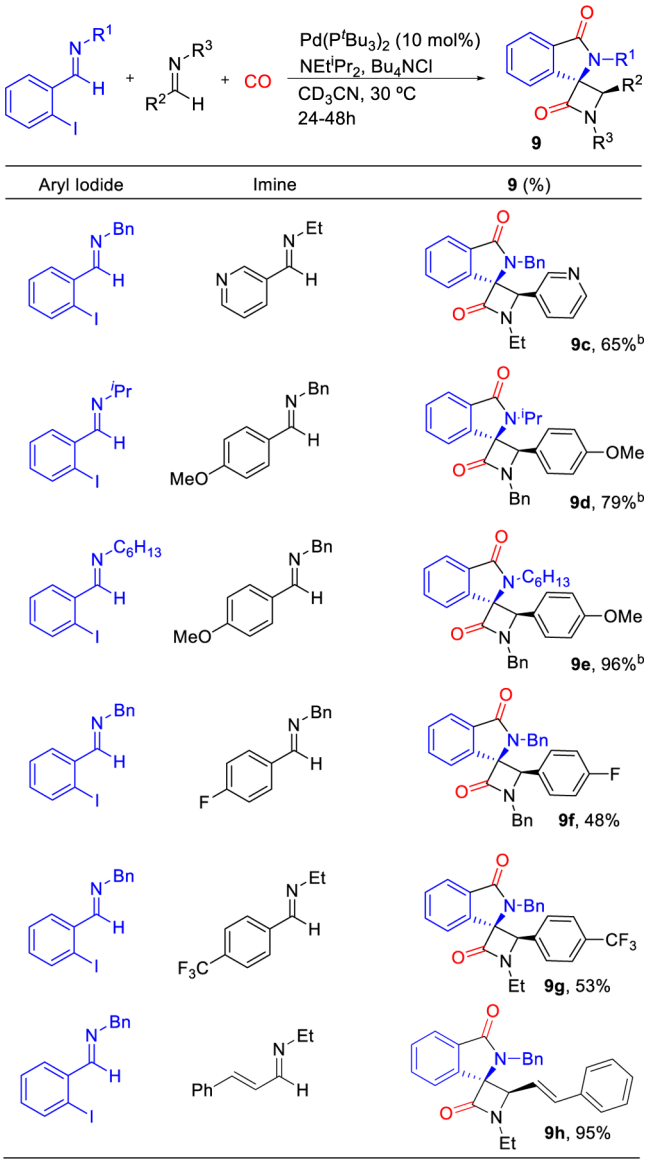
these reagents also make it straightforward to extend this chemistry to more complex polysubstituted and spirocyclic β-lactam products. Importantly, systematic variation of each of the building blocks can allow the generation of families of β-lactams, with minimal synthetic effort relative to classical protocols.

EXPERIMENTAL SECTION

General Procedures. All manipulations were conducted in a glovebox under a nitrogen atmosphere. Unless otherwise noted, all reagents were purchased from commercial sources and used without purification. Research grade carbon monoxide (99.99%) was used as received. Solvents were dried by using a solvent purifier system and stored over activated 3 Å molecular sieves inside the glovebox. Deuterated acetonitrile and benzene were stirred over calcium hydride, vacuum-transferred, degassed, and stored over 4 Å molecular sieves. Imines were prepared using standard literature procedures.[24] Tetrabutylammonium chloride was dried in the glovebox by dissolving in dichloromethane, allowing to stand overnight over activated molecular sieves, filtering, and removing the solvent in vacuo. $Pd(P^tBu_3)_2$ was prepared as previously described.[25] Nuclear magnetic resonance (NMR) characterization was performed on 500 MHz spectrometers for proton and 126 MHz for carbon. ^1H and ^{13}C NMR chemical shifts were referenced to residual solvent. Mass spectra were recorded on a high-resolution electrospray ionization quadrupole mass spectrometer. IR spectra were recorded on a FT-IR with a single reflection platinum ATR module. Note: All reactions with CO were performed in either J-Young NMR tubes rated to withstand 5 bar pressure, thick-walled Schlenk bombs, or Paar reaction vessels. Safety precautions should always be exercised when performing pressurized reactions and when using toxic CO gas.

Catalyst Development for β-Lactam Synthesis via Aryl Iodide Carbonylation. In a glovebox, 4-iodotoluene (6.5 mg, 0.03 mmol), (*p*-tolyl)HC═NBn (25 mg, 0.12 mmol), NEt^iPr_2 (5.8 mg, 0.045 mmol), Bu_4NCl (8.3 mg, 0.03 mmol), $[Pd(allyl)Cl]_2$ (0.5 mg, 1.5 μmol), P^tBu_3 (1.8 mg, 9.0 μmol), and benzyl benzoate standard (3.2 mg, 0.015 mmol) were weighed, dissolved in CD_3CN (0.75 mL), and transferred into a Norell J-Young NMR tube capable of withstanding up to 5 bar pressure. The NMR tube was then sealed with a screw cap and taken out of the glovebox; 5 atm of CO was added, and the tube was warmed to 55 °C. The yield of β-lactam was determined by ^1H NMR analysis relative to the benzyl benzoate internal standard after 18 h.

Table 5. Scope of the Synthesis of Spirocyclic β-Lactams[a]



[a]Aryl iodide (0.024 mmol), imine (0.096 mmol), Bu_4NCl (20 mg, 0.072 mmol), NEt^iPr_2 (9.3 mg, 0.072 mmol), $Pd(P^tBu_3)_2$ (1.2 mg, 0.0024 mmol), and 4 atm CO, MeCN (0.75 mL). [b]NEt^iPr_2 (4.7 mg, 0.036 mmol) and K_2CO_3 (4.9 mg, 0.036 mmol).

Catalyst Development for β-Lactam Synthesis via Aryl Bromide Carbonylation. In a glovebox, $Pd(P^tBu_3)_2$ (3.8 mg, 7.5 μmol), P^tBu_3 (9.1 mg, 0.045 mmol), and Bu_4NCl (42 mg, 0.15 mmol) were weighed and dry-transferred into a thick-walled 50 mL Schlenk bomb equipped with a magnetic stir bar. 4-Bromotoluene (26 mg, 0.15 mmol), (*p*-tolyl)HC═NBn (126 mg, 0.60 mmol), NEt^iPr_2 (29 mg, 0.23 mmol), and benzyl benzoate standard (16 mg, 0.075 mmol) in 1 mL of benzene were added. The vessel was sealed with a Teflon cap, taken out of the glovebox, charged with 5 atm of CO warmed to 80 °C for 48 h. The CO was then removed, and the yield of β-lactam was determined by ^1H NMR analysis.

DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115

Typical Synthesis of β-Lactams with Aryl Iodides. In a glovebox, $Pd(P^tBu_3)_2$ (2.6 mg, 5.0 μmol) and Bu_4NCl (139 mg, 0.5 mmol) were dry-transferred into a thick-walled 25 mL Schlenk bomb equipped with a magnetic stir bar. 4-Iodotoluene (109 mg, 0.5 mmol), (*p*-tolyl)CH═NBn (419 mg, 2.0 mmol), and NEt^iPr_2 (97 mg, 0.75 mmol) were dissolved in 3.3 mL of MeCN and added to the Schlenk bomb. The vessel was sealed with a Teflon cap, taken out of the glovebox, charged with 5 atm of CO, and warmed to 70 °C for 24 h. The CO was removed on a Schlenk line, the solvent removed in vacuo, and the product purified by flash chromatography on silica gel using hexanes/ethyl acetate (4:1) to afford **4a** in 92% yield (260 mg, 0.46 mmol) as a white solid.

