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Note

Synthesis of Pyrrolidine-2-ylidenes from Isoxazolines and Allenes

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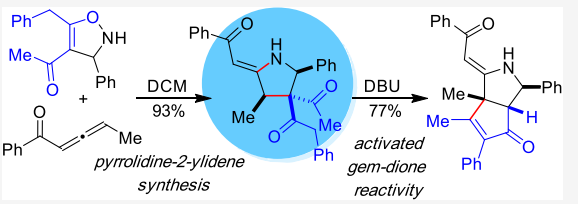
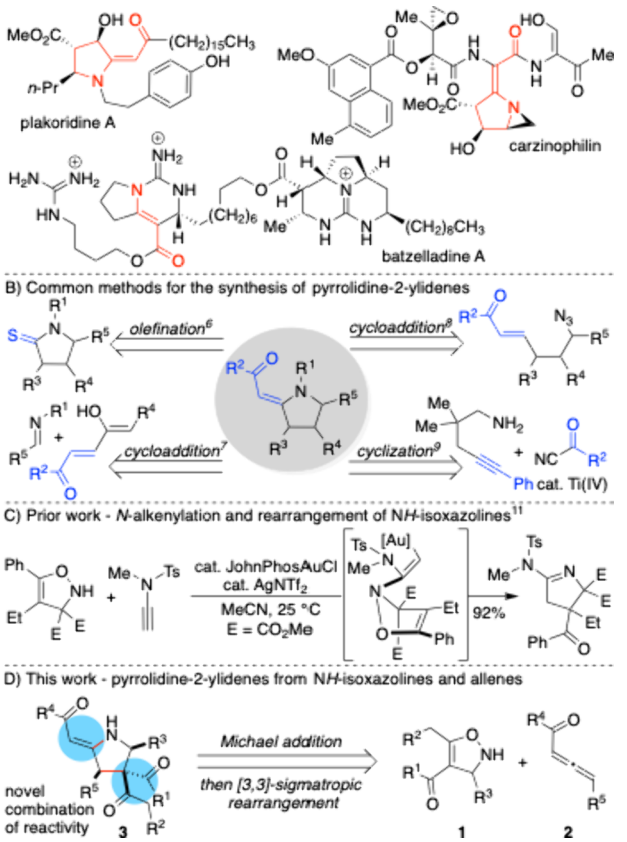
ABSTRACT: A diastereoselective addition and rearrangement reaction has been developed for the synthesis of pyrrolidine-2-ylidenes from N*H*-isoxazolines and electron-deficient allenes. This method proceeds via the rearrangement of a proposed *N*-alkenylisoxazoline intermediate to generate densely functionalized pyrrolidine-2-ylidenes under simple catalyst-free conditions that tolerate ketone substituents and install relative stereochemistry at positions 3 and 4 of the heterocycle. Reaction optimization and the substrate scope are described in addition to studies evaluating the reactivity of the *gem*-dione and enaminone groups of the products.



Pyrrolidine-2-ylidenes are N-heterocycles found in biologically active natural products such as plakoridine A, carzinophilin, azinomycin A, and batzelladine (Scheme 1A).[1−3] The enaminone functional group embedded in these molecules has also been used as an intermediate in the synthesis of other pyrrolidine targets.[4,5] The most common method used for the synthesis of pyrrolidine-2-ylidenes is the olefination of lactams or thiolactams.[1a,6] Additional synthetic approaches to these molecules include using intermolecular cycloaddition of enediones with imines, intramolecular cycloaddition of azides with Michael acceptors, titanium-catalyzed cyclization of ynamines in the presence of acyl cynanides, and ring opening of isoxazoles and isoxazolines (Scheme 1B).[7−10] While these methods have proven to be effective for pyrrolidine-2-ylidene synthesis, olefination reactions limit compatibility with ketone and aldehyde substituents, and installing stereocenters at positions 3 and 4 of these heterocycles is usually dependent on the synthesis of precursors. Recently, we reported that gold-catalyzed N-alkenylation of isoxazolines with ynamides generates *N*-alkenylisoxazoline intermediates that undergo [3,3]-sigmatropic rearrangement to give 2-aminopyrrolines (Scheme 1C).[11] We wondered if the nucleophilic reactivity of N*H*-isoxazolines could also be applied to allenones for the preparation of pyrrolidine-2-ylidenes **3** under mild conditions that would accommodate ketone substituents and install relative stereochemistry. While conjugate additions of N*H*-isoxazolines appear to be straightforward, limited methods for the preparation of N*H*-isoxazolines have inhibited studies of their reactivity and potential to engage in cascade reactions.[11,13] Herein, we describe the synthesis of pyrrolidine-2-ylidenes **3** from N*H*-isoxazolines **1** and allenes **2** via conjugate addition and rearrangement under simple catalyst-free conditions or with the addition of a Lewis acid (Scheme 1D).[12] This reaction gives highly functionalized pyrrolidine-2-

Scheme 1. Pyrrolidine-2-ylidene Targets and Synthesis



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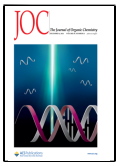

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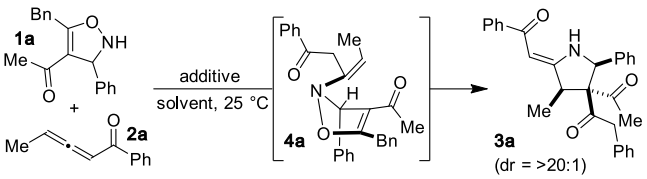
ylidenes with up to three contiguous stereocenters and expands the synthetic utility of N*H*-isoxazolines as modular precursors to diastereoselective rearrangements for stereoselective heterocycle formation. The scope of this method and investigation of the novel reactivity of **3** are described below.

The addition of N*H*-isoxazolines to allenones to generate *N*-alkenylisoxazolines and synthesize pyrrolidines was initially investigated with **1a** and **2a** (Table 1). N*H*-Isoxazoline **1a** was

Table 1. Optimization of the Synthesis of Pyrrolidine-2-ylidenes from Isoxazoline 1a and Allene 2a[a]



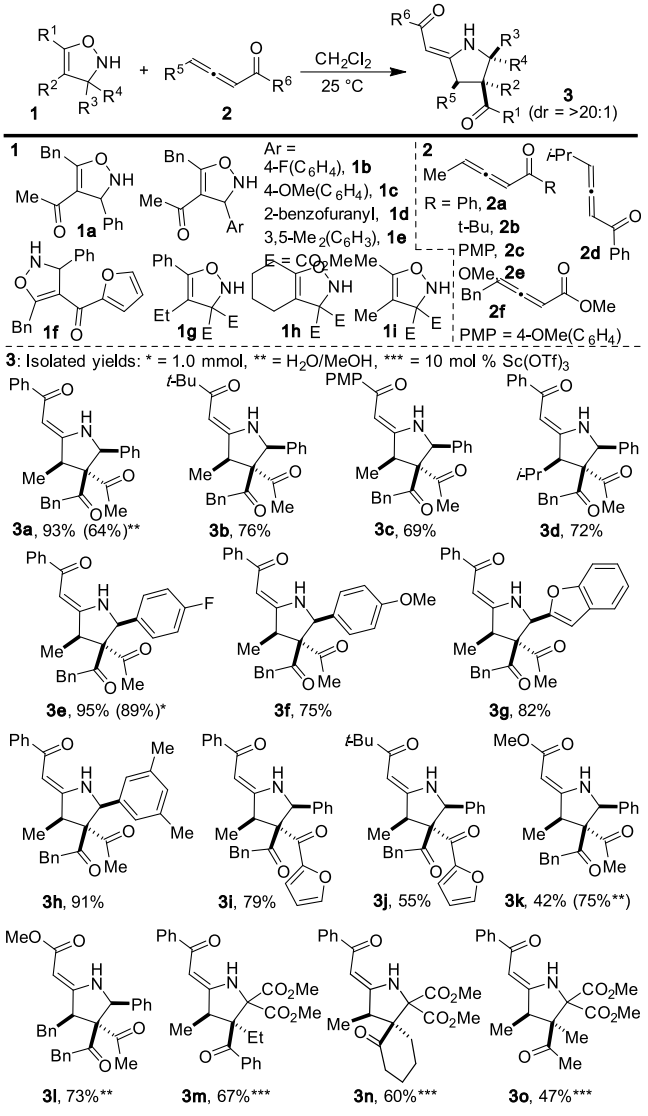
entry	additive	solvent	[**1a**] (M)	yield[b] (%)
1	K_2CO_3	CH_2Cl_2	0.1	80
2	quinoline	CH_2Cl_2	0.1	86
3	–	CH_2Cl_2	0.1	89
4	–	MeOH	0.1	76
5	–	THF	0.1	69
6	–	EtOAc	0.1	78
7	–	acetone	0.1	51
8[c]	–	CH_2Cl_2	0.05	85
9[c,d]	–	CH_2Cl_2	0.05	90

