JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX
Note
pubs.acs.org/joc

A Cross-Metathesis/Aza-Michael Reaction Strategy for the Synthesis of Cyclic and Bicyclic Ureas

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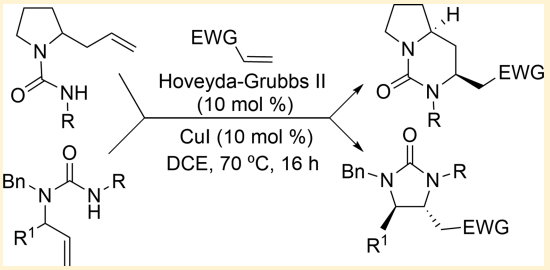
Supporting Information

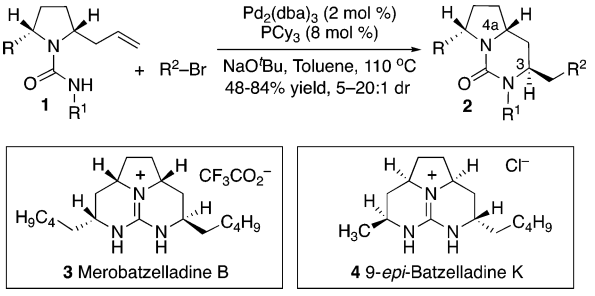
ABSTRACT: The synthesis of cyclic and bicyclic ureas via a ruthenium-catalyzed cross-metathesis / aza-Michael reaction strategy between protected alkenyl ureas and Michael acceptors is described. The substrates for these reactions are generated in 1−3 steps from commercially available materials, and products are formed in moderate yield with up to >20:1 diastereoselectivity.



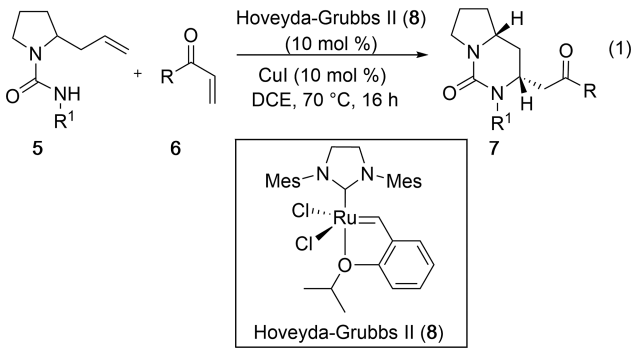
Cyclic and bicyclic ureas are common subunits that are found in many biologically active molecules and natural products, including HIV protease inhibitors,[1] 5-HT_3 receptor antagonists,[2] and NK_1 antagonists.[3] Chiral imidazolidin-2-ones have also been widely utilized as chiral auxiliaries in organic synthesis.[4] In addition, cyclic or bicyclic ureas have been utilized as intermediates in the synthesis of cyclic guanidines,[5] which are also found in a number of biologically active compounds and natural products,[6] including the Batzelladine family of alkaloids. Given the significance of cyclic ureas, many synthetic strategies have been developed to generate these molecules.[7] However, very few of these strategies effect both formation of the ring *and* a carbon−carbon bond in a single one-flask operation.[8]

Our group has previously described a method for the synthesis of cyclic and bicyclic ureas via Pd-catalyzed alkene carboamination reactions[9] between *N*-allylureas and aryl/alkenyl halides that effects the formation of both the ring and a C−C bond and generates products with a high level of diastereoselectivity in most cases (Scheme 1).[10−12] The utility of this method has been demonstrated through its use in the synthesis of (+)-Merobatzelladine B (**3**)[11] and 9-*epi*-batzelladine K (**4**).[12] However, the stereochemical outcome of these reactions is substrate-controlled, and although bicyclic products with a *cis*-relationship between the angular C4a H atom and the C3 alkyl group are formed in high dr, we have been unable to access the analogous *trans*-stereoisomers, which could serve as precursors to many other biologically active batzelladine alkaloids,[5] in acceptably high yield and selectivity using the Pd-catalyzed alkene carboamination strategy.[13]

Scheme 1. Prior Synthesis of Bicyclic Ureas via Pd-Catalyzed Alkene Carboamination Reactions



Herein we describe a new method for the synthesis of bicyclic and cyclic ureas, via a cross-metathesis/aza Michael reaction sequence between ureas **5** bearing pendant alkenes and α,β-unsaturated carbonyl compounds **6**, which provides access to bicyclic urea stereoisomers **7** that cannot be prepared via the Pd-catalyzed alkene carboamination strategy (eq 1). The reaction generates the ring, a C−N bond, and a C−C bond and provides urea products bearing functional groups that can be further elaborated using standard chemistry.



The use of an alkene cross-metathesis/aza-Michael reaction cascade for the construction of heterocycles was first reported by Fustero; unsaturated cbz-protected amines were coupled

Received: June 13, 2018

DOI: 10.1021/acs.joc.8b01492
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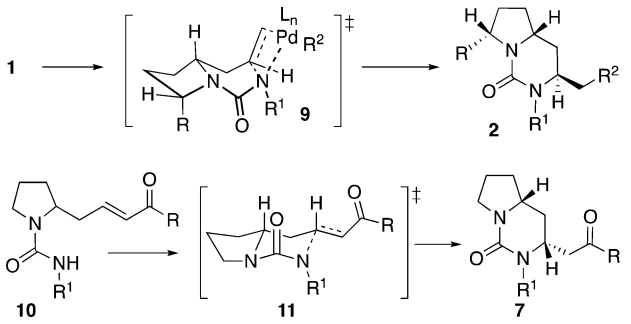
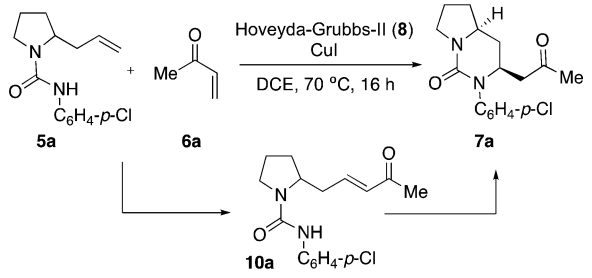
with α,β-unsaturated ketones to afford *N*-cbz-pyrrolidine products in good to excellent yield and moderate stereocontrol.[14] Subsequent studies illustrated this approach could also provide access to cyclic amides[15a] and that a range of α,β-unsaturated carbonyl derivatives were viable substrates.[15] We reasoned this strategy could also be applicable to the construction of cyclic ureas and that this also may provide access to stereoisomers that were not accessible with the Pd-catalyzed carboamination method. The major stereoisomer in the Pd-chemistry derives from *syn*-aminopalladation of the alkene through a boat-like transition state (**1** → **9** → **2**), whereas it seemed the 1,4-addition of the intermediate metathesis product **10** would likely proceed through chairlike transition state **11** to give **7** (Scheme 2).

