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Domino 1,4- and 1,6-Addition Reactions of Ketene Silyl Acetals to Dialkynyl Imines Promoted by Aluminum Chloride: Synthesis of Multifunctionalized β-Lactams

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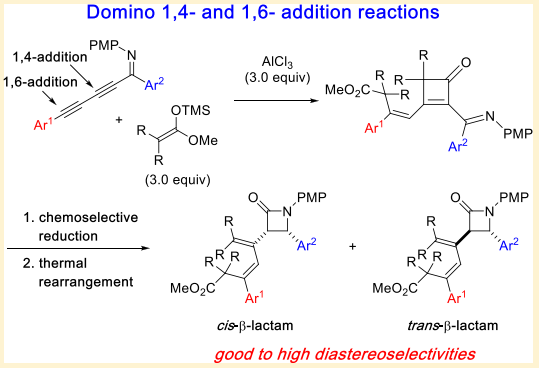
Supporting Information

ABSTRACT: Domino 1,4- and 1,6-addition reactions of ketene silyl acetals to dialkynyl imines are disclosed. Aluminum chloride promoted domino 1,4- and 1,6-addition reactions of ketene silyl acetals to dialkynyl imines to give a variety of alkenyl iminocyclobutenones in moderate to good yields. The chemoselective reduction of alkenyl iminocyclobutenones and the subsequent thermal rearrangement of resulting alkenyl aminocyclobutenones in the presence of appropriate amines provided cis or trans multifunctionalized β-lactams in moderate to high yields with good to high diastereoselectivities.



INTRODUCTION

The development of efficient synthetic methods for nitrogen-containing compounds is extensively investigated because many of them such as amino acids, β-lactams, and vitamins show useful biological activities. Imines, one of the most useful types of nitrogen-containing compounds, are typically prepared by the condensation of carbonyl compounds with primary amines via dehydration. Among various imines, there are α,β-unsaturated alkynyl imines having a triple bond. We have developed new efficient synthetic methods for various nitrogen-containing heterocycles using 1,4-additions of several carbon nucleophiles such as malonic esters, β-keto esters, and ethyl cyanoacetates to α,β-alkynyl imines.[1,2] In 2009, we developed the chemoselective reductions of iminocyclobutenones, which were synthesized using aluminum chloride-promoted 1,4-additions of ketene silyl acetals to α,β-alkynyl imines, to proceed using sodium cyanoborohydride under the influence of an acid to give the racemic aminocyclobutenones in high yields, and the subsequent thermal rearrangement of aminocyclobutenones in the presence of an appropriate amine afforded either racemic *cis*- or *trans*-β-lactams in good yields with high diastereoselectivities.[3] In 2014, we also reported chiral either *cis*- or *trans*-β-lactam synthesis through the enantioselective reduction of iminocyclobutenones catalyzed by a chiral phosphoric acid and the subsequent thermal rearrangement of chiral aminocyclobutenones in the presence of appropriate amines (Scheme 1).[4]

We next envisioned the total synthesis of SCH48461,[5] which is a cholesterol absorption inhibitor, via the synthesis of the chiral β-lactam **4** using the alkynyl iminocyclobutenone **3** as a key intermediate and considered use of the dialkynyl imine **1a** as a novel 1,4-addition acceptor (Scheme 2).[6]

First, we examined the 1,4-addition of an equivalent of ketene silyl acetal **2a** to dialkynyl imine **1a** in the presence of aluminum chloride. The desired alkynyl iminocyclobutenone **3** was not produced; however, the domino 1,4- and 1,6- addition product **5a** was obtained in 27% yield based on **2a** (Scheme 3).

We considered the formation of **5a** via the sequential 1,6-addition of the second nucleophile **2a** to the intermediate **3** generated in situ. 1,6-Addtion reactions of nucleophiles to α,β,γ,δ-unsaturated carbonyl compounds are rare compared to 1,4-addition reactions.[7] Transition-metal-catalyzed asymmetric 1,6-addition reactions have been reported as a represented example.[8] On the other hand, organocatalytic 1,6-addition reactions have been also developed.[9] Among them, 1,6-additon/1,4-addition cascade reactions have been reported by Jørgensen and Ye, respectively.[10] Therefore, we were interested in the formation of the domino 1,4- and 1,6-addition product **5a** albeit in a low yield. Here, we report a novel domino 1,4- and 1,6-addition reaction of ketene silyl acetals to dialkynyl imines.

RESULTS AND DISCUSSION

First, we screened the reaction conditions for the domino 1,4- and 1,6-double addition reactions using more reactive dialkynyl imine **1b** compared to **1a**. Table 1 summarizes the results. Several equivalents of aluminum chloride were

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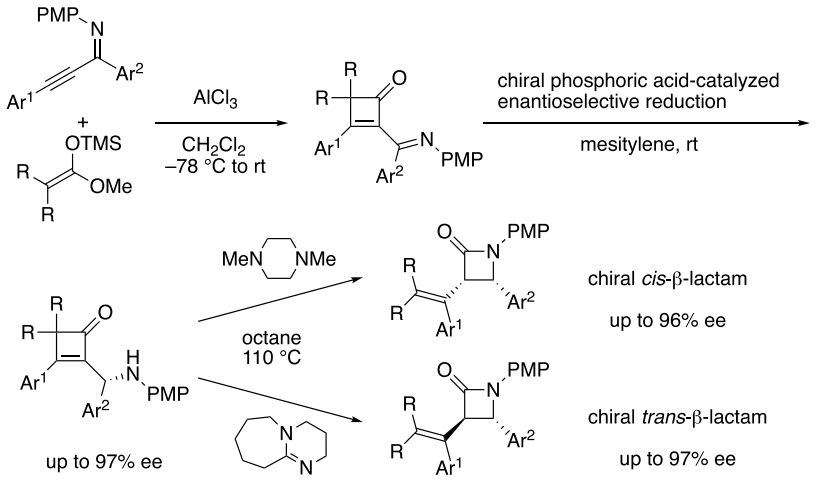
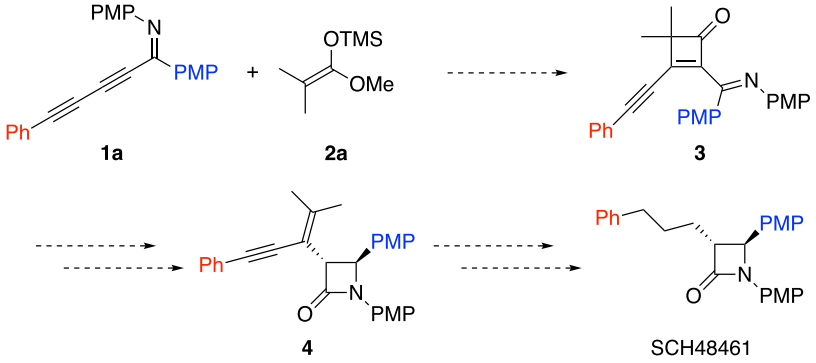
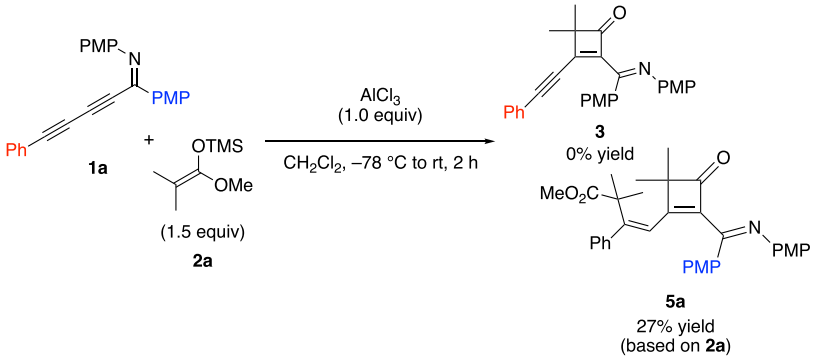
Scheme 1. Stereodivergent Synthesis of *Cis*- and *Trans*-β-Lactams



Scheme 2. Alkynyliminocyclobutenone Synthesis Directed to the Total Synthesis of SCH48461



Scheme 3. 1,4-Addition of Ketene Silyl Acetal 2a to Dialkynyl Imine 1a



examined (entries 1–4). When the reaction of imine **1b** with 3 equiv of the ketene silyl acetal **2a** was carried out in the presence of 3 equiv of aluminum chloride, the desired domino 1,4- and 1,6-addition product **5b** was obtained in 62% yield (entry 3). We next investigated other Lewis acids. Although ethylaluminum dichloride gave **5b** in 57% yield, titanium chloride was not effective (entries 5 and 6).

With the optimized reaction conditions in hands, several dialkynyl imines were subjected to the domino 1,4- and 1,6-addition reaction. The results are summarized in Table 2. We examined the aromatic substituents Ar^2 of the imino carbon. The reaction of imine **1a** under the optimized reaction conditions gave **5a** in 64% yield (entry 1). Dialkynyl imine **1c** having an electron-donating tolyl group afforded **5c** in 59% yield (entry 3). Dialkynyl imine **1d** having an electron-withdrawing 4-chlorophenyl group produced **5d** in 81% yield (entry 4). The reaction of the sterically hindered 2-naphthyl imine **1e** proceeded to give **5e** in 68% yield (entry 5). The imines **1f** and **1g** having a heteroaromatic group gave **5f** and **5g** in moderate yields (entries 6 and 7), respectively. We next examined the aromatic substituents Ar^1 of the terminal alkynyl group. Dialkynyl imines **1h–1j** having a monosubstituted phenyl group afforded **5h–5j** in good to high yields (entries 8–10). The imine **1k** possessing a sterically hindered 2-naphthyl group gave **5k** in 60% yield (entry 11). 2-Thienyl and 5-methyl-2-furyl imines **1l** and **1m** having a heteroaromatic group worked well to give **5l** and **5m** in 70 and 59% yields, respectively (entries 12 and 13). Finally, several ketene silyl

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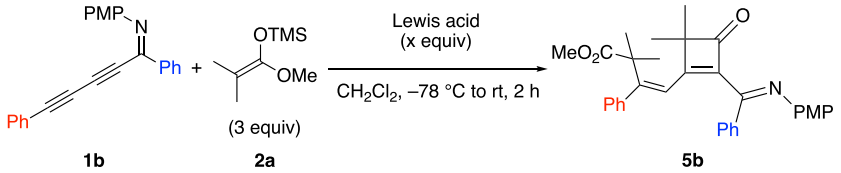
Table 1. Optimization of 1,4- and 1,6-Double Nucleophilic Addition Reaction Conditions

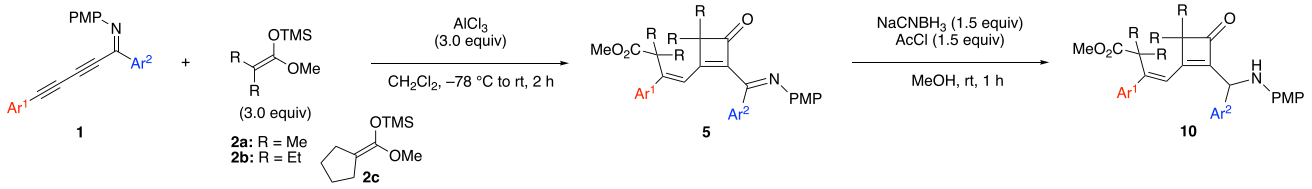


1b 2a 5b

entry	Lewis acid	equiv	yield (%)
1	$AlCl_3$	1	28
2	$AlCl_3$	2	32
3	$AlCl_3$	3	62
4	$AlCl_3$	4	60
5	$EtAlCl_2$	3	57
6	$TiCl_4$	3	0 (76)[a]

[a]Yields of the recovered dialkynyl imine **1b** in parenthesis.

Table 2. Scope of the Substrates in Domino 1,4- and 1,6-Addition Reaction and the Reduction of Iminocyclobutenones 5



entry	Ar^1	Ar^2	R	**5** (yield %)[a]	**10** (yield %)[g]
1	Ph	PMP	Me	**5a** (64)[b]	**10a** (52)
2	Ph	Ph	Me	**5b** (62)	**10b** (88)[h]
3	Ph	4-MeC_6H_4	Me	**5c** (59)[c]	**10c** (78)
4	Ph	4-ClC_6H_4	Me	**5d** (81)	**10d** (75)
5	Ph	2-naphthyl	Me	**5e** (68)[d]	**10e** (73)
6	Ph	2-thienyl	Me	**5f** (56)	**10f** (59)
7	Ph	2-furyl	Me	**5g** (48)[d]	**10g** (62)[i]
8	4-MeC_6H_4	Ph	Me	**5h** (65)	**10h** (70)
9	PMP	Ph	Me	**5i** (84)	**10i** (76)
10	4-ClC_6H_4	Ph	Me	**5j** (66)[e]	**10j** (80)
11	2-naphthyl	Ph	Me	**5k** (60)	**10k** (85)
12	2-thienyl	Ph	Me	**5l** (70)[d]	**10l** (72)
13	5-methyl-2-furyl	Ph	Me	**5m** (59)	**10m** (66)[j]
14[h]	Ph	Ph	Et	**5n** (51)[f]	**10n** (78)
15	Ph	Ph	$-(CH_2)_4-$	**5o** (71)[d]	**10o** (77)

[a]Conditions: dialkynyl imine **1** (0.1 mmol), ketene silyl acetal **2** (0.3 mmol), $AlCl_3$ (0.3 mmol), CH_2Cl_2 (2.0 mL), under Ar at −78 °C to rt, 2 h. [b]**1a** (0.50 mmol). [c]**1c** (0.40 mmol). [d]**1** (1.0 mmol). [e]**1f** (0.50 mmol). [f]**1b** (0.11 mmol), 1.5 h. [g]Conditions: See the Supporting Information for details. [h]0.5 h. [i]AcCl (0.5 equiv). [j]AcCl (1.0 equiv).

acetals were investigated. The reaction of imine **1b** with ketene silyl acetal **2b** having a diethyl group proceeded to afford **5n** on 51% yield (entry 14). The reaction of imine **1b** with **2c** possessing a cyclopentyl group gave **5o** in 71% yield (entry 15).[11,12]

A plausible reaction mechanism is shown in Scheme 4. Metalloallenamine **6** would be generated via a 1,4-addition reaction of the first ketene silyl acetal **2** at the β carbon to the dialkynyl imine **1** activated by aluminum chloride and undergo an intramolecular cyclization to give the alkynyliminocyclobutenoxide **7**. The elimination of aluminum methoxide from the alkynyliminocyclobutenoxide **7** would give the alkynyl iminocyclobutenone **8**. Subsequent 1,6-addition reaction of the second ketene silyl acetal **2** at a delta carbon would proceed to give the metallodienamine **9**. The protonation of the metallodienamine **9** with water to quench the reaction would occur from the less hindered face of the allene moiety to give the 1,4- and 1,6-addition product, *Z*-alkenyliminocyclobutenone **5**. Regarding the regioselective 1,4-addition of the first ketene silyl acetal **2** at the β carbon to the dialkynyl imine **1**, we presume the results of both electronic and steric effects. 1,2-Addition would not proceed because of the steric hindrance at the imino carbon. On the other hand, the delta carbon is less hindered but distal to the electron-withdrawing imino group, and therefore, the 1,6-addition of the first ketene silyl acetal **2** at the delta carbon would not occur. The second ketene silyl acetal **2** would react rapidly at a delta carbon because of the dual effect of the electron-withdrawing imino and keto carbonyl groups. We presume the intermediate **8** would be more reactive than the dialkynyl imine **1** as an electrophile. As a result, the alkynyl iminocyclobutenone **8** was not isolated.

We next examined chemoselective reduction of iminocyclobutenones **5** having four reducible functional groups such as imino, ketone and alkoxy carbonyl, and alkenyl under our previously reported conditions.[3] When sodium cyanoborohy-

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Scheme 4. Plausible Reaction Mechanism

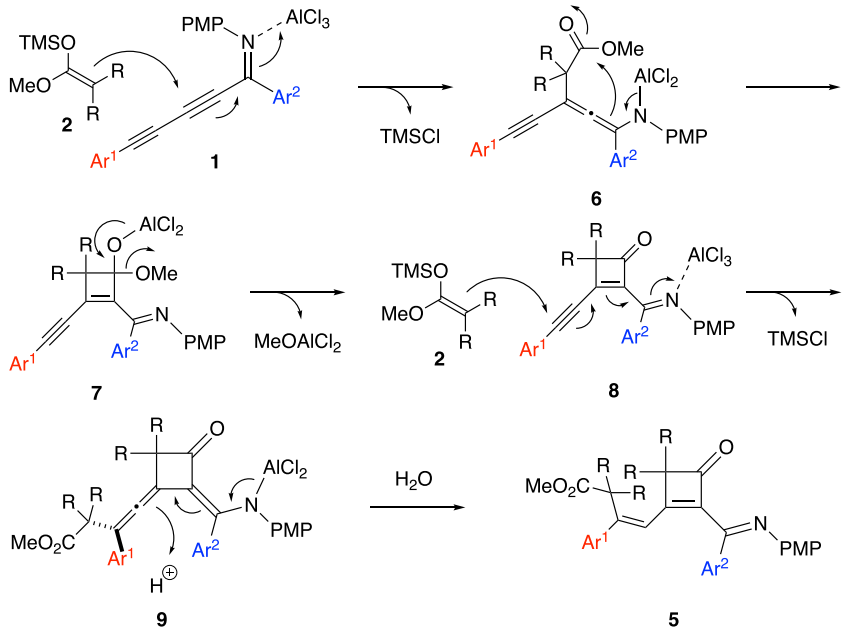
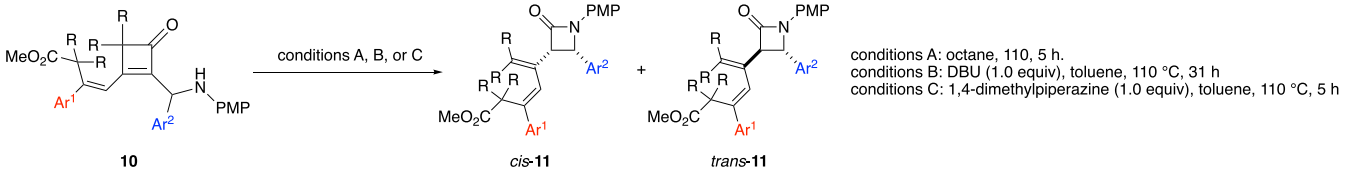


Table 3. Synthesis of *Cis*- or *Trans*-β-Lactams 11 through the Thermal Rearrangement[a]



					conditions A (conditions B)[c]		conditions C	
entry	Ar^1	Ar^2	R	11	yield (%)	cis/trans[b]	yield (%)	cis/trans[b]
1	Ph	PMP	Me	**11a**	60	18/82	86	85/15
2	Ph	Ph	Me	**11b**	69 (80)[d]	23/77 (10/90)	86[j]	86/14
3	Ph	4-MeC_6H_4	Me	**11c**	74 (81)[e]	23/77 (7/93)	89	88/12
4	Ph	4-ClC_6H_4	Me	**11d**	65 (68)	21/79 (<1/>99)	75	90/10
5	Ph	2-naphthyl	Me	**11e**	72	17/83	88	84/16
6	Ph	2-thienyl	Me	**11f**	46 (75)	23/77 (9/91)	79	74/26
7	Ph	2-furyl	Me	**11g**	63 (54)	35/65 (7/93)	69	60/40
8	4-MeC_6H_4	Ph	Me	**11h**	76	18/82	81	87/13
9	PMP	Ph	Me	**11i**	80 (81)	21/79 (20/80)	87	85/15
10	4-ClC_6H_4	Ph	Me	**11j**	73 (81)[e]	23/77 (9/91)	83	91/9
11	2-naphthyl	Ph	Me	**11k**	82	18/82	80	87/13
12	2-thienyl	Ph	Me	**11l**	66 (80)[f]	45/55 (20/80)	89	85/15
13	5-methyl-2-furyl	Ph	Me	**11m**	45 (64)	55/45 (7/93)	69	88/12
14	Ph	Ph	Et	**11n**	82[g]	16/84	78[g]	78/22
15	Ph	Ph	$-(CH_2)_4-$	**11o**	81[h] (97)[i]	23/77 (14/86)	79[h]	88/12

[a]Conditions: see the Supporting Information for details. [b]Determined from the ^1H NMR spectra. [c]Yields and diastereomeric ratios under conditions B are in parentheses. [d]48 h. [e]46 h. [f]24 h. [g]31 h. [h]45 h. [i]60 h. [j]1,4-Dimethylpiperazine (2.0 equiv).

dride was used as a reducing reagent, the reduction of iminocyclobutenones **5** in methanol in the presence of acetyl chloride, which reacted with methanol to generate a limited amount of hydrogen chloride in situ, proceeded chemoselectively at room temperature to give the desired aminocyclobutenones **10** in moderate to high yields (Table 2).

Thermal rearrangement of aminocyclobutenones **10** into β-lactams **11** was next investigated. The results are summarized in Table 3. When the thermal rearrangement of **10a** was carried out in octane at 110 °C for 5 h (conditions A), the desired β-lactam **11a** was obtained in 69% yield with trans selectivity, which was different from the cis selectivity of the thermal rearrangement previously reported.[3] The thermal rearrangement of other aminocyclobutenones **10b−o** proceeded to give the β-lactams **11b−o** in moderate to high yields with trans selectivities except for the β-lactam **11m**. However, trans selectivities were moderate in some aminocyclobutenones **10**. Therefore, the thermal rearrangement of aminocyclobutenones **10** was conducted in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (conditions B). In most cases except for the β-lactam **11i** (entry 9), the β-lactams **11** were obtained with higher trans selectivities

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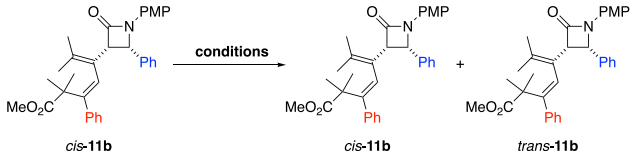
(entries 2−4, 6, 7, 10, 12, 13, and 15). We next examined the *cis*-β-lactam synthesis through the thermal rearrangement of the aminocyclobutenones **10** in the presence of 1,4-dimethylpiperazine (conditions C, Table 3). The desired *cis*-β-lactams **11** were obtained in good to high yields with good to high diastereoselectivities except for the β-lactam **11g** (entry 7).

We undertook some control experiments to clarify the diastereoselectivity in the thermal rearrangement of aminocyclobutenones **10** into *cis*- or *trans*-β-lactams **11**. Isomerization reactions of the isolated *cis*-β-lactam **11b** were examined (Table 4). Isomerization of the *cis*-β-lactam **11b** into the *trans*-lactam **11b** did not occur under the thermodynamic conditions and in the presence of 1,4-dimethylpiperazine presumably due to a lower basicity (entries 1 and 2). On the other hand, isomerization of the *cis*-β-lactam **11b** into the *trans*-β-lactam **11b** proceeded in the presence of DBU having a stronger basicity to give the β-lactam **11b** in a quantitative yield with the cis and trans ratio of 16 to 84 (entry 3).