[a]Conditions: **1a** (1 equiv), **2a** (2 equiv), additive (2 equiv), 25 °C, 1 h. [b]Determined by ^{1}H NMR spectroscopy. CH_2Br_2 used as an internal standard. [c]For 3 h. [d]With 1.5 equiv of **2a**.

prepared as reported by Zhang and co-workers.[13] As described in our previous work, the addition of *N*-hydroxyenamines to allenoates can be achieved in the presence of a mild base to initiate a sigmatropic rearrangement.[14] When a mixture of isoxazoline **1a** and allene **2a** in CH_2Cl_2 was treated with either K_2CO_3 or quinoline, the desired addition and rearrangement product **3a** was observed in good yield (Table 1, entries 1 and 2). Surprisingly, removal of the base additive led to a small increase in yield for **3**, and optimal conditions for the synthesis of **3a** were determined to be simply a 2:3 mixture of **1a** and **2a** in CH_2Cl_2 (Table 1, entry 9). The reaction was shown to be tolerant of other solvents and different concentrations but worked best as a 0.05 M solution (Table 1 entries 4–9). In analogy to our previous work,[11,15] we propose *N*-alkenylisoxazoline **4a** (or related tautomers) as the intermediate in this process that can undergo rearrangement through a boat transition state to form pyrrolidine **3a** with the illustrated relative stereochemistry.

With optimal conditions in hand, the scope of the reaction was investigated by varying the substituents on the allene and the N*H*-isoxazoline. As shown in Scheme 2, allenes with alkyl and aryl ketone functional groups smoothly underwent conversion to **3a**–**3c** with N*H*-isoxazoline **1a**. A somewhat attenuated yield was observed for **3c** presumably due to the lower electrophilicity of **2c**. Branched alkyl groups were also tolerated on the allenone, as shown for **3d**. To interrogate the effect of substituents on the N*H*-isoxazoline, the procedure by Zhang and co-workers[13] was expanded to prepare N*H*-isoxazolines **1b**–**1f**. N*H*-Isoxazolines with aryl and heteroaryl groups adjacent to the N atom were tolerated to give **3e**–**3h**. When the acyl group of **1a** was changed to a furanyl

Scheme 2. Scope of the Synthesis of Pyrrolidine-2-ylidenes



substituent, pyrrolidines **3i** and **3j** were prepared in good yields. More significant changes to the structure of the substrates required additional changes in the reaction conditions. For example, allenoate **2e** gave **3k** in only 42% yield and dr 10:1 under the optimal conditions shown in Table 1 but gave **3k** in 75% yield with dr >20:1 when treated with **1a** in MeOH and H_2O. These protic conditions were also tested for a mixture of **1a** and **2a** but shown to be inferior to the optimized conditions determined in Table 1. The structure and relative stereochemistry of **3** were confirmed with an X-ray crystal structure of **3l**.[16] N*H*-Isoxazolines **1g**–**1i** were prepared from the corresponding azetidine nitrones[11] but did not form the corresponding pyrrolidines under standard conditions. In contrast, when **1g**–**1i** were treated with allene **2a** in the presence of catalytic $Sc(OTf)_3$, pyrrolidines **3m**–**3o**, respectively, were formed in moderate yields. With several examples of pyrrolidine-2-ylidenes **3** in hand, the reactivity of these compounds was evaluated.

Investigations into the reactivity of pyrrolidine-2-ylidenes **3** focused on interrogating the effect of the carbonyl functionalities decorating these molecules. Initial attempts to reduce the enaminone with hydride reagents and hydrogenation were

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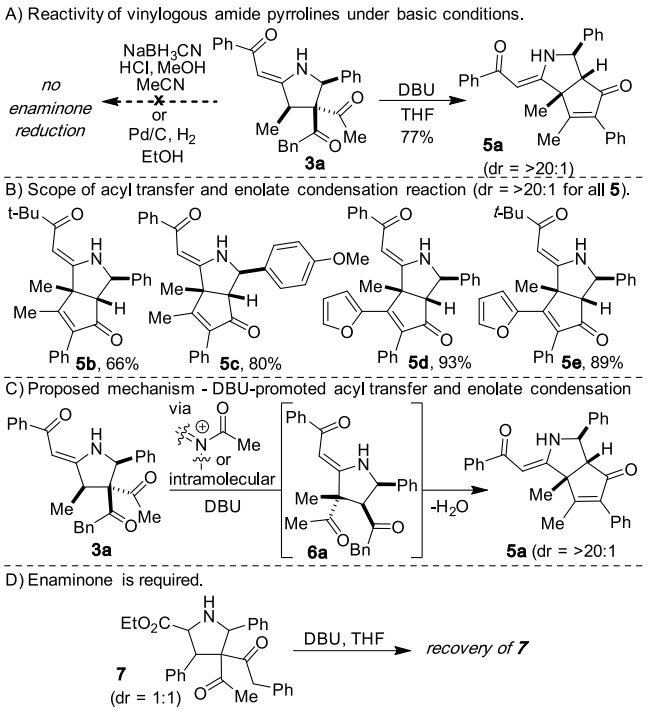
J. Org. Chem. 2024, 89, 17804–17812

met with a lack of reactivity or formation of alternative product mixtures (Scheme 3A). Further analysis showed that treatment

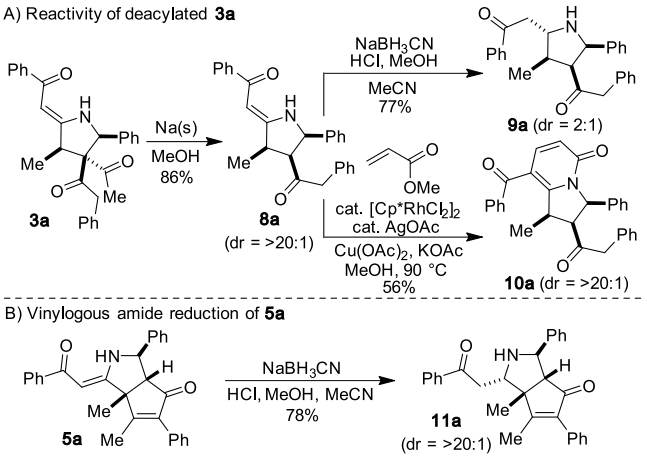
Scheme 3. Conversion of 3 into Fused Pyrrolidines 5



of **3a** with a base leads to the formation of **5a** as a single diastereomer. The relative stereochemistry of **5a** was confirmed by X-ray crystal structure analysis.[16] While a variety of bases such as NaH and KO*t*-Bu were shown to trigger this reactivity, DBU was determined to be optimal for the synthesis of **5a** from **3a**. This reaction was general for several pyrrolidine-2-ylidenes **3** as illustrated by successful formation of **5b**−**5e**, but no reaction was observed for **3m**−**3o**, which do not have *gem*-dione functionalities (Scheme 3B). A proposed mechanism for this reaction is shown in Scheme 3C. Either an intramolecular or a DBU-facilitated acyl migration could form intermediate **6a**,[17] which could be converted into **5a** via enolization at the benzyl ketone followed by addition to the adjacent acyl group and elimination of H_2O. No crossover products were observed when a mixture of **3b** and **3i** was subjected to reaction conditions supporting the absence of solvent-separated fragments during the acyl transfer. Independent synthesis of a diastereomeric mixture of **7** via dipolar cycloaddition[18] followed by treatment with DBU also did not form the analogous fused pyrrolidine, suggesting that the enaminone functionality of **3** is required for the initial acyl transfer (Scheme 3D). These studies identified the *gem*-dione of **3** to be activated by the vinylogous amide toward preferential rearrangement to fused pyrrolidines **5**.