Scheme 2. Bicyclic Urea Stereochemistry



In order to explore the feasibility of this transformation, we examined the reaction of urea **5a** with methyl vinyl ketone (MVK) using the Hoveyda–Grubbs II complex **8** as the catalyst (Table 1), because this catalyst system had provided good results in the previously reported metathesis/Michael cascades. An initial run with 1.5 equiv **6a**, 10 mol % of catalyst **8**, and 10 mol % of CuI at 50 °C afforded the desired product **7a** in 47% yield and 5:1 dr (entry 1).[16] Increasing the temperature to 70 °C, and increasing the amount of **6a** to 5 equiv, afforded **7a** in 70% yield with excellent (>20:1) diastereoselectivity (entry 2). The CuI cocatalyst was essential, as efforts to carry out the transformation in the absence of CuI led to the formation of a 1:1 mixture of **7a**:**10a** in low yield, along with several unidentified side products (entry 5). This suggests that the CuI may be acting as a weak Lewis acid in the Michael addition step, although it was originally included to facilitate the alkene metathesis.[17] An attempt to decrease the catalyst loading to 5 mol % **8** and 5 mol % CuI also led to a mixture of **7a** and **10a** (entry 4). Interestingly, use of the Grubbs II catalyst in place of **8** produced only **10a** (entry 3).

Table 1. Optimization Studies[a]

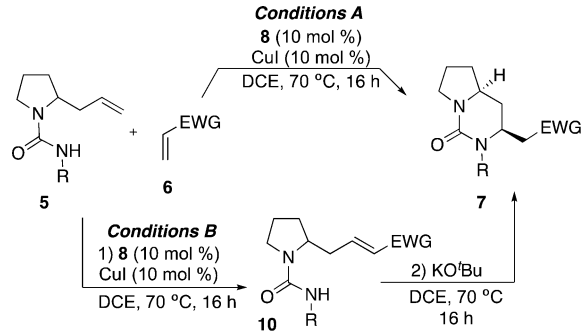


entry	equiv **6a**	mol % **8**	mol % CuI	**7a**:**10a**	yield %[b] (dr)[c]
1	1.5	10	10	>20:1	47 (5:1)[d]
2	5	10	10	>20:1	70 (>20:1)
3	1.5	10[e]	10	<1:20	0[e]
4	5	5	5	10:1	47 (>20:1)
5	5	5	0	1:1	20[f]

[a]Conditions: 1.0 equiv of **5a**, 1.5 or 5 equiv of **6a**, 0–10 mol % CuI, 5–10 mol % **8** DCE, 70 °C, 16 h. [b]Isolated yield (average of two or more experiments). [c]Diastereomeric ratios were determined by ^{1}H NMR analysis. [d]The reaction was conducted at 50 °C. [e]The reaction was conducted with the Grubbs II catalyst in place of **8**. Only the metathesis product **10a** was observed. [f]Several unidentified side products were also formed. The yield in this case was determined by ^{1}H NMR analysis using phenanthrene as an internal standard.

We then explored the scope of this transformation by varying the substituent on the cyclizing nitrogen atom, along with the electron-deficient alkene coupling partner (Table 2).

Table 2. Synthesis of Bicyclic Ureas



entry	R (**5**)	EWG (**6**)	conditions[a]	yield % (**7**)[b] (dr)[c]
1	C_6H_4-*p*-Cl (**5a**)	C(O)Me (**6a**)	A	70 (**7a**) (>20:1)
2	PMP (**5b**)	C(O)Me	A	65 (**7b**) (>20:1)
3	PMB (**5c**)	C(O)Me	A	60 (**7c**) (8:1)
4	C_6H_4-*p*-NO_2 (**5d**)	C(O)Me	B	40 (**7d**) (4:1)
5	C_6H_4-*p*-Cl (**5a**)	CO_2Me (**6b**)	B	38 (**7e**) (3:1)
6	PMP(**5b**)	CO_2Me	B	24 (**7f**) (5:1)
7	PMB (**5c**)	CO_2Me	B	43 (**7g**) (8:1)
8	C_6H_4-*p*-NO_2 (**5d**)	CO_2Me	B	29 (**7h**) (1:1)

[a]Conditions **A**: 1.0 equiv of **5**, 5 equiv of **6**, 10 mol % CuI, 10 mol % **8** DCE, 70 °C, 16 h. [b]Isolated yield (average of two or more experiments). Conditions **B**: (1) 1.0 equiv of **5**, 5 equiv of **6**, 10 mol % CuI, 10 mol % **8** DCE, 70 °C, 16 h; (2) KO^{t}Bu (1.5 equiv), DCE, 70 °C, 16 h. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis.

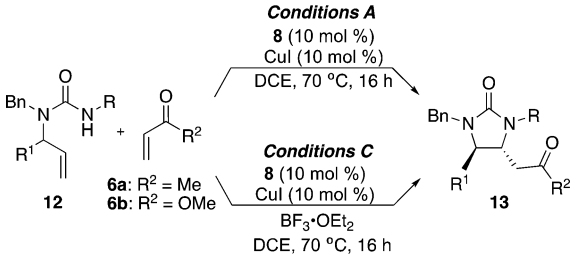
The one-pot cascade metathesis/Michael reactions proceeded smoothly for the coupling of **5a–c** with MVK to provide **7a–c** in good yield with high diastereoselectivity (entries 1–3). However, our initially optimized conditions (Table 2, conditions A) did not afford the bicyclic urea product in the reaction between *p*-nitrophenyl urea **5d** and MVK. Instead, only the cross-metathesis product **10** was generated. However, a two-step sequence (Table 2, conditions B) in which the cross-metathesis product was isolated, and then treated with KO^{t}Bu at 70 °C, led to the formation of **7d** in 40% yield, with moderate (4:1) diastereoselectivity (entry 4). Use of other reagents to effect the Michael addition step, such as $BF_3{\cdot}OEt_2$, $Ti(OiPr)_4$, LiHMDS, or TBAF, failed to provide improved results in this system, although $BF_3{\cdot}OEt_2$ was subsequently found to give higher yields in the formation of monocyclic products (see below). Efforts to employ conditions A in reactions of **5a–d** with methyl acrylate produced only the

DOI: 10.1021/acs.joc.8b01492
J. Org. Chem. XXXX, XXX, XXX–XXX

cross-metathesis product, but the two-step sequence afforded the desired products **7e–h** in low to moderate yield. Diasteroselectivities in this latter set of reactions were highly dependent on the electronic properties of the N-substituent. Substrates **5a–b** bearing a PMP or *p*-chlorophenyl group on the cyclizing nitrogen atom provided **7a–b** with >20:1 dr, and the electron-rich PMB-protected substrate **5c** was converted to **7g** with 8:1 dr. But, in contrast, the *p*-nitrophenyl derivative **5d** provided **7h** with no selectivity (1:1 dr). In this latter case the lack of selectivity might be due to thermodynamically controlled, rather than kinetically controlled, selectivity in the Michael addition step. The origin of the low yield for the formation of **7h** is not entirely clear, as significant amounts of side products were not detected, but the reaction was reproducibly low-yielding. Although the cascade cross-metathesis/Michael reactions were effective with MVK and methyl acrylate, attempts to use other electron-deficient alkenes failed to afford the desired product in useful yields. Reactions involving acrylonitrile returned only **5** along with the metathesis dimer of acrylonitrile, whereas use of crotonaldehyde or acrolein provided small amounts of products (ca. 10–30%) along with complex mixtures of side products, and use of *N*-methoxy-*N*-methylacrylamide gave a complex mixture of products along with some unreacted starting material.