Typical Synthesis of β-Lactams with Aryl Bromides. In a glovebox, $Pd(P^tBu_3)_2$ (12.8 mg, 0.025 mmol), P^tBu_3 (30 mg, 0.15 mmol), and Bu_4NCl (139 mg, 0.5 mmol) were dry-transferred into a thick-walled 50 mL Schlenk bomb equipped with a magnetic stir bar. *p*-BrC_6H_4COEt (107 mg, 0.5 mmol), 1-(benzo[*d*][1,3]dioxol-5-yl)HC═NEt (354 mg, 2.0 mmol), and NEt^iPr_2 (97 mg, 0.75 mmol) were dissolved in 3.3 mL of benzene and transferred into the Schlenk bomb. The vessel was sealed with a Teflon cap, charged with 5 atm of CO, and warmed to 80 °C for 62 h with stirring. The CO was then removed on a Schlenk line, the solvent removed in vacuo, and the product purified by flash chromatography on silica gel using hexanes/ethyl acetate (3:2) to afford **4f** in 55% yield (149.2 mg, 0.27 mmol) as a white solid.

*N-Benzyl-N-(1-benzyl-2-oxo-3,4-di-p-tolylazetidin-3-yl)-4-methylbenzamide (**4a**):* Isolated yield 92% (260 mg, 0.46 mmol); white solid; mp 48−53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.31 (m, 5H), 7.16 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.10−6.95 (m, 11H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 7.3 Hz, 2H), 5.43 (s, 1H), 4.93−4.83 (m, 2H), 4.75 (d, *J* = 17.0 Hz, 1H), 3.79 (d, *J* = 14.6 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.9, 165.7, 139.8, 138.6, 137.8, 137.7, 135.2, 134.1, 132.5, 131.2, 129.8, 129.4, 129.1, 128.9, 128.8, 128.7, 128.6, 128.1, 128.0, 126.7, 126.6, 126.5, 80.7, 66.2, 52.0, 44.1, 21.45, 21.36, 21.27; HRMS calcd for $C_{39}H_{36}O_2N_2Na$ (MNa^+) 587.2669, found 587.2677; FT-IR ATR ν_{CO} = 1749 and 1637 cm^{-1}.

*N-(2,3-Bis(benzo[d][1,3]dioxol-5-yl)-1-(furan-2-ylmethyl)-4-oxoazetidin-3-yl)-N-(furan-2-ylmethyl)-4-(methylthio)benzamide (**4b**):* Isolated yield 80% (253 mg, 0.40 mmol); light yellow solid; mp 76−79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.34−7.29 (m, 2H), 7.22−7.17 (m, 2H), 7.02−6.96 (m, 2H), 6.88 (d, *J* = 1.8 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 2H), 6.63−6.58 (m, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.16 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.99 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.89−5.84 (m, 2H), 5.82−5.77 (m, 2H), 5.64 (dd, *J* = 3.2, 0.9 Hz, 1H), 5.25 (s, 1H), 4.90−4.85 (m, 1H), 4.83 (d, *J* = 15.6 Hz, 1H), 4.77 (dd, *J* = 16.9, 0.9 Hz, 1H), 3.98 (d, *J* = 15.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.6, 166.0, 150.8, 148.4, 147.40, 147.38, 147.2, 142.8, 141.7, 141.4, 132.9, 128.7, 127.9, 127.7, 125.7, 123.4, 122.8, 110.7, 110.2, 110.1, 109.4, 109.2, 107.9, 107.8, 107.3, 101.0, 100.9, 81.0, 66.8, 45.7, 37.1, 15.4; HRMS calcd for $C_{35}H_{29}O_8N_2S$ (M^+ by APCI): 637.1639, found 637.1635; FT-IR ATR ν_{CO} = 1751 and 1637 cm^{-1}.

*N-Benzyl-N-(1-benzyl-2,3-bis(4-fluorophenyl)-4-oxoazetidin-3-yl)-4-methoxybenzamide (**4c**):* Isolated yield 82% (241 mg, 0.41 mmol); white solid; mp 134−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.42 (m, 2H), 7.39−7.31 (m, 3H), 7.20−7.09 (m, 6H), 7.07−6.96 (m, 3H), 6.89−6.82 (m, 2H), 6.77−6.66 (m, 6H), 5.34 (s, 1H), 4.95−4.87 (m, 3H), 3.80 (d, *J* = 14.6 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.8, 165.4, 162.6 (d, *J* = 247.3 Hz), 162.4 (d, *J* = 248.2 Hz), 161.1, 138.0, 134.7, 132.0 (d, *J* = 8.1 Hz), 131.3 (d, *J* = 3.3 Hz), 131.1 (d, *J* = 8.3 Hz), 129.9 (d, *J* = 3.1 Hz), 129.0, 128.97, 128.8, 128.77, 128.3, 128.2, 126.8, 126.79, 115.1 (d, *J* = 21.5 Hz), 114.8 (d, *J* = 21.2 Hz), 113.8, 80.5, 65.7, 55.4, 52.4, 44.3; HRMS calcd for $C_{37}H_{30}O_3N_2F_2Na$ (MNa^+) 611.2117, found 611.2111; FT-IR ATR ν_{CO} = 1748 and 1638 cm^{-1}.

*N-Benzyl-N-(1-benzyl-2-oxo-3,4-di(thiophen-3-yl)azetidin-3-yl)-4-fluorobenzamide (**4d**):* Isolated yield 60% (167 mg, 0.30 mmol); yellow solid; mp 48−50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.36 (td, *J* = 5.0, 2.3 Hz, 3H), 7.18−7.07 (m, 9H), 7.02 (dd, *J* = 5.1, 3.0 Hz, 1H), 6.93 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.90−6.85 (m, 2H), 6.80 (dd, *J* = 4.8, 1.5 Hz, 1H), 6.76−6.70 (m, 2H), 5.39 (s, 1H), 4.91−4.80 (m, 2H), 4.71 (d, *J* = 17.0 Hz, 1H), 3.88 (d, *J* = 14.6 Hz, 1H); ^{13}C NMR (126 MHz, CD_3Cl) δ 172.7, 164.8, 163.5 (d, *J* = 250.4 Hz), 138.3, 136.0, 135.6, 134.9, 132.5 (d, *J* = 3.3 Hz), 129.1 (d, *J* = 9.1 Hz), 129.0, 128.97, 128.7, 128.5, 128.2, 127.7, 127.0, 126.3, 126.1, 125.3, 125.27, 125.18, 115.4 (d, *J* = 21.9 Hz), 62.8, 51.8, 44.4; HRMS calcd for $C_{32}H_{25}O_2N_2FS_2Na$ (MNa^+) 575.1234, found 575.1235; FT-IR ATR ν_{CO} = 1752 and 1637 cm^{-1}.

*N-Benzyl-N-(1-benzyl-2,3-bis(4-fluorophenyl)-4-oxoazetidin-3-yl)-3-methoxybenzamide (**4e**):* Isolated yield 76% (224 mg, 0.38 mmol); white solid; mp 114−116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.42 (m, 2H), 7.41−7.32 (m, 3H), 7.20−7.10 (m, 5H), 7.09−6.97 (m, 3H), 6.90−6.81 (m, 3H), 6.79−6.72 (m, 3H), 6.71−6.66 (m, 2H), 6.59 (dd, *J* = 2.6, 1.5 Hz, 1H), 5.40 (s, 1H), 4.92 (d, *J* = 14.3 Hz, 1H), 4.87 (s, 1H), 4.80 (d, *J* = 16.8 Hz, 1H), 3.81 (d, *J* = 14.6 Hz, 1H), 3.55 (s, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.7, 165.1, 162.7 (d, *J* = 247.3 Hz), 162.5 (d, *J* = 248.4 Hz), 159.4, 138.1, 137.7, 134.7, 131.8 (d, *J* = 8.1 Hz), 131.3 (d, *J* = 3.4 Hz), 131.1 (d, *J* = 8.2 Hz), 129.8 (d, *J* = 3.1 Hz), 129.6, 129.10, 129.06, 128.3, 128.2, 126.8, 126.7, 115.1 (d, *J* = 20.9 Hz), 114.9, 80.3, 65.7, 55.3, 52.1, 44.4; HRMS calcd for $C_{37}H_{30}O_3N_2F_2Na$ (MNa^+) 611.2117, found 611.2118; FT-IR ATR ν_{CO} = 1753 and 1635 cm^{-1}.