Having discovered that the *gem*-dione functionality dominates the reactivity of **3** under basic conditions, we next considered the reactivity of **3** after removal of the acyl group. As shown in Scheme 4A, deacylation of **3a** with NaOMe gave **8a** in good yield and high diastereoselectivity.[19] This compound smoothly underwent sodium cyanoborohydride reduction to give **9a** in good yield, albeit with low diastereoselectivity.[20] Cyclization of **8a** with acrylate gave **10a** in moderate yield and high diastereoselectivity following a

Scheme 4. Reactivity of Deacylated Pyrrolidine-2-ylidenes



procedure reported by Tian, Loh, and co-workers.[21] Further following the trend that the vinylogous amide of **3** reacts as expected in the absence of the *gem*-dione, we also showed that fused pyrrolidine **5a** smoothly underwent reduction to **11a** with $NaBCNH_3$ (Scheme 4B).[20] Taken together, these investigations demonstrate the synthetic utility of **3** and how the *gem*-dione of **3a**−**3l** can be used as a reactivity-controlling element.

In summary, we have discovered a conjugate addition and [3,3]-sigmatropic rearrangement reaction to form pyrrolidine-2-ylidenes from N*H*-isoxazolines and allenes. This diastereoselective transformation occurs under mild catalyst-free conditions and provides access to pyrrolidine-2-ylidenes that are challenging to achieve by other methods. Further studies have also identified an unusual reactivity pattern of these compounds, in which a *gem*-dione preferentially undergoes acyl migration and cyclization under basic conditions. Removal of one of the ketones then allows for the use of known reduction and cyclization conditions of enaminones to functionalize the heterocycle. This work expands the chemical space of accessible pyrrolidine-2-ylidenes and showcases the versatility of N*H*-isoxazoline conjugate addition reactions to initiate cascade reactions for the stereoselective synthesis of different types of pyrrolines.

EXPERIMENTAL SECTION

General Considerations. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded by using a Bruker AV 500 MHz spectrometer at ambient temperature. The data are reported as follows: chemical shift in parts per million from internal tetramethylsilane on the δ scale, multiplicity (br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants (hertz), and integration. Infrared (IR) spectra were recorded at ambient temperature using a Thermo Scientific Nicolet iS5 FT-IR spectrometer with an iD5 ATR sampler. High-resolution mass spectra were acquired on an LTQ hybride ion trap Fourier transform spectrometer using electrospray to ionize the sample and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography (TLC) was performed on 0.25 mm extra hard silica gel plates with a UV_{254} fluorescent indicator. Medium-pressure liquid chromatography was performed using the force flow of the indicated solvent system down columns packed with 60 Å (40−60 μm) of mesh silica gel (SiO_2). All reagents and solvents were obtained from commercial sources and, where appropriate, purified prior to use. CH_2Cl_2, toluene, and tetrahydrofuran (THF) were dried by filtration through alumina according to the procedure of Grubbs.[22] MeOH was dried by filtration through a column loaded

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with activated 4 Å molecular sieves. N*H*-Isoxazolines **1a**−**1f** were prepared following a procedure reported by Zhang and co-workers.[12,11] N*H*-Isoxazolines **1g**−**1i** were prepared following a procedure reported by our group.[11] Allenes **2** were prepared following procedures previously reported by our group and others.[14,23]

General Procedure for Table 1. A 5 mL glass vial was charged with a 0.100 M solution of isoxazoline **1a**[13] in the given solvent, mixed with a 0.150 M solution of allene **2a**[14] in the same solvent, and treated with an additive to form a reaction mixture. The vial was then sealed with a Teflon-sealed screw cap, and the mixture was allowed to stir at 25 °C for the given amount of time. The reaction mixture was then concentrated under vacuum and mixed with 1.0 equiv of 1,4-dimethoxybenzene to act as an internal standard for crude yield determination of pyrrolidine **3a** by ^{1}H NMR spectroscopy.

General Procedure A for the Synthesis of Pyrrolidine-2-ylidenes 3. A 5 mL glass vial was charged with a solution of N*H*-isoxazoline **1** in CH_2Cl_2 (1.50 mL, 0.100 M, 0.150 mmol, 1.00 equiv) and treated with a solution of allene **2** in CH_2Cl_2 (1.50 mL, 0.150 M, 0.225 mmol, 1.50 equiv). The vial was then sealed with a Teflon screw cap and allowed to stir at 25 °C for 2−23 h while the reaction was monitored by TLC. Upon complete consumption of **1**, the reaction mixture was concentrated under vacuum, wet-loaded onto silica gel using CH_2Cl_2 (∼0.5 mL), and purified by medium-pressure chromatography (8−25% EtOAc/hexanes) to afford pyrrolidine-2-ylidenes **3a**−**3j**.

General Procedure B for the Synthesis of Pyrrolidine-2-ylidenes 3. A 20 mL scintillation vial was charged with N*H*-isoxazoline **1** (1.0 equiv), 20% H_2O in MeOH (0.01 M), and allene **2** (2.0 equiv) and sealed with a Teflon screw cap. After the mixture had been stirred for 16 h at 25 °C, pyrrolidine-2-ylidenes **3k** and **3l** precipitated from the reaction mixture and were collected by filtration. The crude product was wet-loaded onto silica gel using CH_2Cl_2 (∼1 mL). Subsequent medium-pressure chromatography (12% EtOAc/hexanes) afforded pyrrolidine-2-ylidenes **3k** and **3l**.

General Procedure C for the Synthesis of Pyrrolidine-2-ylidenes 3. A 5 mL glass vial was charged with $Sc(OTf)_3$ (0.007 g, 0.0150 mmol, 10 mol %), diluted with a solution of N*H*-isoxazoline **1**[11] in CH_2Cl_2 (1.50 mL, 0.100 M, 0.150 mmol, 1.00 equiv), and treated with a solution of allene **2**[14] in CH_2Cl_2 (1.50 mL, 0.150 M, 0.225 mmol, 1.50 equiv). The vial was then sealed with a Teflon screw cap, and the mixture allowed to stir at 25 °C for 2−23 h while the reaction was monitored by TLC. Upon complete consumption of **1**, the reaction mixture was concentrated under vacuum, wet-loaded onto silica gel using CH_2Cl_2 (∼0.5 mL), and purified by medium-pressure chromatography (8−25% EtOAc/hexanes) to afford pyrrolidine-2-ylidenes **3m**−**3o**.

Pyrrolidine-2-ylidene ***3a*** was prepared by general procedure A using N*H*-isoxazoline **1a**[13] (1.50 mL, 0.100 M in CH_2Cl_2, 0.160 mmol, 1.00 equiv) and allene **2a**[14] (1.50 mL, 0.150 M in CH_2Cl_2, 0.218 mmol, 1.36 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 4 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1a** = 0.29, and R_f of **3a** = 0.32; UV_{254} lamp). Chromatography (15% EtOAc/hexanes) afforded pyrrolidine **3a** as a yellow solid (0.065 g, 93%, dr >20:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.93−7.92 (m, 2H), 7.55−7.53 (m, 2H), 7.48−7.42 (m, 3H), 7.40−7.35 (m, 3H), 7.17−7.15 (m, 3H), 6.65−6.63 (m, 2H), 5.90 (s, 1H), 5.80 (s, 1H), 3.32 (q, J = 6.9 Hz, 1H), 3.19 (d, J = 17.2 Hz, 1H), 2.77 (d, J = 17.2 Hz, 1H), 2.36 (s, 3H), 1.56 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 204.8, 201.1, 189.6, 167.9, 140.0, 135.9, 131.9, 131.0, 129.7, 129.0, 128.9, 128.3, 128.3, 127.9, 127.2, 127.0, 85.7, 78.2, 65.3, 49.0, 45.4, 30.2, 12.8; IR (thin film) 3305, 1694, 1614, 1576, 1520, 1453, 1360, 1291, 1259, 1243 cm^{-1}; HRMS (ESI) m/z calcd for $C_{29}H_{28}NO_3$ $(M + H)^+$ 438.2069, found 438.2062; mp 170−172 °C.