With reaction conditions in hand for the synthesis of bicyclic urea products, we sought to expand the scope of this transformation to the synthesis of monocyclic urea products from acyclic *N*-allylurea substrates **12a–e** (Table 3). Reactions

Table 3. Synthesis of Monocyclic Ureas



entry	R	R^1	R^2	conditions[a]	yield %[b] (dr)[c]
1	C_6H_4-*p*-Cl (**12a**)	H	Me	A	66 (**13a**)
2	PMP (**12b**)	H	Me	A	57 (**13b**)
3	C_6H_4-*p*-NO_2 (**12c**)	H	Me	A	61 (**13c**)
4	PMP (**12d**)	Me	Me	A	52 (**13d**) (2:1)
5	C_6H_4-*p*-NO_2 (**12e**)	Me	Me	A	47 (**13e**) (2:1)
6	C_6H_4-*p*-Cl (**12a**)	H	OMe	C	44 (**13f**)
7	PMP (**12b**)	H	OMe	C	41 (**13g**)
8	C_6H_4-*p*-NO_2 (**12c**)	H	OMe	A	71 (**13h**)

[a]Conditions **A**: 1.0 equiv of **5**, 5 equiv of **6**, 10 mol % CuI, 10 mol % **8** DCE, 70 °C, 16 h. [b]Isolated yield (average of two or more experiments). Conditions **C**: (1) 1.0 equiv of **5**, 5 equiv of **6**, 1 equiv of BF_3·OEt_2, 10 mol % CuI, 10 mol % **8** DCE, 70 °C, 16 h. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis.

between unsubstituted substrates **12a–c** and MVK provided the desired cyclic urea products **13a–c** in moderate yield (entries 1–3). In contrast to the reactions between **5d** and MVK, the reaction of nitrophenyl urea substrate **12c** afforded the cyclic urea product **13c** in one step, without the need for a subsequent base-mediated transformation. Substrates **12d–e**, which contain a methyl group in the allylic position, were also converted to cyclic ureas in moderate yield, but diastereoselectivity was poor (2:1 dr; entries 4–5). Efforts to employ a substrate related to **12b** that contained a methyl group at the internal alkene carbon failed to afford the desired product. Instead, only unreacted starting material was observed, which is consistent with the fact that more highly substituted alkenes are much less reactive toward alkene metathesis.[18]

As observed with substrates **5a–d**, efforts to use the standard protocol (conditions A) for reactions of acyclic ureas **12a–b** with methyl acrylate failed to produce acceptable yields of the desired product, and mixtures of cyclic urea and acyclic metathesis products were obtained. Moreover, the two-step procedure used with **5a–d**, in which the metathesis product was treated with KO^{t}Bu to effect the Michael addition (conditions B), was also unsuccessful with **12a–c**. However, we were pleased to find that a modified version of the original Fustero procedure,[15a] in which the metathesis was conducted in one step with the presence of added BF_3·OEt_2 (conditions C), provided cyclic ureas **13f–g** in moderate yield. In contrast, electron-poor urea **12c** was converted to **13h** in one step under the standard conditions A.

In conclusion, we have developed a new cross-metathesis/aza-Michael reaction strategy that effects the transformation of ureas derived from 2-allylpyrrolidine or *N*-allylbenzylamine into bicyclic and monocyclic ureas, respectively, with formation of the ring, a C–N bond, a C–C bond, and introduction of ketone or ester functionality adjacent to the ring. Products in reactions that employ MVK are formed in moderate yield, with moderate to excellent levels of diastereoselectivity, and similar transformations of methyl acrylate provide products in low to moderate yield, with modest diastereoselectivity. The observed high diastereoselectivities likely arise via a kinetically controlled Michael addition reaction that proceeds through a chairlike transition state, whereas lower selectivities may result from thermodynamic control in a reversible Michael addition step.

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. The Hoveyda-Grubbs II catalyst and *N*-Boc-pyrrolidine were purchased from Sigma-Aldrich Chemical Co. and used without further purification. 1,2-Dichloroethane (DCE) was purchased from Acros chemicals and was purified via freeze–pump–thaw prior to use. *tert*-Butyl 2-allylpyrrolidine-1-carboxylate,[19] *N*-benzylprop-2-en-1-amine,[10b] and *N*-benzylbut-3-en-2-amine[10b] were prepared according to published procedures. Dichloromethane, toluene, and tetrahydrofuran were purified using a GlassContour solvent purification system. Boron trifluoride diethyl etherate, tetramethylethylenediamine, methyl vinyl ketone, and methyl acrylate were purified by distillation 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 2–3 *are averages of two or more experiments. Thus, the yields reported in the* Experimental Section *may differ from those shown in* Tables 2–3.

Experimental Procedures and Compound Characterization Data for Substrates. General Procedure 1. *Synthesis of Pyrrolidinyl Ureas.* A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with *tert*-butyl 2-allylpyrrolidine-1-carboxylate[18] (1 equiv) and dichloromethane (0.2 M). The mixture was cooled to 0 °C, and trifluoroacetic acid (1.0 M) was added dropwise. The reaction mixture was warmed to rt, stirred

DOI: 10.1021/acs.joc.8b01492
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overnight, and then was basified to pH > 12 with ammonium hydroxide. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 2-allylpyrrolidine as a volatile oil that was used without purification.

The crude 2-allylpyrrolidine was dissolved in dichloromethane (0.2 M), and the appropriate isocyanate (1.1 equiv) was added. The resulting mixture was stirred at rt overnight and then was concentrated *in vacuo*. The crude urea product was purified via flash chromatography on silica gel usig 40% ethyl acetate in hexanes as the eluent to afford the 2-allylpyrrolidinyl urea, which was stored as a 0.2 M solution in 1,2-dichloroethane.

*2-Allyl-N-(4-chlorophenyl)pyrrolidine-1-carboxamide (**5a**).* The title compound was prepared from *tert*-butyl 2-allylpyrrolidine-1-carboxylate (1.20 g, 6 mmol) and *para*-chlorophenyl isocyanate (1.01 g, 6.66 mmol) according to General Procedure 1. This procedure afforded 1.04 g (65%) of the title compound as a yellow solid, mp 69−70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.31 (m, 2H), 7.26−7.18 (m, 2H), 6.28 (s, 1H), 5.86−5.73 (m, 1H), 5.16−5.05 (m, 2H), 4.08−4.00 (m, 1H), 3.48−3.37 (m, 2H), 2.54 (ddt, J = 3.0, 5.8, 13.5 Hz, 1H), 2.17 (dt, J = 8.4, 13.6 Hz, 1H), 2.07−1.95 (m, 1H), 1.98−1.88 (m, 2H), 1.81 (ddt, J = 2.5, 6.2, 8.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 137.8, 135.0, 128.7, 127.6, 120.7, 117.6, 57.3, 46.4, 38.6, 29.6, 23.7. IR (film) 3305.2, 1641.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{18}ClN_2O$ 265.1108; found 265.1106.

*2-Allyl-N-(4-methoxyphenyl)pyrrolidine-1-carboxamide (**5b**).* The title compound was prepared from *tert*-butyl 2-allylpyrrolidine-1-carboxylate (1.28 g, 6.06 mmol) and *para*-methoxyphenyl isocyanate (0.86 mL, 6.66 mmol) according to General Procedure 1 to afford 1.28 g (81%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.24 (m, 2H), 6.86−6.78 (m, 2H), 6.17 (s, 1H), 5.86−5.73 (m, 1H), 5.13−5.03 (m, 2H), 4.03 (tt, J = 3.5, 7.4 Hz, 1H), 3.76 (s, 3H), 3.44−3.37 (m, 2H), 2.60−2.51 (m, 1H), 2.22−2.11 (m, 1H), 2.04−1.91 (m, 2H), 1.79 (ddt, J = 2.6, 6.1, 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 154.4, 135.2, 132.2, 121.8, 117.4, 114.0, 57.2, 55.5, 46.3, 38.7, 29.5, 23.8. IR (film) 3291.8, 1635.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{21}N_2O_2$ 261.1603; found 261.1602.