*N-(2,3-Bis(benzo[d][1,3]dioxol-5-yl)-1-ethyl-4-oxoazetidin-3-yl)-N-ethyl-4-propionylbenzamide (**4f**):* Isolated yield 55% (149.2 mg, 0.27 mmol); white solid; mp 145−149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05−7.97 (m, 2H), 7.57−7.49 (m, 2H), 7.09 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.98 (d, *J* = 1.8 Hz, 1H), 6.74 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.71 (d, *J* = 1.7 Hz, 1H), 6.62 (dd, *J* = 10.2, 8.1 Hz, 2H), 5.90−5.83 (m, 4H), 5.43 (s, 1H), 3.78−3.70 (m, 1H), 3.65 (dq, *J* = 14.7, 7.4 Hz, 1H), 3.61−3.52 (m, 1H), 3.00 (dq, *J* = 21.0, 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.3 Hz, 3H), 0.71 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 200.1, 172.5, 165.8, 147.56, 147.50, 147.47, 147.44, 141.4, 137.7, 130.0, 128.3, 128.2, 127.0, 123.1, 123.0, 109.9, 109.4, 107.9, 107.7, 101.08, 101.06, 80.1, 66.0, 43.3, 35.2, 32.1, 16.0, 12.7, 8.2; HRMS calcd for $C_{31}H_{30}O_7N_2Na$ (MNa^+) 565.1945, found 565.1965; FT-IR ATR ν_{CO} = 1748, 1687, and 1635 cm^{-1}.

*N-(4-Methoxyphenyl)-1-tosyl-N-(1,2,3-tris(4-methoxyphenyl)-4-oxoazetidin-3-yl)-1H-indole-5-carboxamide (**4g**):* Isolated yield 84% (338.5 mg, 0.42 mmol); yellow solid; mp 133−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−7.70 (m, 1H), 7.65−7.60 (m, 2H), 7.53 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.46 (d, *J* = 3.7 Hz, 1H), 7.36−7.28 (m, 4H), 7.26 (dd, *J* = 8.8, 1.7 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.18−7.12 (m, 2H), 6.81−6.76 (m, 2H), 6.72−6.66 (m, 2H), 6.60−6.56 (m, 3H), 6.50 (dd, *J* = 3.7, 0.8 Hz, 3H), 6.08 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 172.6, 162.7, 159.4, 159.1, 158.8, 156.3, 145.2, 135.1, 135.0, 132.9, 132.3, 132.2, 131.6, 130.8, 130.3, 130.1, 129.9, 127.3, 126.91, 126.87, 126.76, 125.1, 122.2, 119.4, 114.3, 113.5, 113.4, 113.0, 112.9, 109.4, 81.2, 67.1, 55.5, 55.24, 55.20, 55.1, 21.6; HRMS calcd for $C_{47}H_{41}O_8N_3SNa$ (MNa^+) 830.2507, found 830.2525; FT-IR ATR ν_{CO} = 1742 and 1642 cm^{-1}.

*N-(4-Methoxybenzyl)-N-(1-(4-methoxybenzyl)-2-oxo-3,4-diphenylazetidin-3-yl)-[1,1′-biphenyl]-4-carboxamide (**4h**):* Isolated yield 82% (271 mg, 0.41 mmol); white solid; mp 79−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.51 (m, 2H), 7.51−7.47 (m, 2H), 7.47−7.39 (m, 4H), 7.39−7.33 (m, 1H), 7.24−7.15 (m, 7H), 7.13−7.02 (m, 5H), 6.91−6.86 (m, 2H), 6.53 (q, *J* = 8.9 Hz, 4H), 5.44 (s, 1H), 4.91 (d, *J* = 14.6 Hz, 1H), 4.88−4.78 (m, 2H), 3.83 (s, 3H), 3.78 (d, *J* = 14.6 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.7, 165.5, 159.5, 158.4, 142.6, 140.3, 135.9, 135.6, 134.3, 130.4, 130.3, 129.9, 129.4, 129.0, 128.2, 128.15, 128.11, 127.96, 127.95, 127.90, 127.3, 127.2, 127.1, 127.0, 114.3, 113.5, 81.1, 66.1, 55.4, 55.3, 51.7, 43.7; HRMS calcd for $C_{44}H_{38}O_4N_2Na$ (MNa^+) 681.2724, found 681.2721; FT-IR ATR ν_{CO} = 1749 and 1636 cm^{-1}.

*N-Benzyl-N-(1-benzyl-2-oxo-3,4-diphenylazetidin-3-yl)-4-butylbenzamide (**4i**):* Isolated yield 70% (202 mg, 0.35 mmol); clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.39−7.32 (m, 3H), 7.21−7.14 (m, 7H), 7.11−6.94 (m, 10H), 6.63 (d, *J* = 7.3 Hz, 2H), 5.47 (s, 1H), 4.96 (d, *J* = 14.7 Hz, 1H), 4.88 (s, 2H), 3.83 (d, *J* = 14.7 Hz, 1H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.56−1.46 (m, 2H), 1.29 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 174.0, 165.7, 145.0, 138.3, 135.5, 135.0, 134.3, 134.2, 129.9, 129.4, 129.01, 128.99, 128.3, 128.2, 128.12, 128.11, 128.0, 127.94, 127.91, 126.85,

DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115

126.76, 126.6, 81.2, 66.2, 52.3, 44.3, 35.5, 33.5, 22.2, 14.0; HRMS calcd for $C_{40}H_{38}O_2N_2Na$ (MNa^+) 601.2826, found 601.2821; FT-IR ATR ν_{CO} = 1751 and 1637 cm^{-1}.

Typical Synthesis of Cross-Coupled β-Lactams. In a glovebox, $Pd(P^tBu_3)_2$ (13 mg, 0.025 mmol) and Bu_4NCl (139 mg, 0.5 mmol) were added to a 4 mL vial equipped with a magnetic stir bar. (*p*-tolyl)HC═NBn (105 mg, 0.5 mmol), 4-iodotoluene (545 mg, 2.5 mmol), and NEt^iPr_2 (97 mg, 0.75 mmol) were dissolved in 3.3 mL of MeCN and transferred into the vial. The vial was closed with a pierced plastic cap, placed inside a Parr steel autoclave, sealed, and charged with 10 atm CO. The autoclave was stirred at 40 °C for 24 h. The CO was then removed, and the vessel was brought back into the glovebox. The crude solution was transferred into a thick-walled 25 mL Schlenk bomb; the solvent was evaporated in vacuo; the remaining oil was dissolved in 3.5 mL of benzene, and (3-furanyl)HC═NEt (123 mg, 1.0 mmol) was added. The reactor was sealed with a Teflon cap and heated at 70 °C with stirring for 18 h. The β-lactam product was isolated by flash chromatography on silica gel with hexanes/ethyl acetate 4:1 to afford β-lactam **5a** in 94% yield (224 mg, 0.47 mmol) as a pale yellow solid.

*N-Benzyl-N-(1-ethyl-2-(furan-3-yl)-4-oxo-3-(p-tolyl)azetidin-3-yl)-4-methylbenzamide (**5a**):* Isolated yield 94% (224 mg, 0.47 mmol); light yellow solid; mp 152−154 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.39 (m, 3H), 7.25−7.20 (m, 2H), 7.16 (t, *J* = 1.8 Hz, 1H), 7.14−7.08 (m, 3H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.97 (d, *J* = 8.1 Hz, 2H), 6.88 (dd, *J* = 7.4, 2.2 Hz, 2H), 6.08 (d, *J* = 1.7 Hz, 1H), 5.62 (s, 1H), 4.87 (d, *J* = 16.9 Hz, 1H), 4.79 (d, *J* = 16.9 Hz, 1H), 3.58 (dq, *J* = 14.6, 7.4 Hz, 1H), 2.99 (dq, *J* = 14.2, 7.2 Hz, 1H), 2.29 (s, 3H), 2.25 (s, 3H), 1.15 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 174.0, 165.3, 142.6, 142.2, 139.9, 138.5, 137.9, 133.8, 132.1, 129.2, 128.9, 128.6, 128.0, 126.7, 126.6, 126.5, 120.6, 110.3, 79.8, 59.6, 51.9, 35.0, 21.3, 21.1, 12.5; HRMS calcd for $C_{31}H_{30}O_3N_2Na$ (MNa^+) 501.2149, found 501.2150; FT-IR ATR ν_{CO} = 1750 and 1634 cm^{-1}.