Pyrrolidine-2-ylidene ***3a*** was prepared by general procedure B using N*H*-isoxazoline **1a**[13] (9.75 mL, 0.020 M in CH_2Cl_2, 0.195 mmol, 1.00 equiv) and allene **2a**[14] (9.75 mL, 0.030 M in CH_2Cl_2, 0.303 mmol, 1.56 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 16 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1a** = 0.29, and R_f of **3a** = 0.32; UV_{254} lamp). Chromatography (15% EtOAc/hexanes) afforded pyrrolidine **3a** as a yellow solid (0.054 g, 64%, dr >20:1). ^{1}H and ^{13}C{^{1}H} NMR data matched the values presented above.

Pyrrolidine-2-ylidene ***3b*** was prepared by general procedure A using N*H*-isoxazoline **1a**[13] (1.80 mL, 0.100 M in CH_2Cl_2, 0.184 mmol, 1.00 equiv) and allene **2b** (1.80 mL, 0.120 M in CH_2Cl_2, 0.220 mmol, 1.20 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 23 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1a** = 0.29, and R_f of **3b** = 0.53; UV_{254} lamp). Chromatography (12% EtOAc/hexanes) afforded pyrrolidine **3b** as a yellow solid (0.058 g, 76%, dr >20:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.50−7.48 (m, 2H), 7.37−7.34 (m, 3H), 7.17−7.14 (m, 3H), 6.62−6.60 (m, 2H), 5.70 (s, 1H), 5.37 (s, 1H), 3.23 (q, J = 6.9 Hz, 1H), 3.18 (d, J = 17.3 Hz, 1H), 2.76 (d, J = 17.3 Hz, 1H), 2.35 (s, 3H), 1.48 (d, J = 6.9 Hz, 3H), 1.19 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 205.6, 205.0, 201.4, 166.6, 136.0, 132.1, 129.7, 128.9, 128.7, 128.2, 127.8, 127.0, 84.4, 78.0, 65.0, 49.0, 45.3, 41.9, 30.2, 27.8, 12.8; IR (thin film) 3308, 1738, 1695, 1624, 1525, 1498, 1454, 1360, 1300, 1264 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{32}NO_3$ $(M + H)^+$ 418.2382, found 418.2379; mp 114−116 °C.

Pyrrolidine-2-ylidene ***3c*** was prepared by general procedure A using N*H*-isoxazoline **1a**[13] (1.80 mL, 0.100 M in CH_2Cl_2, 0.188 mmol, 1.00 equiv) and allene **2c** (1.80 mL, 0.150 M in CH_2Cl_2, 0.270 mmol, 1.44 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 5 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1a** = 0.29, and R_f of **3c** = 0.21; UV_{254} lamp). Chromatography (20% EtOAc/hexanes) afforded pyrrolidine **3c** as an orange solid (0.061 g, 69%, dr >20:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.92−7.91 (m, 2H), 7.54−7.52 (m, 2H), 7.38−7.36 (m, 3H), 7.16−7.15 (m, 3H), 6.94−6.92 (m, 2H), 6.64−6.63 (m, 2H), 5.86 (s, 1H), 5.78 (s, 1H), 3.85 (s, 3H), 3.31 (q, J = 7.2 Hz, 1H), 3.19 (d, J = 17.2 Hz, 1H), 2.79 (d, J = 17.2 Hz, 1H), 2.36 (s, 3H), 1.56 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 204.9, 201.2, 188.7, 167.2, 162.0, 136.0, 132.7, 132.0, 129.7, 129.1, 129.0, 128.8, 128.2, 127.9, 127.0, 113.5, 85.2, 78.1, 65.1, 55.4, 48.9, 45.4, 30.2, 12.9; IR (thin film) 3305, 1693, 1613, 1600, 1573, 1522, 1490, 1454, 1290, 1243 cm^{-1}; HRMS (ESI) m/z calcd for $C_{30}H_{30}NO_4$ $(M + H)^+$ 468.2175, found 468.2175; mp 152−162 °C.

Pyrrolidine-2-ylidene ***3d*** was prepared by general procedure A using N*H*-isoxazoline **1a**[13] (1.80 mL, 0.100 M in CH_2Cl_2, 0.186 mmol, 1.00 equiv) and allene **2d** (1.80 mL, 0.170 M in CH_2Cl_2, 0.300 mmol, 1.61 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 4 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1a** = 0.29, and R_f of **3d** = 0.42; UV_{254} lamp). Chromatography (12% EtOAc/hexanes) afforded pyrrolidine **3d** as an orange solid (0.062 g, 72%, dr >20:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.74 (s, 1H), 7.91−7.89 (m, 2H), 7.48−7.39 (m, 6H), 7.32−7.30 (m, 2H), 7.20−7.13 (m, 3H), 6.70−6.69 (m, 2H), 6.07 (s, 1H), 5.46 (s, 1H), 3.76 (d, J = 18.1 Hz, 1H), 3.54 (d, J = 6.9 Hz, 1H), 2.84 (d, J = 18.1 Hz, 1H), 2.56 (s, 3H), 2.42 (sextet, J = 6.8 Hz, 1H), 1.33 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 205.8, 202.7, 189.5, 168.4, 140.1, 135.0, 133.2, 131.0, 129.9, 129.3, 129.1, 128.3, 128.1, 127.4, 127.2, 126.7, 87.0, 77.9, 67.9, 58.7, 50.2, 29.9, 27.3, 23.7, 22.7; IR (thin film) 2959, 1738, 1708, 1610, 1578, 1521, 1453, 1366, 1263, 1231 cm^{-1}; HRMS (ESI) m/z calcd for $C_{31}H_{32}NO_3$ $(M + H)^+$ 466.2382, found 466.2379; mp 116−117 °C.

Pyrrolidine-2-ylidene ***3e*** was prepared by general procedure A using N*H*-isoxazoline **1b** (1.45 mL, 0.100 M in CH_2Cl_2, 0.124 mmol, 1.00 equiv) and allene **2a**[14] (1.30 mL, 0.150 M in CH_2Cl_2, 0.196 mmol, 1.58 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 5 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1b** = 0.26, and R_f of **3e** = 0.29; UV_{254} lamp). Chromatography (15% EtOAc/hexanes) afforded pyrrolidine **3e** as a yellow solid (0.054 g, 95%, dr >20:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.92−7.91 (m, 2H), 7.54−7.51 (m, 2H), 7.47−7.42 (m, 3H), 7.19−7.18 (m, 3H), 7.05 (t, J = 8.6 Hz, 2H), 6.70−6.68 (m, 2H), 5.90 (s, 1H), 5.74 (s, 1H), 3.30 (q, J = 6.9 Hz, 1H), 3.16 (d, J = 16.9 Hz, 1H), 2.84 (d, J = 16.9 Hz, 1H), 2.31 (s, 3H), 1.57 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 205.0, 200.8, 189.7 167.8, 162.9 (d, J = 248.4 Hz), 139.9, 131.6, 131.1, 129.9 (2C), 129.6, 128.4, 128.3, 127.2 (2C), 115.8 (d, J = 21.3 Hz), 85.8, 78.1, 64.8, 48.9, 45.2, 30.2, 13.0; IR (thin

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J. Org. Chem. 2024, 89, 17804−17812

film) 3290, 1694, 1613, 1579, 1517, 1323, 1297, 1251, 1149, 1121 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{27}FNO_3$ $(M + H)^+$ 456.1975, found 456.1970; mp 157−160 °C.

Pyrrolidine-2-ylidene ***3e*** *(1 mmol scale)* was prepared by general procedure A using N*H*-isoxazoline **1b** (10.0 mL, 0.100 M in CH_2Cl_2, 1.00 mmol, 1.00 equiv) and allene **2a**[14] (10.0 mL, 0.125 M in CH_2Cl_2, 1.25 mmol, 1.25 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 12 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1b** = 0.26, and R_f of **3e** = 0.29; UV_{254} lamp). Chromatography (15% EtOAc/hexanes) afforded pyrrolidine **3e** as a yellow solid (0.405 g, 89%, dr >20:1). ^1H and $^{13}C\{^1H\}$ NMR data matched the values presented above.