Table 4. Control Experiments (1)

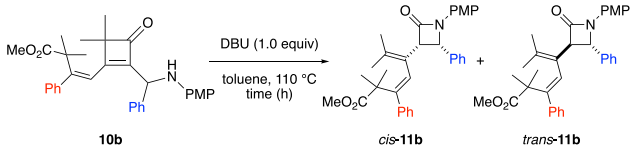


entry	conditions	yield (%)	cis/trans[a]
1	octane, 110 °C, 31 h	98	100/0
2	1,4-dimethylpiperazine (1.0 equiv), toluene, 110 °C, 31 h	99	100/0
3	DBU (1.0 equiv), toluene, 110 °C, 48 h	quant	16/84

[a]Determined from the ^{1}H NMR spectra.

The effect of the reaction time in the presence of DBU was further investigated (Table 5). When the reactions of **10b** were carried out for a short reaction time, the *cis*-β-lactam **11b** was obtained predominantly (entries 1 and 3). The trans selectivity improved as the reaction time became prolonged (entries 4−6). On the other hand, when the reaction of **10b** was carried out in the absence of DBU in toluene at 110 °C for 3 h, the β-lactam **11b** was obtained in 57% yield with the cis and trans ratio of 30:70 (entry 2). These results suggest that *cis*-β-lactam **11b** would be kinetically produced even in the presence of DBU and then isomerize into the thermodynamically more stable *trans*-β-lactam **11b**.

Table 5. Control Experiments (2)



entry	time (h)	**11b** (%)	cis/trans[a]	**10b** (%)
1	3	78	68/32	7
2[b]	3	57	30/70	15
3	5	79	54/46	
4	10	79	48/52	
5	24	79	22/78	
6	48	80	10/90	

[a]Determined from the ^{1}H NMR spectra. [b]The reaction was carried out in the absence of DBU.

A plausible reaction mechanism for the thermal rearrangement of aminocyclobutenones **10** into β-lactams **11** is shown in Scheme 5. The aminoketene **12** would be generated by ring opening of the aminocyclobutenone **10** and undergo a cyclization to give the ammonium intermediate **13** having a trans stereochemistry between PMP and Ar[2] groups to minimize their steric repulsion. An intramolecular proton transfer of **13** would proceed directly from the α-face to give the *trans*-β-lactam **11**. On the other hand, the protonation of the enol intermediate **14** would occur from the less hindered β-face of the enol to give the *cis*-β-lactam **11** predominantly. Regarding the role of 1,4-dimethylpiperazine and DBU, we presume the formation of a bulky proton source to protonate the enolate intermediate **15**. In the presence of DBU having a stronger basicity for a long reaction time, the *cis*-β-lactam **11** would isomerize into the thermodynamically more stable *trans*-β-lactam **11** via the enolate **16**.

CONCLUSIONS

We have developed the domino 1,4- and 1,6-addition reactions of the ketene silyl acetals to the dialkynyl imines to give the alkenyl iminocyclobutenones in moderate to good yields.[13] We have also found that the chemoselective reduction of alkenyl iminocyclobutenones and the subsequent thermal rearrangement of alkenyl aminocyclobutenones in the presence of appropriate amines provided cis or trans multifunctionalized β-lactams in moderate to high yields with good to high diastereoselectivities.[14] The present β-lactam synthesis via the domino 1,4- and 1,6-addition reactions is attractive because β-lactams having multifunctional groups such as alkenyl, aromatic, imino, and alkoxycarbonyl can be obtained.

EXPERIMENTAL SECTION

General Aspects. Melting point (mp) determinations were performed using a YAMATO MP-21 instrument and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECX400P spectrometer (400 MHz), a JEOL JNM α-500 spectrometer (500 MHz), or a JNM-ECZ500R spectrometer (500 MHz) with tetramethylsilane as an internal standard. ^{13}C{^{1}H} NMR spectra were recorded on a JEOL JNM-ECX400P spectrometer (100 MHz), a JEOL JNM α-500 spectrometer (125 MHz), or a JEOL JNM-ECZ500R spectrometer (125 MHz). Chemical shifts are reported in δ units, parts per million from the central peak of $CDCl_3$ (δ 77.0) as an internal reference. High-resolution mass spectra (EI) were recorded on a JEOL JMS-700D mass spectrometer employed with a quadrupole doublet based lens system. Benzene was predried with $CaCl_2$, distilled, and stored over molecular sieves 4 Å. Methanol (MeOH) was distilled from magnesium methoxide and dried over molecular sieves 3 Å. Toluene was predried with $CaCl_2$, distilled, and stored over molecular sieves 4 Å. Tetrahydrofuran was distilled from benzophenone ketyl immediately before use or purified by Glass Contour Organic Solvent Purification System of Nikko Hansen & Co., Ltd. Dichloromethane (CH_2Cl_2) was predried with P_2O_5, distilled from CaH_2, and stored over molecular sieves 4 Å. Octane was distilled and stored over molecular sieves 4 Å. Triethylamine (Et_3N) was distilled from CaH_2 and stored over molecular sieves 4 Å. Purification of products was performed by column chromatography on silica gel (Kanto Chemical Co. Inc., Silica Gel 60 N (spherical, neutral)) and/or preparative thin-layer chromatography (TLC) on silica gel (Wakogel B-5F). All reactions

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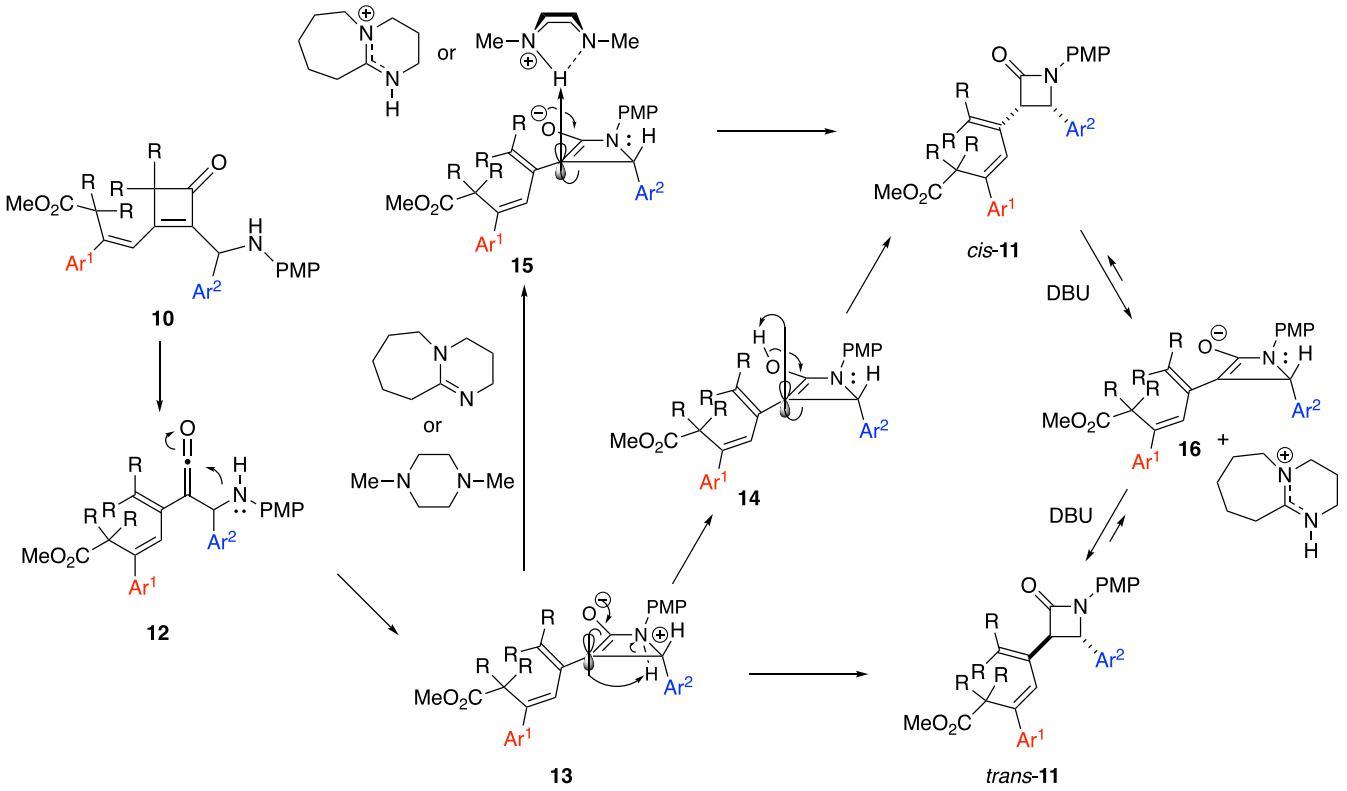
Scheme 5. Plausible Reaction Mechanism for the Thermal Rearrangement

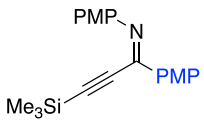


were carried out under an argon atmosphere. For reactions that require heating, an oil bath was used.

Procedure for the Preparation of Dialkynyl Imines 1 (See Tables S1–S3 in the Supporting Information). Amides **S1a–g** were prepared according to the literature method.[15–19]

Synthesis of Alkynyl Imines S3a–g (See Table S1 in the Supporting Information). In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon was placed amide **S1a**[15] (2.06 g, 8.0 mmol) in thionyl chloride (3.81 g, 32.0 mmol) at room temperature. The reaction mixture was stirred at 75–80 °C for 1.5 h and then cooled down to room temperature. The excess thionyl chloride and volatile materials were evaporated and dried in vacuo to give the crude imidoyl chloride **S2a** (2.19 g). In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $Pd(OAc)_2$ (18.0 mg, 0.08 mmol), PPh_3 (21.0 mg, 0.08 mmol), and the crude imidoyl chloride **S2a** (2.19 g) in degassed triethylamine (12 mL) at room temperature, and to the mixture was added trimethylsilylacetylene (1.18 g, 12.0 mmol). The reaction mixture was stirred at 70–80 °C for 2 h and then cooled down to room temperature. The mixture was diluted with diethyl ether (12 mL) and filtered through a Celite pad. The Celite pad was washed with diethyl ether (60 mL). The combined organic layers were washed with H_2O (12 mL) and brine (12 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 14:1) to give alkynyl imine **S3a** (2.11 g, 78% (two steps)) as a yellow solid.

*(Z)-N,1-Bis(4-methoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-imine (**S3a**).*



S3a

Yellow solid; mp 89–91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18–8.16 (m, 2H), 7.30–7.26 (m, 2H), 7.02–6.94 (m, 4H), 3.91 (s, 3H), 3.87 (s, 3H), 0.23 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.8, 157.2, 147.5, 144.3, 130.3, 129.7, 129.6, 122.9, 113.6, 113.5, 104.1, 97.9, 55.4, 55.4, -0.7; IR (KBr) 2958, 2146, 1604, 1558, 1508, 1459, 1250, 1165, 1031, 840, 761, 509 cm^{-1}; HRMS (EI): calcd for $C_{20}H_{23}NO_2Si$ $(M)^+$ 337.1498, found 337.1505.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon was placed amide **S1b**[2] (3.97 g, 17.5 mmol) in thionyl chloride (8.33 g, 70.0 mmol) at room temperature. The reaction mixture was stirred at 75–80 °C for 1.5 h and then cooled down to room temperature. The excess thionyl chloride and volatile materials were evaporated and dried in vacuo to give the crude imidoyl chloride **S2b** (4.28 g). In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $Pd(OAc)_2$ (39.2 mg, 0.175 mmol), PPh_3 (46.0 mg, 0.175 mmol), and the crude imidoyl chloride **S2b** (4.28 g) in degassed triethylamine (15 mL) at room temperature, and to the mixture was added trimethylsilylacetylene (2.58 g, 26.3 mmol). The reaction mixture was stirred at 70–80 °C for 2 h and then cooled down to room temperature. The mixture was diluted with diethyl ether (15 mL) and filtered through a Celite pad. The Celite pad was washed with diethyl ether (75 mL). The combined organic layers were washed with H_2O (15 mL) and brine (15 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 14:1) to give alkynyl imine **S3b** (3.01 g, 73% (two steps)) as a yellow oil.

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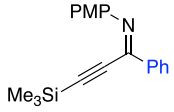
*(Z)-N-(4-Methoxyphenyl)-1-phenyl-3-(trimethylsilyl)prop-2-yn-1-imine (**S3b**).*

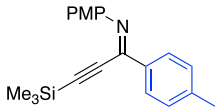


S3b

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.16 (m, 2H), 7.45−7.42 (m, 3H), 7.29−7.25 (m, 2H), 6.93−6.90 (m, 2H), 3.82 (s, 3H), 0.19 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.5, 147.9, 144.0, 137.4, 130.7, 128.2, 127.9, 123.0, 113.5, 104.5, 97.9, 55.4, −0.7; IR (neat) 2958, 2146, 1666, 1601, 1504, 1448, 1248, 1176, 1040, 842, 759, 694 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{21}NOSi$ $(M)^+$ 307.1392, found 307.1382.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon was placed amide **S1c**[16] (4.46 g, 18.5 mmol) in thionyl chloride (8.80 g, 73.9 mmol) at room temperature. The reaction mixture was stirred at 75−80 °C for 1.5 h and then cooled down to room temperature. The excess thionyl chloride and volatile materials were evaporated and dried in vacuo to give the crude imidoyl chloride **S2c** (4.20 g). In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $Pd(OAc)_2$ (41.5 mg, 0.185 mmol), PPh_3 (48.5 mg, 0.185 mmol), and the crude imidoyl chloride **S2c** (4.20 g) in degassed triethylamine (20 mL) at room temperature, and to the mixture was added trimethylsilylacetylene (2.73 g, 27.8 mmol). The reaction mixture was stirred at 70−80 °C for 2 h and then cooled down to room temperature. The mixture was diluted with diethyl ether (20 mL) and filtered through a Celite pad. The Celite pad was washed with diethyl ether (100 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 14:1) to give alkynyl imine **S3c** (2.22 g, 63% (two steps)) as a yellow solid.

*(Z)-N-(4-Methoxyphenyl)-1-(p-tolyl)-3-(trimethylsilyl)prop-2-yn-1-imine (**S3c**).*

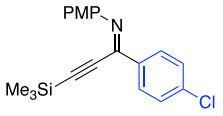


S3c

Yellow solid; mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.04 (m, 2H), 7.25−7.22 (m, 4H), 6.91−6.89 (m, 2H), 3.82 (s, 3H), 2.41 (s, 3H), 0.18 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.3, 148.0, 144.2, 141.1, 134.8, 129.0, 127.9, 123.0, 113.5, 104.2, 98.0, 55.5, 21.5, -0.7; IR (KBr) 2961, 2147, 1727, 1603, 1552, 1502, 1461, 1238, 1181, 1108, 1044, 865, 761, 744, 641 cm^{-1}; HRMS (EI): calcd for $C_{20}H_{23}NOSi$ $(M)^+$ 321.1549, found 321.1551.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon was placed amide **S1d**[17] (8.66 g, 33.1 mmol) in thionyl chloride (15.7 g, 132.3 mmol) at room temperature. The reaction mixture was stirred at 75−80 °C for 1.5 h and then cooled down to room temperature. The excess thionyl chloride and volatile materials were evaporated and dried in vacuo to give the crude imidoyl chloride **S2d** (9.27 g). In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $Pd(OAc)_2$ (74.0 mg, 0.33 mmol), PPh_3 (87.0 mg, 0.33 mmol), and the crude imidoyl chloride **S2d** (9.27 g) in degassed triethylamine (25 mL) at room temperature, and to the mixture was added trimethylsilylacetylene (4.91 g, 50.0 mmol). The reaction mixture was stirred at 70−80 °C for 2 h and then cooled down to room temperature. The mixture was diluted with diethyl ether (25 mL) and filtered through a Celite pad. The Celite pad was washed with diethyl ether (125 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 14:1) to give alkynyl imine **S3d** (10.75 g, 95% (two steps)) as a yellow solid.

*(Z)-1-(4-Chlorophenyl)-N-(4-methoxyphenyl)-3-(trimethylsilyl)-prop-2-yn-1-imine (**S3d**).*

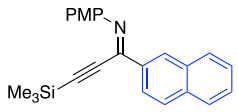


S3d

Yellow solid; mp 81−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.09 (m, 2H), 7.42-7.40 (m, 2H), 7.29−7.25 (m, 2H), 6.92−6.90 (m, 2H), 3.84 (s, 3H), 0.20 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 146.4, 143.7, 136.8, 135.9, 129.2, 123.2, 113.6, 105.0, 97.6, 55.5, -0.7; IR (KBr) 2958, 2147, 1604, 1591, 1502, 1401, 1247, 1167, 1041, 863, 760, 641 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{20}ClNOSi$ $(M)^+$ 341.1003, found 341.0995.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon was placed amide **S1e**[18] (5.63 g, 20.3 mmol) in thionyl chloride (9.66 g, 81.2 mmol) at room temperature. The reaction mixture was stirred at 75−80 °C for 1.5 h and then cooled down to room temperature. The excess thionyl chloride and volatile materials were evaporated and dried in vacuo to give the crude imidoyl chloride **S2e** (5.97 g). In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $Pd(OAc)_2$ (46.0 mg, 0.203 mmol), PPh_3 (53.0 mg, 0.203 mmol), and the crude imidoyl chloride **S2e** (5.97 g) in degassed triethylamine (20 mL) at room temperature, and to the mixture was added trimethylsilylacetylene (2.99 g, 30.5 mmol). The reaction mixture was stirred at 70−80 °C for 2 h and then cooled down to room temperature. The mixture was diluted with diethyl ether (20 mL) and filtered through a Celite pad. The Celite pad was washed with diethyl ether (100 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 14:1) to give alkynyl imine **S3e** (6.09 g, 84% (two steps)) as a yellow solid.

*(Z)-N-(4-Methoxyphenyl)-1-(naphthalen-2-yl)-3-(trimethylsilyl)-prop-2-yn-1-imine (**S3e**).*



S3e

Yellow solid; mp 72−74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.67 (m, 1H), 7.43−7.41 (m, 1H), 7.32-7.31 (m, 2H), 7.09−7.07 (m, 1H), 6.90−6.88 (m, 2H), 3.82 (s, 3H), 0.21 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.6, 147.8, 144.1, 135.0, 134.7, 132.9, 129.4, 129.1, 127.9, 127.7, 127.3, 126.3, 124.0, 123.1, 113.6, 104.7, 98.0, 55.5, -0.6; IR (KBr) 2957, 2143, 1604, 1502, 1353, 1290, 1251, 1190, 1128, 1039, 951, 841, 754 cm^{-1}; HRMS (EI): calcd for $C_{23}H_{23}NOSi$ $(M)^+$ 357.1549, found 357.1557.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon was placed amide **S1f**[19] (4.70 g, 20.0 mmol) in thionyl

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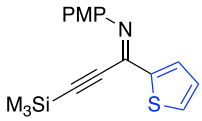
chloride (9.52 g, 80.0 mmol) at room temperature. The reaction mixture was stirred at 75−80 °C for 1.5 h and then cooled down to room temperature. The excess thionyl chloride and volatile materials were evaporated and dried in vacuo to give the crude imidoyl chloride **S2f** (5.11 g). In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $Pd(OAc)_2$ (48.4 mg, 0.200 mmol), PPh_3 (53.0 mg, 0.200 mmol), and the crude imidoyl chloride **S2f** (5.11 g) in degassed triethylamine (20 mL) at room temperature, and to the mixture was added trimethylsilylacetylene (1.96 g, 20.0 mmol). The reaction mixture was stirred at 70−80 °C for 2 h and then cooled down to room temperature. The mixture was diluted with diethyl ether (20 mL) and filtered through a Celite pad. The Celite pad was washed with diethyl ether (100 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9:1) to give alkynyl imine **S3f** (6.22 g, 99% (two steps)) as a yellow oil.

*(E)-N-(4-Methoxyphenyl)-1-(thiophen-2-yl)-3-(trimethylsilyl)-prop-2-yn-1-imine (**S3f**).*

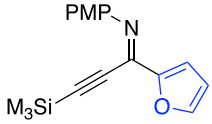


S3f

Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.70 (m, 1H), 7.43−7.33 (m, 3H), 7.10−7.08 (m, 1H), 6.92−6.90 (m, 2H), 3.82 (s, 3H), 0.23 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.6, 145.1, 143.0, 141.6, 130.5, 129.7, 127.4, 123.6, 113.4, 102.9, 97.1. 55.3, −0.7; IR (neat) 2958, 2146, 1604, 1556, 1500, 1426, 1248, 1202, 1165, 1035, 984, 839, 760, 711 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{19}NOSSi$ $(M)^+$ 313.0957, found 313.0968.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon was placed amide **S1g**[19] (2.65 g, 12.2 mmol) in thionyl chloride (5.81 g, 48.8 mmol) at room temperature. The reaction mixture was stirred at 75−80 °C for 1.5 h and then cooled down to room temperature. The excess thionyl chloride and volatile materials were evaporated and dried in vacuo to give the crude imidoyl chloride **S2g** (2.52 g). In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $Pd(PPh_3)_2Cl_2$ (86.0 mg, 0.122 mmol) and the crude imidoyl chloride **S2g** (2.52 g) in degassed benzene (18 mL) at room temperature, and to the mixture was added trimethyl-[(tributylstannyl)ethynyl]silane[20] (5.20 g, 13.4 mmol). The reaction mixture was stirred at 70 °C for 5 h and then cooled down to room temperature. After benzene was evaporated, the mixture was diluted with diethyl ether (30 mL), filtered through a Celite pad, washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give alkynyl imine **S3g** (2.35 g, 70% (two steps)) as a yellow oil.

*(E)-1-(Furan-2-yl)-N-(4-methoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-imine (**S3g**).*

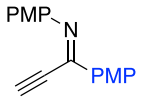


S3g

Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 1.2 Hz, 1H), 7.35−7.32 (m, 2H), 7.03 (d, J = 2.9 Hz, 1H), 6.91−6.88 (m, 1H), 6.52 (dd, J = 1.2, 2.9 Hz, 1H), 3.82 (s, 3H), 0.20 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 157.6, 145.1, 143.0, 141.6, 130.5, 129.7, 127.4, 123.6, 113.4, 102.9, 97.1, 55.3, −0.7; IR (neat) 2958, 2835, 2151, 1550, 1504, 1474, 1393, 1248, 1205, 1163, 1060, 1009, 841, 755, 594 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{19}NO_2Si$ $(M)^+$ 297.1185 found 297.1191.