*2-Allyl-N-(4-methoxybenzyl)pyrrolidine-1-carboxamide (**5c**).* The title compound was prepared from *tert*-butyl 2-allylpyrrolidine-1-carboxylate (2.01 g, 9.5 mmol) and *para*-methoxybenzyl isocyanate (1.5 mL, 10.5 mmol) according to General Procedure 1. This procedure afforded 0.324 g (49%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.21 (m, 2H), 6.90−6.80 (m, 2H), 5.77 (dddd, J = 6.5, 7.7, 10.2, 16.9 Hz, 1H), 5.10−4.99 (m, 2H), 4.45 (s, 1H), 4.36 (q, J = 14.4 Hz, 2H), 3.97 (tt, J = 3.2, 6.9 Hz, 1H), 3.79 (s, 3H), 3.34−3.23 (m, 2H), 2.56−2.47 (m, 1H), 2.13 (dddd, J = 1.2, 8.0, 8.9, 13.7 Hz, 1H), 1.99−1.83 (m, 3H), 1.76 (ddt, J = 2.6, 6.1, 8.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 156.6, 135.3, 131.9, 129.1, 117.2, 113.9, 56.9, 55.3, 46.1, 44.1, 38.8, 29.4, 23.6. IR (film) 3321.8, 1624.3, cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_2$ 275.1760; found 275.1758.

*2-Allyl-N-(4-nitrophenyl)pyrrolidine-1-carboxamide (**5d**).* The title compound was prepared from *tert*-butyl 2-allylpyrrolidine-1-carboxylate (0.50 g, 2.4 mmol) and *para*-nitrophenyl isocyanate (0.43 g, 2.6 mmol) according to General Procedure 1. This procedure afforded 0.324 g (49%) of the title compound as a yellow solid, mp 99−102 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 9.1 Hz, 2H), 7.61−7.54 (m, 2H), 6.59 (s, 1H), 5.82 (ddt, J = 7.2, 10.3, 17.2 Hz, 1H), 5.18−5.09 (m, 2H), 4.09 (dt, J = 5.0, 10.4 Hz, 1H), 3.53−3.46 (m, 2H), 2.56 (dt, J = 5.5, 12.2 Hz, 1H), 2.27−2.15 (m, 2H), 2.12−2.01 (m, 1H), 2.04−1.94 (m, 1H), 1.85 (ddq, J = 2.8, 3.6, 6.4, 9.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 145.3, 142.3, 134.7, 125.1, 118.0, 57.6, 46.5, 38.5, 29.7, 23.7. IR (film) 3325, 1654.9 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{18}N_3O_3$ 276.1348; found 276.1343.

General Procedure 2. *Synthesis of N-Benzyl-N-allylureas.* A flame-dried round-bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with the appropriate benzylamine (1 equiv), dichloromethane (1.0 M), and the appropriate isocyanate (1.4 equiv). The resulting mixture was stirred at rt overnight and then was concentrated *in vacuo* to yield the crude urea product, which was purified via flash chromatography on silica gel using 20% ethyl acetate in hexanes as the eluent.

*1-Allyl-1-benzyl-3-(4-chlorophenyl)urea (**12a**).* The title compound was prepared from *N*-benzylprop-2-en-1-amine[10a] (0.997 g, 6.6 mmol) and 4-chlorophenyl isocyanate (1.44 g, 9.4 mmol) using General Procedure 2. This procedure afforded 1.68 g (85%) of the title compound as a peach color solid, mp 84−85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.33 (m, 2H), 7.37−7.27 (m, 3H), 7.27−7.17 (m, 4H), 6.45 (s, 1H), 5.85 (ddt, J = 5.4, 10.5, 17.3 Hz, 1H), 5.35−5.26 (m, 2H), 4.58 (s, 2H), 3.97 (dt, J = 1.7, 5.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 137.7, 137.4, 133.7, 128.9, 128.8, 127.9, 127.8, 127.5, 120.9, 117.6, 50.6, 50.0. IR (film) 3325.6, 1636.6, cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{18}ClN_2O$ 301.1108; found 301.1114.

*1-Allyl-1-benzyl-3-(4-methoxyphenyl)urea (**12b**).* The title compound was prepared from *N*-benzylprop-2-en-1-amine[10b] (0.996 g, 6.6 mmol) and 4-methoxyphenyl isocyanate (1.1 mL, 9.3 mmol) using General Procedure 2. This procedure afforded 1.53 g (79%) of the title compound as a white-tan solid, mp 88−90 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 7.23−7.17 (m, 2H), 6.84−6.78 (m, 2H), 6.37 (s, 1H), 5.85 (ddt, J = 5.4, 10.5, 17.2 Hz, 1H), 5.33−5.23 (m, 2H), 4.57 (s, 2H), 3.96 (dt, J = 1.7, 5.5 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 155.7, 137.7, 133.8, 132.1, 128.8, 127.6, 127.5, 122.0, 117.4, 114.0, 55.5, 50.5, 49.9. IR (film) 3326.0, 1634.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{21}N_2O_2$ 297.1603; found 297.1604.

*1-Allyl-1-benzyl-3-(4-nitrophenyl)urea (**12c**).* The title compound was prepared from *N*-benzylprop-2-en-1-amine (1.00 g, 6.6 mmol) and 4-nitrophenyl isocyanate (1.54 g, 9.4 mmol) using General Procedure 2. This procedure afforded 1.51 g (74%) of the title compound as a pale yellow solid, mp 106−108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14−8.09 (m, 2H), 7.48−7.42 (m, 2H), 7.41−7.34 (m, 3H), 7.32 (dt, J = 1.7, 6.1 Hz, 2H), 6.88 (s, 1H), 5.87 (ddt, J = 5.4, 10.6, 17.2 Hz, 1H), 5.38−5.30 (m, 2H), 4.60 (s, 2H), 4.00 (dt, J = 1.7, 5.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 145.3, 142.4, 136.9, 133.4, 129.0, 128.0, 127.5, 125.0, 118.4, 118.0, 50.8, 50.2. IR (film) 3341.3, 1657.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{18}N_3O_3$ 312.1348; found 312.1351.

*1-Benzyl-1-(but-3-en-2-yl)-3-(4-methoxyphenyl)urea (**12d**).* The title compound was prepared from *N*-benzylbut-3-en-2-amine (0.302 g, 1.86 mmol) and 4-methoxyphenyl isocyanate (0.34 mL, 2.61 mmol) using General Procedure 2. This procedure afforded 0.512 g (88%) of the title compound as an orange-pink solid, mp 87−89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.37 (m, 5H), 7.10−7.03 (m, 2H), 6.81−6.73 (m, 2H), 6.23 (s, 1H), 5.99 (ddd, J = 4.4, 10.6, 17.5 Hz, 1H), 5.31−5.20 (m, 2H), 5.00 (dtt, J = 2.4, 5.3, 7.3 Hz, 1H), 4.53 (d, J = 17.1 Hz, 1H), 4.37 (d, J = 17.1 Hz, 1H), 3.74 (s, 3H), 1.33 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 155.7, 139.2, 138.0, 132.1, 129.0, 127.7, 126.9, 121.9, 116.2, 114.0, 55.5, 53.2, 47.4, 16.6. IR (film) 3322.7, 1633.5 cm^{-1} HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{23}N_2O_2$ 311.1760; found 311.1764.