Pyrrolidine-2-ylidene ***3f*** was prepared by general procedure A using N*H*-isoxazoline **1c**[11] (0.500 mL, 0.100 M in CH_2Cl_2, 0.062 mmol, 1.00 equiv) and allene **2a**[14] (0.500 mL, 0.230 M in CH_2Cl_2, 0.114 mmol, 1.84 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 6 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1c** = 0.20, and R_f of **3f** = 0.31; UV_{254} lamp). Chromatography (17% EtOAc/hexanes) afforded pyrrolidine **3f** as an orange solid (0.022 g, 75%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.93−7.91 (m, 2H), 7.46−7.41 (m, 5H), 7.18−7.17 (m, 3H), 6.89−6.87 (m, 2H), 6.72−6.70 (m, 2H), 5.88 (s, 1H), 5.72 (s, 1H), 3.81 (s, 3H), 3.28 (q, *J* = 7.0 Hz, 1H), 3.20 (d, *J* = 17.1 Hz, 1H), 2.80 (d, *J* = 17.0 Hz, 1H), 2.33 (s, 3H), 1.55 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.0, 201.1, 189.5, 167.9, 160.0, 140.1, 132.0, 131.0, 129.7, 129.2, 128.3, 128.2, 127.4, 127.2, 127.0, 114.3, 85.5, 78.0, 65.1, 55.4, 48.9, 45.3, 30.2, 12.8; IR (thin film) 3303, 1695, 1608, 1576, 1509, 1364, 1293, 1241, 1175, 1050 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{30}NO_4$ $(M + H)^+$ 468.2175, found 468.2174; mp 157−159 °C.

Pyrrolidine-2-ylidene ***3g*** was prepared by general procedure A using N*H*-isoxazoline **1d**[11] (1.50 mL, 0.100 M in CH_2Cl_2, 0.156 mmol, 1.00 equiv) and allene **2a**[14] (1.50 mL, 0.180 M in CH_2Cl_2, 0.276 mmol, 1.77 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 7 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1d** = 0.26, and R_f of **3g** = 0.32; UV_{254} lamp). Chromatography (15% EtOAc/hexanes) afforded pyrrolidine **3g** as a yellow solid (0.061 g, 82%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.95−7.93 (m, 2H), 7.57−7.55 (m, 1H), 7.50−7.44 (m, 4H), 7.35−7.32 (m, 1H), 7.29−7.26 (m, 1H), 7.15−7.14 (m, 3H), 6.90 (s, 1H), 6.81−6.79 (m, 2H), 5.97 (s, 1H), 5.68 (s, 1H), 3.77 (d, *J* = 17.6 Hz, 1H), 3.62 (q, *J* = 7.2 Hz, 1H), 3.31 (d, *J* = 17.5 Hz, 1H), 2.42 (s, 3H), 1.51 (d, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 203.7, 202.4, 190.0, 167.4, 154.9, 151.6, 139.6, 132.3, 131.3, 129.8, 128.4, 128.2, 127.6, 127.3, 127.0, 125.3, 123.6, 121.5, 111.5, 107.3, 87.0, 78.0, 60.2, 48.3, 44.9, 29.1, 12.9; IR (thin film) 2921, 1697, 1614, 1578, 1522, 1453, 1364, 1293, 1241, 1174 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{28}NO_4$ $(M + H)^+$ 478.2018, found 478.2014; mp 110−114 °C.

Pyrrolidine-2-ylidene ***3h*** was prepared by general procedure A using N*H*-isoxazoline **1e** (1.50 mL, 0.100 M in CH_2Cl_2, 0.148 mmol, 1.00 equiv) and allene **2a**[14] (1.50 mL, 0.160 M in CH_2Cl_2, 0.240 mmol, 1.60 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 4 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1e** = 0.68, and R_f of **3h** = 0.39; UV_{254} lamp). Chromatography (12% EtOAc/hexanes) afforded pyrrolidine **3h** as a yellow solid (0.063 g, 91%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.93−7.91 (m, 2H), 7.46−7.41 (m, 3H), 7.17−7.16 (m, 3H), 7.08 (s, 2H), 6.98 (s, 1H), 6.64−6.62 (m, 2H), 5.88 (s, 1H), 5.72 (s, 1H), 3.29−3.24 (m, 2H), 2.74 (d, *J* = 17.5 Hz, 1H), 2.42 (s, 3H), 2.29 (s, 6H), 1.55 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 204.7, 201.0, 189.6, 167.8, 140.1, 138.8, 135.5, 132.2, 130.9, 130.6, 129.7, 128.3, 128.1, 127.2, 126.9, 125.6, 85.5, 78.1, 65.4, 49.1, 45.7, 30.2, 21.4, 12.6; IR (thin film) 2918, 1698, 1615, 1578, 1526, 1455, 1379, 1256, 1286, 1244 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{32}NO_3$ $(M + H)^+$ 466.2382, found 466.2378; mp 68−72 °C.

Pyrrolidine-2-ylidene ***3i*** was prepared by general procedure A using isoxazoline **1f**[11] (1.50 mL, 0.090 M in CH_2Cl_2, 0.132 mmol, 1.00 equiv) and allene **2a**[14] (1.50 mL, 0.140 M in CH_2Cl_2, 0.203 mmol, 1.54 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 16 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1f** = 0.47, and R_f of **3i** = 0.39; UV_{254} lamp). Chromatography (11% EtOAc/hexanes) afforded pyrrolidine **3i** as a brown solid (0.051 g, 79%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.45 (s, 1H), 7.92−7.90 (m, 2H), 7.56−7.55 (m, 2H), 7.49−7.48 (m, 1H), 7.45−7.35 (m, 7H), 7.13−7.12 (m, 3H), 6.63−6.62 (m, 1H), 6.60−6.58 (m, 2H), 6.26 (s, 1H), 5.88 (s, 1H), 3.38 (q, *J* = 7.1 Hz, 1H), 3.04 (d, *J* = 17.4 Hz, 1H), 2.25 (d, *J* = 17.4 Hz, 1H), 1.48 (d, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 199.5, 189.6, 185.0, 168.3, 151.6, 147.0, 140.3, 136.4, 132.8, 130.8, 129.5, 129.1 (2C), 128.2, 127.9 (2C), 127.2, 126.7, 120.5, 113.5, 85.3, 76.3, 64.9, 49.2, 48.1, 12.3; IR (thin film) 3264, 1711, 1656, 1612, 1577, 1562, 1521, 1496, 1455, 1366 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{32}H_{28}NO_4$ $(M + H)^+$ 490.2018, found 490.2025; mp 136−138 °C.

Pyrrolidine-2-ylidene ***3j*** was prepared by general procedure A using N*H*-isoxazoline **1f**[11] (5.60 mL, 0.100 M in CH_2Cl_2, 0.558 mmol, 1.00 equiv) and allene **2b** (5.60 mL, 0.195 M in CH_2Cl_2, 1.09 mmol, 1.94 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 18 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1f** = 0.47, and R_f of **3j** = 0.56; UV_{254} lamp). Chromatography (7% EtOAc/hexanes) afforded pyrrolidine **3j** as a yellow solid (0.144 g, 55%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.52−7.50 (m, 2H), 7.46−7.45 (m, 1H), 7.43 (s, 1H), 7.37−7.31 (m, 3H), 7.12−7.11 (m, 3H), 6.61−6.60 (m, 1H), 6.58−6.57 (m, 2H), 6.15 (s, 1H), 5.34 (s, 1H), 3.26 (q, *J* = 7.2 Hz, 1H), 3.02 (d, *J* = 17.5 Hz, 1H), 2.21 (d, *J* = 17.4 Hz, 1H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.17 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.4, 199.6, 185.2, 167.1, 151.7, 146.9, 136.6, 132.9, 129.5, 129.0, 128.9, 127.9 (2C), 126.7, 120.4, 113.4, 83.9, 76.2, 64.7, 49.2, 48.0, 41.8, 27.9, 12.1; IR (thin film) 2964, 1708, 1651, 1620, 1522, 1496, 1456, 1387, 1368, 1295 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{32}NO_4$ $(M + H)^+$ 470.2331, found 470.2335; mp 135−140 °C.