Synthesis of Alkynyl Imines S4a−e (See Table S2 in the Supporting Information). In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed alkynyl imine **S3a** (2.11 g, 6.25 mmol) in methanol (65 mL) at room temperature, and to the mixture was added anhydrous potassium carbonate (86.4 mg, 0.625 mmol). The reaction mixture was stirred at room temperature for 0.5 h and then cooled down to 0 °C. The mixture was filtered, and the solid was washed with cold methanol to give alkynyl imine **S4a** (1.42 g, 85%) as a yellow solid.

*(E)-N,1-Bis(4-methoxyphenyl)prop-2-yn-1-imine (**S4a**).*

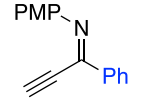


S4a

Yellow solid; mp 137−139 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14−8.11 (m, 2H), 7.17−7.15 (m, 2H), 6.97−6.91 (m, 4H), 3.87 (s, 3H), 3.83 (s, 3H), 3.33 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 157.2, 147.0, 144.2, 130.1, 129.7, 122.5, 113.8, 113.7, 84.9, 76.9, 55.4; IR (KBr) 3169, 2952, 2090, 1607, 1554, 1508, 1468, 1315, 1249, 1207, 1170, 1108, 1027, 838, 738, 671 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{15}NO_2$ $(M)^+$ 265.1103, found 265.1108.

In a 200 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed alkynyl imine **S3b** (5.41 g, 17.6 mmol) in methanol (90 mL) at room temperature, and to the mixture was added anhydrous potassium carbonate (243 mg, 1.76 mmol). The reaction mixture was stirred at room temperature for 0.5 h and then cooled down to 0 °C. The mixture was filtered and the solid was washed with cold methanol to give alkynyl imine **S4b** (3.01 g, 73%) as a yellow solid.

*(E)-N-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-imine (**S4b**).*



S4b

Yellow solid; mp 101−102 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20−8.17 (m, 2H), 7.47−7.44 (m, 3H), 7.23−7.19 (m, 2H), 6.94−6.92 (m, 2H), 3.82 (s, 3H), 3.35 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.5, 147.4, 143.9, 137.1, 131.0, 128.3, 127.9, 122.6, 113.8, 85.2, 76.8, 55.4; IR (KBr) 3175, 2955, 2087, 1604, 1558, 1505, 1443, 1249, 1207, 1108, 1031, 1033, 839, 750, 693 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{13}NO$ $(M)^+$ 235.0997, found 235.0991.

In a 200 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed alkynyl imine **S3c** (4.56 g, 14.2 mmol) in methanol (60 mL) at room temperature, and to the mixture was added anhydrous potassium carbonate (196 mg, 1.42 mmol). The reaction mixture was stirred at room temperature for 0.5 h and then cooled down to 0 °C. The mixture was filtered and the solid was washed with cold methanol to give alkynyl imine **S4c** (2.22 g, 63%) as a yellow solid.

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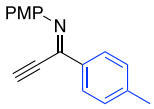
*(E)-N-(4-Methoxyphenyl)-1-(p-tolyl)prop-2-yn-1-imine (**S4c**).*

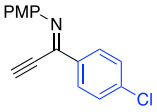


S4c

Yellow solid; mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.26−7.24 (m, 2H), 7.19−7.17 (m, 2H), 6.93−6.91 (m, 2H), 3.83 (s, 3H), 3.34 (s, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.3, 147.6, 144.0, 141.5, 134.6, 129.1, 127.9, 122.5, 113.8, 85.0, 76.9, 55.4, 21.5; IR (KBr) 3188, 2954, 2092, 1606, 1559, 1503, 1449, 1295, 1253, 1209, 1174, 1110, 1028, 838, 822, 744, 668 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{15}NO$ $(M)^+$ 249.1154, found 249.1146.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed alkynyl imine **S3d** (3.42 g, 10.0 mmol) in methanol (70 mL) at room temperature, and to the mixture was added anhydrous potassium carbonate (138 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 0.5 h and then cooled down to 0 °C. The mixture was filtered and the solid was washed with cold methanol to give alkynyl imine **S4d** (2.09 g, 77%) as a yellow solid.

*(E)-1-(4-Chlorophenyl)-N-(4-methoxyphenyl)prop-2-yn-1-imine (**S4d**).*

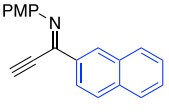


S4d

Yellow solid; mp 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.11 (m, 2H), 7.43−7.41 (m, 2H), 7.25−7.21 (m, 2H), 6.94−6.92 (m, 2H), 3.84 (s, 3H), 3.39 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.8, 145.9, 143.5, 137.1, 135.7, 129.2, 128.5, 122.7, 113.8, 85.5, 76.6, 55.4; IR (KBr) 3183, 3006, 2091, 1712, 1576, 1506, 1363, 1224, 1173, 1110, 1027, 839, 750, 664 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{12}ClNO$ $(M)^+$ 269.0607, found 269.0608.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed alkynyl imine **S3e** (6.03 g, 16.9 mmol) in methanol (60 mL) at room temperature, and to the mixture was added anhydrous potassium carbonate (234 mg, 1.69 mmol). The reaction mixture was stirred at room temperature for 0.5 h and then cooled down to 0 °C. The mixture was filtered and the solid was washed with cold methanol to give alkynyl imine **S4e** (4.12 g, 85%) as a yellow solid.

*(E)-N-(4-Methoxyphenyl)-1-(naphthalen-2-yl)prop-2-yn-1-imine (**S4e**).*

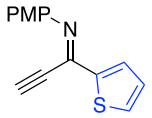


S4e

Yellow solid; mp 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.35−8.32 (m, 1H), 7.97-7.86 (m, 3H), 7.55−7.53 (m, 2H), 7.27−7.21 (m, 2H), 6.96−6.94 (m, 2H), 3.84 (s, 3H), 3.44 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.6, 174.3, 143.9, 134.8, 132.9, 129.6, 129.1, 128.0, 127.7, 127.4, 126.5, 123.8, 122.7, 113.8, 85.3, 76.9, 55.4; IR (KBr) 3181, 2962, 2091, 1605, 1565, 1506, 1398, 1294, 1253, 1206, 1168, 1094, 1030, 837, 742 cm^{-1}; HRMS (EI): calcd for $C_{20}H_{15}NO$ $(M)^+$ 285.1154, found 285.1159.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed alkynyl imine **S3f** (498 mg, 1.6 mmol) in methanol (3.5 mL) at room temperature, and to the mixture was added anhydrous potassium carbonate (22.1 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 0.5 h and then cooled down to 0 °C. Methanol was evaporated in vacuo. The mixture was diluted with ethyl acetate (20 mL), washed with H_2O (10 mL) and brine (10 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 8:1) to give alkynyl imine **S4f** (338 mg, 87%) as a yellow oil.

*(E)-N-(4-Methoxyphenyl)-1-(thiophen-2-yl)prop-2-yn-1-imine (**S4f**).*

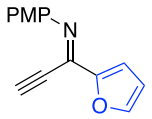


S4f

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (m, 1H), 7.43−7.42 (m, 1H), 7.26−7.23 (m, 2H), 7.08−7.06 (m, 1H), 6.91−6.89 (m, 2H), 3.80 (s, 3H), 3.32 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.4, 144.7, 142.8, 141.4, 131.0, 130.1, 127.5. 123.1, 113.7, 83.8, 76.2, 55.3; IR (neat) 3280, 2955, 2097, 1605, 1564, 1502, 1441, 1426, 1355, 1202, 1166, 1107, 1031, 956, 836, 751, 714, 683 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{11}NOS$ $(M)^+$ 241.0561, found 241.0563.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed alkynyl imine **S3g** (2.35 g, 8.60 mmol) in methanol (38 mL) at room temperature, and to the mixture was added anhydrous potassium carbonate (119 mg, 0.86 mmol). The reaction mixture was stirred at room temperature for 0.5 h and then cooled down to 0 °C. Methanol was evaporated in vacuo. The mixture was diluted with ethyl acetate (40 mL), washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give alkynyl imine **S4g** (1.24 g, 64%) as an orange oil.

*(E)-1-(Furan-2-yl)-N-(4-methoxyphenyl)prop-2-yn-1-imine (**S4g**).*



S4g

Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.68 (m, 1H), 7.42−7.41 (m, 1H), 7.25−7.24 (m, 2H), 7.07−7.05 (m, 1H), 6.91−6.89 (m, 2H), 3.78 (s, 3H), 3.32 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.6, 144.6, 142.7, 141.3, 130.9, 130.1, 127.5, 123.1, 113.6, 83.8, 76.1, 55.2; IR (KBr) 3280, 2095, 1601, 1499, 1470, 1295, 1244, 1202, 1168, 1041, 835, 751, 571 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{11}NO_2$ $(M)^+$ 225.0790, found 225.0794.

Synthesis of Dialkynyl Imines 1a−o (See Table S3 in the Supporting Information). In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (351 mg, 0.50 mmol), CuI (191 mg, 1.00 mmol), PPh_3 (262 mg, 1.00 mmol), and alkynyl bromide **S5a**[21] (1.09 g, 6.00 mmol) in degassed triethylamine (30 mL) at room temperature, and to the mixture was added alkynyl imine **S4a** (1.33 g, 5.00 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was

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washed with dichloromethane (120 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 12:1) to give dialkynyl imine **1a** (0.603 g, 33%) as a yellow solid.

*(Z)-N,1-Bis(4-methoxyphenyl)-5-phenylpenta-2,4-diyn-1-imine (**1a**).* Yellow solid; mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.11 (m, 2H), 7.50−7.49 (m, 2H), 7.35−7.25 (m, 5H), 6.95−6.93 (m, 4H), 3.82 (s, 3H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 157.6, 146.1, 144.0, 132.7, 130.4, 129.9, 129.6, 128.5, 122.9, 120.8, 113.9, 113.7, 84.7, 80.6, 75.0, 73.1, 55.4; IR (KBr) 3052, 2996, 2954, 2927, 2907, 2837, 2207, 2138, 1602, 1576, 1547, 1507, 1461, 1442, 1337, 1295, 1250, 1204, 1176, 1169, 1109, 1025, 950, 837, 763, 745 cm^{-1}; HRMS (EI): calcd for $C_{25}H_{19}NO_2$ $(M)^+$ 365.1416, found 365.1407.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (1.05 g, 1.5 mmol), CuI (574 mg, 3.0 mmol), PPh_3 (787 mg, 3.0 mmol), and alkynyl bromide **S5a**[21] (3.26 g, 18.0 mmol) in degassed triethylamine (35 mL) at room temperature, and to the mixture was added alkynyl imine **S4b** (3.53 g, 15.0 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (120 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9:1) to give dialkynyl imine **1b** (2.13 g, 38%) as a yellow solid.

*(Z)-N-(4-Methoxyphenyl)-1,5-diphenylpenta-2,4-diyn-1-imine (**1b**).* Yellow solid; mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.16 (m, 2H), 7.52−7.45 (m, 5H), 7.34−7.30 (m, 5H), 6.97−6.95 (m, 2H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.8, 146.6, 143.7, 137.4, 132.7, 132.4, 130.9, 129.9, 129.2, 128.6, 128.5, 128.4, 127.8, 123.0, 120.7, 113.9, 85.0, 81.0, 74.9, 73.0, 55.4; IR (KBr) 3418, 3183, 2835, 2360, 2088, 1885, 1505, 1444, 1251, 1108, 1031. 839, 743, 690, 524, 518 cm^{-1}; HRMS (EI): calcd for $C_{24}H_{17}NO$ $(M)^+$ 335.1310, found 335.1317.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (421 mg, 0.60 mmol), CuI (230 mg, 1.20 mmol), PPh_3 (315 mg, 1.20 mmol), and alkynyl bromide **S5a**[21] (1.41 g, 7.80 mmol) in degassed triethylamine (30 mL) at room temperature, and to the mixture was added alkynyl imine **S4c** (1.50 g, 6.0 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (120 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/dichloromethane = 1:1) to give dialkynyl imine **1c** (1.06 g, 51%) as a yellow solid.

*(Z)-N-(4-Methoxyphenyl)-5-phenyl-1-(p-tolyl)penta-2,4-diyn-1-imine (**1c**).* Yellow solid; mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 2H), 7.51−7.49 (m, 2H), 7.38−7.35 (m, 1H), 7.32−7.24 (m, 6H), 6.95−6.93 (m, 2H), 3.81 (s, 3H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 146.7, 144.0, 141.4, 134.9, 132.7, 129.9, 129.1, 128.5, 127.9, 122.9, 120.9, 113.9, 84.8, 80.7, 75.0, 73.1, 55.4, 21.5; IR (KBr) 3095, 3053, 2925, 2833, 2207, 2138, 1604, 1573, 1544, 1499, 1460, 1334, 1292, 1249, 1206, 1166, 1108, 1031, 950, 836, 760, 714, 688 cm^{-1}; HRMS (EI): calcd for $C_{25}H_{19}NO$ $(M)^+$ 349.1467, found 349.1467.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (351 mg, 0.50 mmol), CuI (190 mg, 1.0 mmol), PPh_3 (262 mg, 1.0 mmol), and alkynyl bromide **S5a**[21] (1.36 g, 7.5 mmol) in degassed triethylamine (20 mL) at room temperature, and to the mixture was added alkynyl imine **S4d** (1.35 g, 5.0 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (80 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1) to give dialkynyl imine **1d** (642 mg, 37%) as a yellow solid.

*(Z)-1-(4-Chlorophenyl)-N-(4-methoxyphenyl)-5-phenylpenta-2,4-diyn-1-imine (**1d**).* Yellow solid; mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.10 (m, 2H), 7.54−7.52 (m, 2H), 7.44−7.31 (m, 7H), 6.98−6.95 (m, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.1, 145.1, 143.4, 137.0, 136.0, 132.7, 130.0, 129.1, 128.6, 128.6, 123.2, 120.7, 113.9, 85.3, 81.3, 74.5, 72.9, 55.4; IR (KBr) 3060, 3042, 3013, 2985, 2971, 2943, 2209, 1617, 1602, 1563, 1502, 1446, 1328, 1290, 1243, 1208, 1170, 1033, 956, 832, 752, 691, 665, 634, 591 cm^{-1}; HRMS (EI): calcd for $C_{24}H_{16}ClNO$ $(M)^+$ 369.0920, found 369.0910.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (107 mg, 0.15 mmol), CuI (57.1 mg, 0.30 mmol), PPh_3 (78.9 mg, 0.30 mmol), and alkynyl bromide **S5a**[21] (489 mg, 2.7 mmol) in degassed triethylamine (4.5 mL) at room temperature, and to the mixture was added alkynyl imine **S4e** (430 mg, 1.5 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (40 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9:1) to give dialkynyl imine **1e** (346 mg, 60%) as a yellow solid.

*(Z)-N-(4-Methoxyphenyl)-1-(naphthalen-2-yl)-5-phenylpenta-2,4-diyn-1-imine (**1e**).* Yellow solid; mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.34−8.32 (m, 2H), 8.01−7.99 (m, 1H), 7.91−7.89 (m, 2H), 7.58−7.53 (m, 4H), 7.42−7.34 (m, 5H), 7.00−6.98 (m, 2H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.8, 146.5, 143.8, 135.1, 132.9, 132.8, 130.0, 129.4, 129.1, 128.6, 128.1, 127.8, 127.4, 126.5, 123.9, 123.1, 113.9, 85.0, 81.0, 75.0, 73.2, 55.5;;IR (KBr) 3069, 3001, 2959, 2926, 2833, 2208, 2135, 1598, 1563, 1499, 1461, 1355, 1328, 1292, 1239, 1211, 1193, 1128, 1100, 1031, 932, 875, 835, 799, 757, 684 cm^{-1}; HRMS (EI): calcd for $C_{28}H_{19}NO$ $(M)^+$ 385.1467, found 385.1464.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (107 mg, 0.15 mmol), CuI (57.1 mg, 0.30 mmol), PPh_3 (78.9 mg, 0.30 mmol), and alkynyl bromide **S5a**[21] (543 mg, 3.0 mmol) in degassed triethylamine (7.0 mL) at room temperature, and to the mixture was added alkynyl imine **S4f** (360 mg, 1.5 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (40 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1) to give dialkynyl imine **1f** (211 mg, 42%) as a yellow solid.

*(E)-N-(4-Methoxyphenyl)-5-phenyl-1-(thiophen-2-yl)penta-2,4-diyn-1-imine (**1f**).* Yellow solid; mp 95−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.71 (m, 1H), 7.52−7.51 (m, 2H), 7.44−7.32 (m, 6H), 7.10−7.08 (m, 1H), 6.94−6.93 (m, 2H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 144.9, 142.8, 140.6, 132.7, 130.7, 130.0, 129.9, 128.5, 127.6, 123.4, 120.6, 113.8, 84.9, 79.6, 73.9, 72.9, 55.3; IR (KBr) 3051, 3007, 2926, 2866, 2212, 2124, 1600, 1554, 1498, 1423, 1335, 1292, 1247, 1202, 1168, 1031, 903, 850, 835, 760, 718, 689 cm^{-1}; HRMS (EI): calcd for $C_{22}H_{15}NOS$ $(M)^+$ 341.0847, found 341.0859.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (360 mg, 0.51 mmol), CuI

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(197 mg, 1.0 mmol), PPh_3 (270 mg, 1.0 mmol), and alkynyl bromide **S5a**[21] (1.11 g, 6.2 mmol) in degassed triethylamine (25 mL) at room temperature, and to the mixture was added alkynyl imine **S4g** (1.16 g, 5.1 mmol). The reaction mixture was stirred at 60−65 °C for 5 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (120 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1) to give dialkynyl imine **1g** (646 mg, 39%) as a yellow semisolid.

*(E)-1-(Furan-2-yl)-N-(4-methoxyphenyl)-5-phenylpenta-2,4-diyn-1-imine (**1g**).* Yellow semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73−7.72 (m, 1H), 7.54−7.52 (m, 2H), 7.46−7.32 (m, 6H), 7.11−7.10 (m, 1H), 6.96−6.93 (m, 2H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 144.9, 142.9, 140.6, 132.7, 130.7, 130.0, 130.0, 128.5, 127.6, 123.5, 120.7, 113.9, 85.0, 79.6, 74.0, 73.0, 55.4; IR (neat) 3144, 3051, 3010, 2961, 2920, 2839, 2193, 2136, 1600, 1564, 1501, 1471, 1447, 1323, 1290, 1236, 1205, 1167, 1098, 1073, 1032, 960, 829, 754, 689, 663, 590 cm^{-1}; HRMS(EI): calcd for $C_{22}H_{15}NO_2$ $(M)^+$ 325.1103, found 325.1101.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (421 mg, 0.60 mmol), CuI (230 mg, 1.2 mmol), PPh_3 (315 mg, 1.2 mmol), and alkynyl bromide **S5b**[22] (1.40 g, 7.2 mmol) in degassed triethylamine (30 mL) at room temperature, and to the mixture was added alkynyl imine **S4b** (1.41 g, 6.0 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (120 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/dichloromethane = 1:1) to give dialkynyl imine **1h** (662 mg, 30%) as a yellow solid.

*(Z)-N-(4-Methoxyphenyl)-1-phenyl-5-(p-tolyl)penta-2,4-diyn-1-imine (**1h**).* Yellow solid; mp 82−83 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19−8.16 (m, 2H), 7.46−7.40 (m, 5H), 7.30 (m, 2H), 7.13−7.11 (m, 2H), 6.97−6.94 (m, 2H), 3.82 (s, 3H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.8, 146.6, 143.7, 140.5, 137.4, 132.6, 130.9, 129.3, 128.3, 127.8, 123.0, 117.6, 113.9, 85.4, 81.3, 74.7, 72.5, 55.3, 21.6; IR (KBr) 3084, 3034, 2954, 2898, 2832, 2208, 1600, 1554, 1503, 1461, 1444, 1338, 1292, 1245, 1207, 1172, 1102, 1031, 951, 926, 836, 816, 777, 757, 694, 661 cm^{-1}; HRMS (EI): calcd for $C_{25}H_{19}NO$ $(M)^+$ 349.1467, found 349.1467.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (421 mg, 0.60 mmol), CuI (230 mg, 1.2 mmol), PPh_3 (315 mg, 1.2 mmol), and alkynyl bromide **S5c**[22] (1.52 g, 7.2 mmol) in degassed triethylamine (30 mL) at room temperature, and to the mixture was added alkynyl imine **S4b** (1.41 g, 6.0 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (120 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/dichloromethane = 1:1) to give dialkynyl imine **1i** (598 mg, 27%) as a yellow solid.

*(Z)-N,5-Bis(4-methoxyphenyl)-1-phenylpenta-2,4-diyn-1-imine (**1i**).* Yellow solid; mp 98−99 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18−8.16 (m, 2H), 7.44−7.42 (m, 5H), 7.32−7.30 (m, 2H), 6.96−6.93 (m, 2H), 6.81−6.79 (m, 2H), 3.79 (s, 3H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8, 157.7, 146.6, 143.7, 137.4, 134.4, 130.8, 128.2, 127.8, 123.0, 114.2, 113.8, 112.4, 85.5, 81.5, 74.6, 72.1, 55.3, 55.2; IR (KBr) 3035, 2961, 2920, 2837, 2210, 2132, 1654, 1604, 1558, 1509, 1501, 1468, 1445, 1338, 1292, 1252, 1208, 1175, 1105, 1027, 946, 836, 799, 776, 755, 734, 690 cm^{-1}; HRMS (EI): calcd for $C_{25}H_{19}NO_2$ $(M)^+$ 365.1416, found 365.1412.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (140 mg, 0.20 mmol), CuI (76.2 mg, 0.40 mmol), PPh_3 (104 mg, 0.40 mmol), and alkynyl bromide **S5d**[22] (780 g, 3.6 mmol) in degassed triethylamine (10 mL) at room temperature, and to the mixture was added alkynyl imine **S4b** (470 mg, 2.0 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (40 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/dichloromethane = 1:1) to give dialkynyl imine **1j** (407 mg, 55%) as a yellow solid.

*(Z)-5-(4-Chlorophenyl)-N-(4-methoxyphenyl)-1-phenylpenta-2,4-diyn-1-imine (**1j**).* Yellow solid; mp 88−90 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17−8.15 (m, 2H), 7.48−7.44 (m, 5H), 7.33−7.29 (m, 4H), 6.97−6.95 (m, 2H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.9, 146.5, 143.7, 137.3, 136.2, 133.9, 131.0, 129.0, 128.4, 127.8, 123.0, 119.3, 113.9, 83.6, 80.6, 75.4, 74.0, 55.4; IR (KBr) 3031, 2992, 2953, 2834, 2208, 2134, 1602, 1579, 1548, 1503, 1462, 1448, 1338, 1291, 1247, 1206, 1173, 1106, 1072, 1034, 952, 927, 836, 816, 774, 760, 694 cm^{-1}; HRMS (EI): calcd for $C_{24}H_{16}ClNO$ $(M)^+$ 369.0920, found 369.0932.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (421 mg, 0.60 mmol), CuI (230 mg, 1.20 mmol), PPh_3 (315 mg, 1.20 mmol), and alkynyl bromide **S5e**[23] (1.80 g, 7.80 mmol) in degassed triethylamine (30 mL) at room temperature, and to the mixture was added alkynyl imine **S4b** (1.41 g, 6.0 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (120 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/dichloromethane = 1:1) to give dialkynyl imine **1k** (1.00 g, 43%) as a yellow solid.