*1-Benzyl-1-(but-3-en-2-yl)-3-(4-nitrophenyl)urea (**12e**).* The title compound was prepared from *N*-benzylbut-3-en-2-amine (0.135 g, 0.84 mmol) and 4-nitrophenyl isocyanate (0.193 g, 1.2 mmol) using General Procedure 2. This procedure afforded 0.088 g (32%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.05 (d, J = 9 Hz, 2H), 7.46−7.39 (m, 2H), 7.39−7.32 (m, 3H), 7.34−7.27 (m, 2H), 6.75 (s, 1H), 6.00 (ddd, J = 4.4, 10.4, 17.6 Hz, 1H), 5.35−5.28 (m, 2H), 4.97 (s, 1H), 4.58 (d, J = 16.9 Hz, 1H), 4.41 (d, J = 16.9 Hz, 1H), 1.37 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 145.2, 142.4, 138.7, 137.2, 129.3, 128.2, 126.8, 125.0, 118.2, 117.0, 52.8, 47.8, 16.6. IR (film) 3390.6, 1653.2 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}N_3O_3$ 326.1505; found 326.1501.

Experimental Procedures and Compound Characterization Data for Products of the Metathesis/Michael Reaction Sequence. General Procedure 3 (Conditions A). A flame-dried

DOI: 10.1021/acs.joc.8b01492
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Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the Hoveyda-Grubbs II catalyst (0.02 mmol, 10 mol %) and copper iodide (0.02 mmol, 10 mol %). The flask was purged with nitrogen and charged with the appropriate urea substrate (0.2 mmol) in 1,2-dichloroethane (0.2 M), and the resulting mixture was stirred for 5 min at rt. Methyl vinyl ketone or methyl acrylate (1.0 mmol) was added, and the reaction mixture was heated to 70 °C with stirring overnight. The reaction mixture was then cooled to rt and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford the desired product.

General Procedure 4 (Conditions B). The reaction was carried out according to General Procedure 3. The cross-metathesis product (**10**) was purified by flash chromatography on silica gel and then transferred as a solution in 1,2-dichloroethane (1 mL) to a nitrogen-filled flame-dried Schlenk tube equipped with a stir bar that had been charged with potassium *tert*-butoxide (1.5 equiv). The mixture was heated to 70 °C with stirring overnight, then was cooled to rt, and quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with dichloromethane (3 × 2 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford the desired product.

General Procedure 5 (Conditions C). A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the Hoveyda-Grubbs II catalyst (0.02 mmol, 10 mol %) and copper iodide (0.02 mmol, 10 mol %). The flask was purged with nitrogen, and the appropriate substrate (0.2 mmol) in 1,2-dichloroethane (0.2 M) was added. The resulting mixture was stirred for 5 min at rt, and then methyl acrylate (1.0 mmol) and boron trifluoride diethyl etherate (0.2 mmol) were added. The reaction mixture was heated to 70 °C with stirring overnight and then was cooled to rt, and the reaction was quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with dichloromethane (3 × 2 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford the desired product.

(±)-(3S,4aS*)-2-(4-Chlorophenyl)-3-(2-oxopropyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (**7a**).* The title compound was prepared from 2-allyl-*N*-(4-chlorophenyl) pyrrolidine-1-carboxamide (52 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 50% ethyl acetate in hexanes →100% ethyl acetate as the eluent). This procedure afforded 52.7 mg (86%) as a brown solid, mp 110−112 °C. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 4.29 (ddt, J = 3.8, 8.1, 14.9 Hz, 1H), 3.69−3.57 (m, 1H), 3.48 (dd, J = 5.0, 9.4 Hz, 2H), 2.48 (ddt, J = 3.2, 12.6, 28.4 Hz, 2H), 2.33 (ddd, J = 2.8, 8.6, 17.5 Hz, 1H), 2.23−2.10 (m, 1H), 1.96 (s 3H), 1.79 (dddt, J = 3.0, 6.6, 9.6, 12.7 Hz, 2H), 1.56−1.35 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.0, 154.3, 139.2, 132.3, 130.5, 129.0, 54.7, 53.0, 48.5, 45.9, 35.7, 33.5, 30.7, 23.1. IR (film) 3425.6, 1712.6, 1631.3 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{20}ClN_2O_2$ 307.1213; found 307.1215.

(±)-(3S,4aS*)-2-(4-Methoxyphenyl)-3-(2-oxopropyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (**7b**).* The title compound was prepared from 2-allyl-*N*-(4-methoxyphenyl) pyrrolidine-1-carboxamide (52 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 40% ethyl acetate in hexanes →100% ethyl acetate as the eluent). This procedure afforded 24.4 mg (75%) of the title compound as a purple solid, mp 103−106 °C. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.27 (ddt, J = 4.0, 8.1, 12.0 Hz, 1H), 3.79 (s, 3H), 3.64 (tt, J = 4.5, 10.3 Hz, 1H), 3.56−3.47 (m, 2H), 2.57 (dd, J = 4.2, 17.4 Hz, 1H), 2.44 (dt, J = 3.4, 12.7 Hz, 1H), 2.32 (dd, J = 8.4, 17.5 Hz, 1H), 2.20−2.10 (m, 1H), 1.89 (s, 3H), 1.80 (ttd, J = 6.6, 9.3, 12.3 Hz, 2H), 1.56−1.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.3, 158.2, 133.3, 130.5, 114.2, 55.4, 54.8, 53.4, 48.6, 46.0, 35.7, 33.6, 30.7, 29.7, 23.2. IR (film) 3412.2, 1713.2, 1635.4 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_3$ 303.1709; found 303.1707.

(±)-(3S,4aS*)-2-(4-Methoxybenzyl)-3-(2-oxopropyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (**7c**).* The title compound was prepared from 2-allyl-*N*-(4-methoxybenzyl) pyrrolidine-1-carboxamide (55 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 50% ethyl acetate in hexanes →100:0 ethyl acetate as the eluent). This procedure afforded 45 mg (71%) of the title compound as a purple solid, mp 109−112 °C. 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 (500 MHz, $CDCl_3$) δ 7.27−7.13 (m, 2H), 6.88−6.80 (m, 2H), 4.82 (d, J = 15.9 Hz, 1H), 4.29 (d, J = 15.9 Hz, 1H), 3.89−3.84 (m, 1H), 3.78 (s, 3H), 3.80−3.71 (m, 1H), 3.65−3.40 (m, 3H), 2.86 (dd, J = 4.0, 16.9 Hz, 1H), 2.38−2.25 (m, 2H), 2.14−2.02 (m, 1H), 1.99 (s, 2H), 1.93 (dtt, J = 11.8, 7.0, 2.3 Hz, 1H), 1.78 (ttd, J = 6.9, 9.3, 12.4 Hz, 1H), 1.45 (tdd, J = 7.3, 9.8, 11.9 Hz, 1H), 1.36−1.23 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.3, 158.5, 156.3, 131.1, 128.4, 113.9, 55.3, 54.2, 50.7, 47.9, 47.2, 46.1, 35.9, 33.7, 30.8, 23.2. IR (film) 3444.4, 1712.3, 1612.6 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_3$ 317.1865; found 317.1855.