Pyrrolidine-2-ylidene ***3k*** was prepared by general procedure B using N*H*-isoxazoline **1a**[13] (4.20 mL, 0.020 M, 0.084 mmol, 1.00 equiv) and allene **2e**[23a] (4.20 mL, 0.030 M, 0.127 mmol, 1.50 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 16 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1a** = 0.29, and R_f of **3k** = 0.37; UV_{254} lamp). Chromatography (12% EtOAc/hexanes) afforded pyrrolidine **3k** as a white solid (0.025 g, 75%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (bs, 1H), 7.51−7.49 (m, 2H), 7.36−7.34 (m, 3H), 7.17−7.14 (m, 3H), 6.65−6.63 (m, 2H), 5.66 (s, 1H), 4.69 (s, 1H), 3.68 (s, 3H), 3.20−3.17 (m, 2H), 2.79 (d, *J* = 17.2 Hz, 1H), 2.32 (s, 3H), 1.44 (d, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.0, 201.3, 171.1, 165.5, 136.3, 132.1, 129.7, 128.9, 128.7, 128.2, 127.8, 127.0, 78.0, 77.3, 64.5, 50.4, 48.9, 44.8, 30.2, 12.7; IR (thin film) 3361, 1737, 1694, 1660, 1589, 1579, 1483, 1453, 1363, 1294 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{25}NO_4$ $(M + H)^+$ 392.1784, found 392; mp 118−120 °C.

Pyrrolidine-2-ylidene ***3k*** was prepared by general procedure A using N*H*-isoxazoline **1a**[13] (1.95 mL, 0.100 M, 0.195 mmol, 1.00 equiv) and allene **2e**[23a] (1.95 mL, 0.165 M, 0.322 mmol, 1.65 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 16 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1a** = 0.29, and R_f of **3k** = 0.37; UV_{254} lamp). Chromatography (12% EtOAc/hexanes) afforded pyrrolidine **3k** as a white solid (0.032 g, 42%, dr 10:1). ^1H and $^{13}C\{^1H\}$ NMR data matched the values presented above.

Pyrrolidine-2-ylidene ***3l*** was prepared by general procedure B using isoxazoline **1a**[13] (0.0559 g, 0.200 mmol, 1.00 equiv), allene **2f**[23b] (0.0753 g, 0.400 mmol, 2.00 equiv), and 10 mL of 20% H_2O in MeOH. After the mixture had been stirred for 16 h, pyrrolidine **3l** precipitated from the reaction mixture and was collected by filtration (0.0683 g, 73%, dr >20:1). A single crystal suitable for X-ray crystallographic analysis was obtained by recrystallization of this solid in iPrOAc (2.0 mL) with hexane (18 mL) at−20 °C. CCDC deposition number 2390522: ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.49−7.47 (m, 2H), 7.41−7.37 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.21−7.18 (m, 5H), 6.74−6.72 (m, 2H), 5.65 (s, 1H), 4.70 (s, 1H), 3.64 (s, 3H), 3.57 (dd, *J* = 7.8, 2.4 Hz, 1H), 3.39 (dd, *J* = 16.0, 7.9 Hz, 1H), 3.30 (d, *J* = 17.1 Hz, 1H), 2.98 (dd, *J* = 16.0, 3.1 Hz, 1H), 2.77 (d, *J* = 17.2 Hz, 1H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 204.9, 201.7, 171.1, 165.5,

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J. Org. Chem. 2024, 89, 17804−17812

139.5, 136.1, 132.2, 129.8, 129.1, 129.0 (2C), 128.3 (2C), 127.8, 127.0, 126.9, 78.5, 78.2, 65.1, 51.2, 50.4, 49.1, 34.9, 30.0; IR (thin flim) 3374, 1693, 1664, 1593, 1581, 1497, 1479, 1454, 1427, 1400 cm^{-1}; HRMS (ESI) m/z calcd for $C_{30}H_{30}NO_4$ $(M + H)^+$ 468.2175, found 468.2176; mp 133−138 °C.

Pyrrolidine-2-ylidene ***3m*** was prepared by general procedure C using N*H*-isoxazoline **1g**[11] (1.50 mL, 0.100 M in CH_2Cl_2, 0.150 mmol, 1.00 equiv), 10 mol % $Sc(OTf)_3$ (0.0070 g, 0.015 mmol, 0.10 equiv), and allene **2a**[14] (1.50 mL, 0.150 M in CH_2Cl_2, 0.225 mmol, 1.50 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 18 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1g** = 0.53, and R_f of **3m** = 0.34; UV_{254} lamp). Chromatography (12% EtOAc/hexanes) afforded pyrrolidine **3m** as a yellow solid (0.045 g, 67%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.70 (s, 1H), 7.95 (d, J = 6.6 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.47−7.41 (m, 4H), 7.37 (t, J = 7.9 Hz, 2H), 5.92 (s, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.40 (q, J = 7.3 Hz, 1H), 2.39−2.32 (m, 1H), 2.05−1.98 (m, 1H), 1.38 (d, J = 7.3 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 202.5, 189.7, 168.6, 168.4, 168.2, 139.8, 139.6, 131.4, 131.1, 128.3 (2C), 128.1, 127.3, 87.2, 79.8, 66.2, 53.5, 53.3, 48.6, 29.3, 14.6, 9.8; IR (thin film) 2969, 1738, 1660, 1614, 1580, 1533, 1445, 1365, 1323, 1304 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{28}NO_6$ $(M + H)^+$ 450.1917, found 450.1915; mp 96−102 °C.

Pyrrolidine-2-ylidene ***3n*** was prepared by general procedure C using N*H*-isoxazoline **1h**[11] (0.9 mL, 0.093 M in CH_2Cl_2, 0.084 mmol, 1.00 equiv), 10 mol % $Sc(OTf)_3$ (0.007 g, 0.015 mmol, 0.10 equiv), and allene **2a**[14] (0.9 mL, 0.131 M in CH_2Cl_2, 0.118 mmol, 1.40 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 18 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1h** = 0.53, and R_f of **3n** = 0.18; UV_{254} lamp). Chromatography (20% EtOAc/hexanes) afforded pyrrolidine **3n** as a yellow solid (0.020 g, 60%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 7.88 (d, J = 7.7 Hz, 2H), 7.45−7.38 (m, 3H), 5.74 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.34 (q, J = 7.3 Hz, 1H), 2.67−2.63 (m, 1H), 2.40−2.34 (m, 1H), 2.25−2.18 (m, 1H), 1.99−1.94 (m, 3H), 1.90−1.77 (m, 2H), 1.33 (d, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 208.7, 189.5, 168.6, 168.4, 167.6, 140.0, 130.9, 128.2, 127.3, 87.1, 79.5, 61.0, 53.4, 53.1, 49.1, 42.6, 33.4, 23.3, 21.9, 14.6; IR (thin film) 2969, 2948, 1738, 1614, 1579, 1531, 1446, 1365, 1228, 1217 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{26}NO_6$ $(M + H)^+$ 400.1760, found 400.1747; mp 146−151 °C.

Pyrrolidine-2-ylidene ***3o*** was prepared by general procedure C using N*H*-isoxazoline **1i**[11] (2.0 mL, 0.098 M in CH_2Cl_2, 0.195 mmol, 1.00 equiv), 10 mol % $Sc(OTf)_3$ (0.010 g, 0.020 mmol, 0.10 equiv), and allene **2a**[14] (4.0 mL, 0.110 M in CH_2Cl_2, 0.439 mmol, 2.25 equiv). The reaction mixture was stirred at 25 °C and monitored by TLC for 18 h (TLC eluent, 30% EtOAc/hexanes; R_f of **1i** = 0.50, and R_f of **3o** = 0.24; UV_{254} lamp). Chromatography (20% EtOAc/hexanes) afforded pyrrolidine **3o** as an orange solid (0.054 g, 47%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.90 (d, J = 7.5 Hz, 2H), 7.44−7.38 (m, 3H), 5.83 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.16 (q, J = 7.3 Hz, 1H), 2.04 (s, 3H), 1.44 (s, 3H), 1.09 (d, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 206.0, 189.7, 168.5, 167.8, 167.2, 139.6, 131.2, 128.3, 127.3, 87.6, 78.6, 60.7, 53.5, 53.4, 47.3, 29.3, 17.9, 10.5; IR (thin film) 2949, 1757, 1731, 1702, 1613, 1578, 1520, 1438, 1378, 1355 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{24}NO_6$ $(M + H)^+$ 374.1604, found 374.1590; mp 133−138 °C.