*N-(1-Benzyl-2-oxo-4-(thiophen-3-yl)-3-(4-(trifluoromethyl)-phenyl)azetidin-3-yl)-N-ethyl-4-methoxybenzamide (**5b**):* Isolated yield 67% (189 mg, 0.33 mmol); light brown solid; mp 118−121 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.37−7.30 (m, 5H), 7.25−7.20 (m, 2H), 7.10 (dd, *J* = 3.1, 1.2 Hz, 1H), 7.04 (dd, *J* = 5.0, 3.0 Hz, 1H), 6.95−6.88 (m, 2H), 6.78 (dd, *J* = 5.0, 1.3 Hz, 1H), 5.35 (s, 1H), 4.99 (d, *J* = 14.8 Hz, 1H), 3.97 (d, *J* = 14.8 Hz, 1H), 3.84 (s, 4H), 3.68 (dq, *J* = 14.5, 7.1 Hz, 1H), 0.67 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.8, 165.6, 161.1, 140.5, 135.7, 135.0, 130.3 (q, *J* = 32.2 Hz), 129.7, 129.1, 129.0, 128.8, 128.6, 128.2, 127.6, 125.5, 125.1, 124.9 (q, *J* = 3.6 Hz), 123.0, 114.0, 80.5, 62.8, 55.5, 44.6, 44.0, 15.9; HRMS calcd for $C_{31}H_{27}O_3N_2F_3SNa$ (MNa^+) 587.1587, found 587.1589; FT-IR ATR ν_{CO} = 1749 and 1636 cm^{-1}.

*N-Benzyl-N-(1-hexyl-2-(4-methoxyphenyl)-4-oxo-3-(1-tosyl-1H-indol-3-yl)azetidin-3-yl)-3,5-dimethylbenzamide (**5c**):* Isolated yield 65% (250 mg, 0.32 mmol); light yellow solid; mp 58−61 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.1 Hz, 1H), 7.79 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.61−7.54 (m, 2H), 7.38 (s, 1H), 7.17−7.10 (m, 3H), 7.04−6.96 (m, 4H), 6.95−6.87 (m, 3H), 6.82 (d, *J* = 1.7 Hz, 2H), 6.66 (dd, *J* = 8.2, 1.2 Hz, 2H), 6.52−6.44 (m, 2H), 5.55 (s, 1H), 4.85 (d, *J* = 16.6 Hz, 1H), 4.69−4.60 (m, 1H), 3.66 (s, 3H), 3.50 (dt, *J* = 13.9, 7.8 Hz, 1H), 2.81 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 6H), 1.49 (q, *J* = 7.3 Hz, 2H), 1.36−1.22 (m, 7H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 174.0, 165.6, 159.7, 144.8, 138.3, 138.1, 136.8, 135.3, 134.6, 131.5, 130.2, 129.8, 129.0, 128.5, 128.0, 127.0, 126.9, 126.7, 126.4, 124.8, 124.7, 124.5, 123.2, 116.8, 113.4, 112.9, 76.4, 65.6, 55.3, 52.2, 40.6, 31.5, 27.2, 26.9, 22.7, 21.7, 21.2, 14.2; HRMS calcd for $C_{47}H_{49}O_5N_3SNa$ (MNa^+) 790.3285, found 790.3290; FT-IR ATR ν_{CO} = 1751 and 1639 cm^{-1}.

*N-Benzyl-N-(1,2-bis(4-methoxyphenyl)-4-oxo-3-(p-tolyl)azetidin-3-yl)-4-methylbenzamide (**5d**):* Isolated yield 70% (220 mg, 0.37 mmol); yellow solid; mp 102−106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.3 Hz, 2H), 7.26−7.20 (m, 6H), 7.04 (d, *J* = 7.9 Hz, 2H), 7.02−6.95 (m, 3H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.81−6.72 (m, 4H), 6.69−6.63 (m, 2H), 6.00 (s, 1H), 4.91 (d, *J* = 16.8 Hz, 1H), 4.86 (d, *J* = 16.9 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 174.0, 163.0, 159.3, 156.4, 140.1, 138.4, 137.84, 134.0, 131.8, 130.8, 130.3, 129.8, 129.0, 128.6, 128.1, 126.9, 126.7, 126.6, 126.6, 119.3, 114.3, 113.5, 80.3, 67.1, 55.5, 55.2, 52.4, 21.5, 21.2; HRMS calcd for $C_{39}H_{36}O_4N_2Na$ (MNa^+) 619.2567, found 619.2576; FT-IR ATR ν_{CO} = 1736 and 1633 cm^{-1}.

*N-(3-(Benzo[d][1,3]dioxol-5-yl)-1-(furan-2-ylmethyl)-2-oxo-4-(p-tolyl)azetidin-3-yl)-4-bromo-N-ethylbenzamide (**5e**):* Isolated yield 77% (227 mg, 0.39 mmol); light yellow solid; mp 130−134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58−7.51 (m, 2H), 7.36 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.31−7.27 (m, 2H), 7.10−7.03 (m, 3H), 7.01−6.93 (m, 3H), 6.58 (d, *J* = 8.2 Hz, 1H), 6.29 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.13 (dd, *J* = 3.2, 0.7 Hz, 1H), 5.84 (dd, *J* = 10.0, 1.5 Hz, 2H), 5.28 (s, 1H), 4.88 (d, *J* = 15.7 Hz, 1H), 3.94 (d, *J* = 15.6 Hz, 1H), 3.80−3.71 (m, 1H), 3.63−3.52 (m, 1H), 2.26 (s, 3H), 0.70 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 172.4, 166.0, 148.5, 147.4, 147.4, 142.8, 137.9, 136.2, 131.9, 130.9, 129.9, 129.0, 128.7, 128.5, 124.2, 123.2, 110.6, 110.1, 109.1, 107.6, 101.0, 80.8, 66.8, 43.5, 37.0, 21.3, 15.9; HRMS calcd for $C_{31}H_{27}O_5N_2BrNa$ (MNa^+) 609.0996, found 609.1000; FT-IR ATR ν_{CO} = 1748 and 1631 cm^{-1}.

*N-Benzyl-N-(1-benzyl-2-(2,6-dichlorophenyl)-3-(4-fluorophenyl)-4-oxoazetidin-3-yl)-4-methoxybenzamide (**5f**):* Isolated yield 63% (201 mg, 0.31 mmol); white solid; mp 112−116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.40 (m, 2H), 7.37 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.26−7.25 (m, 3H), 7.23−7.19 (m, 2H), 7.17−7.10 (m, 4H), 7.07−7.02 (m, 2H), 6.99 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.96−6.89 (m, 2H), 6.76−6.68 (m, 4H), 5.99 (s, 1H), 4.84 (d, *J* = 17.3 Hz, 1H), 4.77 (d, *J* = 17.2 Hz, 1H), 4.72 (d, *J* = 14.3 Hz, 1H), 3.79 (d, *J* = 14.4 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 172.9, 165.3, 162.5 (d, *J* = 247.9 Hz), 160.9, 138.6, 138.1, 136.7, 133.6, 131.6 (d, *J* = 8.0 Hz), 130.5 (d, *J* = 3.4 Hz), 130.3, 129.5, 129.4, 129.3, 128.8, 128.7, 128.4, 128.0, 127.0, 126.2, 114.4 (d, *J* = 21.1 Hz), 113.6, 78.5, 63.7, 55.4, 52.1, 46.2; HRMS calcd for $C_{37}H_{29}Cl_2FN_2NaO_3$ (MNa^+) 661.1431, found 661.1430; FT-IR ATR ν_{CO} = 1754 and 1637 cm^{-1}.