(±)-(3S,4aS*)-2-(4-Nitrophenyl)-3-(2-oxopropyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (**7d**).* The title compound was prepared from 2-allyl-*N*-(4-nitrophenyl) pyrrolidine-1-carboxamide (55 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 4. The cross-metathesis step afforded 45 mg (71%) of (±)-(*E*)-*N*-(4-nitrophenyl)-2-(4-oxopent-2-en-1-yl)-pyrrolidine-1-carboxamide (**10d**) as a brown oil (chromatography was performed using 40% ethyl acetate in hexanes →100% ethyl acetate as the eluent). ^{1}H NMR (500 MHz, $CDCl_3$) 8.17 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 6.79 (dt, J = 7.3, 15.1 Hz, 1H), 6.56 (s, 1H), 6.13 (d, J = 15.8 Hz, 1H), 4.26 (dq, J = 4.3, 8.3 Hz, 1H), 3.53 (s, 1H), 3.48 (d, J = 7.7 Hz, 1H), 2.76 (dt, J = 5.3, 11.9 Hz, 1H), 2.45−2.34 (m, 1H), 2.25 (s, 3H), 2.04 (dtd, J = 6.8, 11.7, 13.0, 26.1 Hz, 3H), 1.83−1.75 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.28, 152.72, 145.05, 143.86, 143.70, 133.29, 124.89, 118.20, 56.83, 46.46, 37.14, 29.57, 27.15, 24.06. IR (film) 3356.4, 2970.5, 1662.6, 1542.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{20}N_3O_4$ 318.1454; found 318.1453.

Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 100% ethyl acetate as the eluent) afforded 39 mg (65%; 45% over two steps from **5d**) of the title compound as a white-tan solid, mp 143−147 °C. The compound was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, J = 7.7, 9.6 Hz, 2H), 7.48−7.41 (d, J = 9 Hz, 2H), 4.68 (dq, J = 2.6, 3.3, 9.5 Hz, 1H), 3.70−3.56 (m, 2H), 3.55−3.47 (m, 1H), 2.78 (dd, J = 9.7, 17.9 Hz, 1H), 2.70−2.61 (m, 1H), 2.28 (ddd, J = 2.1, 3.7, 13.5 Hz, 1H), 2.23−2.14 (m, 1H), 2.10−1.93 (m, 4H), 1.92−1.75 (m, 2H), 1.61−1.41 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.6, 153.0, 148.0, 144.4, 128.4, 126.4, 124.3, 124.0, 53.1, 46.0, 33.7, 31.5, 30.6, 23.3. IR (film) 2973.4, 1711.9, 1640 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{20}N_3O_4$ 318.1454; found 318.1453.

(±)-(3S,4aS*)-Methyl 2-(2-(4-chlorophenyl)-1-oxooctahydropyrrolo[1,2-c]pyrimidin-3-yl)acetate (**7e**).* The title compound was prepared from 2-allyl-*N*-(4-chlorophenyl) pyrrolidine-1-carboxamide (53 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 4. The cross-metathesis step afforded 41 mg (63%) of (*E*)-4-{1-[(4-chlorophenyl)carbamoyl]pyrrolidin-2-yl]but-2-enoate (**10e**) as a purple oil (chromatography was performed using 40% ethyl acetate in hexanes as the eluent). The compound was obtained as a 4:1 mixture of *E*/*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.31 (m, 2H), 7.26−7.17 (m, 2H), 6.91 (dt, J = 7.5, 15.3 Hz, 1H), 6.26 (s, 1H), 5.88 (dt, J = 1.4, 15.6 Hz, 1H), 4.17 (dq, J = 3.6,

DOI: 10.1021/acs.joc.8b01492
J. Org. Chem. XXXX, XXX, XXX−XXX

10.2 Hz, 1H), 3.72 (s, 3H), 3.49−3.36 (m, 2H), 2.73 (dddd, J = 1.5, 3.6, 6.9, 14.0 Hz, 1H), 2.44−2.33 (m, 1H), 2.06−1.89 (m, 3H), 1.80−1.71 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 153.6, 145.2, 137.6, 128.8, 128.5, 123.3, 120.9, 56.6, 51.5, 46.4, 36.7, 29.5, 24.0. IR (film) 3329.9, 1719.5, 1642.9 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{20}ClN_2O_3$ 323.1162; found 323.1161.

Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 40% ethyl acetate in hexanes →100% ethyl acetate as the eluent) afforded 25 mg (63%, 38% over two steps from **5a**) of the title compound as a white solid, mp 117−118 °C. The compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 2H), 7.17 (dd, J = 8.6, 1.7 Hz, 2H), 4.23 (ddt, J = 4.1, 8.5, 11.2 Hz, 1H), 3.72−3.60 (m, 1H), 3.56 (s, 3H), 3.53−3.45 (m, 2H), 2.57−2.40 (m, 2H), 2.19−2.12 (m, 2H), 2.05−1.92 (m, 1H), 1.82 (ddt, J = 15.1, 12.0, 4.5 Hz, 1H), 1.60−1.47 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 154.2, 139.0, 130.6, 129.1, 54.6, 54.0, 51.7, 45.9, 39.9, 35.6, 33.8, 31.7, 23.1. IR (film) 1733.2, 1639.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{20}ClN_2O_3$ 323.1162; found 323.1163.

(±)-(3S,4aS*)-Methyl 2-[2-(4-methoxyphenyl)-1-oxooctahydropyrrolo[1,2-c]pyrimidin-3-yl]acetate (**7f**).* The title compound was prepared from 2-allyl-*N*-(4-methoxyphenyl) pyrrolidine-1-carboxamide (52 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 4. The cross-metathesis step afforded 54 mg (85%) of methyl (*E*)-4-{1-[(4-methoxyphenyl)carbamoyl]pyrrolidin-2-yl}but-2-enoate (**10f**) as a brown/tan oil (chromatography was performed using 40% ethyl acetate in hexanes as the eluent). The compound was obtained as a 5:1 mixture of *E*/*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.24 (m, 2H), 6.97−6.87 (m, 1H), 6.85−6.78 (m, 2H), 6.13 (s, 1H), 5.98−5.84 (m, 1H), 4.20−4.06 (m, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.47−3.35 (m, 2H), 2.74 (dddd, J = 1.6, 3.6, 7.0, 14.1 Hz, 1H), 2.38 (dddd, J = 1.4, 8.0, 9.0, 14.2 Hz, 1H), 2.03−1.96 (m, 3H), 1.74 (ddt, J = 3.4, 5.4, 12.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 155.8, 154.3, 145.5, 131.9, 123.2, 122.1, 114.1, 56.5, 55.5, 51.5, 46.3, 36.9, 29.7, 24.0. IR (film) 3322.7, 2950.0, 1719.1, 1639.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_4$ 319.1658; found 319.1656.

Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 100% ethyl acetate as the eluent) afforded 46 mg (84%, 71% over two steps from **5b**) of the title compound as a yellow solid, mp 107−110 °C. The compound was obtained as a 5:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 2H), 6.90−6.84 (m, 2H), 4.23−4.15 (m, 1H), 3.79 (s, 3H), 3.65 (s, 1H), 3.57 (s, 1H), 3.54 (s, 3H), 3.51 (dd, J = 4.9, 9.4 Hz, 2H), 2.45 (td, J = 3.7, 13.7, 14.8 Hz, 2H), 2.18 (dt, J = 7.4, 14.5 Hz, 2H), 2.00−1.93 (m, 1H), 1.81 (s, 1H), 1.55 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4 158.3, 154.7, 133.2, 130.1, 114.2, 55.4, 54.7, 54.2, 51.6, 46.0, 40.1, 35.6, 33.6, 23.1. IR (film) 1734.2, 1634.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_4$ 319.1658; found 319.1661.