*(Z)-N-(4-Methoxyphenyl)-5-(naphthalen-2-yl)-1-phenylpenta-2,4-diyn-1-imine (**1k**).* Yellow solid; mp 166−167 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (m, 2H), 8.07 (s, 1H), 7.79−7.77 (m, 3H), 7.52−7.46 (m, 6H), 7.34−7.32 (m, 2H), 6.99−6.97 (m, 2H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.9, 146.7, 143.8, 137.5, 133.7, 133.5, 132.7, 130.9, 128.4, 128.3, 128.2, 127.9, 127.9, 127.8, 127.6, 126.9, 123.0, 118.0, 114.0, 85.5, 81.2, 75.2, 73.4, 55.4; IR (KBr) 3073, 2964, 2898, 2833, 2168, 1547, 1503, 1442, 1417, 1368, 1317, 1292, 1251, 1195, 935, 911, 835, 774, 755, 739, 693, 665 cm^{-1}; HRMS (EI): calcd for $C_{28}H_{19}NO$ $(M)^+$ 385.1467, found 385.1481.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (421 mg, 0.60 mmol), CuI (230 mg, 1.20 mmol), PPh_3 (315 mg, 1.20 mmol), and alkynyl bromide **S5f**[23] (1.46 g, 7.8 mmol) in degassed triethylamine (30 mL) at room temperature, and to the mixture was added alkynyl imine **S4b** (1.41 g, 6.0 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (120 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/dichloromethane = 1:1) to give dialkynyl imine **1l** (729 mg, 36%) as a yellow solid.

*(Z)-N-(4-Methoxyphenyl)-1-phenyl-5-(thiophen-2-yl)penta-2,4-diyn-1-imine (**1l**).* Yellow solid; mp 92−93 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17−8.15 (m, 2H), 7.48−7.44 (m, 3H), 7.39−7.38 (m, 1H), 7.36−7.34 (m, 1H), 7.31−7.29 (m,2H), 7.00−6.95 (m, 3H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 146.3, 143.5, 137.1, 135.3, 130.8, 129.7, 128.2, 127.6, 127.1, 122.8, 120.8,

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113.7, 80.5, 77.9, 76.8, 76.5, 55.2; IR (KBr) 3062, 2952, 2833, 2185, 1603, 1546, 1504, 1442, 1418, 1368, 1292, 1252, 1195, 1169, 1108, 1081, 1065, 1029, 939, 911, 837, 806, 774, 756, 738, 694 cm^{-1}; HRMS (EI): calcd for $C_{22}H_{15}NOS$ $(M)^+$ 341.0874 found 341.0879.

In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a Dimroth condenser, and an argon balloon were placed $PdCl_2(PPh_3)_2$ (359 mg, 0.51 mmol), CuI (196 mg, 1.02 mmol), PPh_3 (268 mg, 1.02 mmol), and alkynyl bromide **S5g**[24] (1.13 g, 6.1 mmol) in degassed triethylamine (25 mL) at room temperature, and to the mixture was added alkynyl imine **S4b** (1.61 g, 5.1 mmol). The reaction mixture was stirred at 60−65 °C for 2 h and then cooled down to room temperature. The mixture was filtered through a Celite pad and it was washed with dichloromethane (100 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/dichloromethane = 1:1) to give alkynyl imine **1m** (601 mg, 35%) as a red oil.

*(Z)-N-(4-Methoxyphenyl)-5-(5-methylfuran-2-yl)-1-phenylpenta-2,4-diyn-1-imine (**1m**).* Red oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16−8.13 (m, 2H), 7.46−7.28 (m, 5H), 6.96−6.94 (m, 2H), 6.73 (s, 1H), 6.01−6.00 (m, 1H), 3.83 (s, 3H), 2.30 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.9, 156.1, 146.3, 143.6, 137.2, 134.1, 130.9, 128.3, 127.8, 123.0, 121.2, 113.9, 107.8, 80.6, 78.4, 78.2, 75.0, 55.3, 14.0; IR (neat) 3054, 2958, 2929, 2835, 2189, 1603, 1548, 1528, 1502, 1445, 1377, 1335, 1293, 1246, 1205, 1172, 1167, 1107, 1073, 1030, 956, 905, 834, 786, 768, 757, 688, 661 cm^{-1}; HRMS (EI): calcd for $C_{23}H_{17}NO_2$ $(M)^+$ 339.1259, found 339.1243.

Procedure for the Preparation of Ketene Silyl Acetals 2. Ketene silyl acetals **2a**[25] and **2c**[26] were prepared according to the literature method.

Synthesis of Ketene Silyl Acetal 2b (See Page S3 in the Supporting Information). In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed diisopropylamine (1.82 g, 18.0 mmol) in diethyl ether (30 mL) at 0 °C and to the mixture was added *n*-butyllithium (11.0 mL, 1.62 M in hexane, 17.9 mmol) at 0 °C. After 0.5 h, methyl 2-ethylbutanoate (1.95 g, 15.0 mmol) was added to the mixture. After the solution was stirred for 30 min at 0 °C, trimethylsilyl chloride (1.94 g, 17.9 mmol) was added at 0 °C to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The solvents were evaporated in vacuo. The resulting mixture was diluted with hexane (50 mL) and filtered through a Celite pad. The filtrate was evaporated in vacuo and then the residue was purified by distillation under reduced pressure to give the silyl ketene acetal **2b** (2.18 g, 72%) as a colorless oil:

*[(2-Ethyl-1-methoxybut-1-en-1-yl)oxy]trimethylsilane (**2b**).* Colorless oil; bp 60−61 °C/0.9 kPa; ^1H NMR (400 MHz, $CDCl_3$) δ 3.50 (s, 3H), 2.00 (q, J = 7.3 Hz, 2H), 1.95 (q, J = 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H), 0.21 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.3, 103.0, 56.9, 20.9, 20.5, 13.7, 12.8, −0.1; IR (neat) 2963, 2937, 1689, 1462, 1253, 1167, 1146, 1043, 949, 921, 846, 758 cm^{-1}; HRMS (EI): calcd for $C_{10}H_{22}O_2Si$ $(M)^+$ 202.1389, found 202. 1389.

Experimental Procedure for the Scope of the Substrates in Domino 1,4- and 1,6-Addition Reactions. In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (60.0 mg, 0.45 mmol) and dialkynyl imine **1a** (183 mg, 0.50 mmol) in dichloromethane (6.5 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (262 mg, 1.5 mmol) in dichloromethane (2.5 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (15 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5a** (173 mg, 64%) as a yellow oil.

*Methyl (Z)-4-(2-((E)-(4-Methoxyphenyl)((4-methoxyphenyl)-imino)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**5a**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.67 (m, 2H), 7.40−7.33 (m, 3H), 6.92−6.90 (m, 2H), 6.85−6.83 (m, 2H), 5.95−5.94 (m, 1H), 5.85 (s, 1H), 5.70 (m, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 2.13 (s, 3H) 1.26 (s, 6H), 1.09 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.3, 175.6, 175.5, 157.8, 156.8, 153.6, 147.9, 146.1, 144.7, 138.4, 136.9, 130.6, 128.2, 127.8, 121.8, 116.1, 114.0, 113.7, 107.6, 63.4, 55.4, 52.1, 49.0, 25.3, 20.3, 13.6; IR (neat) 3062, 2931, 2844, 2137, 1604, 1502, 1442, 1170, 1091, 953, 760, 690 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{35}NO_5$ $(M)^+$ 537.2515, found 537.2493.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (60.0 mg, 0.45 mmol) and dialkynyl imine **1b** (33.5 mg, 0.10 mmol) in dichloromethane (1.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (52.3 mg, 0.30 mmol) in dichloromethane (1.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5b** (31.5 mg, 62%) as a yellow oil.

*Methyl (Z)-4-(2-((E)-((4-Methoxyphenyl)imino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**5b**).* Yellow semisolid, 31.5 mg, 62 ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.66 (m, 2H), 7.43−7.39 (m, 3H), 7.16−7.15 (3H, s), 6.85−6.75 (m, 6H), 6.07 (s, 1H), 3.81 (s, 3H), 3.56 (s, 3H), 1.22 (s, 6H), 0.74 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.6, 176.2, 175.1, 158.0, 156.7, 156.0, 144.6, 140.0, 137.6, 137.1, 130.9, 128.9, 128.4, 128.1, 128.0, 121.8, 118.7, 113.8, 63.2, 55.5, 52.0, 49.9, 25.1, 20.1; IR (neat) 2966, 1724, 1647, 1577, 1513, 1366, 1245, 1034, 753, 697 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{33}NO_4$ $(M)^+$ 507.2410, found 507.2392.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (160 mg, 1.20 mmol) and dialkynyl imine **1c** (140 mg, 0.40 mmol) in dichloromethane (4.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (209 mg, 1.2 mmol) in dichloromethane (2.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (15 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 6:1) to give 1,4- and 1,6-addition adduct **5c** (123 mg, 59%) as a yellow oil.

*Methyl (Z)-4-(2-((E)-((4-Methoxyphenyl)imino)(p-tolyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**5c**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58−7.56 (m, 2H), 7.21−7.17 (m, 5H), 6.84−6.75 (m, 6H), 6.08 (s, 1H), 3.81(s, 3H), 3.56 (s, 3H), 2.40 (s, 3H), 1.22 (s, 6H), 0.70 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.9, 176.0, 175.1, 157.8, 156.6, 155.8, 144.8, 141.3, 140.3, 137.7, 134.4, 129.1, 128.9, 128.3, 128.0, 127.9, 121.8, 118.7, 113.8, 63.1, 55.5, 52.0, 49.9, 25.1, 21.5, 20.1; IR (neat) 2954, 2910, 2836, 1755, 1738, 1602, 1500, 1244, 1142, 1034, 838, 706 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{35}NO_4$ $(M)^+$ 521.2566, found 521.2561.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (40.4 mg, 0.30 mmol) and dialkynyl imine **1d** (33.6 mg, 0.10 mmol) in dichloromethane (1.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (52.3 mg, 0.30 mmol) in dichloromethane (1.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added

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to quench the reaction. The mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5d** (42.0 mg, 81%) as a yellow oil.

Procedure for the Scaling-Up Reaction. In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (1.20 g, 9.0 mmol) and dialkynyl imine **1d** (1.04 g, 3.0 mmol) in dichloromethane (19 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (1.57 g, 9.0 mmol) in dichloromethane (6.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (25 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (25 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give 1,4- and 1,6-addition adduct **5d** (1.14 g, 70%) as a yellow oil.

*Methyl (Z)-4-(2-((E)-(4-Chlorophenyl)((4-methoxyphenyl)imino)-methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**5d**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.54 (m, 2H), 7.35−7.33 (m, 2H), 7.14−7.12 (m, 3H), 6.85−6.74 (m, 6H), 6.01 (s, 1H), 3.81 (s, 3H), 3.57 (s, 3H), 1.23 (s, 6H), 0.80 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.4, 176.7, 175.0, 156.9, 156.5, 156.4, 144.4, 139.1, 137.5, 137.0, 135.5, 129.3, 128.8, 128.5, 128.3, 128.0, 121.8, 118.3, 113.8, 63.3, 55.5, 52.0, 49.9, 25.2, 20.1; IR (neat) 3084, 3018, 2954, 2898, 1737, 1602, 1560, 1501, 1462, 1382, 1362, 1244, 1142, 1088, 1033, 963, 913, 839, 731, 706 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{32}ClNO_4$ $(M)^+$, 541.2020, found 541.2048.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (400 mg, 3.0 mmol) and dialkynyl imine **1e** (386 mg, 1.0 mmol) in dichloromethane (10 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (523 mg, 3.0 mmol) in dichloromethane (3.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5e** (379 mg, 68%) as a yellow oil.

*Methyl (Z)-4-(2-((E)-((4-Methoxyphenyl)imino)(naphthalen-2-yl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**5e**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 2H), 7.48−7.37 (m, 3H), 7.17−7.16 (m, 3H), 6.85−6.76 (m, 6H), 6.07 (s, 1H), 3.82 (s, 3H), 3.56 (s, 3H), 1.22 (s, 6H), 0.74 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.5, 176.3, 175.1, 157.8, 156.7, 156.0, 144.7, 140.0, 137.6, 130.1, 128.9, 128.4, 128.3, 128.1, 128.0, 121.8, 118.6, 113.8, 63.1, 55.5, 52.1, 49.9, 25.1, 20.1; IR (neat) 2955, 2836, 1736, 1603, 1570, 1503, 1460, 1363, 1243, 1142, 1104, 1033, 963, 837, 755, 698 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{35}NO_4$ $(M)^+$ 557.2566, found 557.2518.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (40.9 mg, 0.31 mmol) and dialkynyl imine **1f** (34.2 mg, 0.10 mmol) in dichloromethane (1.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (52.8 mg, 0.30 mmol) in dichloromethane (1.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5f** (28.9 mg, 56%) as a yellow oil.

*Methyl (Z)-4-(2-((Z)-((4-Methoxyphenyl)imino)(thiophen-2-yl)-methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**5f**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 0.9, 5.0 Hz, 1H), 7.19−7.14 (m, 3H), 7.05−7.00 (m, 2H), 6.83−6.76 (m, 6H), 6.08 (s, 1H), 3.81 (s, 3H), 3.58 (s, 3H), 1.25 (s, 6H), 079 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.2. 176.4, 175.1, 156.9, 156.5, 151.9, 143.7, 138.5, 137.5, 130.6, 130.1, 128.8, 128.3, 127.9, 127.5, 122.4, 118.4, 113.7, 63.3, 55.5, 52.1, 50.0, 25.2, 20.0; IR (neat) 3040, 2954, 2898, 1755, 1735, 1602, 1574, 1461, 1426, 1244, 1142, 1033, 925, 838, 762, 706 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{31}NO_4S$ $(M)^+$ 513.1974, found 513.1993.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (400 mg, 3.0 mmol) and dialkynyl imine **1g** (325 mg, 1.0 mmol) in dichloromethane (8. 0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (523 mg, 3.0 mmol) in dichloromethane (5.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate/triethylamine = 75:25:8) to give 1,4- and 1,6-addition adduct **5g** (240 mg, 48%) as a yellow oil.

*Methyl (Z)-4-(2-((Z)-Furan-2-yl((4-methoxyphenyl)imino)-methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**5g**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.43 (m, 1H), 7.17−7.15 (m, 2H), 7.04−7.01 (m, 2H), 6.83−6.67 (m, 6H), 6.08 (s, 1H), 3.81 (s, 3H), 3.58 (s, 3H), 1.25 (s, 6H), 0.79 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.3, 176.4, 175.1, 156.8. 156.6, 151.9, 143.8, 143.7, 138.4, 137.5, 130.7, 130.2, 128.8, 127.9, 127.5, 122.4, 118.4, 113.7, 63.3, 55.5, 52.1, 50.0, 25.2, 20.0; IR (neat) 3051, 2975, 2844, 1734, 1599, 1502, 1243, 1142, 1032, 837, 693 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{31}NO_5$ $(M)^+$ 497.2202, found 497.2227.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (40.0 mg, 0.30 mmol) and dialkynyl imine **1h** (34.9 mg, 0.10 mmol) in dichloromethane (1.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (52.3 mg, 0.30 mmol) in dichloromethane (1.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5h** (34.1 mg, 65%) as an orange oil.

*Methyl (Z)-4-(2-((E)-((4-Methoxyphenyl)imino)(naphthalen-2-yl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**5h**).* Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.61 (m, 2H), 7.43−7.41 (m, 1H),7.38−7.34 (m, 2H), 6.93−6.91 (m, 2H), 6.83−6.81 (m, 2H), 6.76−6.73 (m, 2H), 6.68−6.66 (m, 2H), 6.00 (s, 1H), 3.80 (s, 3H), 3.56 (s, 3H), 2.17 (s, 3H) 1.20 (s, 6H), 0.79 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.7, 176.7, 175.2, 157.9, 156.6, 156.3, 144.8, 139.5, 138.1, 137.0, 134.5, 130.8, 128.7, 128.7, 128.3, 128.1, 121.7, 118.3, 113.7, 63.1, 55.5, 52.0. 50.0, 25.1, 21.1, 20.2; IR (neat) 3062, 2954, 2876, 2835, 1754, 1736, 1602, 1559, 1500, 1460, 1382, 1362, 1243, 1142, 1090, 1032, 963, 839, 756, 706 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{35}NO_4$ $(M)^+$ 521.2566, found 521.2575.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (40.0 mg, 0.30 mmol) and dialkynyl imine **1i** (36.5 mg, 0.10 mmol) in dichloromethane (1.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution

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of ketene silyl acetal **2a** (52.3 mg, 0.30 mmol) in dichloromethane (1.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5i** (44.9 mg, 84%) as an orange oil.

*Methyl (Z)-3-(4-Methoxyphenyl)-4-(2-((E)-((4-methoxyphenyl)-imino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethylbut-3-enoate (**5i**).* Orange oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.61 (m, 2H), 7.43−7.36 (m, 2H), 6.85−6.83 (m, 2H), 6.79−6.77 (m, 3H), 6.73−6.71 (m, 2H), 6.64−6.62 (m, 2H), 6.00 (s, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 3.57 (s, 3H), 1.21 (s, 6H), 0.83 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.8, 176.7, 175.2, 159.4, 157.9, 156.6, 156.1, 144.8, 139.4, 137.0, 130.8, 130.0, 129.6, 128.2, 128.0, 121.7, 118.5, 113.7, 113.4, 63.1, 55.5, 55.0, 52.0, 50.1, 25.1, 20.2; IR (neat); 3062, 3018, 2942, 1735, 1620, 1501, 1460, 1361, 1242, 1177, 1143, 1103, 1034, 963, 838, 755, 706 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{35}NO_5$ $(M)^+$ 537.2515, found 537.2515.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (200 mg, 1.5 mmol) and dialkynyl imine **1j** (185 mg, 0.5 mmol) in dichloromethane (2.5 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (262 mg, 1.5 mmol) in dichloromethane (2.5 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5j** (178 mg, 66%) as an orange oil.

*Methyl (Z)-3-(4-Chlorophenyl)-4-(2-((E)-((4-methoxyphenyl)-imino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethylbut-3-enoate (**5j**).* Orange oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−7.58 (m, 2H), 7.46−7.42 (m, 1H), 7.38−7.32 (m, 2H), 7.06−7.04 (m, 2H), 6.85−6.83 (m, 2H), 6.77−6.73 (m, 4H), 5.97 (s, 1H), 3.79 (s, 3H), 3.56 (s, 3H), 1.21 (s, 6H), 0.87 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.1, 176.0, 174.7, 157.6, 156.6, 154.1, 144.5, 139.8, 136.5, 135.7, 134.3, 131.0, 130.5, 130.1, 128.2, 128.2, 127.7, 121.6, 118.7, 113.7, 63.1, 55.4, 52.0, 49.6, 25.0, 20.1; IR (neat) 2996, 2954, 2833, 1735, 1604, 1508, 1460, 1364, 1245, 1170, 1142, 1032, 963, 838, 770, 706 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{32}ClNO_4$ $(M)^+$ 541.2020, found 541.1998.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (40.0 mg, 0.30 mmol) and dialkynyl imine **1k** (38.3 mg, 0.10 mmol) in dichloromethane (1.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (52.3 mg, 0.30 mmol) in dichloromethane (1.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5k** (33.4 mg, 60%) as an orange oil.

*Methyl (Z)-4-(2-((E)-((4-Methoxyphenyl)imino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-(naphthalen-2-yl)but-3-enoate (**5k**).* Orange oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.66 (m, 2H), 7.43 −7.42 (m, 3H), 7.13−7.11 (m, 1H), 6.85−6.79 (m, 4H), 6.71−6.70 (m, 1H), 6.51−6.50 (m, 1H), 6.07 (s, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 1.25 (s, 6H), 0.93 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.4, 176.6, 175.2, 157.9, 156.6, 155.9, 144.8, 139.8, 136.6, 135.0, 132.7, 132.6, 130.8, 127.9, 127.8, 127.7, 127.7, 126.5, 126.4, 126.3, 121.7, 118.8, 113.8, 63.2, 55.5, 52.1, 50.0, 25.3, 20.3; IR (neat) 3029, 2954, 2887, 1735, 1605, 1501, 1460, 1243, 1141, 1032, 837, 751 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{35}NO_4$ $(M)^+$ 557.2566, found 557.2528.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (400 mg, 3.0 mmol) and dialkynyl imine **1l** (341 mg, 1.0 mmol) in dichloromethane (8. 0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (523 mg, 3.0 mmol) in dichloromethane (6.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate/triethylamine = 10:1:1) to give 1,4- and 1,6-addition adduct **5l** (365 mg, 70%) as a yellow oil.

*Methyl (E)-4-(2-((E)-((4-Methoxyphenyl)imino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-(thiophen-2-yl)but-3-enoate (**5l**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.67 (m, 2H), 7.45−7.37 (m, 3H), 7.13−7.11 (m, 1H), 6.85−6.51 (m, 4H), 6.72−6.70 (m, 1H), 6.51−6.50 (m, 1H), 6.07 (s, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 1.25 (s, 6H), 0.93 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.6, 176.2, 175.1, 157.8, 156.7, 149.2, 144.7, 140.1, 137.0, 137.0, 130.9, 129.4, 128.4, 128.1, 127.0, 126.8, 121.7, 120.7, 113.8, 63.6, 55.5, 52.2, 50.2, 25.0, 20.2; IR (neat) 3051, 2950, 2887, 1734, 1606, 1563, 1501, 1460, 1365, 1244, 1143, 1032, 836, 755, 696 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{31}NO_4S$ $(M)^+$ 513.1987, found 513.1987.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (40.0 mg, 0.30 mmol) and dialkynyl imine **1m** (39.3 mg, 0.10 mmol) in dichloromethane (1.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2a** (52.3 mg, 0.30 mmol) in dichloromethane (1.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5m** (29.9 mg, 59%) as an orange oil.