*N-(3-(3-Bromophenyl)-1-ethyl-2-(1-ethyl-1H-imidazol-2-yl)-4-oxoazetidin-3-yl)-N-ethyl-4-methoxybenzamide (**5g**):* Isolated yield 65% (170 mg, 0.32 mmol); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 9.6 Hz, 2H), 5.57 (s, 1H), 4.55−4.33 (m, 1H), 4.22 (h, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 3.79−3.72 (m, 2H), 3.65 (dq, *J* = 13.5, 6.7, 6.1 Hz, 1H), 3.09 (dq, *J* = 14.4, 7.3 Hz, 1H), 1.39 (t, *J* = 7.3 Hz, 3H), 1.14 (t, *J* = 7.3 Hz, 3H), 0.77 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.5, 164.8, 161.0, 140.5, 138.1, 132.0, 131.3, 129.4, 129.2, 128.7, 127.8, 122.0, 119.9, 114.0, 80.0, 58.3, 55.5, 44.0, 40.8, 35.3, 16.9, 16.0, 12.4; HRMS calcd for $C_{26}H_{30}O_3N_4Br$ (MH^+) 525.1496, found 525.1496; FT-IR ATR ν_{CO} = 1752 and 1628 cm^{-1}.

*N-(3-(Benzo[d][1,3]dioxol-5-yl)-1-hexyl-2-(4-(methylthio)phenyl)-4-oxoazetidin-3-yl)-N-benzyl-3-methoxybenzamide (**5h**):* Isolated yield 72% (229 mg, 0.36 mmol); yellow solid; mp 36−38 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.14 (m, 3H), 7.09−7.03 (m, 6H), 6.97 (d, *J* = 1.7 Hz, 1H), 6.89 (dt, *J* = 7.5, 1.1 Hz, 1H), 6.85 (ddd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 6.78 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.69 (dd, *J* = 2.4, 1.5 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 5.83 (dd, *J* = 14.1, 1.5 Hz, 2H), 5.57 (s, 1H), 4.87 (d, *J* = 16.8 Hz, 1H), 4.82 (d, *J* = 16.8 Hz, 1H), 3.58 (s, 3H), 3.57−3.52 (m, 1H), 2.84−2.76 (m, 1H), 2.43 (s, 3H), 1.51 (q, *J* = 8.0 Hz, 2H), 1.35−1.26 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.6, 165.7, 159.5, 147.35, 147.32, 138.55, 138.49, 138.1, 131.3, 129.7, 129.5, 129.1, 128.1, 126.8, 126.7, 125.9, 123.8, 118.9, 116.5, 111.5, 110.5, 107.5, 101.0, 80.3, 66.6, 55.3, 52.2, 40.2, 31.5, 27.4, 26.9, 22.7, 15.7, 14.2; HRMS calcd for $C_{38}H_{41}O_5N_2S$ (M^+ by APCI) 637.2731, found 637.2738; FT-IR ATR ν_{CO} = 1748 and 1637 cm^{-1}.

*N-Benzyl-N-(1-benzyl-3-(4-fluorophenyl)-2-oxo-4-(1-tosyl-1H-indol-3-yl)azetidin-3-yl)-4-methylbenzamide (**5i**):* Isolated yield 79% (295 mg, 0.39 mmol); white solid; mp 79−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.52−7.45 (m, 3H), 7.35−7.29 (m, 4H), 7.23 (dt, *J* = 7.2, 3.0 Hz, 3H), 7.13−6.95 (m, 11H), 6.70 (d, *J* = 7.2 Hz, 2H), 6.46 (t, *J* = 8.7 Hz, 2H), 5.59 (s, 1H), 4.93−4.87 (m, 2H), 4.84 (d, *J* = 16.8 Hz, 1H), 3.77 (d, *J* = 14.7 Hz, 1H), 2.40 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.9, 165.0, 162.3 (d, *J* = 247.8 Hz), 145.2, 140.3, 138.0, 135.2, 134.9, 134.7, 133.7, 131.9 (d, *J* = 3.2 Hz), 131.5 (d, *J* = 8.2 Hz), 130.0, 129.5, 129.1, 129.0, 128.9, 128.3, 128.2, 126.9, 126.82, 126.80, 126.7, 124.8, 123.5, 121.0,

DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115

116.6, 114.7 (d, J = 21.1 Hz), 113.4, 79.9, 59.9, 52.1, 44.5, 21.7, 21.5.; HRMS calcd for $C_{46}H_{38}O_4N_3FNaS$ (MNa^+) 770.2459, found 770.2478; FT-IR ATR ν_{CO} = 1752 and 1636 cm^{-1}.

*N-Benzyl-N-(1-benzyl-2-(9H-fluoren-2-yl)-4-oxo-3-(p-tolyl)-azetidin-3-yl)-4-fluorobenzamide (**5j**):* Isolated yield 67% (216 mg, 0.34 mmol); white solid; mp 85−90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.44−7.40 (m, 3H), 7.36 (q, J = 6.1, 4.8 Hz, 4H), 7.30 (t, J = 7.7 Hz, 1H), 7.19 (dd, J = 7.2, 1.7 Hz, 2H), 7.14 (d, J = 7.8 Hz, 1H), 7.10−7.05 (m, 3H), 7.02 (t, J = 7.4 Hz, 2H), 6.90−6.82 (m, 4H), 6.63 (d, J = 7.4 Hz, 2H), 5.53 (s, 1H), 4.94 (d, J = 14.7 Hz, 1H), 4.88 (d, J = 17.0 Hz, 1H), 4.75 (d, J = 17.0 Hz, 1H), 3.88 (d, J = 14.7 Hz, 1H), 3.83 (d, J = 22.2 Hz, 1H), 3.70 (d, J = 21.8 Hz, 1H); ^{13}C NMR (126 MHz, CD_3Cl) δ 173.0, 165.6, 163.3 (d, J = 249.9 Hz), 143.7, 143.0, 141.7, 141.6, 138.4, 138.1, 135.1, 133.2 (d, J = 3.4 Hz), 132.9, 132.2, 129.7, 129.2, 129.0, 128.8, 128.7 (d, J = 8.6 Hz), 128.3, 128.1, 127.9, 126.90, 126.86, 126.77, 126.5, 126.4, 125.2, 120.1, 119.4, 115.3 (d, J = 21.8 Hz), 80.9, 66.5, 52.1, 44.4, 36.9, 21.2; HRMS calcd for $C_{44}H_{35}O_2N_2FNa$ (MNa^+) 665.2575, found 665.2592; FT-IR ATR ν_{CO} = 1749 and 1638 cm^{-1}.

Typical Synthesis of Spirocyclic β-Lactams. In a glovebox, $Pd(P^tBu_3)_2$ (25 mg, 0.05 mmol) and Bu_4NCl (417 mg, 1.5 mmol) were dry-transferred into a thick-walled 50 mL Schlenk bomb. (*o*-IC_6H_4)-CH═NBn (161 mg, 0.50 mmol), (*p*-$MeOC_6H_4$)CH═NBn (451 mg, 2.0 mmol), and NEt^iPr_2 (194 mg, 1.5 mmol) were dissolved in 16 mL of MeCN and added. The vessel was sealed with a Teflon cap, taken out of the glovebox, charged with 4 atm of CO, and stirred at 30 °C for 48 h. The CO was then removed, and the product was purified by flash chromatography on silica gel using hexanes/ethyl acetate (3:1) to afford **9b** in 79% yield (187 mg, 0.40 mmol) as a white solid.

*(E)-N-Benzyl-1-(2-iodophenyl)methanimine (**8a**):* Isolated yield 71% (5.80 g, 18 mmol); clear liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.04 (dd, J = 7.8, 1.8 Hz, 1H), 7.87 (dd, J = 7.9, 1.2 Hz, 1H), 7.41−7.33 (m, 5H), 7.33−7.26 (m, 1H), 7.11 (td, J = 7.6, 1.8 Hz, 1H), 4.89 (d, J = 1.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 139.7, 139.1, 137.1, 132.2, 129.1, 128.7, 128.5, 128.2, 127.2, 100.3, 65.1; HRMS calcd for $C_{14}H_{13}IN$ (MH^+) 322.0087, found 322.0084.

*(E)-1-(2-Iodophenyl)-N-isopropylmethanimine (**8b**):* Isolated yield 36% (850 mg, 3.1 mmol); clear liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.95 (dd, J = 7.8, 1.8 Hz, 1H), 7.83 (dd, J = 7.9, 1.2 Hz, 1H), 7.34 (td, J = 7.5, 7.0, 0.9 Hz, 1H), 7.06 (td, J = 7.6, 1.8 Hz, 1H), 3.63 (hept, J = 6.3 Hz, 1H), 1.28 (d, J = 6.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.6, 139.5, 137.3, 131.8, 128.9, 128.4, 100.0, 61.4, 24.2; HRMS calcd for $C_{10}H_{13}IN$ (MH^+) 274.0087, found 274.0080.