General Procedure D for the Synthesis of Fused Pyrrolidines 5 from 3. A 20 mL scintillation vial was charged with pyrrolidine **3** (0.700 mmol, 1.00 equiv), DBU (0.910 mmol, 1.30 equiv), and 10 mL of THF to form a 0.07 M solution of **3**. The reaction mixture was stirred at 25 °C for ∼1 h and monitored by TLC using a UV_{254} lamp. Once pyrrolidine **3** was completely consumed, the mixture was concentrated and the resulting crude residue was wet-loaded onto silica gel using CH_2Cl_2 and purified by medium-pressure chromatography (5−15% EtOAc/hexanes) to afford fused pyrrolidines **5**.

Fused Pyrrolidine ***5a*** was prepared by general procedure D using pyrrolidine **3a** (0.743 mmol, 1.00 equiv), DBU (0.966 mmol, 1.30 equiv), and THF (10.0 mL). The reaction mixture was stirred at 25 °C and monitored by TLC for 1 h (TLC eluent, 30% EtOAc/hexanes; R_f of **3a** = 0.32, and R_f of **5a** = 0.63; UV_{254} lamp). Chromatography (5% EtOAc/hexanes) afforded fused pyrrolidine **5a** as a white solid (0.241 g, 77%, dr >20:1). A single crystal suitable for X-ray crystallographic analysis was obtained by recrystallization of this solid in $CHCl_3$ (1.0 mL) with heptane (10 mL) by diffusion at −10 °C. CCDC deposition number 2370375:[15] ^1H NMR (500 MHz, $CDCl_3$) δ 10.61 (s, 1H), 7.96 (d, J = 6.4 Hz, 2H), 7.51−7.42 (m, 6H), 7.40−7.37 (m, 4H), 7.32−7.31 (m, 3H), 6.06 (s, 1H), 5.17 (d, J = 3.5 Hz, 1H), 2.89 (d, J = 3.5 Hz, 1H), 2.36 (s, 3H), 1.67 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 204.1, 189.5, 172.1, 169.0, 142.6, 140.0, 139.8, 131.2, 130.8, 129.4, 129.2, 128.4 (2C), 128.3, 128.0, 127.2, 125.5, 86.9, 63.9, 63.1, 58.1, 23.4, 14.3; IR (thin film) 2968, 1739, 1707, 1624, 1596, 1579, 1538, 1491, 1479, 1456 cm^{-1}; HRMS (ESI) m/z calcd for $C_{29}H_{26}NO_2$ $(M + H)^+$ 420.1964, found 420.1964; mp 202−205 °C.

Fused Pyrrolidine ***5b*** was prepared by general procedure D using pyrrolidine **3b** (0.575 mmol, 1.00 equiv), DBU (0.748 mmol, 1.30 equiv), and THF (8.0 mL). The reaction mixture was stirred at 25 °C and monitored by TLC for 1 h (TLC eluent, 30% EtOAc/hexanes; R_f of **3b** = 0.53, and R_f of **5b** = 0.60; UV_{254} lamp). Chromatography (10% EtOAc/hexanes) afforded fused pyrrolidine **5b** as a yellow solid (0.152 g, 66%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.44−7.41 (m, 2H), 7.39−7.34 (m, 5H), 7.30−7.29 (m, 3H), 5.53 (s, 1H), 5.04 (d, J = 3.67 Hz, 1H), 2.83 (d, J = 3.7 Hz, 1H), 2.28 (s, 3H), 1.59 (s, 3H), 1.23 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.4, 204.3, 172.3, 167.7, 142.8, 139.5, 130.8, 129.4, 129.1, 128.4, 128.3, 127.9, 125.5, 85.6, 63.6, 63.0, 57.9, 41.9, 27.9, 23.5, 14.2; IR (thin film) 2969, 1738, 1704, 1621, 1538, 1482, 1453, 1376, 1269, 1217 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{30}NO_2$ $(M + H)^+$ 400.2277, found 400.2272; mp 62−68 °C.

Fused Pyrrolidine ***5c*** was prepared by general procedure D using pyrrolidine **3f** (0.629 mmol, 1.00 equiv), DBU (0.817 mmol, 1.30 equiv), and THF (9.0 mL). The reaction mixture was stirred at 25 °C and monitored by TLC for 1 h (TLC eluent, 30% EtOAc/hexanes; R_f of **3f** = 0.31, and R_f of **5c** = 0.47; UV_{254} lamp). Chromatography (10% EtOAc/hexanes) afforded fused pyrrolidine **5c** as a white solid (0.225 g, 80%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.51−7.42 (m, 5H), 7.38−7.35 (m, 1H), 7.31−7.29 (m, 4H), 6.92 (d, J = 8.8 Hz, 2H), 6.04 (s, 1H), 5.11 (d, J = 3.5 Hz, 1H), 3.81 (s, 3H), 2.86 (d, J = 3.5 Hz, 1H), 2.35 (s, 3H), 1.68 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 204.2, 189.4, 172.1, 168.8, 159.4, 140.0, 139.8, 134.6, 131.1, 130.8, 129.4, 128.4 (2C), 128.3, 127.2, 126.8, 114.5, 86.8, 63.6, 63.3, 58.2, 55.4, 23.5, 14.3; IR (thin film) 3015, 2969, 1765, 1606, 1576, 1527, 1510, 1477, 1441, 1375 cm^{-1}; HRMS (ESI) m/z calcd for $C_{30}H_{28}NO_3$ $(M + H)^+$ 450.2069, found 450.2075; mp 107−112 °C.

Fused Pyrrolidine ***5d*** was prepared by general procedure D using pyrrolidine **3i** (0.470 mmol, 1.00 equiv), DBU (0.611 mmol, 1.30 equiv), and THF (6.5 mL). The reaction mixture was stirred at 25 °C and monitored by TLC for 1 h (TLC eluent, 30% EtOAc/hexanes; R_f of **3i** = 0.39, and R_f of **5d** = 0.59; UV_{254} lamp). Chromatography (15% EtOAc/hexanes) afforded fused pyrrolidine **5d** as a yellow solid (0.205 g, 93%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.78 (s, 1H), 7.82−7.80 (m, 2H), 7.75 (s, 1H), 7.45−7.39 (m, 10H), 7.34−7.31 (m, 1H), 7.28−7.26 (m, 2H), 6.45−6.44 (m, 1H), 6.34 (s, 1H), 6.27−6.26 (m, 1H), 5.31−5.30 (m, 1H), 2.99−2.99 (m, 1H), 1.97 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 203.5, 189.8, 169.8, 157.5, 149.4, 144.4, 142.7, 140.1, 137.7, 131.9, 131.0, 129.1, 129.0 (2C), 128.7, 128.3, 127.9, 127.2, 125.5, 118.2, 112.9, 87.6, 64.3, 63.5, 57.8, 25.2; IR (thin film) 3143, 1738, 1689, 1609, 1574, 1525, 1498, 1463, 1343, 1307 cm^{-1}; HRMS (ESI) m/z calcd for $C_{32}H_{26}NO_3$ $(M + H)^+$ 472.1913, found 472.1908; mp 199−202 °C.

Fused Pyrrolidine ***5e*** was prepared by general procedure D using pyrrolidine **3j** (0.132 mmol, 1.00 equiv), DBU (0.174 mmol, 1.32 equiv), and THF (2.0 mL). The reaction mixture was stirred at 25 °C and monitored by TLC for 1 h (TLC eluent, 30% EtOAc/hexanes; R_f of **3j** = 0.56, and R_f of **5e** = 0.72; UV_{254} lamp). Chromatography (6% EtOAc/hexanes) afforded fused pyrrolidine **5e** as a yellow solid (0.053 g, 89%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.25 (s,

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J. Org. Chem. 2024, 89, 17804−17812

1H), 7.66 (s, 1H), 7.43−7.38 (m, 7H), 7.31−7.29 (m, 1H), 7.26−7.24 (m, 2H), 6.40−6.39 (m, 1H), 6.22−6.21 (m, 1H), 5.72 (s, 1H), 5.18 (d, J = 3.0 Hz, 1H), 2.93 (d, J = 2.9 Hz, 1H), 1.92 (s, 3H), 1.09 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.8, 203.7, 168.4, 157.9, 149.4, 144.2, 142.9, 137.6, 131.9, 129.1, 129.0, 128.9, 128.6, 127.8, 125.5, 117.8, 112.6, 86.4, 64.1, 63.4, 57.7, 41.9, 27.8, 25.4; IR (thin film) 2963, 1697, 1621, 1586, 1537, 1465, 1339, 1223, 1160, 1122 cm^{-1}; HRMS (ESI) m/z calcd for $C_{30}H_{30}NO_3$ $(M + H)^+$ 452.2226, found 452.2234; mp 65−70 °C.