*Methyl (E)-4-(2-((E)-((4-Methoxyphenyl)imino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-(5-methylfuran-2-yl)but-3-enoate (**5m**).* Orange oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 2H), 7.42−7.32 (m, 3H), 6.92−6.90 (m, 2H), 6.84−6.83 (m, 2H), 5.94 (d, J = 3.21, 1H), 5.85 (s, 1H), 5.69 (d, J = 3.21, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 2.13 (s, 3H) 1.26 (s, 6H), 1.09 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.3, 175.6, 175.5, 157.8, 156.8, 153.6, 147.9, 146.1, 144.7, 138.4, 136.9, 130.6, 128.2, 127.8, 121.8, 116.1, 114.0, 113.7, 107.6, 63.4, 55.4, 52.1, 49.0, 25.3, 20.3, 13.6; IR (neat) 3004, 2965, 2924, 1713, 1421, 1361, 1222, 1091, 918, 734, 647 cm^{-1}; HRMS (EI): calcd for $C_{32}H_{33}NO_5$ $(M)^+$, 511.2359, found 511.2350.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (40.0 mg, 0.30 mmol) and dialkynyl imine **1b** (39.3 mg, 0.10 mmol) in dichloromethane (1.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2b** (59.6 mg, 0.30 mmol) in dichloromethane (1.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 6:1) to give 1,4- and 1,6-addition adduct **5n** (28.9 mg, 51%) as an orange oil.

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*Methyl (Z)-4-(4,4-Diethyl-2-((E)-((4-methoxyphenyl)imino)(phenyl)methyl)-3-oxocyclobut-1-en-1-yl)-2,2-diethyl-3-phenylbut-3-enoate (**5n**).* Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.71 (m, 2H), 7.46−7.38 (m, 3H), 7.20−7.16 (m, 3H), 6.84−6.77 (m, 4H), 6.71−6.67 (m, 2H), 6.22 (s, 1H), 3.77 (s, 3H), 3.54 (s, 3H), 1.71 (dq, J = 7.3, 14.5 Hz, 2H), 1.54 (dq, J = 7.3, 14.5 Hz, 2H), 1.30 (dq, J = 7.3, 14.5 Hz, 2H), 0.78 (dq, J = 7.3, 14.5, 2H), 0.70 (t, J = 7.3 Hz, 6H), 0.67 (t, J = 7.3 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.6, 174.1, 173.5, 157.6, 156.7, 153.5, 145.0. 142.7, 137.6, 130.7, 128.4, 128.3, 127.9, 122.0, 121.3, 113.9, 72.9, 58.1, 55.5, 51.7, 25.5, 24.2, 10.3, 8.3; IR (neat) 3062, 2952, 2866, 1751, 1607, 1572, 1502, 1442, 1297, 1241, 1168, 1105, 1035, 911, 835, 730, 702 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{41}NO_4$ $(M)^+$ 563.3036, found 563.3031.

In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed $AlCl_3$ (400 mg, 3.0 mmol) and dialkynyl imine **1b** (335 mg, 1.0 mmol) in dichloromethane (6.0 mL) at room temperature. The mixture was stirred at −78 °C for 10 min and to the mixture was added a solution of ketene silyl acetal **2c** (601 mg, 3.0 mmol) in dichloromethane (6.0 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 1,4- and 1,6-addition adduct **5o** (400 mg, 71%) as an orange oil.

*Methyl 1-((Z)-2-(2-((E)-((4-Methoxyphenyl)imino)(phenyl)methyl)-3-oxospiro[3.4]oct-1-en-1-yl)-1-phenylvinyl)cyclopentane-1-carboxylate (**5o**).* Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.52 (m, 2H), 7.42−7.38 (m, 1H), 7.35−7.31 (m, 2H), 7.08−7.00 (m, 3H), 6.80−6.77 (m, 4H), 6.66−6.64 (m, 2H), 6.00 (s, 1H), 3.80 (s, 3H), 3.56 (s, 3H), 2.10−2.07 (m, 2H), 1.74−1.70 (m, 2H), 1.60−1.54 (m, 8H), 14.2−1.35 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.7, 147.6, 157.5, 156.7, 154.1, 144.8, 140.5, 138.0, 128.2, 128.1, 128.0, 121.9, 118.6, 113.6, 72.3, 62.2, 55.5, 52.2, 35.4, 31.0, 26.0, 23.3; IR (neat) 3052, 2968, 2877, 1742, 1608, 1502, 1454, 1380, 1295, 1245, 1127, 1034, 911, 836, 732, 696 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{37}NO_4$ $(M)^+$ 559.2723, found 559.2749.

Experimental Procedure for the Scope of the Substrates in the Reduction of Iminocyclobutenones 5. In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5a** (46.1 mg, 0.086 mmol) in MeOH (1.0 mL) at room temperature. A solution of $NaCNBH_3$ (8.1 mg, 0.13 mmol) in MeOH (0.5 mL) and acetyl chloride in MeOH (0.95 mL, 0.13 mmol), which was prepared from acetyl chloride (0.10 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (toluene/diethyl ether = 6:1) to give the aminocyclobutenone **10a** (24.2 mg, 52%) as an orange oil.

*Methyl (Z)-4-(2-((4-Methoxyphenyl)((4-methoxyphenyl)amino)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**10a**).* Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.21 (m, 5H), 7.01−7.00 (m, 2H), 6.84−6.83 (m, 2H), 6.72−6.70 (m, 2H), 6.52 (s, 1H), 6.48−6.47 (m, 2H), 4.68 (s, 1H), 4.20 (s, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 0.73 (s, 3H), 0.69 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.0, 175.6, 172.2, 158.9, 155.1, 152.3, 143.8, 140.7, 138.3, 132.4, 128.4, 128.2, 128.1, 118.4, 115.3, 114.5, 114.0, 63.0, 55.7, 55.2, 54.4, 52.2, 49.9, 25.6, 25.6, 20.5, 20.4; IR (neat) 3384, 2954, 1739, 1617, 1511, 1461, 1246, 1175, 1139, 1033, 825, 765, 708 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_5$ $(M)^+$ 539.2672, found 539.2685.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5b** (254 mg, 0.50 mmol) in MeOH (4.0 mL) at room temperature. A solution of $NaCNBH_3$ (47.1 mg, 0.75 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.83 mL, 0.75 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 0.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give the aminocyclobutenone **10b** (225 mg, 88%) as a yellow oil.

*Methyl (Z)-4-(2-(((4-Methoxyphenyl)amino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**10b**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.30 (m, 4H), 7.24−7.21 (m, 4H), 7.02−6.99 (m, 2H), 6.72−6.70 (m,2H), 6.52 (s, 1H), 6.49−6.46 (m, 2H), 4.72 (s, 1H), 4.29 (s, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 0.73 (s, 3H), 0.71 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.9, 175.6, 172.5, 155.3, 152.4, 143.5, 140.6, 140.4, 138.3, 128.8, 128.7, 128.4, 128.2, 127.4, 127.0, 118.3, 115.2, 114.5, 63.1, 55.7, 55.0, 52.2, 49.9, 25.6, 25.6, 20.5, 20.3; IR (neat) 3395, 2953, 1738, 1622, 1512, 1459, 1244, 1143, 1035, 821, 755, 701 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{35}NO_4$ $(M)^+$ 509.2566, found 509.2560.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5c** (52.2 mg, 0.10 mmol) in MeOH (1.0 mL) at room temperature. A solution of $NaCNBH_3$ (9.4 mg, 0.15 mmol) in MeOH (0.5 mL) and acetyl chloride in MeOH (1.1 mL, 0.15 mmol), which was prepared from acetyl chloride (0.10 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (toluene/diethyl ether = 6:1) to give the aminocyclobutenone **10c** (40.9 mg, 78%) as a yellow oil.

*Methyl (Z)-4-(2-(((4-Methoxyphenyl)amino)(p-tolyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**10c**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.23 (m, 5H), 7.03−7.01 (m, 2H), 6.90−6.88 (m, 2H), 6.71−6.68 (m, 2H), 6.44−6.42 (m, 3H), 4.57 (s, 1H), 4.28 (s, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 2.19 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.81 (s, 3H), 0.80 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.8, 175.7, 172.5, 155.8, 152.3, 142.9, 140.6, 140.4, 138.3, 135.3, 129.0, 128.5, 127.3, 126.9, 118.0, 115.1, 114.5, 62.9, 55.7, 54.8, 52.1, 49.8, 25.6, 25.6, 21.1, 20.4, 20.3; IR (neat) 3388, 2952, 1738, 1621, 1511, 1460, 1242, 1142, 1037, 818, 771, 705 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_4$ $(M)^+$ 523.2723, found 523.2747.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5d** (108.4 mg, 0.20 mmol) in MeOH (2.0 mL) at room temperature. A solution of $NaCNBH_3$ (18.9 mg, 0.30 mmol) in MeOH (0.5 mL) and acetyl chloride in MeOH (0.73 mL, 0.30 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (toluene/diethyl ether = 8:1) to give the aminocyclobutenone **10d** (81.5 mg, 75%) as a yellow oil.

Procedure for the Scaling-Up Reaction. In a 100 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5d** (1.14 g, 2.1 mmol) in MeOH (20 mL) at room temperature. A solution of $NaCNBH_3$ (199 mg, 3.2 mmol) in MeOH (5.0 mL) and acetyl chloride in MeOH (7.7 mL, 3.2 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to

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the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4/1) to give the aminocyclobutenone **10d** (913 mg, 80%) as a yellow oil.

*Methyl (Z)-4-(2-((4-Chlorophenyl)((4-methoxyphenyl)amino)-methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**10d**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.20 (m, 7H), 7.02−6.99 (m, 2H), 6.71−6.69 (m, 2H), 6.45−6.41 (m, 3H), 4.58 (s, 1H), 4.24 (s, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 0.79 (s, 3H), 0.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.5, 175.5, 172.7, 155.8, 152.4, 142.5, 140.2, 138.9, 128.7, 128.6, 128.5, 128.3, 128.2, 118.0, 115.3, 114.4, 63.1, 55.6, 54.3, 52.2, 49.8, 25.6, 20.4, 20.3; IR (neat) 3379, 2953, 1737, 1621, 1510, 1465, 1244, 1143, 1091, 1037, 1015, 821, 757, 705 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{34}ClNO_4$ $(M)^+$ 543.2176, found 543.2190.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5e** (223 mg, 0.40 mmol) in MeOH (4.0 mL) at room temperature. A solution of $NaCNBH_3$ (37.3 mg, 0.60 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.46 mL, 0.60 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give the aminocyclobutenone **10e** (163 mg, 73%) as a yellow oil.

*Methyl (Z)-4-(2-(((4-Methoxyphenyl)amino)(naphthalen-2-yl)-methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**10e**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.75 (m, 4H), 7.46−7.43 (m, 3H), 7.21−7.15 (m, 3H), 7.01−7.00 (m, 2H), 6.70−6.68 (m, 2H), 6.53−6.50 (m, 3H), 4.89 (s, 1H), 4.46 (s, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.75 (s, 3H), 0.74 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 175.5, 172.6, 155.3, 152.3, 143.2, 140.6, 238.2, 137.8, 133.3, 132.8, 128.7, 128.5, 128.4, 128.2, 127.9, 126.0, 125.6, 125.0, 118.3, 115.2, 114.5, 63.1, 55.6, 55.2, 52.1, 49.8, 25.5, 20.4, 20.3; IR (neat) 3370, 2953, 1738, 1620, 1511, 1460, 1243, 1142, 1037, 819, 750, 705 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{37}NO_4$ $(M)^+$ 559.2723, found 559.2710.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5f** (104 mg, 0.20 mmol) in MeOH (1.5 mL) at room temperature. A solution of $NaCNBH_3$ (18.9 mg, 0.30 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (0.73 mL, 0.30 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 6:1) to give the aminocyclobutenone **10f** (65.5 mg, 59%) as a yellow oil.

*Methyl (Z)-4-(2-(((4-Methoxyphenyl)amino)(thiophen-2-yl)-methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**10f**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.24 (m, 3H), 7.17−7.17 (m, 1H), 7.02−7.00 (m, 2H), 6.89−6.88 (m, 1H), 6.89−6.88 (m, 1H), 6.82 (s, 1H), 6.74−6.72 (m, 2H), 6.54−6.51 (m, 2H), 6.49 (s, 1H), 4.81 (s, 1H), 4.25 (s, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 0.84 (s, 3H), 076 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.3, 174.5, 172.7 155.9, 152.8, 144.1, 142.4, 140.2, 138.2, 128.7, 128.4, 128.2, 126.6, 124.8, 124.7, 118.1, 115.8, 114.5, 63.1, 55.6, 52.1, 50.8, 49.9, 25.6, 20.4, 20.3; IR (neat) 3372, 2954, 1739, 1623, 1510, 1463, 1371, 1240, 1143, 1034, 825, 770, 706 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{33}NO_4S$ $(M)^+$ 515.2130, found 515.2112.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5g** (49.8 mg, 0.10 mmol) in MeOH (1.0 mL) at room temperature. A solution of $NaCNBH_3$ (9.4 mg, 0. mmol) in MeOH (0.5 mL) and acetyl chloride in MeOH (0.36 mL, 0.05 mmol), which was prepared from acetyl chloride (0.10 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.0 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate/triethylamine = 80:20:3) to give the aminocyclobutenone **10g** (31.2 mg, 62%) as a yellow oil.

*Methyl (Z)-4-(2-(Furan-2-yl((4-methoxyphenyl)amino)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-phenylbut-3-enoate (**10g**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 1H), 7.28−7.23 (m, 3H), 7.02−6.98 (m, 2H), 6.75−6.72 (m, 2H), 6.56−6.53 (m, 2H), 6.49 (s, 1H), 6.28-6.25 (m, 1H), 6.11 (d, J = 3.1 Hz, 1H), 4.65 (s, 1H), 4.15 (brs, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 0.84 (s, 3H), 0.76 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.5, 175.5, 173.5, 155.9, 152.8, 152.2, 142.0, 140.7, 140.3, 138.2, 128.8, 128.3, 128.2, 118.0, 115.8, 114.5, 110.3, 107.2, 63.1, 55.7, 52.2, 49.9, 49.2, 25.7, 25.6, 20.4, 20.4; IR (neat) 3382, 2953, 1739, 1624, 1511, 1461, 1372, 1241, 1144, 1014, 822, 738, 709 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{33}NO_5$ $(M)^+$ 499.2359, found 499.2367.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5h** (209 mg, 0.40 mmol) in MeOH (4.0 mL) at room temperature. A solution of $NaCNBH_3$ (37.7 mg, 0.60 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.46 mL, 0.60 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give the aminocyclobutenone **10h** (148 mg, 70%) as a yellow oil.

*Methyl (Z)-4-(2-(((4-Methoxyphenyl)amino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-(p-tolyl)but-3-enoate (**10h**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.28−7.20 (m, 5H), 7.03−7.01 (m, 2H), 6.90−6.88 (m, 2H), 6.71−6.68 (m, 2H), 6.44−6.42 (m, 3H), 4.57 (s, 1H), 4.28 (s, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 2.19 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.81 (s, 3H), 0.80 (s, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 197.8, 175.7, 172.5, 155.8, 152.3, 142.9, 140.6, 140.4, 138.3, 129.0, 128.5, 127.3, 126.9, 118.0, 115.1, 114.5, 62.9, 55.7, 54.8, 49.8, 25.6, 25.6, 21.1, 20.4, 20.3; IR (neat) 3393, 2952, 1738, 1620, 1512, 1459, 1242, 1142, 1035, 820, 753, 700 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_4$ $(M)^+$ 523.2723, found 523.2727.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5i** (161 mg, 0.30 mmol) in MeOH (3.0 mL) at room temperature. A solution of $NaCNBH_3$ (28.3 mg, 0.45 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.1 mL, 0.45 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 2.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified

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by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give the aminocyclobutenone **10i** (123 mg, 76%) as a yellow oil.

*Methyl (Z)-3-(4-Methoxyphenyl)-4-(2-(((4-methoxyphenyl)-amino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethylbut-3-enoate (**10i**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.19 (m, 5H), 6.94−6.92 (m, 2H), 6.74−6.68 (m, 4H), 6.44−6.42 (m, 3H), 4.56 (s, 1H), 4.29 (s, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 175.8, 172.5, 159.7, 155.6, 152.3, 142.8, 140.6, 140.5, 130.4, 129.9, 128.6, 127.3, 126.9, 118.0, 115.1, 114.5, 113.7, 62.9, 55.7, 55.0, 54.9, 52.2, 50.0, 25.7, 25.6, 20.5, 20.4; IR (neat) 3384, 2953, 1738, 1612, 1511, 1459, 1245, 1177, 1142, 1031, 829, 751, 699 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_5$ $(M)^+$ 539.2672, found 539.2671.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5j** (217 mg, 0.40 mmol) in MeOH (4.0 mL) at room temperature. A solution of $NaCNBH_3$ (37.7 mg, 0.60 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.46 mL, 0.60 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (toluene/diethyl ether = 7:1) to give the aminocyclobutenone **10j** (174 mg, 80%) as a yellow oil.

*Methyl (Z)-3-(4-Chlorophenyl)-4-(2-(((4-methoxyphenyl)amino)-(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethylbut-3-enoate (**10j**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.23 (m, 5H), 7.20−7.17 (m, 2H), 6.94−6.92 (m, 2H), 6.73−6.71 (m, 2H), 6.51 (s, 1H), 6.50−6.47 (m, 2H), 4.75 (s, 1H), 4.20 (s, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 1.32 (s, 6H), 0.80 (s, 3H), 0.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.4, 175.3, 172.3, 153.6, 152.5, 143.9, 140.6, 140.0, 130.2, 128.7, 128.5, 127.6, 126.9, 118.8, 115.3, 114.6, 63.1, 55.6, 55.0, 52.4, 49.7, 25.5, 20.5; IR (neat) 3384, 2955, 1739, 1624, 1511, 1461, 1242, 1143, 1095, 1023, 919, 827, 754, 697 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{34}ClNO_4$ $(M)^+$ 543.2176, found 543.2185.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5k** (223 mg, 0.40 mmol) in MeOH (4.0 mL) at room temperature. A solution of $NaCNBH_3$ (37.7 mg, 0.60 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.46 mL, 0.60 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give the aminocyclobutenone **10k** (191 mg, 85%) as an orange oil.

*Methyl (Z)-4-(2-(((4-Methoxyphenyl)amino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-(naphthalen-2-yl)but-3-enoate (**10k**).* Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.68 (m, 3H), 7.45−7.44 (m, 3H), 7.20−7.11 (m, 6H), 6.65−6.63 (m, 2H), 6.57 (s, 1H), 6.36−6.34 (m, 2H), 4.63 (s, 1H), 4.19 (s, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 1.37 (s, 6H), 0.74 (s, 3H), 0.72 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.6, 175.6, 172.6, 155.2, 152.3, 143.5, 140.6, 140.0, 135.7, 132.8, 132.7, 128.5, 128.1, 127.9, 127.8, 127.7, 126.8, 126.5, 126.4, 118.6, 115.2, 114.5, 63.1, 55.6, 54.9, 52.2, 49.9, 25.7, 20.5, 20.4; IR (neat) 3387, 2952, 1738, 1620, 1512, 1460, 1243, 1141, 1035, 820, 752, 700 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{37}NO_4$ $(M)^+$ 559.2723, found 559.2719.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5l** (205 mg, 0.40 mmol) in MeOH (4.0 mL) at room temperature. A solution of $NaCNBH_3$ (37.7 mg, 0.60 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.46 mL, 0.60 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give the aminocyclobutenone **10l** (149 mg, 72%) as a yellow oil.

*Methyl (E)-4-(2-(((4-Methoxyphenyl)amino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-(thiophen-2-yl)-but-3-enoate (**10l**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.18 (m, 4H), 7.17−7.16 (m, 2H), 6.82−6.76 (m, 2H), 6.70−6.68 (m, 2H), 6.46−6.44 (m, 2H), 6.38 (s, 1H), 4.59 (s, 1H), 4.30 (s, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.2, 175.4, 172.2, 152.2, 148.1, 143.4, 140.5, 138.2, 128.5, 128.5, 127.2, 127.1, 127.0, 126.9, 119.4, 115.1, 114.3, 63.1, 55.5, 55.0, 52.2, 50.1, 25.3, 25.3, 20.3, 20.1; IR (neat) 3371, 2952, 1738, 1618, 1512, 1459, 1383, 1242, 1145, 1037, 822, 754, 701 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{33}NO_4S$ $(M)^+$ 515.2130, found 515.2134.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5m** (189 mg, 0.37 mmol) in MeOH (3.8 mL) at room temperature. A solution of $NaCNBH_3$ (36.9 mg, 0.59 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.39 mL, 0.35 mmol), which was prepared from acetyl chloride (0.10 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 0.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by preparative silica gel TLC (hexane/ethyl acetate = 5:1) to give the aminocyclobutenone **10m** (124 mg, 66%) as an orange oil.

*Methyl (E)-4-(2-(((4-Methoxyphenyl)amino)(phenyl)methyl)-4,4-dimethyl-3-oxocyclobut-1-en-1-yl)-2,2-dimethyl-3-(5-methylfuran-2-yl)but-3-enoate (**10m**).* Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.67 (m, 2H), 7.40−7.33 (m, 3H), 6.92−6.90 (m, 2H), 6.85−6.83 (m, 2H), 5.95−5.94 (d, J =3.4 Hz, 1H), 5.85 (s, 1H), 5.70 (d, J =3.4 Hz, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 2.13 (s, 3H) 1.26 (s, 6H), 1.09 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.3, 175.6, 175.5, 157.8, 156.8, 153.6, 147.9, 146.1, 144.7, 138.4, 136.9, 130.6, 128.2, 127.8, 121.8, 116.1, 114.0, 113.7, 107.6, 63.4, 55.4, 52.1, 49.0, 25.3, 20.3, 13.6; IR (neat) 3365, 2952, 1738, 1680, 1511, 1460, 1240, 1036, 821, 778, 700 cm^{-1}; HRMS (EI): calcd for $C_{32}H_{35}NO_5$ $(M)^+$ 513.2515, found 513.2495.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5n** (141 mg, 0.25 mmol) in MeOH (4.0 mL) at room temperature. A solution of $NaCNBH_3$ (23.6 mg, 0.38 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.39 mL, 0.38 mmol), which was prepared from acetyl chloride (0.10 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 8:1) to give the aminocyclobutenone **10n** (110 mg, 78%) as a yellow oil.