*(E)-N-Hexyl-1-(2-iodophenyl)methanimine (**8c**):* Isolated yield 53% (1.41 g, 5.5 mmol); clear liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.93 (dd, J = 7.8, 1.8 Hz, 1H), 7.84 (dd, J = 8.0, 1.2 Hz, 1H), 7.36 (tt, J = 8.0, 1.0 Hz, 1H), 7.13−7.04 (m, 1H), 3.66 (td, J = 7.0, 1.4 Hz, 2H), 1.71 (p, J = 7.0 Hz, 2H), 1.41−1.30 (m, 6H), 0.95−0.83 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 139.7, 137.3, 131.9, 128.9, 128.5, 100.0, 61.7, 31.8, 30.9, 27.1, 22.8, 14.2; HRMS calcd for $C_{13}H_{19}IN$ (MH^+) 316.0557, found 316.0552.

*1,2′-Dibenzyl-2-(2-iodophenyl)spiro[azetidine-3,1′-isoindoline]-3′,4-dione (**9a**):* Isolated yield 40% (114 mg, 0.20 mmol); white solid; mp 165−166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.78 (m, 1H), 7.68 (dd, J = 7.9, 1.2 Hz, 1H), 7.48−7.42 (m, 5H), 7.41−7.36 (m, 3H), 7.32 (td, J = 7.6, 1.2 Hz, 1H), 7.18−7.10 (m, 3H), 7.01 (dd, J = 7.8, 1.8 Hz, 2H), 6.92 (td, J = 7.7, 1.7 Hz, 1H), 6.82−6.76 (m, 1H), 5.19 (d, J = 14.4 Hz, 1H), 5.08 (s, 1H), 4.40 (d, J = 16.0 Hz, 1H), 4.18 (d, J = 14.5 Hz, 1H), 3.96 (d, J = 16.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 166.9, 143.4, 140.5, 137.2, 136.3, 135.3, 132.6, 131.3, 130.4, 129.5, 129.4, 128.9, 128.3, 128.1, 127.4, 127.2, 126.9, 124.1, 120.6, 98.0, 81.6, 70.1, 46.5, 46.0; HRMS calcd for $C_{30}H_{23}IN_2NaO_2$ (MNa^+) 593.0696, found 593.0692; FT-IR ATR ν_{CO} = 1760 and 1704 cm^{-1}.

*1,2′-Dibenzyl-2-(4-methoxyphenyl)spiro[azetidine-3,1′-isoindoline]-3′,4-dione (**9b**):* Isolated yield 79% (187 mg, 0.40 mmol); white solid; mp 146−147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.79 (m, 1H), 7.49−7.41 (m, 5H), 7.40−7.35 (m, 2H), 7.20−7.12 (m, 3H), 7.03 (ddd, J = 7.5, 4.1, 1.2 Hz, 4H), 6.86−6.78 (m, 3H), 5.18 (d, J = 14.4 Hz, 1H), 4.93 (s, 1H), 4.44 (d, J = 16.0 Hz, 1H), 4.22 (d, J = 14.4 Hz, 1H), 3.92 (d, J = 16.0 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 166.4, 160.0, 142.7, 136.4, 135.5, 132.7, 130.8, 129.4, 129.3, 128.7, 128.0, 127.6, 127.4, 126.9, 125.6, 124.1, 120.7, 114.7, 81.3, 66.5, 55.3, 46.2, 45.9; HRMS calcd for $C_{31}H_{26}O_3N_2Na$ (MNa^+) 497.1836, found 497.1849; FT-IR ATR ν_{CO} = 1756 and 1703 cm^{-1}.

*2′-Benzyl-1-ethyl-4-(pyridin-3-yl)spiro[azetidine-3,1′-isoindoline]-2,3′-dione (**9c**):* Isolated yield 65% (125 mg, 0.33 mmol); white solid; mp 169−171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 2.4 Hz, 1H), 8.41 (dd, J = 4.9, 1.6 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.69 (td, J = 7.5, 1.2 Hz, 1H), 7.61−7.51 (m, 2H), 7.35 (dt, J = 8.0, 2.0 Hz, 1H), 7.11 (dd, J = 5.2, 2.0 Hz, 3H), 7.07 (dd, J = 7.9, 4.8 Hz, 1H), 6.93 (dd, J = 7.2, 2.5 Hz, 2H), 5.21 (s, 1H), 4.30 (d, J = 16.1 Hz, 1H), 4.07 (d, J = 16.1 Hz, 1H), 3.99 (dq, J = 14.7, 7.4 Hz, 1H), 3.35 (dq, J = 14.2, 7.1 Hz, 1H), 1.42 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 165.8, 150.3, 147.6, 142.2, 136.0, 134.0, 133.1, 130.8, 130.0, 129.9, 128.2, 127.0, 126.9, 124.5, 123.8, 120.5, 82.0, 65.5, 46.5, 37.1, 13.4; HRMS calcd for $C_{24}H_{22}O_2N_3$ (MH^+) 384.1707, found 384.1696; FT-IR ATR ν_{CO} = 1755 and 1708 cm^{-1}.

*1-Benzyl-2′-isopropyl-2-(4-methoxyphenyl)spiro[azetidine-3,1′-isoindoline]-3′,4-dione (**9d**):* Isolated yield 79% (169 mg, 0.40 mmol); white solid; mp 59−61 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−7.70 (m, 1H), 7.45−7.37 (m, 7H), 7.06 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.85−6.81 (m, 1H), 5.26 (d, J = 14.3 Hz, 1H), 4.86 (s, 1H), 4.23 (d, J = 14.3 Hz, 1H), 3.81 (s, 3H), 3.29 (hept, J = 6.9 Hz, 1H), 1.38 (d, J = 6.7 Hz, 3H), 0.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 166.9, 160.0, 142.1, 135.4, 132.5, 132.2, 129.4, 129.33, 129.27, 128.7, 127.9, 125.9, 123.5, 120.5, 114.6, 82.6, 66.7, 55.5, 49.7, 46.2, 19.4, 19.2; HRMS calcd for $C_{27}H_{26}O_3N_2Na$ (MNa^+) 449.1836, found 449.1848; FT-IR ATR ν_{CO} = 1759 and 1693 cm^{-1}.

*1-Benzyl-2′-hexyl-2-(4-methoxyphenyl)spiro[azetidine-3,1′-isoindoline]-3′,4-dione (**9e**):* Isolated yield 96% (225 mg, 0.48 mmol); white solid; mp 58−60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79−7.73 (m, 1H), 7.47−7.37 (m, 7H), 7.06 (d, J = 8.4 Hz, 2H), 6.94−6.88 (m, 2H), 6.85−6.80 (m, 1H), 5.26 (d, J = 14.3 Hz, 1H), 4.89 (s, 1H), 4.25 (d, J = 14.3 Hz, 1H), 3.82 (s, 3H), 3.00 (ddd, J = 13.8, 11.3, 5.4 Hz, 1H), 2.81 (ddd, J = 13.9, 11.1, 5.0 Hz, 1H), 1.54 (dddd, J = 11.4, 10.1, 8.9, 5.1 Hz, 1H), 1.26−1.15 (m, 2H), 1.15−1.03 (m, 3H), 1.03−0.93 (m, 1H), 0.84 (t, J = 7.3 Hz, 3H), 0.67−0.57 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 167.2, 160.1, 142.4, 135.4, 132.3, 131.3, 129.4, 129.4, 129.3, 128.8, 127.6, 126.0, 123.8, 120.5, 114.7, 81.3, 66.5, 55.5, 46.2, 43.5, 31.5, 27.4, 26.9, 22.7, 14.2; HRMS calcd for $C_{30}H_{32}N_2NaO_3$ (MNa^+) 491.2305, found 491.2296; FT-IR ATR ν_{CO} = 1761 and 1703 cm^{-1}.