(±)-(3S,4aS*)-Methyl 2-(2-(4-methoxybenzyl)-1-oxooctahydropyrrolo[1,2-c]pyrimidin-3-yl)acetate (**7g**).* The title compound was prepared from 2-allyl-*N*-(4-methoxybenzyl) pyrrolidine-1-carboxamide (55 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 4. The cross-metathesis step afforded 48 mg (72%) of (*E*)-methyl 4-{1-[(4-methoxybenzyl)carbamoyl]pyrrolidin-2-yl}but-2-enoate (**10g**) as a pink-purple oil (chromatography was performed using 40% ethyl acetate in hexanes as the eluent). The compound was obtained as a >20:1 mixture of *E*/*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.16 (m, 2H), 6.97−6.81 (m, 3H), 5.86 (dt, J = 1.5, 15.6 Hz, 1H), 4.44 (s, 1H), 4.41−4.29 (m, 1H), 4.35 (s, 1H), 4.11 (ddd, J = 3.1, 5.5, 9.8 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.32−3.19 (m, 2H), 2.70 (dddd, J = 1.5, 3.6, 7.0, 14.0 Hz, 1H), 2.42−2.31 (m, 1H), 1.99−1.85 (m, 2H), 1.75−1.66 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 158.9, 156.5, 145.7, 131.7, 129.1, 123.1, 114.0, 56.3, 55.3, 51.5, 46.0, 44.1, 37.1, 29.5, 23.9. IR (film) 3333.9, 1719.5, 1626.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_4$ 333.1814; found 333.1806.

Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 100% ethyl acetate as the eluent) afforded 26 mg (54%, 39% over two steps from **5c**) of the title compound as a yellow oil. The compound was obtained as a 8:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.14 (m, 2H), 6.84 (d, J = 8.2 Hz, 2H), 5.02 (d, J = 15.9 Hz, 1H), 4.21 (d, J = 15.9 Hz, 1H), 3.78 (s, 2H), 3.64 (d, J = 14.9 Hz, 3H), 3.63−3.40 (m, 3H), 2.77 (dd, J = 3.9, 15.2 Hz, 1H), 2.31−2.20 (m, 2H), 2.11 (qd, J = 3.8, 7.3 Hz, 1H), 2.05−1.89 (m, 1H), 1.93 (s, 1H), 1.86−1.72 (m, 1H), 1.54−1.35 (m, 2H), 0.39 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 158.6, 156.1, 130.8, 128.5, 113.9, 55.2, 54.1, 51.7, 51.3, 46.7, 46.1, 39.0, 35.5, 33.5, 23.2. IR (film) 1734.0, 1614.3 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_4$ 333.1814; found 333.1810.

*Methyl 2[(2-(4-Nitrophenyl)-1-oxooctahydropyrrolo[1,2-c]-pyrimidin-3-yl]acetate (**7h**).* The title compound was prepared from 2-allyl-*N*-(4-nitrophenyl) pyrrolidine-1-carboxamide (55 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 4. The cross-metathesis step afforded 36 mg (54%) of (*E*)-methyl 4-{1-[(4-nitrophenyl)carbamoyl]pyrrolidin-2-yl}but-2-enoate (**10h**) as a brown oil (chromatography was performed using 40% ethyl acetate in hexanes as the eluent). The compound was obtained as a 4:1 mixture of *E*/*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.31 (m, 2H), 7.26−7.18 (m, 2H), 6.91 (dt, J = 7.5, 15.3 Hz, 1H), 6.26 (s, 2H), 5.89 (dt, J = 1.5, 15.5 Hz, 1H), 4.18 (dq, J = 3.7, 10.2 Hz, 1H), 3.72 (s, 3H), 3.49−3.36 (m, 2H), 2.73 (dddd, J = 1.4, 3.7, 6.8, 13.7 Hz, 1H), 2.44−2.34 (m, 1H), 2.07−1.95 (m, 2H), 1.75 (tq, J = 3.8, 5.0, 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 152.7, 145.2, 144.8, 142.4, 125.1, 123.6, 118.2, 56.8, 51.6, 46.5, 36.5, 29.5, 24.0. IR (film) 3357.3, 1718.3, 1654.4 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{20}N_3O_5$ 334.1403; found 334.1401.

Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 100% ethyl acetate as the eluent) afforded 19.4 mg (58%, 31% over two steps from **5d**) of the title compound as a yellow solid, mp 99−100 °C. 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 (500 MHz, $CDCl_3$) δ 8.24−8.16 (m, 4H), 7.50−7.42 (m, 4H), 4.61 (dtd, J = 1.9, 5.1, 10.6 Hz, 1H), 4.39 (ddt, J = 4.0, 8.4, 10.7 Hz, 1H), 3.75−3.46 (m, 12H), 2.67−2.43 (m, 4H), 2.34−2.16 (m, 4H), 2.08−1.95 (m, 2H), 1.90−1.79 (m, 3H), 1.67−1.51 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 153.3, 152.9, 148.0, 146.7, 145.5, 144.5, 128.7, 126.7, 124.3, 124.0, 54.5, 53.6, 52.8, 51.9, 46.5, 46.0, 39.7, 37.6, 35.6, 33.7, 33.5, 31.6, 23.3, 23.0. IR (film) 1733.7, 1644.3 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{20}N_3O_5$ 334.1403; found 334.1403.

*1-Benzyl-3-(4-chlorophenyl)-4-(2-oxopropyl)imidazolidin-2-one (**13a**).* The title compound was prepared from 1-allyl-1-benzyl-3-(4-chlorophenyl)urea (60 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 20% ethyl acetate in hexanes → 40% ethyl acetate in hexanes as the eluent). This procedure afforded 48 mg (70%) of the title compound as a brown solid, mp 89−92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.35 (m, 2H), 7.35−7.18 (m, 5H), 4.59 (dddd, J = 2.8, 4.7, 8.6, 10.0 Hz, 1H), 4.47−4.36 (m, 2H), 3.64 (t, J = 9.1 Hz, 1H), 2.97−2.88 (m, 2H), 2.59 (dd, J = 10.1, 18.3 Hz, 1H), 2.37 (s, 1H), 2.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.2, 157.3, 137.0, 136.5, 129.1, 128.8, 128.7, 128.3, 127.7, 121.8, 49.1, 48.1, 47.9, 46.1, 30.5. IR (film) 1699.5, 1493.4 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{20}ClN_2O_2$ 343.1213; found 343.1212.

*1-Benzyl-3-(4-methoxyphenyl)-4-(2-oxopropyl)imidazolidin-2-one (**13b**).* The title compound was prepared from 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea (60 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 20% ethyl acetate in hexanes → 40% ethyl acetate in hexanes as the eluent). This procedure afforded 43 mg (63%) of the title compound as a brown solid, mp 110−111 °C. ^{1}H NMR (500

DOI: 10.1021/acs.joc.8b01492
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MHz, $CDCl_3$) δ 7.38−7.21 (m, 7H), 6.95−6.86 (m, 2H), 4.55−4.42 (m, 2H), 4.38 (d, J = 14.9 Hz, 1H), 3.79 (s, 3H), 3.63 (t, J = 9.0 Hz, 1H), 2.94−2.86 (m, 2H), 2.57 (dd, J = 10.0, 18.2 Hz, 1H), 2.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.4, 158.2, 156.7, 136.8, 131.2, 128.7, 128.3, 127.6, 124.0, 114.4, 55.5, 50.3, 48.3, 48.1, 46.5, 30.5. IR (film) 1694.4, 1511.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{23}N_2O_3$ 339.1709; found 339.1713.