*Methyl (Z)-4-(4,4-Diethyl-2-(((4-methoxyphenyl)amino)(phenyl)-methyl)-3-oxocyclobut-1-en-1-yl)-2,2-diethyl-3-phenylbut-3-enoate (**10n**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.20 (m, 9H), 7.01−6.99 (m, 2H), 6.72−6.69 (m, 2H), 6.62−6.61 (m, 1H), 6.50−6.46 (m, 2H), 4.77 (s, 1H), 4.35 (brs, 1H), 3.70 (s, 3H), 3.62 (s, 3H), 1.87−1.76 (m, 2H), 1.72-1.64 (m, 2H), 1.32-1.21 (m, 2H), 0.83−0.75 (m, 6H), 0.71−0.51 (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 174.5, 168.0, 152.6, 152.4, 146.8, 140.7, 138.2,

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128.6, 128.4, 128.2, 128.0, 127.4, 126.9, 121.6, 115.1, 114.5, 72.6, 57.9, 55.7, 55.0, 51.8, 25.4, 25.4, 24.7, 24.5, 9.9, 9.8, 8.4, 8.3; IR (neat) 3398, 2965, 1736, 1617, 1511, 1455, 1234, 1128, 1036, 822, 755, 703 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{43}NO_4$ $(M)^+$ 565.3192, found 565.3175.

In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 1,4- and 1,6-addition adduct **5o** (205 mg, 0.40 mmol) in MeOH (4.0 mL) at room temperature. A solution of $NaCNBH_3$ (37.7 mg, 0.60 mmol) in MeOH (1.0 mL) and acetyl chloride in MeOH (1.46 mL, 0.60 mmol), which was prepared from acetyl chloride (0.30 mL) and MeOH (10 mL), was added to the mixture. The resulting mixture was stirred at room temperature for 1.5 h. After removing MeOH in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1) to give the aminocyclobutenone **10o** (173 mg, 77%) as a yellow solid.

*Methyl (Z)-1-(2-(2-(((4-Methoxyphenyl)amino)(phenyl)methyl)-3-oxospiro[3.4]oct-1-en-1-yl)-1-phenylvinyl)cyclopentane-1-carboxylate (**10o**).* Yellow solid; mp 115−117 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28−7.10 (m, 8H), 7.07−7.05 (m, 2H), 6.68−6.64 (m, 2H), 6.40 (s, 1H), 6.33−6.31 (m, 2H), 4.26 (brs, 1H), 4.21 (s, 1H), 3.69 (s, 3H), 3.69 (s, 3H), 2.30−2.22 (m, 2H), 1.75−1.54 (m, 10H), 1.47−1.36 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 196.9, 175.1, 169.4, 154.0, 152.1, 144.1, 140.4, 140.4, 138.8, 128.4, 128.3, 128.2, 127.1, 126.8, 118.6, 115.1, 114.3, 71.9, 61.8, 55.5, 55.0, 52.3, 36.2, 35.9, 31.2, 31.0, 26.0, 23.4, 23.3; IR (KBr) 3359, 2951, 2867, 1739, 1720, 1610, 1513, 1492, 1445, 1231, 1168, 1036, 933, 817, 742, 699 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{39}NO_4$ $(M)^+$ 561.2879, found 561.2878.

Experimental Procedure for the Synthesis of β-Lactams 11 through Thermal Rearrangement. Entry 1: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10a** (27.0 mg, 0.05 mmol) in octane (2.5 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 3/1, three times) to give the mixture of *cis*- and *trans*-β-lactams **11a** (16.1 mg, 60%, cis/trans = 18/82).

Entry 1 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10a** (27.0 mg, 0.05 mmol) and 1,4-dimethylpiperazine (5.7 mg, 0.05 mmol) in toluene (2.5 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 2.5/1, three times) to give the mixture of *cis*- and *trans*-β-lactams **11a** (23.3 mg, 86%, cis/trans = 85/15).

Methyl (Z)-5-((2S,3R*)-1,2-Bis(4-methoxyphenyl)-4-oxoazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (trans-**11a**).* Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24−7.16 (m, 5H), 7.06-7.04 (m, 2H), 7.00−6.99 (m, 2H), 6.84−6.78 (m, 4H), 6.29 (s, 1H), 4.26 (d, J = 2.1 Hz, 1H), 3.96 (d, J = 2.1 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.51 (s, 3H), 1.61 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 177.0, 165.5, 159.5, 155.7, 146.7, 139.4, 134.0, 131.4, 130.2, 128.9, 127.6, 127.2, 126.9, 126.3, 122.9, 118.2, 114.3, 114.1, 63.5, 59.4, 55.4, 55.2, 51.8, 48.4, 26.1, 26.0, 22.9, 20.4; IR (neat) 2925, 2854, 1740, 1610, 1513, 1452, 1381, 1249, 1141, 1032, 830, 769, 708 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_5$ $(M)^+$ 539.2672, found 539.2677.

Methyl (Z)-5-((2S,3S*)-1,2-Bis(4-methoxyphenyl)-4-oxoazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (cis-**11a**).* Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.20−7.12 (m, 7H), 6.87−6.79 (m, 4H), 5.59 (s, 1H), 5.13 (d, J = 5.7 Hz, 1H), 4.44 (d, J = 5.7 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.65 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.3, 165.7, 159.2, 155.8, 146.0, 140.1, 133.1, 131.8, 128.8, 128.1, 127.6, 127.3, 126.9, 126.4, 122.1, 118.2, 114.3, 113.6, 59.6, 58.8, 55.5, 55.2, 51.8, 48.2, 26.0, 25.5, 22.1, 20.5; IR (neat) 2924, 2855, 1740, 1515, 1464, 1385, 1249, 1134, 1035, 926, 838 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_5$ $(M)^+$ 539.2672, found 539.2675.

Entry 2: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10b** (25.5 mg, 0.050 mmol) in octane (2.5 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 3/1, twice) to give the mixture of *cis*- and *trans*-β-lactams **11b** (17.5 mg, 69%, cis/trans = 23/77).

Entry 2 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10b** (39.9 mg, 0.074 mmol) and DBU (11.3 mg, 0.074 mmol) in toluene (3.7 mL) at room temperature. The mixture was stirred at 110 °C for 48 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 4/1, twice) to give the mixture of *cis*- and *trans*-β-lactams **11b** (31.9 mg, 80%, cis/trans = 10/90).

Entry 2 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10b** (28.7 mg, 0.053 mmol) and 1,4-dimethylpiperazine (12.1 mg, 0.106 mmol) in toluene (2.7 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 6/1, twice) to give *cis*-β-lactam **11b** (21.2 mg, 74%) and *trans*-β-lactam **11b** (3.5 mg, 12%).

Methyl (Z)-5-((3R,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (trans-**11b**).* Orange oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.27 (m, 3H), 7.23−7.16 (m, 5H), 7.13−7.11 (m, 2H), 7.01−6.99 (m, 2H), 6.29 (s, 1H), 4.33 (d, J = 2.4 Hz, 1H), 3.98 (d, J = 2.4 Hz, 1H), 3.75 (s, 3H), 3.51 (s, 3H), 1.63 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 177.0, 165.4, 155.8, 146.8, 139.3, 138.3, 134.2, 131.4, 128.9, 128.8, 128.1, 127.6, 126.9, 126.2, 125.9, 122.8, 118.2, 114.2, 63.4, 59.7, 55.4, 51.8, 48.4, 26.1, 26.0, 22.9, 20.4; IR (neat) 2987, 2929, 1742, 1511, 1452, 1384, 1247, 1141, 1032, 831, 752, 702 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{35}NO_4$ $(M)^+$ 509.2566, found 509.2567.

Methyl (Z)-5-((3S,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (cis-**11b**).* Colorless solid; mp 180−181 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 5H), 7.22−7.12 (m, 7H), 6.83−6.79 (m, 2H), 5.54 (s, 1H), 5.17 (d, J = 6.0 Hz, 1H), 4.49 (d, J = 6.0 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.19 (s, 3H), 1.11 (s. 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 177.3, 165.6, 155.8, 146.1, 140.0, 135.7, 133.3, 131.8, 128.9, 128.0, 127.3, 126.8, 126.4, 122.0, 118.2, 114.3, 59.9, 58.8, 55.5, 51.8, 48.2, 29.7, 26.0, 25.5, 22.0, 20.6; IR (KBr) 2987, 2918, 1749, 1512, 1465, 1387, 1245, 1145, 1025, 826, 774, 734, 705 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{35}NO_4$ $(M)^+$ 509.2566, found 509.2563.

Entry 3: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10c** (47.0 mg, 0.090 mmol) in octane (4.5 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11c** (8.0 mg, 17%) and *trans*-β-lactam**11c** (26.6 mg, 57%).

Entry 3 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth

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condenser, and an argon balloon were placed aminocyclobutenone **10c** (33.6 mg, 0.064 mmol) and DBU (9.8 mg, 0.064 mmol) in toluene (3.2 mL) at room temperature. The mixture was stirred at 110 °C for 46 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 4/1, twice) to give the mixture of *cis*- and *trans*-*β*-lactams **11c** (27.4 mg, 81%, cis/trans = 7/93).

Entry 3 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10c** (42.8 mg, 0.082 mmol) and 1,4-dimethylpiperazine (9.4 mg, 0.082 mmol) in toluene (4.1 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-*β*-lactam **11c** (33.8 mg, 79%) and *trans*-*β*-lactam**11c** (4.5 mg, 10%).

Methyl (Z)-5-((3S,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-(p-tolyl)-azetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (trans-**11c**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.15 (m, 5H), 7.11−7.09 (m, 2H), 7.03−6.99 (m, 4H), 6.80−6.76 (m, 2H), 6.28 (s, 1H), 4.31 (d, J = 2.5 Hz, 1H), 3.97 (d, J = 2.5 Hz, 1H), 3.75 (s, 3H), 3.51 (s, 3H), 2.31 (s, 3H), 1.61 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.0, 165.5, 155.7, 146.7, 139.4, 137.9, 135.3, 134.0, 131.4, 129.6, 128.8, 127.6, 126.9, 126.2, 125.8, 122.9, 118.2, 114.1, 63.4, 59.6, 55.4, 51.8, 48.4, 26.1, 26.0, 22.9, 21.1, 20.4; IR (neat) 2926, 2861, 1742, 1512, 1449, 1383, 1244, 1140, 1032, 828, 707 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_4$ $(M)^+$ 523.2723, found 523.2733.

Methyl (Z)-5-((3R,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-(p-tolyl)-azetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (cis-**11c**).* Yellow solid; mp 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.29 (m, 2H), 7.20−7.08 (m, 9H), 6.82−6.78 (m, 2H), 5.59 (s, 1H), 5.13 (d, J = 6.0 Hz, 1H), 4.46 (d, J = 6.0 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 2.34 (s, 3H), 1.35 (s, 6H), 1.20 (s, 3H), 1.13 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.3, 165.7, 155.8, 146.0, 140.1, 137.6, 133.1, 132.6, 131.9, 128.9, 127.3, 126.9, 126.8, 126.4, 122.1, 118.2, 114.3, 59.8, 58.8, 55.4, 51.8, 48.2, 26.0, 25.5, 22.1, 21.2, 20.5; IR (KBr) 2987, 2915, 1744, 1510, 1450, 1386, 1245, 1178, 1141, 1035, 835, 792, 708 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_4$ $(M)^+$ 523.2723, found 523.2730.

Entry 4: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10d** (27.2 mg, 0.05 mmol) in octane (2.5 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 3/1, twice) to give the mixture of *cis*- and *trans*-*β*-lactams **11d** (16.6 mg, 65%, cis/trans = 21/79).

Entry 4 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10d** (24.4 mg, 0.045 mmol) and DBU (6.8 mg, 0.045 mmol) in toluene (2.3 mL) at room temperature. The mixture was stirred at 110 °C for 31 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 3/1, three times) to give the mixture of *cis*- and *trans*-*β*-lactams **11d** (16.7 mg, 68%, cis/trans = <1/>99).

Entry 4 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10d** (27.2 mg, 0.05 mmol) and 1,4-dimethylpiperazine (5.7 mg, 0.05 mmol) in toluene (2.5 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 3/1, twice) to give the mixture of *cis*- and *trans*-*β*-lactams **11d** (20.4 mg, 75%, cis/trans = 90/10).

Procedure for the Scaling-Up Reaction. Entry 4 with DBU: In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10d** (297 mg, 0.54 mmol) and DBU (83 mg, 0.54 mmol) in toluene (20 mL) at room temperature. The mixture was stirred at 110 °C for 31 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give the mixture of *cis*- and *trans*-*β*-lactams **11d** (230 mg, 77%, cis/trans = 6/94).

Entry 4 with 1,4-dimethylpiperazine: In a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10d** (327 mg, 0.60 mmol) and 1,4-dimethylpiperazine (69 mg, 0.60 mmol) in toluene (22 mL) at room temperature. The mixture was stirred at 110 °C for 7 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give the mixture of *cis*- and *trans*-*β*-lactams **11d** (272 mg, 83%, cis/trans = 92/8).

Methyl (Z)-5-((2S,3R*)-2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (trans-**11d**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.21 (m, 3H), 7.19−7.12 (m, 4H), 7.03−6.98 (m, 4H), 6.82−6.78 (m, 2H), 6.29 (s, 1H), 4.25 (d, J = 2.1 Hz, 1H), 3.94 (d, J = 2.1 Hz, 1H), 3.76 (s, 3H), 3.50 (s, 3H), 1.65 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.0, 165.1, 155.9, 146.9, 139.4, 137.0, 134.7, 129.3, 128.9, 128.3, 127.8, 127.3, 127.1, 126.2, 122.7, 118.2, 114.4, 114.3, 63.3, 60.0, 55.4, 51.9, 48.3, 26.1, 25.9, 22.9, 20.4; IR (neat) 2986, 2937, 1745, 1512, 1449, 1382, 1249, 1141, 1029, 830, 760, 706 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{34}ClNO_4$ $(M)^+$ 543.2176, found 543.2164.

*Methyl (Z)-5-((2S,3S)-2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (cis-**11d**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 4H), 7.20−7.12 (m, 7H), 6.84−6.79 (m, 2H), 5.52 (s, 1H), 5.14 (d, J = 6.0 Hz, 1H), 4.48 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 1.35 (s, 6H), 1.19 (s, 3H), 1.15 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.2, 165.3, 156.0, 146.5, 139.9, 134.5, 133.8, 133.7, 131.5, 128.8, 128.5, 128.2, 127.4, 126.5, 121.8, 118.2, 114.4, 59.3, 58.8, 55.5, 51.9, 48.2, 26.1, 25.5, 22.1, 20.6; IR (neat) 2925, 2857, 1741, 1512, 1462, 1382, 1249, 1177, 1138, 1026, 828, 753, 703 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{34}ClNO_4$ $(M)^+$ 543.2176, found 543.2168.

Entry 5: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10e** (49.3 mg, 0.088 mmol) in octane (4.4 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 6/1, twice) to give *cis*-*β*-lactam **11e** (6.0 mg, 12%) and *trans*-*β*-lactam**11e** (29.3 mg, 60%).

Entry 5 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10e** (43.4 mg, 0.078 mmol) and 1,4-dimethylpiperazine (8.9 mg, 0.078 mmol) in toluene (3.9 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 6/1, twice) to give *cis*-*β*-lactam **11e** (32.8 mg, 76%) and *trans*-*β*-lactam**11e** (5.3 mg, 12%).

Methyl (Z)-5-((2S,3R*)-1-(4-Methoxyphenyl)-2-(naphthalen-2-yl)-4-oxoazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (trans-**11e**).* Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.74 (m, 3H), 7.56 (s, 1H), 7.50−7.44 (m, 2H), 7.27−7.18 (m, 6H), 7.07−7.04 (m, 2H), 6.79−6.75 (m, 2H), 6.34 (s, 1H), 4.50 (d, J = 2.3 Hz, 1H), 4.08 (d, J = 2.3 Hz, 1H), 3.73 (s, 3H), 3.52 (s, 3H), 1.64 (s,

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3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.0, 165.4, 155.8, 146.9, 139.4, 135.9, 134.4, 133.3, 133.2, 131.5, 129.1, 128.9, 127.8, 127.8, 127.7, 127.0, 126.4, 126.3, 126.2, 123.2, 122.8, 118.2, 114.2, 63.4, 59.9, 55.4, 51.8, 48.4, 26.2, 26.0, 23.0, 20.4; IR (neat) 2927, 2867, 1740, 1596, 1511, 1449, 1385, 1245, 1183, 1140, 1031, 826, 754 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{37}NO_4$ $(M)^+$ 559.2723, found 559.2722.

Methyl (Z)-5-((2S,3S*)-1-(4-Methoxyphenyl)-2-(naphthalen-2-yl)-4-oxoazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (cis-**11e**).* Yellow solid; mp 169−170 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85−7.76 (m, 3H), 7.71 (s, 1H), 7.50−7.46 (m, 2H), 7.35−7.29 (m, 3H), 7.18−7.12 (m, 5H), 6.81−6.77 (m, 2H), 5.62 (s, 1H), 5.31 (d, J = 6.0 Hz, 1H), 4.56 (d, J = 6.0 Hz, 1H), 3.74 (s, 3H), 3.56 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.2, 165.6, 155.9, 146.1, 140.0, 133.5, 133.4, 133.1, 131.9, 128.8, 128.0, 127.9, 127.7, 127.3, 126.8, 126.4, 126.3, 126.2, 124.5, 122.0, 118.2, 114.3, 60.2, 59.0, 55.4, 51.7, 48.2, 26.0, 25.5, 22.1, 20.6; IR (KBr) 2987, 2934, 1732, 1595, 1512, 1445, 1393, 1299, 1248, 1183, 1143, 1037, 834, 775, 707 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{37}NO_4$ $(M)^+$ 559.2723, found 559.2706.

Entry 6: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10f** (16.0 mg, 0.031 mmol) in octane (1.6 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11f** (1.7 mg, 11%) and *trans*-β-lactam **11f** (5.7 mg, 35%).

Entry 6 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10f** (29.0 mg, 0.056 mmol) and DBU (8.6 mg, 0.056 mmol) in toluene (2.8 mL) at room temperature. The mixture was stirred at 110 °C for 31 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11f** (1.9 mg, 7%) and *trans*-β-lactam **11f** (19.8 mg, 68%).

Entry 6 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10f** (29.9 mg, 0.058 mmol) and 1,4-dimethylpiperazine (6.6 mg, 0.058 mmol) in toluene (2.9 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11f** (17.4 mg, 58%) and *trans*-β-lactam **11f** (6.1 mg, 21%).

Methyl (Z)-5-((3R,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-(thiophen-2-yl)azetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (trans-**11f**).* Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24−7.16 (m, 6H), 7.00−6.98 (m, 2H), 6.93−6.89 (m, 2H), 6.83−6.80 (m, 2H), 6.26 (s, 1H), 4.63 (d, J = 2.1 Hz, 1H), 4.15 (d, J = 2.1 Hz, 1H), 3.76 (s, 3H), 3.52 (s, 3H), 1.62 (s, 3H), 1.44 (s. 3H), 1.34 (s, 3H), 1.31 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 177.0, 165.1, 155.9, 147.0, 142.3, 139.2, 134.6, 131.3, 128.7, 127.6, 127.0, 126.9, 126.0, 125.6, 125.5, 122.5, 118.3, 114.2, 64.2, 55.7, 55.4, 51.9, 48.4, 26.1, 25.9, 23.0, 20.4; IR (neat) 2981, 2933, 1745, 1512, 1446, 1381, 1248, 1183, 1139, 1032, 831, 706 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{33}NO_4S$ $(M)^+$ 515.2112, found 515.2133.

Methyl (Z)-5-((3S,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-(thiophen-2-yl)azetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (cis-**11f**).* Yellow solid; mp 160−161 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.33 (m, 2H), 7.27−7.26 (m, 1H), 7.23−7.14 (m, 5H), 6.97−6.95 (m, 2H), 6.84−6.82 (m, 2H), 5.82 (s, 1H), 5.41 (d, J = 6.1 Hz, 1H), 4.46 (d, J = 6.1 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 177.3, 165.2, 155.9, 146.2, 140.2, 139.6, 133.8, 131.4, 128.8, 127.3, 126.9, 126.6, 126.4, 126.1, 125.6, 121.9, 118.3, 114.2, 59.3, 56.3, 55.4, 51.8, 48.2, 26.0, 25.4, 22.1, 20.6; IR (KBr) 2925, 2854, 1745, 1513, 1457, 1381, 1248, 1144, 1022, 943, 823, 701 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{33}NO_4S$ $(M)^+$ 515.2112, found 515.2117.

Entry 7: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10g** (19.0 mg, 0.038 mmol) in octane (1.9 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether/triethylamine = 100/10/3) to give *cis*-β-lactam **11g** (4.2 mg, 22%) and *trans*-β-lactam **11g** (7.7 mg, 41%).

Entry 7 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10g** (33.6 mg, 0.064 mmol) and DBU (9.8 mg, 0.064 mmol) in toluene (3.2 mL) at room temperature. The mixture was stirred at 110 °C for 31 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether/triethylamine = 100/10/3) to give *cis*-β-lactam **11g** (1.2 mg, 4%) and *trans*-β-lactam **11g** (15.5 mg, 50%).

Entry 7 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10g** (27.4 mg, 0.055 mmol) and 1,4-dimethylpiperazine (6.3 mg, 0.055 mmol) in toluene (2.8 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether/triethylamine = 100/10/3, twice) to give *cis*-β-lactam **11g** (11.2 mg, 41%) and *trans*-β-lactam **11g** (7.6 mg, 28%).

Methyl (Z)-5-((2S,3R*)-2-(Furan-2-yl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (trans-**11g**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.36 (m, 1H), 7.25−7.13 (m, 5H), 6.97−6.95 (m, 2H), 6.83−6.81 (m, 2H), 6.33−6.32 (m, 1H), 6.27−6.26 (m, 1H), 6.25 (s, 1H), 4.45 (d, J = 2.6 Hz, 1H), 4.32 (d, J = 2.6 Hz, 1H), 3.77 (s, 3H), 3.55 (s, 3H), 1.60 (s, 3H), 1.45 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177,0 165.2, 155.9, 150.8, 147.0, 143.0, 139.2, 134.2, 131.5, 128.7, 127.6, 126.8, 126.0, 122.4, 118.1, 114.2, 110.5, 109.0, 59.7, 55.5, 53.2, 51.9, 48.4, 26.0, 25.9, 21.9, 20.2; IR (neat) 2987, 2939, 1745, 1588, 1512, 1448, 1382, 1246, 1141, 1025, 828, 752, 602 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{33}NO_5$ $(M)^+$ 499.2359, found 499.2380.

Methyl (Z)-5-((2S,3S*)-2-(Furan-2-yl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-2,2,6-trimethyl-3-phenylhepta-3,5-dienoate (cis-**11g**).* Yellow solid; mp 124−125 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.37 (m, 1H), 7.32−7.30 (m, 2H), 7.21−7.15 (m, 5H), 6.84−6.81 (m, 2H), 6.34−6.33 (m, 1H), 6.28−6.27 (m, 1H), 5.99 (s, 1H), 5.17 (d, J = 5.5 Hz, 1H), 4.41 (d, J = 5.5 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 1.43 (s, 3H), 1.30 (s, 3H), 1.24 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.4, 165.1, 155.9, 149.9, 146.2, 142.7, 140.3, 133.1, 131.6, 128.8, 128.3, 126.5, 126.4, 122.1, 118.0, 114.3, 110.4, 109.1, 58.3, 55.5, 54.2, 51.8, 48.2, 26.0, 25.4, 21.9, 20.2; IR (KBr) 2980, 2943, 1753, 1512, 1446, 1378, 1248, 1149, 1032, 910, 828, 746 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{33}NO_5$ $(M)^+$ 499.2359, found 499.2362.