*1,2′-Dibenzyl-2-(4-fluorophenyl)spiro[azetidine-3,1′-isoindoline]-3′,4-dione (**9f**):* Isolated yield 48% (110 mg, 0.24 mmol); white solid; mp 195−197 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.80 (m, 1H), 7.51−7.42 (m, 5H), 7.40−7.35 (m, 2H), 7.18−7.13 (m, 3H), 7.09−7.04 (m, 2H), 7.02−6.93 (m, 4H), 6.86−6.81 (m, 1H), 5.18 (d, J = 14.4 Hz, 1H), 4.94 (s, 1H), 4.40 (d, J = 16.0 Hz, 1H), 4.21 (d, J = 14.5 Hz, 1H), 3.94 (d, J = 15.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 166.4, 162.9 (d, J = 248.7 Hz), 142.5, 136.2, 135.2, 132.8, 130.7, 129.62, 129.60, 129.44, 129.36, 128.9, 128.14, 128.12 (d, J = 7.6 Hz), 127.3, 127.0, 124.2, 120.7, 116.4 (d, J = 21.8 Hz), 81.5, 66.3, 46.4, 46.1; HRMS calcd for $C_{30}H_{23}O_2N_2FNa$ (MNa^+) 485.1636, found 485.1646; FT-IR ATR ν_{CO} = 1765 and 1704 cm^{-1}.

*2′-Benzyl-1-ethyl-4-(4-(trifluoromethyl)phenyl)spiro[azetidine-3,1′-isoindoline]-2,3′-dione (**9g**):* Isolated yield 53% (120 mg, 0.27 mmol); white solid; mp 108−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dt, J = 7.5, 0.9 Hz, 1H), 7.69 (td, J = 7.6, 1.2 Hz, 1H), 7.62−7.53 (m, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.11−7.04 (m, 3H), 6.94−6.85 (m, 2H), 5.25 (s, 1H), 4.26 (d, J = 16.1 Hz, 1H), 4.11 (d, J = 16.2 Hz, 1H), 4.01 (dq, J = 14.7, 7.4 Hz, 1H), 3.35 (dq, J = 14.2, 7.1 Hz, 1H), 1.43 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 165.9, 142.4, 138.1, 136.1, 133.1, 131.1 (q, J = 32.7 Hz), 130.8, 130.0, 129.1, 128.1, 127.0, 126.8, 126.1 (q, J = 3.7 Hz), 124.5, 123.7 (q, J = 272.3 Hz), 120.6, 82.2, 67.0, 46.6, 37.1, 13.4; HRMS calcd for $C_{26}H_{21}O_2N_2F_3Na$ (MNa^+) 473.1447, found 473.1463; FT-IR ATR ν_{CO} = 1750 and 1701 cm^{-1}.

*(E)-2′-Benzyl-1-ethyl-4-styrylspiro[azetidine-3,1′-isoindoline]-2,3′-dione (**9h**):* Isolated yield 95% (194 mg, 0.48 mmol); light yellow solid; mp 141−144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dt, J = 7.5, 1.0 Hz, 1H), 7.66 (td, J = 7.6, 1.2 Hz, 1H), 7.58−7.49 (m, 2H), 7.34−

DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115

7.29 (m, 2H), 7.24−7.14 (m, 6H), 6.80−6.73 (m, 2H), 6.50 (d, J = 15.7 Hz, 1H), 5.85 (dd, J = 15.7, 8.9 Hz, 1H), 5.15 (d, J = 16.3 Hz, 1H), 4.69 (dd, J = 8.9, 0.8 Hz, 1H), 4.59 (d, J = 16.4 Hz, 1H), 3.67 (dq, J = 14.5, 7.3 Hz, 1H), 3.32 (dq, J = 14.3, 7.2 Hz, 1H), 1.35 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 165.3, 142.1, 137.5, 137.2, 134.9, 132.8, 131.0, 129.7, 128.7, 128.6, 128.5, 127.3, 127.1, 126.8, 124.3, 122.9, 120.8, 82.1, 68.3, 47.4, 36.1, 13.7; HRMS calcd for $C_{27}H_{25}O_2N_2$ (MH^+) 409.1911, found 409.1922; FT-IR ATR ν_{CO} = 1758 and 1698 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02405.

^{1}H and ^{13}C NMR spectra for products (PDF)

Crystallographic data for **9g** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ashfaq.bengali@qatar.tamu.edu.

*E-mail: bruce.arndtsen@mcgill.ca

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This publication was made possible by funding through an NPRP award (5-156-1-037) from the Qatar National Research Fund (member of Qatar Foundation). Martin Torres and De La Higuera Macias would like to thank the CONACyT (Mexican National Council of Science and Technology) for providing funding for doctoral studies. The statements made herein are solely the responsibility of the authors.

■ REFERENCES

(1) (a) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; p 621. (b) Testero, S. A.; Fisher, J. F.; Mobashery, S. β-Lactam Antibiotics. In *Burger's Medicinal Chemistry, Drug Discovery and Development*; Abraham, D. J., Rotella, D. P., Eds.; Wiley: Hoboken, NJ, 2010; pp 259−404. (c) von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Habich, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5072. (d) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publications: New York, 1993.

(2) (a) Rothstein, J. D.; Patel, S.; regan, M. R.; Haenggeli, C.; Huang, Y. H.; Bergles, D. E.; Jin, L.; Hoberg, M. D.; Vidensky, S.; Chung, D. S.; Toan, S. V.; Bruijn, L. I.; Su, Z.-Z.; Gupta, P.; Fisher, P. B. *Nature* **2005**, *433*, 73. (b) Miller, T. M.; Cleveland, D. W. *Science* **2005**, *307*, 361. (c) Xing, B.; Rao, J.; Liu, R. *Mini-Rev. Med. Chem.* **2008**, *8*, 455. (d) Palomo, C.; Aizpurua, J. M.; Benito, A.; Miranda, J. I.; Fratila, R. M.; Matute, C.; Domercq, M.; Gago, F.; Martin-Santamaria, S.; Linden, A. *J. Am. Chem. Soc.* **2003**, *125*, 16243. (e) Feledziak, M.; Michaux, C.; urbach, A.; Labar, G.; Muccioli, G. G.; Lambert, D. M.; Marchand-Brynaert, J. *J. Med. Chem.* **2009**, *52*, 7054. (f) Bonneau, P. R.; Hasani, F.; Plouffe, C.; Malenfant, E.; LaPlante, S. R.; Guse, I.; Ogilvie, W. W.; Plante, R.; Davidson, W. C.; Hopkins, J. L.; Morelock, M. M.; Cordingley, M. G.; Déziel, R. *J. Am. Chem. Soc.* **1999**, *121*, 2965. (g) Jamieson, A. G.; Boutard, N.; Beauregard, K.; Bodas, M. S.; Ong, H.; Quiniou, C.; Chemtob, S.; Lubell, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 7917.

(3) (a) Hashimoto, K. *Prog. Polym. Sci.* **2000**, *25*, 1411. (b) Gangloff, N.; Ulbricht, J.; Lorson, T.; Schlaad, H.; Luxenhofer, R. *Chem. Rev.* **2016**, *116*, 1753. (c) Deming, T. J. *Adv. Drug Delivery Rev.* **2002**, *54*, 1145. (d) Dane, E. L.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2012**, *134*, 16255−16264. (e) Zhang, J.; Kissounko, D. A.; Lee, S. E.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 1589. (f) Deming, T. J.; Cheng, J. *J. Am. Chem. Soc.* **2001**, *123*, 9457. (g) Mowery, B. P.; Lee, S. E.; Kissounko, D. A.; Epand, R. F.; Epand, R. M.; Weisblum, B.; Stahl, S. S.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 15474. (h) Macías, A.; Ramallal, A. M.; Alonso, E.; del Pozo, C.; González, J. *J. Org. Chem.* **2006**, *71*, 7721.

(4) For a recent review, see: Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437.

(5) (a) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395. (b) Dale-Skinner, J. W.; Bonev, B. In *New Strategies Combating Bacterial Infection*; Ahmad, I., Aqil, F., Eds.; Wiley-VCH: Weinheim, Germany, 2009; pp 1−46. (c) Lewis, K. *Nat. Rev. Drug Discovery* **2013**, *12*, 371. (d) Walsh, C. T.; Wencewicz, T. A. *J. Antibiot.* **2014**, *67*, 7.