*1-Benzyl-3-(4-nitrophenyl)-4-(2-oxopropyl)imidazolidin-2-one (**13c**).* The title compound was prepared from 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (60 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 20% ethyl acetate in hexanes → 40% ethyl acetate in hexanes as the eluent) to afford 44 mg (62%) yellow solid, mp 132−135 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 9.5 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.40−7.25 (m, 5H), 4.76−4.67 (m, 1H), 4.51−4.37 (m, 2H), 3.67 (t, J = 9.2 Hz, 1H), 3.04−2.94 (m, 2H), 2.69 (dd, J = 10.3, 18.5 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.9, 156.2, 144.5, 142.2, 135.9, 128.8, 128.3, 128.0, 125.0, 117.8, 48.7, 47.9, 47.8, 45.7, 30.5. IR (film) 3404.4, 2924.0, 1704.3, 1593.4, 1500.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{20}N_3O_4$ 354.1454; found 354.1451.

(4R,5R*)-1-Benzyl-3-(4-methoxyphenyl)-5-methyl-4-(2-oxopropyl)imidazolidin-2-one (**13d**).* The title compound was prepared from 1-benzyl-1-(but-3-en-2-yl)-3-(4-methoxyphenyl)urea (62 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 20% ethyl acetate in hexanes → 40% ethyl acetate in hexanes as the eluent). This procedure afforded 40 mg (56%) of the title compound as a brown oil. The compound was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.19 (m, 5H), 6.89 (dd, J = 2.6, 9.2 Hz, 2H), 4.86 (d, J = 15.3 Hz, 1H), 4.17 (dt, J = 3.5, 9.2 Hz, 1H), 4.05 (d, J = 15.3 Hz, 1H), 3.79 (s, 3H), 3.84−3.71 (m, 1H), 3.14 (qd, J = 3.8, 6.2 Hz, 1H), 2.82−2.72 (m, 1H), 2.50 (dd, J = 9.2, 17.9 Hz, 1H), 1.98 (s, 3H), 1.29 (d, J = 6.2 Hz, 3H), 1.04 (d, J = 6.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.5, 157.1, 156.4, 137.4, 131.3, 128.6, 128.2, 127.5, 123.5, 114.4, 57.6, 55.5, 54.4, 45.9, 45.0, 30.7, 18.2. IR (film) 3362.5, 2932.6, 1693.8, 1511.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{25}N_2O_3$ 353.1865; found 353.1866.

(4R,5R*)-1-Benzyl-5-methyl-3-(4-nitrophenyl)-4-(2-oxopropyl)-imidazolidin-2-one (**13e**).* The title compound was prepared from 1-benzyl-1-(but-3-en-2-yl)-3-(4-nitrophenyl)urea (40 g, 0.12 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 20% ethyl acetate in hexanes →25% ethyl acetate in hexanes as the eluent). This procedure afforded 21 mg (48%) of the title compound as a white-tan solid, mp 155−158 °C. The compound was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24−8.17 (m, 2H), 7.76−7.68 (m, 2H), 7.36 (dd, J = 6.5, 8.0 Hz, 2H), 7.35−7.26 (m, 3H), 4.93 (d, J = 15.2 Hz, 1H), 4.37−4.27 (m, 1H), 4.03 (d, J = 15.1 Hz, 1H), 3.14 (qd, J = 2.0, 6.3 Hz, 1H), 2.86 (dd, J = 2.3, 18.5 Hz, 1H), 2.56 (dd, J = 10.2, 18.5 Hz, 1H), 2.06 (s, 3H), 1.31 (d, J = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.9, 155.2, 144.9, 142.0, 136.6, 128.9, 128.1, 127.9, 125.1, 117.1, 56.1, 54.2, 45.2, 44.9, 30.6, 18.3. IR (film) 1709.5, 1595.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{22}N_3O_4$ 368.1610; found 368.1608.

*Methyl 2-[1-Benzyl-3-(4-chlorophenyl)-2-oxoimidazolidin-4-yl]-acetate (**13f**).* The title compound was prepared from 1-allyl-1-benzyl-3-(4-chlorophenyl)urea (60 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 5 (chromatography was performed using 25% ethyl acetate in hexanes → 40% ethyl acetate in hexanes as the eluent). This procedure afforded 34 mg (47%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.14 (m, 9H), 4.61−4.45 (m, 2H), 4.40 (d, J = 14.8 Hz, 1H), 3.80−3.56 (m, 3H), 3.10 (dd, J = 4.5, 9.5 Hz, 1H), 2.78 (dd, J = 3.2, 16.4 Hz, 1H), 2.44 (dd, J = 9.9, 16.3 Hz, 1H), 1.46 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 136.4, 129.1, 128.7, 128.3, 127.0, 125.1, 122.5, 121.2, 52.0, 50.8, 50.1, 48.0, 47.6, 37.0. IR (film) 1732.7, 1703.0, 1594.2 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{20}ClN_2O_3$ 359.1162; found 359.1161.

*Methyl 2-[1-Benzyl-3-(4-methoxyphenyl)-2-oxoimidazolidin-4-yl]acetate (**13g**).* The title compound was prepared from 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea (60 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 5 (chromatography was performed using 25% ethyl acetate in hexanes → 40% ethyl acetate in hexanes as the eluent). This procedure afforded 35 mg (48%) of the title compound as a white-tan solid, mp 64−67 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.23 (m, 7H), 6.96−6.86 (m, 2H), 4.54−4.43 (m, 2H), 4.39 (d, J = 14.8 Hz, 1H), 3.79 (d, J = 1.3 Hz, 3H), 3.60 (d, J = 1.3 Hz, 3H), 3.07 (ddd, J = 1.2, 5.4, 9.3 Hz, 1H), 2.75 (dt, J = 2.2, 16.3 Hz, 1H), 2.42 (ddd, J = 1.2, 9.8, 16.3 Hz, 1H), 1.25 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 158.2, 156.8, 136.8, 128.7, 128.3, 127.6, 124.3, 114.4, 55.5, 51.8, 51.2, 48.1, 47.9, 37.4, 29.7. IR (film) 1733.7, 1699.7, cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{23}N_2O_4$ 355.1658; found 355.1657.

*Methyl 2-[1-Benzyl-3-(4-nitrophenyl)-2-oxoimidazolidin-4-yl]-acetate (**13h**).* The title compound was prepared from 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (62 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 25% ethyl acetate in hexanes as the eluent). This procedure afforded 52 mg (70%) of the title compound as a yellow solid, mp 130−132 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25−8.18 (m, 2H), 7.77−7.69 (m, 2H), 7.36 (dd, J = 6.4, 7.9 Hz, 2H), 7.34−7.26 (m, 3H), 4.72−4.63 (m, 1H), 4.51 (d, J = 14.9 Hz, 1H), 4.45 (d, J = 14.9 Hz, 1H), 3.67 (s, 3H), 3.64 (t, J = 9.0 Hz, 1H), 3.17 (dd, J = 3.2, 9.6 Hz, 1H), 2.84 (dd, J = 2.7, 16.5 Hz, 1H), 2.53 (dd, J = 10.1, 16.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 156.2, 144.4, 142.4, 135.8, 128.9, 128.3, 128.0, 125.1, 117.9, 52.2, 49.6, 47.9, 47.3, 36.6. IR (film) 1707.8, 1594.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{20}N_3O_5$ 370.1403; found 370.1402.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01492.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the University of Michigan for financial support of this work. The authors also thank Dr. Nick Babij for conducting preliminary experiments in this area.

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