Entry 8: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10h** (38.4 mg, 0.073 mmol) in octane (3.7 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11h** (5.4 mg, 14%) and *trans*-β-lactam **11h** (23.9 mg, 62%).

Entry 8 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10h** (35.7 mg, 0.068 mmol) and 1,4-dimethylpiper-

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azine (7.8 mg, 0.068 mmol) in toluene (3.4 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 6/1) to give *cis*-β-lactam **11h** (25.1 mg, 70%) and *trans*-β-lactam **11h** (3.8 mg, 11%).

Methyl (Z)-5-((3R,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-(p-tolyl)hepta-3,5-dienoate (trans-**11h**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.27 (m, 3H), 7.18−7.10 (m, 4H), 6.98−6.96 (m, 2H), 6.90−6.87 (m, 2H), 6.81−6.77 (m, 2H), 6.26 (s, 1H), 4.38 (d, *J* = 2.8 Hz, 1H), 3.98 (d, *J* = 2.8 Hz, 1H), 3.75 (s, 3H), 3.50 (s, 3H), 2.31 (s, 3H), 1.62 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.1, 165.5, 155.7, 146.8, 138.5, 136.4, 136.2, 134.1, 131.5, 128.9, 128.7, 128.3, 128.1, 125.9, 122.9, 118.2, 114.1, 63.4, 59.5, 55.4, 51.8, 48.4, 26.1, 26.0, 22.9, 21.2, 20.4; IR (neat) 2981, 2926, 1749, 1596, 1512, 1453, 1385, 1246, 1183, 1144, 1032, 829, 750, 698 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_4$ (M)$^+$ 523.2723, found 523.2726.

Methyl (Z)-5-((3S,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-(p-tolyl)hepta-3,5-dienoate (cis-**11h**).* Yellow solid; mp 140−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 5H), 7.22−7.20 (m, 2H), 7.07−7.05 (m, 2H), 7.00−6.98 (m, 2H), 6.83−6.79 (m, 2H), 5.51 (s, 1H), 5.16 (d, *J* = 6.0 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 2.28 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.3, 165.7, 155.8, 146.0, 136.9, 135.8, 133.2, 131.8, 128.7, 128.2, 128.0, 127.9, 126.9, 126.6, 122.1, 118.2, 114.3, 59.9, 58.8, 55.4, 51.8, 48.2, 26.0, 25.5, 22.0, 21.1, 20.7; IR (neat) 2987, 2925, 1747, 1512, 1455, 1391, 1297, 1249, 1142, 1030, 826, 773, 697 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_4$ (M)$^+$ 523.2723, found 523.2724.

Entry 9: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10i** (23.8 mg, 0.044 mmol) in octane (2.2 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1) to give *cis*-β-lactam **11i** (4.6 mg, 17%) and *trans*-β-lactam **11i** (16.9 mg, 63%).

Entry 9 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10i** (39.4 mg, 0.073 mmol) and DBU (11.0 mg, 0.073 mmol) in toluene (3.7 mL) at room temperature. The mixture was stirred at 110 °C for 31 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 3/1, twice) to give the mixture of *cis*- and *trans*-β-lactams **11i** (31.9 mg, 81%, cis/trans = 20/80).

Entry 9 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10i** (36.5 mg, 0.068 mmol) and 1,4-dimethylpiperazine (7.8 mg, 0.068 mmol) in toluene (3.4 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1) to give *cis*-β-lactam **11i** (27.1 mg, 74%) and *trans*-β-lactam **11i** (4.8 mg, 13%).

Methyl (Z)-3-(4-Methoxyphenyl)-5-((3R,4S*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethylhepta-3,5-dienoate (trans-**11i**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.27 (m, 3H), 7.19−7.14 (m, 4H), 6.94−6.92 (m, 2H), 6.80−6.78 (m, 2H), 6.72−6.70 (m, 2H), 6.26 (s, 1H), 4.39 (d, *J* = 2.4 Hz, 1H), 3.99 (d, *J* = 2.4 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.51 (s, 3H), 1.61 (s, 3H), 1,39 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.1, 165.5, 158.4, 155.8, 146.5, 138.4, 134.0, 131.6, 131.4, 129.9, 129.0, 128.1, 126.0, 125.9, 122.9, 118.2, 114.2, 113.1, 63.4, 59.7, 55.4, 55.1, 51.8, 48.6, 26.1, 26.0, 22.9, 20.4; IR (neat) 2934, 2848, 1607, 1513, 1455, 1384, 1247, 1141, 1033, 832, 753, 699 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_5$ (M)$^+$ 539.2672, found 539.2678.

Methyl (Z)-3-(4-Methoxyphenyl)-5-((3S,4S*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethylhepta-3,5-dienoate (cis-**11i**).* Yellow solid; mp 137−140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.28 (m, 5H), 7.22−7.20 (m, 2H), 7.12−7.11 (m, 2H), 6.83-6.80 (m, 2H), 6.75−6.72 (m, 2H), 5.50 (s, 1H), 5.18 (d, *J* = 5.8 Hz, 1H), 4.51 (d, *J* = 5.8 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.63 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.3, 165.7, 158.0, 155.8, 145.7, 135.7, 133.2, 132.4, 131.8, 130.0, 128.2, 127.9, 126.8, 126.7, 122.1, 118.2, 114.3, 112.7, 59.8, 58.8, 55.5, 55.0, 51.8, 48.3, 26.0, 25.5, 22.0, 20.6; IR (KBr) 2987, 2944, 1747, 1607, 1512, 1455, 1387, 1251, 1146, 1033, 938, 834, 565 cm^{-1}; HRMS (EI): calcd for $C_{34}H_{37}NO_5$ (M)$^+$ 539.2672, found 539.2669.

Entry 10: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10j** (54.4 mg, 0.10 mmol) in octane (5.0 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1) to give *cis*-β-lactam **11j** (9.3 mg, 17%) and *trans*-β-lactam **11j** (30.8 mg, 56%).

Entry 10 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10j** (17.8 mg, 0.033 mmol) and DBU (5.0 mg, 0.033 mmol) in toluene (1.7 mL) at room temperature. The mixture was stirred at 110 °C for 31 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 3/1) to give the mixture of *cis*- and *trans*-β-lactams **11j** (14.5 mg, 81%, cis/trans = 9/91).

Entry 10 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10j** (54.4 mg, 0.10 mmol) and 1,4-dimethylpiperazine (11.4 mg, 0.10 mmol) in toluene (5.0 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1) to give *cis*-β-lactam **11j** (41.1 mg, 75%) and *trans*-β-lactam **11j** (4.1 mg, 8%).

Methyl (Z)-3-(4-Chlorophenyl)-5-((3R,4S*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethylhepta-3,5-dienoate (trans-**11j**).* Yellow solid; mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 3H), 7.20−7.13 (m, 6H), 6.99−6.96 (m, 2H), 6.81−6.77 (m, 2H), 6.30 (s, 1H), 4.43 (d, *J* = 2.1 Hz, 1H), 4.00 (d, *J* = 2.1 Hz, 1H), 3.75 (s, 3H), 3.54 (s, 3H), 1.58 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.8, 165.2, 155.9, 145.8, 138.2, 137.8, 134.3, 132.9, 131.3, 130.2, 129.1, 128.3, 127.8, 126.7, 125.9, 122.7, 118.1, 114.3, 63.3, 60.0, 55.4, 51.9, 48.3, 26.1, 25.9, 22.9, 20.4; IR (KBr) 2987, 2934, 1751, 1511, 1452, 1386, 1246, 1142, 1030, 830, 731 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{34}ClNO_4$ (M)$^+$ 543.2176, found 543.2179.

*Methyl (Z)-3-(4-Chlorophenyl)-5-((3S,4S)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethylhepta-3,5-dienoate (cis-**11j**).* Yellow solid; mp 140−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 5H), 7.21−7.15 (m, 6H), 6.84−6.80 (m, 2H), 5.54 (s, 1H), 5.19 (d, *J* = 5.7 Hz, 1H), 4.51 (d, *J* = 5.7 Hz, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.0, 165.5, 155.9, 145.1, 138.6, 135.6, 133.5, 132.3, 131.7, 130.4, 128.2, 128.0, 127.5, 127.4, 126.7, 122.0, 118.2, 114.3, 59.8, 58.5, 55.4, 51.8, 48.1, 26.0, 25.4, 22.0, 20.5; IR (KBr) 2981, 2937, 1740, 1513, 1452, 1387, 1298, 1250, 1175, 1143, 1034, 835, 776, 698 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{34}ClNO_4$ (M)$^+$ 543.2176, found 543.2180.

Entry 11: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an

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argon balloon was placed aminocyclobutenone **10k** (63.0 mg, 0.113 mmol) in octane (5.5 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11k** (9.5 mg, 15%) and *trans*-β-lactam **11k** (41.9 mg, 67%).

Entry 11 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10k** (59.5 mg, 0.106 mmol) and 1,4-dimethylpiperazine (12.1 mg, 0.106 mmol) in toluene (5.3 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11k** (41.7 mg, 70%) and *trans*-β-lactam **11k** (6.1 mg, 10%).

Methyl (Z)-5-((3R,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-(naphthalen-2-yl)hepta-3,5-dienoate (trans-**11k**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.78 (m, 1H), 7.68–7.66 (m, 1H), 7.59–7.57 (m, 1H), 7.25–7.23 (m, 3H), 7.21–7.19 (m, 1H), 7.17–7.15 (m, 2H), 7.06–7.04 (m, 2H), 6.81–6.79 (m, 2H), 6.38 (s, 1H), 4.42 (d, J = 2.1 Hz, 1H), 4.00 (d, J = 2.1 Hz, 1H), 3.76 (s, 3H), 3.54 (s, 3H), 1.64 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.0, 165.4, 155.8, 146.8, 138.2, 137.0, 134.3, 132.8, 132.3, 128.9, 128.1, 128.0, 127.5, 127.5, 127.4, 126.9, 126.6, 125.9, 125.8, 125.8, 122.9, 118.2, 114.2, 63.4, 59.8, 55.4, 51.9, 48.6, 26.3, 26.1, 23.1, 20.4; IR (neat) 2987, 2928, 1741, 1595, 1512, 1453, 1389, 1246, 1183, 1139, 1032, 832, 749 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{37}NO_4$ $(M)^+$ 559.2723, found 559.2700.

*Methyl (Z)-5-((3S,4S)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-(naphthalen-2-yl) hepta-3,5-dienoate (cis-**11k**).* Yellow solid; mp 158–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78–7.74 (m, 1H), 7.69–7.67 (m, 1H), 7.43–7.39 (m, 3H), 7.35–7.29 (m, 5H), 7.23–7.21 (m, 2H), 7.21–7.19 (m, 1H), 7.17–7.15 (m, 2H), 6.83–6.81 (m, 2H), 5.63 (s, 1H), 5.19 (d, J = 6.1 Hz, 1H), 4.52 (d, J = 6.1 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 1.39 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H), 1.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.3, 165.6, 155.9, 146.1, 137.8, 135.7, 133.5, 133.0, 132.2, 131.8, 128.2, 128.1, 128.0, 128.0, 127.4, 127.3, 127.2, 126.8, 126.5, 125.4, 122.1, 118.2, 114.3, 63.4, 59.8, 55.4, 51.9, 48.6, 26.3, 26.1, 23.1, 20.4; IR (KBr) 2981, 2928, 1747, 1513, 1453, 1389, 1298, 1246, 1175, 1140, 1031, 827, 775, 755, 703 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{37}NO_4$ $(M)^+$ 559.2723, found 559.2700.

Entry 12: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10l** (22.1 mg, 0.043 mmol) in octane (2.1 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 4/1, twice) to give the mixture of *cis*- and *trans*-β-lactams **11l** (14.6 mg, 66%, cis/trans = 45/55).

Entry 12 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10l** (25.8 mg, 0.050 mmol) and DBU (7.6 mg, 0.050 mmol) in toluene (2.5 mL) at room temperature. The mixture was stirred at 110 °C for 24 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11l** (4.2 mg, 16%) and *trans*-β-lactam **11l** (16.4 mg, 64%).

Entry 12 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10l** (28.7 mg, 0.056 mmol) and 1,4-dimethylpiperazine (6.4 mg, 0.056 mmol) in toluene (2.8 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 4/1, twice) to give the mixture of *cis*- and *trans*-β-lactams **11l** (25.6 mg, 89%, cis/trans = 85/15).

Methyl (E)-5-((3R,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-(thiophen-2-yl)hepta-3,5-dienoate (trans-**11l**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 4H), 7.18–7.15 (m, 2H), 7.09–7.07 (m, 2H), 6.96–6.94 (m, 1H), 6.78–6.75 (m, 3H), 6.34 (s, 1H), 4.52 (d, J = 2.4 Hz, 1H), 4.10 (d, J = 2.4 Hz, 1H), 3.74 (s, 3H), 3.43 (s, 3H), 1.68 (s, 3H), 1.56 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.1, 165.6, 155.9, 140.3, 139.9, 138.3, 135.9, 131.3, 128.9, 128.1, 126.9, 126.4, 126.4, 125.9, 125.2, 123.0, 118.3, 114.2, 63.2, 59.2, 55.4, 51.9, 49.0, 29.7, 26.3, 25.8, 22.8, 20.4; IR (neat) 2924, 2855, 1740, 1511, 1458, 1385, 1249, 1140, 1069, 1034, 832, 747, 700 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{33}NO_4S$ $(M)^+$ 515.2112, found 515.2119.

Methyl (E)-5-((3S,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-(thiophen-2-yl)hepta-3,5-dienoate (cis-**11l**).* Yellow solid; mp 139–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 5H), 7.23–7.21 (m, 2H), 7.15–7.14 (m, 1H), 6.90–6.86 (m, 2H), 6.83–6.79 (m, 2H), 5.57 (s, 1H), 5.19 (d, J = 6.0 Hz, 1H), 4.56 (d, J = 6.0 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 1.52 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.2, 165.4, 155.8, 140.3, 139.4, 135.8, 134.5, 131.8, 128.7, 128.2, 128.0, 127.0, 126.8, 126.0, 124.7, 122.0, 118.2, 114.3, 59.7, 58.9, 55.4, 51.9, 48.8, 25.8, 25.3, 21.8, 20.8; IR (KBr) 2994, 2925, 1736, 1511, 1452, 1386, 1242, 1143, 1028, 834, 782, 730 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{33}NO_4S$ $(M)^+$ 515.2112, found 515.2105.

Entry 13: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10m** (21.2 mg, 0.041 mmol) in octane (2.1 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate/triethylamine = 31/2/1, three times) to give *cis*-β-lactam **11m** (5.3 mg, 25%) and *trans*-β-lactam **11m** (4.3 mg, 20%).

Entry 13 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10m** (34.4 mg, 0.067 mmol) and DBU (10.2 mg, 0.067 mmol) in toluene (3.4 mL) at room temperature. The mixture was stirred at 110 °C for 31 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, three times) to give *cis*-β-lactam **11m** (1.5 mg, 4%) and *trans*-β-lactam **11m** (20.5 mg, 60%).

Entry 13 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10m** (34.6 mg, 0.0067 mmol) and 1,4-dimethylpiperazine (7.7 mg, 0.067 mmol) in toluene (0.9 mL) at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, three times) to give the mixture of *cis*- and *trans*-β-lactams **11m** (24.0 mg, 69%, cis/trans = 88/12).

*Methyl (E)-5-((3R,4S)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-(5-methylfuran-2- yl)hepta-3,5-dienoate (trans-**11m**).* Orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.28 (m, 3H), 7.17–7.11 (m, 4H), 6.76–6.74 (m, 2H), 6.23 (d, J = 3.1 Hz, 1H), 6.09 (s, 1H), 5.94 (d, J = 3.7 Hz, 1H), 4.71 (d, J = 2.4 Hz, 1H), 4.18 (d, J = 2.4 Hz, 1H), 3.72 (s, 3H), 3.47 (s, 3H), 2.20 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.5, 165.9, 155.8, 150.8, 150.2, 138.4, 137.4, 134.1, 131.2, 128.9, 128.0, 125.9, 123.5, 122.5, 118.3, 114.1, 110.9, 107.1, 62.8, 58.9, 55.4, 51.8, 46.9, 26.0, 25.7, 22.0, 21.2, 13.4; IR (neat) 2987, 2937, 1741, 1596, 1513, 1453, 1386, 1245, 1183, 1145, 1031, 833, 754, 700 cm^{-1}; HRMS (EI): calcd for $C_{32}H_{35}NO_5$ $(M)^+$ 513.2515, found 513.2532.

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Methyl (E)-5-((3S,4S*)-1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2,6-trimethyl-3-(5-methylfuran-2-yl)hepta-3,5-dienoate (cis-**11m**).* Orange solid; mp 123−124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.20 (m, 7H), 6.81−6.79 (m, 2H), 5.94 (d, J = 3.1 Hz, 1H), 5.81 (d, J = 2.1 Hz, 1H), 5.40 (s, 1H), 5.20 (d, J = 5.8 Hz, 1H), 4.70 (d, J = 5.8 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 2.17 (s, 3H), 1.71 (s, 3H), 1.31 (s, 6H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.8, 165.6, 155.8, 150.3, 150.2, 135.7, 135.5, 134.7, 131.8, 128.2, 127.8, 126.9, 124.1, 122.5, 118.2, 114.2, 110.7, 106.9, 59.6, 59.1, 55.4, 51.9, 29.7, 25.6, 21.8, 21.0, 13.5; IR (KBr) 2918, 2854, 1743, 1513, 1454, 1387, 1244, 1142, 1029, 826, 734, 608 cm^{-1}; HRMS (EI): calcd for $C_{32}H_{35}NO_5$ (M)$^+$ 513.2515, found 513.2495.

Entry 14: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10n** (23.9 mg, 0.042 mmol) in octane (2.1 mL) at room temperature. The mixture was stirred at 110 °C for 31 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 6/1, twice) to give *cis*-β-lactam **11n** (3.1 mg, 13%) and *trans*-β-lactam **11n** (16.5 mg, 69%).

Entry 14 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10n** (28.8 mg, 0.051 mmol) and 1,4-dimethylpiperazine (5.8 mg, 0.051 mmol) in toluene (2.6 mL) at room temperature. The mixture was stirred at 110 °C for 31 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 6/1, twice) to give *cis*-β-lactam **11n** (17.4 mg, 61%) and *trans*-β-lactam **11n** (5.0 mg, 17%).

Methyl (Z)-2,2,6-Triethyl-5-((3R,4S*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-3-phenylocta-3,5-dienoate (trans-**11n**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.23 (m, 4H), 7.20−7.12 (m, 4H), 7.06−7.03 (m, 2H), 7.00−6.98 (m, 2H), 6.79−6.76 (m, 2H), 6.33 (s, 1H), 4.17 (d, J = 2.5 Hz, 1H), 3.95 (d, J = 2.5 Hz, 1H), 3.75 (s, 3H), 3.48 (s, 3H), 2.32−2.23 (m, 1H), 2.08−1.99 (m, 1H), 1.92−1.82 (m, 2H), 1.76−1.59 (m, 4H), 0.88 (t, J = 7.3 Hz, 3H), 0.78 (t, J = 7.3 Hz, 3H), 0.75 (t, J = 7.3 Hz, 3H), 0.59 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.0, 165.4, 155.7, 145.5, 143.6, 139.2, 138.2, 131.4, 129.0, 128.9, 128.2, 127.6, 127.0, 125.9, 122.1, 118.2, 114.1, 63.2, 59.4, 56.1, 55.4, 51.6, 26.0, 24.7, 24.5, 23.4, 13.2, 12.0, 8.3, 8.3; IR (neat) 2967, 2880, 1749, 1643, 1512, 1454, 1388, 1298, 1247, 1134, 1072, 1033, 830, 750, 701 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{43}NO_4$ (M)$^+$ 565.3192, found 565.3170.

Methyl (Z)-2,2,6-Triethyl-5-((3S,4S*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-3-phenylocta-3,5-dienoate (cis-**11n**).* Colorless solid; mp 135−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.27 (m, 5H), 7.23−7.11 (m, 7H), 6.83−6.80 (m, 2H), 6.83−6.80 (m, 2H), 5.58 (s, 1H), 5.17 (d, J = 5.7 Hz, 1H), 4.44 (brs, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 1.94−1.72 (m, 5H), 1.55-1.40 (m, 3H), 0.81 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H), 0.39 (brs, 3H), 0.18 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.2, 165.6, 155.8, 144.3, 143.8, 140.3, 135.9, 131.8, 128.8, 128.3, 127.9, 127.1, 126.9, 126.3, 121.5, 118.3, 114.3, 59.9, 58.3, 55.6, 55.5, 51.5, 25.5, 24.6, 24.0, 23.9, 11.7, 11.5, 8.6, 7.7; IR (KBr) 3026, 2969, 2880, 1750, 1511, 1457, 1386, 1297, 1246, 1180, 1130, 1031, 824, 772, 735, 705 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{43}NO_4$ (M)$^+$ 565.3192, found 565.3187.

Entry 15: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon was placed aminocyclobutenone **10o** (26.2 mg, 0.047 mmol) in octane (2.3 mL) at room temperature. The mixture was stirred at 110 °C for 45 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11o** (4.8 mg, 18%) and *trans*-β-lactam **11o** (16.3 mg, 63%).

Entry 15 with DBU: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10o** (31.0 mg, 0.055 mmol) and DBU (8.4 mg, 0.055 mmol) in toluene (2.8 mL) at room temperature. The mixture was stirred at 110 °C for 60 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (hexane/ethyl acetate = 5/2, twice) to give the mixture of *cis*- and *trans*-β-lactams **11o** (30.1 mg, 97%, cis/trans = 14/86).

Entry 15 with 1,4-dimethylpiperazine: In a 30 mL two-neck round-bottom flask equipped with a magnetic stirring bar, a glass stopper, a Dimroth condenser, and an argon balloon were placed aminocyclobutenone **10o** (34.6 mg, 0.062 mmol) and 1,4-dimethylpiperazine (7.1 mg, 0.062 mmol) in toluene (3.1 mL) at room temperature. The mixture was stirred at 110 °C for 45 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (toluene/diethyl ether = 7/1, twice) to give *cis*-β-lactam **11o** (24.3 mg, 71%) and *trans*-β-lactam **11o** (2.9 mg, 8%).