(6) (a) Fu, N.; Tidwell, T. T. *Tetrahedron* **2008**, *64*, 10465. (b) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771. (c) Konaklieva, M. I.; Plotkin, B. J. Asymmetric Synthesis of β-Lactams via the Staudinger Reaction. In *Amino Acids, Peptides and Proteins in Organic Chemistry: Protection Reactions, Medicinal Chemistry, Combinatorial Synthesis*; Hughes, A. B., Ed.; Wiley-VCH: Weinheim, Germany, 2011; Vol. *4*, p 293. (d) Wright, S. W. Staudinger Ketene-Imine Cycloaddition. In *Name Reactions for Carbocyclic Ring Formations*; Li, J. J., Ed.; John Wiley & Sons, Inc.: New York, 2010; Vol. *1*, p 45.

(7) Reviews: (a) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592. (b) Alcaide, B.; Almendros, P.; Luna, A. The Chemistry of 2-Azetidinones (β-Lactams). In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, Germany, 2011; Vol. *4*, p 2117. (c) Tuba, R. *Org. Biomol. Chem.* **2013**, *11*, 5976.

(8) Carbonylative approaches: (a) Zhou, Z.; Alper, H. *J. Org. Chem.* **1996**, *61*, 1256. (b) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518. (c) Lu, S.-M.; Alper, H. *J. Org. Chem.* **2004**, *69*, 3558. (d) Fontana, F.; Tron, G. C.; Barbero, N.; Ferrini, S.; Thomas, S. P.; Aggarwal, V. K. *Chem. Commun.* **2010**, *46*, 267. (e) Li, W.; Liu, C.; Zhang, H.; Ye, K.; Zhang, G.; Zhang, W.; Duan, Z.; You, S.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 2443. (f) Paul, N. D.; Chirila, A.; Lu, H.; Zhang, X. P.; de Bruin, B. *Chem. - Eur. J.* **2013**, *19*, 12953. (g) Xie, P.; Qian, B.; Huang, H.; Xia, C. *Tetrahedron Lett.* **2012**, *53*, 1613. (h) Tanaka, H.; Hai, A. K. M. A.; Sadakane, M.; Okumoto, H.; Torii, S. *J. Org. Chem.* **1994**, *59*, 3040.

(9) Other recent metal-catalyzed methods: (a) Alcaide, B.; Almendros, P.; Carrascosa, R.; Casarrubios, L.; Soriano, E. *Chem. - Eur. J.* **2015**, *21*, 2200. (b) Zhao, Q.; Li, C. *Org. Lett.* **2008**, *10*, 4037. (c) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206. (d) Jiao, L.; Zhang, Q.; Liang, Y.; Zhang, S.; Xu, J. *J. Org. Chem.* **2006**, *71*, 815. (e) Lawlor, M. D.; Lee, T. W.; Danheiser, R. L. *J. Org. Chem.* **2000**, *65*, 4375.

(10) Review: (a) Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2198. Recent examples: (b) Wolosewicz, K.; Michalak, M.; Adamek, J.; Furman, B. *Eur. J. Org. Chem.* **2016**, *2016*, 2212. (c) Kabala, K.; Grzeszczyk, B.; Stecko, S.; Furman, B.; Chmielewski, M. *J. Org. Chem.* **2015**, *80*, 12038. (d) Zhang, X.; Hsung, R. P.; Li, H.; Zhang, Y.; Johnson, W. L.; Figueroa, R. *Org. Lett.* **2008**, *10*, 3477.

(11) Review: (a) Mandal, B.; Basu, B. *Top. Heterocycl. Chem.* **2012**, *30*, 85. Recent examples: (b) Isoda, M.; Sato, K.; Funakoshi, M.; Omura, K.; Tarui, A.; Omote, M.; Ando, A. *J. Org. Chem.* **2015**, *80*, 8398. (c) Smith, S. R.; Douglas, J.; Prevet, H.; Shapland, P.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2014**, *79*, 1626. (d) Yoshimura, T.; Takuwa, M.; Tomohara, K.; Uyama, M.; Hayashi, K.; Yang, P.; Hyakutake, R.; Sasamori, T.; Tokitoh, N.; Kawabata, T. *Chem. - Eur. J.* **2012**, *18*, 15330. (e) Evans, C. D.; Mahon, M. F.; Andrews, P. C.; Muir, J.; Bull, S. D. *Org. Lett.* **2011**, *13*, 6276.

(12) (a) Li, Z.; Sharma, U. K.; Liu, Z.; Sharma, N.; Harvey, J. N.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2015**, *2015*, 3957. (b) Cornier, P. G.; Delpiccolo, C. M. L.; Boggián, D. B.; Mata, E. G. *Tetrahedron Lett.* **2013**, *54*, 4742. (c) Vishwanatha, T. M.; Narendra, N.; Sureshbabu, V. V. *Tetrahedron Lett.* **2011**, *52*, 5620. (d) Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2008**, *73*, 9762. (e) Kolb, J.; Beck, B.; Dömling, A. *Tetrahedron Lett.* **2002**, *43*, 6897.

(13) Dhawan, R.; Dghaym, R. D.; St. Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 3927.

(14) For reviews on Münchnones, see: (a) Gingrich, H. L.; Baum, J. S. Mesoionic Oxazoles. In *Chemistry of Heterocyclic Compounds: Oxazoles*;

DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115

Turchi, I. J., Ed.; John Wiley & Sons, Inc.: New York, 1986. (b) Gribble, G. W. Mesoionic Oxazoles. In *The Chemistry of Heterocyclic Compounds, Vol. 60: Oxazoles: Synthesis, Reactions, and Spectroscopy, Part A*; Palmer, D. C., Ed.; John Wiley & Sons, Inc.: New York, 2003. (c) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432. (d) Reissig, H. U.; Zimmer, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 9708.

(15) Huisgen, R.; Funke, E.; Schaefer, F. C.; Knorr, R. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 367.

(16) (a) Torres, G. M.; Quesnel, J. S.; Bijou, D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2016**, *138*, 7315. (b) Bontemps, S.; Quesnel, J. S.; Worrall, K.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8948.

(17) (a) Quesnel, J. S.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2013**, *135*, 16841. (b) Quesnel, J. S.; Kayser, L. V.; Fabrikant, A.; Arndtsen, B. A. *Chem. - Eur. J.* **2015**, *21*, 9550.

(18) *N*-Acyl iminium salts generated from imines and acid chlorides undergo decomposition in the presence of amine base at temperatures above 65 °C (unpublished results).

(19) For example, the use of ^{i}PrCH═NBn leads to exclusive enamide formation.

(20) The stereochemistry of all β-lactam products was determined by NOE analysis. See Supporting Information for details.

(21) For a recent discussion of the stereochemistry of β-lactam formation, see: Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060.

(22) Reviews: (a) Bari, S.; Bhalla, A. *Top. Heterocycl. Chem.* **2010**, *22*, 49. (b) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673. (c) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2011**, *67*, 1989. (d) Benfatti, F.; Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1946. (e) Sandanayaka, V. P.; Prashad, A. S.; Yang, Y.; Williamson, R. T.; Lin, Y. I.; Mansour, T. S. *J. Med. Chem.* **2003**, *46*, 2569. For representative examples, see: (f) Bhalla, A.; Bari, S. S.; Bhalla, J.; Khullar, S.; Mandal, S. *Tetrahedron Lett.* **2016**, *57*, 2822. (g) Bittermann, H.; Gmeiner, P. *J. Org. Chem.* **2006**, *71*, 97. (h) Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673.

(23) Cho, C. S.; Chu, D. Y.; Lee, D. Y.; Shim, S. C.; Kim, T. J.; Lim, W. T.; Heo, N. H. *Synth. Commun.* **1997**, *27*, 4141.

(24) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489.

(25) Quesnel, J. S.; Kayser, L. V.; Fabrikant, A.; Arndtsen, B. A. *Chem. - Eur. J.* **2015**, *21*, 9550.

DOI: 10.1021/acs.joc.6b02405
J. Org. Chem. 2016, 81, 12106−12115