Methyl 1-((Z)-3-Cyclopentylidene-3-((3R,4S*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-1-phenylprop-1-en-1-yl)-cyclopentane-1-carboxylate (trans-**11o**).* Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.27 (m, 3H), 7.21−7.11 (m, 7H), 7.08−7.06 (m, 2H), 6.79−6.76 (m, 2H), 6.33 (s, 1H), 4.44 (d, J = 2.6 Hz, 1H), 3.84 (d, J = 2.6 Hz, 1H), 3.75 (s, 1H), 3.56 (s, 3H), 2.22-1.93 (m, 5H), 1.88-1.74 (m, 2H), 1.70-1.55 (m, 5H), 1.53-1.42 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.6, 165.5, 155.8, 147.4, 144.6, 140.0, 138.5, 131.4, 128.9, 128.6, 128.1, 127.8, 127.3, 126.9, 125.8, 119.9, 118.2, 114.2, 64.5, 60.5, 59.6, 55.4, 52.1, 36.4, 35.9, 32.9, 30.6, 26.3, 26.0, 23.3, 23.2; IR (neat) 2952, 2873, 1748, 1512, 1448, 1389, 1295, 1247, 1171, 1031, 828, 754, 700 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{39}NO_4$ (M)$^+$ 561.2879, found 561.2898.

Methyl 1-((Z)-3-Cyclopentylidene-3-((3S,4S*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-1-phenylprop-1-en-1-yl)-cyclopentane-1-carboxylate (cis-**11o**).* Yellow solid; mp 124−126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.27 (m, 5H), 7.23−7.14 (m, 7H), 6.83−6.79 (m, 2H), 5.59 (s, 1H), 5.11 (d, J = 5.7 Hz, 1H), 4.23 (d, J = 5.7 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 2.15−2.01 (m, 4H), 1.80−1.75 (m, 1H), 1.69−1.42 (m, 8H), 1.30−1.20 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.7, 165.8, 155.9, 147.4, 142.8, 140.3, 135.7, 131.8, 128.7, 128.6, 128.1, 127.8, 127.6, 126.9, 126.7, 119.2, 118.2, 114.3, 60.5, 59.4, 59.4, 55.5, 51.9, 36.6, 35.4, 32.4, 31.2, 26.1, 26.1, 23.3, 23.2; IR (KBr) 3032, 2952, 2873, 1748, 1512, 1444, 1388, 1298, 1246, 1175, 1110, 1029, 823, 776, 704 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{39}NO_4$ (M)$^+$ 561.2879, found 561.2871.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02364.

Experimental details, spectral data, and copies of ^{1}H and ^{13}C{^{1}H} NMR spectra charts (PDF)

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Notes

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REFERENCES

(1) For a review on synthesis of nitrogen-containing heterocycles using conjugate addition reactions of nucleophiles to α,β-unsaturated imines, see: (a) Hachiya, I.; Mizota, I.; Shimizu, M. Synthesis Of Nitrogen-Containing Heterocycles Using Conjugate Addition Reactions of Nucleophiles to α,β-Unsaturated Imines. *Heterocycles* **2012**, *85*, 993−1016. For our recent examples of alkynyl imines, see: (b) Hachiya, I.; Kugisaki, N.; Agata, R.; Matsumoto, H.; Yamada, Y.; Shimizu, M. Synthesis of (±)-muscopyridine analogue using ring-expansion reaction of cyclic b-keto ester via conjugate addition to alkynyl imine. *Tetrahedron* **2015**, *71*, 5824−5829. (c) Hachiya, I.; Shimada, S.; Fukutomi, M.; Miura, R.; Shimizu, M. Synthesis of α-Carbolines Using Palladium-Catalyzed Intramolecular Amination of 3-(2-Chlorophenyl)-2-Aminopyridines. *ChemistrySelect* **2019**, *4*, 469−472.

(2) For selected recent examples of alkynyl imines, see: (a) Johnson, P. L.; Renga, J. M.; Galliford, C. V.; Whiteker, G. T.; Giampietro, N. C. Synthesis of Novel Fluoropicolinate Herbicides by Cascade Cyclization of Fluoroalkyl Alkynylimines. *Org. Lett.* **2015**, *17*, 2905−2907. (b) Wang, Y.; Jiang, L.; Li, L.; Dai, J.; Xiong, D.; Shao, Z. An Arylation Strategy to Propargylamines: Catalytic Asymmetric Friedel−Crafts-type Arylation Reactions of C-AlkynylImines. *Angew. Chem., Int. Ed.* **2016**, *55*, 15142−15146. (c) Liu, L.; Chen, D.; Yao, J.; Zong, Q.; Wang, J.; Zhou, H. CuX-Activated N-Halosuccinimide: Synthesis of 3-Haloquinolines via Electrophilic Cyclization of Alkynyl Imines. *J. Org. Chem.* **2017**, *82*, 4625−4630. (d) Kondoh, A.; Terada, M. Brønsted Base-Catalyzed Umpolung Intramolecular Cyclization of Alkynyl Imines. *Chem. − Eur. J.* **2018**, *24*, 3998−4001.

(3) Hachiya, I.; Yoshitomi, T.; Yamaguchi, Y.; Shimizu, M. Stereodivergent Synthesis of β-Lactams Using Thermal Rearrangement of Aminocyclobutenones. *Org. Lett.* **2009**, *11*, 3266−3268.

(4) Hachiya, I.; Ito, A.; Shimizu, M. Chiral β-Lactam Synthesis through the Enantioselective Reduction of Iminocyclobutenones and the Thermal Rearrangement of Aminocyclobutenones. *Asian J. Org. Chem.* **2014**, *3*, 614−618.

(5) (a) Burnett, D. A. Asymmetric synthesis and absolute stereochemistry of cholesterol absorption inhibitor, SCH 48461. *Tetrahedron Lett.* **1994**, *35*, 7339−7342. (b) Braun, M.; Galle, D. A Simple Stereoselective Synthesis of the Cholesterol Absorption Inhibitor (-)-SCH 48461. *Synthesis* **1996**, *1996*, 819−820. (c) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. Stereoselective synthesis of 2-azetidinones as cholesterol-absorption inhibitors. *Tetrahedron: Asymmetry* **1999**, *10*, 4841−4849.

(6) Dialkynyl imines 1 were prepared using the palladium-catalyzed cross coupling reactions of alkynyl bromides with ethynyl imines. See the Supporting Information for detail.

(7) For a review on conjugate addition reactions of carbon nucleophiles to electron-deficient dienes, see: Csákÿ, A. G.; de la Herrán, G.; Murcia, M. C. Conjugate addition reactions of carbon nucleophiles to electron-deficient dienes. *Chem. Soc. Rev.* **2010**, *39*, 4080−4102.

(8) For selected recent examples on transition metal-catalyzed 1,6-addition reactions, see: (a) Nishimura, T.; Makino, H.; Nagaosa, M.; Hayashi, T. Rhodium-Catalyzed Enantioselective 1,6-Addition of Arylboronic Acids to Enynamides: Asymmetric Synthesis of Axially Chiral Allenylsilanes. *J. Am. Chem. Soc.* **2010**, *132*, 12865−12867. (b) Sawano, T.; Ashouri, A.; Nishimura, T.; Hayashi, T. Cobalt-Catalyzed Asymmetric 1,6-Addition of (Triisopropylsilyl)-acetylene to α,β,γ,δ-Unsaturated Carbonyl Compounds. *J. Am. Chem. Soc.* **2012**, *134*, 18936−18939. (c) Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. Enantioselective Synthesis of Allylboronates and Allylic Alcohols by Copper-Catalyzed 1,6-Boration. *Angew. Chem., Int. Ed.* **2014**, *53*, 4186−4190. (d) Wang, Z.; Kang, T.; Yao, Q.; Ji, J.; Liu, X.; Lin, L.; Feng, X. Scandium-Catalyzed Asymmetric 1,6-Addition of 3-Substituted Oxindoles to Linear Dienyl Ketones. *Chem. − Eur. J.* **2015**, *21*, 7709−7712. (e) Meng, F.; Li, X.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. Catalytic enantioselective 1,6-conjugate additions of propargyl and allyl groups. *Nature* **2016**, *537*, 387−393. (f) Bertuzzi, G.; Lenti, L.; Bisag, D. G.; Fochi, M.; Petrini, M.; Bernardi, L. γ-Regioselective Functionalization of 3-Alkenylindoles via 1,6-Addition to Extended Alkylideneindolenine Intermediates. *Adv. Synth. Catal.* **2018**, *360*, 1296−1302. (g) Abbas, S. Y.; Zhao, P.; Overman, L. E. 1,6-Addition of Tertiary Carbon Radicals Generated From Alcohols or Carboxylic Acids by Visible-Light Photoredox Catalysis. *Org. Lett.* **2018**, *20*, 868−871. (h) Li, W.; Xu, X.; Yang Liu, Y.; Gao, H.; Cheng, Y.; Li, P. Enantioselective Organocatalytic 1,6-Addition of Azlactones to para-Quinone Methides: An Access to α,α-Disubstituted and β,β-Diaryl-α-amino acid Esters. *Org. Lett.* **2018**, *20*, 1142−1145. (i) Sun, Z.; Sun, B.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric 1,6-Conjugate Addition of Amides to p-Quinone Methides. *Org. Lett.* **2018**, *20*, 3070−3073. (j) Chen, S.; Wu, L.; Shao, Q.; Yang, G.; Zhang, W. Pd(II)-Catalyzed asymmetric 1,6-conjugate addition of arylboronic acids to Meldrum's acid-derived dienes. *Chem. Commun.* **2018**, *54*, 2522−2525. (k) Guo, Y.; Kootstra, J.; Harutyunyan, S. R. Catalytic Regio- and Enantioselective Alkylation of Conjugated Dienyl Amides. *Angew. Chem., Int. Ed.* **2018**, *57*, 13547−13550.

(9) For a review on organocatalytic 1,6-addition reactions, see: (a) Chauhan, P.; Kaya, U.; Enders, D. Advances in Organocatalytic 1,6-Addition Reactions: Enantioselective Construction of Remote Stereogenic Centers. *Adv. Synth. Catal.* **2017**, *359*, 888−912. For recent selected examples on organocatalytic 1,6-addition reactions, see: (b) Uraguchi, D.; Yoshioka, K.; Ooi, T. Complete diastereodivergence in asymmetric 1,6-addition reactions enabled by minimal modification of a chiral catalyst. *Nat. Commun.* **2017**, *8*, No. 14793. (c) Yoshioka, K.; Yamada, K.; Uraguchi, D.; Ooi, T. Unique site-selectivity control in asymmetric Michael addition of azlactone to alkenyl dienyl ketones enabled by P-spiro chiral iminophosphorane catalysis. *Chem. Commun.* **2017**, *53*, 5495−5498. (d) Zhang, Z.-P.; Chen, L.; Li, X.; Cheng, J.-P. Organocatalytic Asymmetric Sequential 1,6-Addition/Acetalization of 1-Oxotetralin-2-carbaldehyde to ortho-Hydroxyphenyl-Substituted para-Quinone Methides for Synthesis of Spiro-3,4-dihydrocoumarins. *J. Org. Chem.* **2018**, *83*, 2714−2724. (e) Santra, S.; Porey, A.; Jana, B.; Guin, J. N-Heterocyclic carbenes as chiral Brønsted base catalysts: a highly diastereo- and enantioselective 1,6-addition reaction. *Chem. Sci.* **2018**, *9*, 6446−6450. (f) Zhu, Y.; Wang, D.; Huang, Y. Phosphine Sequentially Catalyzed Domino 1,6-Addition/Annulation: Access to Functionalized Chromans and Tetrahydroquinolines with an Ethynyl-Substituted All-Carbon Quaternary Center. *Org. Lett.* **2019**, *21*, 908−912.

(10) For recent examples on 1,6-addition/1,4-addition reactions, see: (a) Poulsen, P. H.; Feu, K. S.; Paz, B. M.; Jensen, F.; Jørgensen, K. A. Organocatalytic Asymmetric 1,6-Addition/1,4-Addition Sequence to 2,4-Dienals for the Synthesis of Chiral Chromans. *Angew. Chem., Int. Ed.* **2015**, *54*, 8203−8207. (b) Sun, X.; Fei, J.; Zou, C.; Lu, M.; Ye, J. Remote stereocontrolled asymmetric 1,6-addition/1,4-addition cascade reactions between cyclic dienones and 2-indolinethiones. *RSC Adv.* **2016**, *6*, 106676−106679.

(11) For selected recent examples on ketene silyl acetals, see: (a) Katayev, D.; Matoušek, V.; Koller, R.; Togni, A. Lewis Acid Catalyzed Synthesis of α-Trifluoromethyl Esters and Lactones by Electrophilic Trifluoromethylation. *Org. Lett.* **2015**, *17*, 5898−5901. (b) Martin, A.; Vors, J.-P.; Baudoin, O. Synthesis of Conformationally Constrained Esters and Amines by Pd-Catalyzed α-Arylation of Hindered Substrates. *ACS Catal.* **2016**, *6*, 3941−3945. (c) Zhou, F.; Yamamoto, H. A Disulfonimide Catalyst for Highly Enantioselective Mukaiyama−Mannich Reaction. *Org. Lett.* **2016**, *18*, 4974−4977. (d) Martin, A.; Vors, J.-P.; Baudoin, O. Synthesis of Conformationally Constrained Esters and Amines by Pd-Catalyzed α-Arylation of Hindered Substrates. *ACS Catal.* **2016**, *6*, 3941−3945. (e) Zhou, F.; Yamamoto, H. A Powerful Chiral Phosphoric Acid Catalyst for Enantioselective Mukaiyama-Mannich Reactions. *Angew. Chem., Int. Ed.* **2016**, *55*, 8970−8974. (f) Esumi, N.; Suzuki, K.; Nishimoto, Y.;

DOI: 10.1021/acs.joc.9b02364
J. Org. Chem. XXXX, XXX, XXX−XXX

Yasuda, M. Synthesis of 1,4-Dicarbonyl Compounds from Silyl Enol Ethers and Bromocarbonyls, Catalyzed by an Organic Dye under Visible-Light Irradiation with Perfect Selectivity for the Halide Moiety over the Carbonyl Group. *Org. Lett.* **2016**, *18*, 5704−5707. (g) Jiang, X.; Hartwig, J. F. Iridium-Catalyzed Enantioselective Allylic Substitution of Aliphatic Esters with Silyl Ketene Acetals as the Ester Enolates. *Angew. Chem, Int. Ed.* **2017**, *56*, 8887−8891. (h) Gatzenmeier, T.; Kaib, P. S. J.; Lingnau, J. B.; Goddard, R.; List, B. The Catalytic Asymmetric Mukaiyama-Michael Reaction of Silyl Ketene Acetals with α,β-Unsaturated Methyl Esters. *Angew. Chem, Int. Ed.* **2018**, *57*, 2464−2468. (i) Chan, J. Z.; Chang, Y.; Wasa, M. B(C6F5)3-Catalyzed C−H Alkylation of N-Alkylamines Using Silicon Enolates without External Oxidant. *Org. Lett.* **2019**, *21*, 984−988.

(12) Although ketene silyl acetals 2d (R = Cl), 2e (R = OMe), and [(1-methoxyprop-1-en-1-yl)oxy]trimethylsilane (2f) were examined, the desired 1,4- and 1,6-addition products were not obtained.

(13) For reviews on cyclobutenones, see: (a) Chen, P.-h.; Dong, G. Cyclobutenones and Benzocyclobutenones: Versatile Synthons in Organic Synthesis. *Chem. − Eur. J.* **2016**, *22*, 18290−18315. For recent examples on cyclobutenones, see: (b) Pirwerdjan, R.; Priebbenow, D. L.; Becker, P.; Lamers, P.; Bolm, C. Exploring the Reactivity of N-Alkynylated Sulfoximines: [2 + 2]-Cycloadditions. *Org. Lett.* **2013**, *15*, 5397−5399. (c) Rodriguez, K. X.; Kaltwasser, N.; Toni, T. A.; Ashfeld, B. L. Rearrangement of an Intermediate Cyclopropyl Ketene in a RhII-Catalyzed Formal [4 + 1]-Cycloaddition Employing Vinyl Ketenes as 1,4-Dipoles and Donor−Acceptor Metallocarbenes. *Org. Lett.* **2017**, *19*, 2482−2485. (d) Gao, S.; Hu, X. Nickel-catalyzed ring-opening of α-hydroxycyclobutenones with a remarkable ligand effect. *Chem. Commun.* **2017**, *53*, 10540−10543. (e) Rodriguez, K. X.; Pilato, T. C.; Ashfeld, B. L. An unusual stereoretentive 1,3-quaternary carbon shift resulting in an enantioselective RhII-catalyzed formal [4+1]-cycloaddition between diazo compounds and vinyl ketenes. *Chem. Sci.* **2018**, *9*, 3221−3226. (f) Yu, Y.; Zhang, Y.; Xiao, L.-Y.; Peng, Q.-Q.; Zhao, Y.-L. Thermally induced formal [4+2] cycloaddition of 3-aminocyclobutenones with electron-deficient alkynes: facile and efficient synthesis of 4-pyridones. *Chem. Commun.* **2018**, *54*, 8229−8232. (g) Xu, W.-B.; Li, C.; Wang, J. RhI-Catalyzed Carbonylative [3+1] Construction of Cyclobutenones via C−C σ-Bond Activation of Cyclopropenes. *Chem. − Eur. J.* **2018**, *24*, 15786−15790. (h) Qin, Q.; Luo, X.; Wei, J.; Zhu, Y.; Wen, X.; Song, S.; Jiao, N. Acetonitrile Activation: An Effective Two-Carbon Unit for Cyclization. *Angew. Chem., Int. Ed.* **2019**, *58*, 4376−4380.

(14) For selected reviews on the synthesis of β-lactams, see: (a) Brandi, A.; Cicchi, S.; Cordero, F. M. Novel Syntheses of Azetidines and Azetidinones. *Chem. Rev.* **2008**, *108*, 3988−4035. (b) Xu, J. Synthesis of β-lactams withpelectron-withdrawing substituents. *Tetrahedron* **2012**, *68*, 10696−10747. (c) Pitts, C. R.; Lectka, T. Chemical Synthesis of β-Lactams: Asymmetric Catalysis and Other Recent Advances. *Chem. Rev.* **2014**, *114*, 7930−7953. For selected recent examples on a variety of β-lactam syntheses, see: (d) Li, C.; Jiang, K.; Ouyang, Q.; Liu, T.-Y.; Chen, Y.-C. [3+1]- and [3+2]-Cycloadditions of Azaoxyallyl Cations and Sulfur Ylides. *Org. Lett.* **2016**, *18*, 2738−2741. (e) Zidan, A.; Garrec, J.; Cordier, M.; El-Naggar, A. M.; Abd El-Sattar, N. E. A.; Ali, A. K.; Hassan, M. A.; El Kaim, L. β-Lactam Synthesis through Diodomethane Addition to Amide Dianions. *Angew. Chem., Int. Ed.* **2017**, *56*, 12179−12183. (f) Shu, T.; Zhao, L.; Li, S.; Chen, X.-Y.; von Essen, C.; Rissanen, K.; Enders, D. Asymmetric Synthesis of Spirocyclic β-Lactams through Copper-Catalyzed Kinugasa/Michael Domino Reactions. *Angew. Chem., Int. Ed.* **2018**, *57*, 10985−10988.

(15) Van den Nieuwendijk, A. M. C. H.; Pietra, D.; Heitman, L.; Göeblyös, A.; IJzerman, A. P. Synthesis and Biological Evaluation of 2,3,5-Substituted [1,2,4]Thiadiazoles as Allosteric Modulators of Adenosine Receptors. *J. Med. Chem.* **2004**, *47*, 663−672.

(16) Obata, A.; Ano, Y.; Chatani, N. Nickel-catalyzed C−H/N−H annulation of aromatic amides with alkynes in the absence of a specific chelation system. *Chem. Sci.* **2017**, *8*, 6650−6655.

(17) Kakuta, H.; Zheng, X.; Oda, H.; Harada, S.; Sugimoto, Y.; Sasaki, K.; Tai, A. Cyclooxygenase-1-Selective Inhibitors Are Attractive Candidates for Analgesics That Do Not Cause Gastric Damage. Design and in Vitro/in Vivo Evaluation of a Benzamide-Type Cyclooxygenase-1 Selective Inhibitor. *J. Med. Chem.* **2008**, *51*, 2400−2411.

(18) Gonec, T.; Bobal, P.; Sujan, J.; Pesko, M.; Guo, J.; Kralova, K.; Pavlacka, L.; Vesely, L.; Kreckova, E.; Kos, J.; Coffey, A.; Kollar, P.; Imramovsky, A.; Placek, L.; Jampilek, J. J. Investigating the Spectrum of Biological Activity of Substituted Quinoline-2-Carboxamides and Their Isosteres. *Molecules* **2012**, *17*, 613−644.

(19) Lee, C. K.; Yu, J. S.; Ji, Y. R. Determination of aromaticity indices of thiophene and furan by nuclear magnetic resonance spectroscopic analysis of their anilides. *J. Heterocycl. Chem.* **2002**, *39*, 1219−1227.

(20) Logue, M. W.; Teng, K. Palladium-catalyzed reactions of acyl chlorides with (1-alkynyl)tributylstannanes. A convenient synthesis for 1-alkynyl ketones. *J. Org. Chem.* **1982**, *47*, 2549−2553.

(21) Nie, X.; Wang, G. Synthesis and Self-Assembling Properties of Diacetylene-Containing Glycolipids. *J. Org. Chem.* **2006**, *71*, 4734−4741.

(22) Chen, X. Y.; Wang, L.; Frings, M.; Bolm, C. Copper-Catalyzed N-Alkynylations of Sulfoximines with Bromoacetylenes. *Org. Lett.* **2014**, *16*, 3796−3799.

(23) Beltran, F.; Miesch, L. Tertiary Enamide-Triggered SEAr: Domino Allylation and Enamine-Type Addition. *Org. Lett.* **2019**, *21*, 1569−1573.

(24) Moodapelly, S. K.; Sharma, G. V. M.; Doddi, V. R. Controlled Reactivity of 1,8-Diazabicyclo[5.4.0]undec-7-ene(DBU) in the Selective Synthesis of 1-(Bromoethynyl)arenes. *Adv. Synth. Catal.* **2017**, *359*, 1535−1540.

(25) Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. Pestalotiopsin A. Enantioselective Construction of Potential Building Blocks Derived from Antipodal Cyclobutanol Intermediates. *J. Org. Chem.* **2007**, *72*, 7125−7134.

(26) Martin, A.; Vors, J.-P.; Baudoin, O. Synthesis of Conformationally Constrained Esters and Amines by Pd-Catalyzed α-Arylation of Hindered Substrates. *ACS Catal.* **2016**, *6*, 3941−3945.

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