Deacylation of 3a and Synthesis of 8a. A 20 mL scintillation vial was charged with sodium metal (0.0250 g, 1.09 mmol) and purged with N_2.[24] The vial was cooled to 0 °C with an ice bath, and MeOH (6.0 mL) was added slowly. After being stirred for 15 min, the reaction mixture was allowed to warm to ambient temperature. A second scintillation vial was charged with pyrrolidine **3a** (0.178 g, 0.407 mmol, 1.00 equiv) and MeOH (3.0 mL), and the mixture added in one portion to the freshly prepared NaOMe solution. The reaction mixture was then stirred for 2 h, and the reaction quenched with aqueous NH_4Cl (10 mL). The mixture was diluted with EtOAc (∼75 mL), washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The resulting crude residue was then wet-loaded onto silica gel using (0.5 mL) CH_2Cl_2 and purified by medium-pressure chromatography (10% EtOAc/hexanes), to afford deacylated pyrrolidine **8a** as an orange solid (0.138 g, 86%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.90−7.88 (m, 2H), 7.46−7.38 (m, 6H), 7.31−7.30 (m, 2H), 7.27−7.23 (m, 3H), 6.93−6.91 (m, 2H), 5.79 (s, 1H), 4.94 (d, J = 8.8 Hz, 1H), 3.61 (d, J = 15.2 Hz, 1H), 3.46 (d, J = 15.1 Hz, 1H), 3.41−3.36 (m, 1H), 3.07 (t, J = 8.9 Hz, 1H), 1.17 (d, J = 6.97 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 206.2, 189.3, 169.6, 140.1, 139.8, 132.3, 130.9, 129.5, 129.2, 128.8 (2C), 128.2, 127.4, 127.1, 126.6, 85.6, 66.1, 64.5, 51.7, 43.1, 16.6; IR (thin film) 3260, 1719, 1607, 1577, 1525, 1498, 1481, 1453, 1394, 1366 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{26}NO_2$ $(M + H)^+$ 396.1964, found 396.1971; mp 113−116 °C.

Reduction of Pyrrolidine 8a and Synthesis of 9a.[20a] A 20 mL scintillation vial was charged with deacylated pyrrolidine **8a** (0.130 mmol, 1.00 equiv), $NaBH_3CN$ (0.510 mmol, 3.92 equiv), and 5 mL of MeCN to form a 0.026 M solution. A solution of HCl in MeOH (2.00 mL, 1.00 M) was added dropwise to the mixture, and the mixture allowed to stir at 25 °C for ∼16 h and monitored by TLC (TLC eluent, 25% acetone/pentane; R_f of **8a** = 0.56, and R_f of **9a** = 0.18; UV_{254} lamp). Once **8a** was fully consumed, the reaction was quenched with saturated $NaHCO_3$ (∼10 mL) and the mixture extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (∼25 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The resulting crude residue was wet-loaded onto silica gel using CH_2Cl_2 (0.5−1.0 mL) and purified by medium-pressure chromatography (10−15% acetone/pentane) to afford reduced pyrrolidine **9a** as a yellow oil (0.040 g, 77%, dr 2:1): ^1H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 7.96−7.95 (m, 2H), 7.57−7.54 (m, 1H), 7.47−7.44 (m, 2H), 7.36−7.28 (m, 5H), 7.26−7.20 (m, 3H), 6.95−6.93 (m, 2H), 4.36 (d, J = 8.7 Hz, 1H), 3.69 (td, J = 8.8, 3.2 Hz, 1H), 3.52 (d, J = 15.2 Hz, 1H), 3.41 (d, J = 15.2 Hz, 1H), 3.27 (dd, J = 17.1, 3.2 Hz, 1H), 3.18−3.13 (m, 1H), 2.99 (t, J = 8.7 Hz, 1H), 2.55 (bs, 1H), 2.38−2.31 (m, 1H), 0.98 (t, J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, major diastereomer) δ 208.3, 199.6, 143.4, 137.0, 133.2, 133.1, 129.6, 128.9, 128.6 (2C), 128.1, 127.8, 127.0, 126.6, 67.1, 65.9, 61.4, 51.5, 44.1, 44.0, 16.5; ^1H NMR (500 MHz, $CDCl_3$, minor diastereomer) δ 7.97−7.96 (m, 2H), 7.58−7.55 (m, 1H), 7.48−7.45 (m, 2H), 7.35−7.28 (m, 5H), 7.25−7.21 (m, 3H), 7.00−6.98 (m, 2H), 4.38 (d, J = 8.4 Hz, 1H), 3.92−3.88 (m, 1H), 3.55 (d, J = 15.3 Hz, 1H), 3.47 (d, J = 15.5 Hz, 1H), 3.16−3.14 (m, 2H), 2.80−2.77 (m, 1H), 2.64−2.59 (m, 1H), 2.48 (bs, 1H), 0.98 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, minor diastereomer) δ 208.4, 199.4, 142.8, 137.1, 133.4, 133.2, 129.6, 128.6 (2C), 128.6, 128.0, 127.5, 127.0, 126.6, 66.5, 65.1, 56.2, 51.1, 41.0, 39.4, 16.4; IR (thin film) 2956, 1705, 1681, 1597, 1580, 1531, 1494, 1449, 1404, 1378 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{28}NO_2$ $(M + H)^+$ 398.2120, found 398.2123.

Synthesis of 10a from 8a. Pyrrolidine **10a** was made from **8a** using an adapted literature procedure.[21] In an inert atmosphere glovebox, a 5 mL conical vial was charged with $[RhCp^*Cl_2]_2$ (0.003 g, 0.005 mmol, 11 mol %), AgOAc (0.001 g, 0.006 mmol, 13 mol %), $Cu(OAc)_2$ (0.017 g, 0.094 mmol, 2 equiv), KOAc (0.009 g, 0.092 mmol, 2 equiv), and pyrrolidine **8a** (0.018 g, 0.046 mmol, 1 equiv). The vial was then removed from the glovebox and flushed onto a N_2 manifold with a needle. A solution of methyl acrylate (0.008 g, 0.093 mmol, 2 equiv) in MeOH (2 mL) was added to the solids in one portion. The reaction vial was then capped with a Teflon-lined cap and heated in an oil bath at 90 °C for 16 h. The product mixture was concentrated under vacuum, wet-loaded onto silica gel using CH_2Cl_2 (0.5−1.0 mL), and purified by medium-pressure chromatography (15% EtOAc/hexanes) to afford **10a** as a brown solid (0.012 g, 56%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 7.70−7.69 (m, 2H), 7.68−7.66 (m, 1H), 7.60−7.57 (m, 1H), 7.52−7.49 (m, 2H), 7.38−7.35 (m, 2H), 7.31−7.28 (m, 3H), 7.24−7.23 (m, 3H), 6.89−6.87 (m, 2H), 6.43 (d, J = 9.5 Hz, 1H), 6.02 (s, 1H), 4.23 (q, J = 7.2 Hz, 1H), 3.90 (s, 2H), 3.18 (s, 1H), 1.21 (d, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.3, 193.4, 160.6, 160.5, 142.4, 139.4, 138.5, 132.7, 132.3, 129.6, 129.2, 129.1, 129.0, 128.6, 127.8, 127.6, 125.0, 117.2, 112.3, 65.2, 60.7, 49.0, 42.6, 20.6; IR (thin film) 2922, 1713, 1675, 1638, 1598, 1528, 1495, 1453, 1413, 1318 cm^{-1}; HRMS (ESI) m/z calcd for $C_{30}H_{26}NO_3$ $(M + H)^+$ 448.1915, found 448.1913; mp 47−50 °C.

Reduction of Fused Pyrrolidine 5a to 11a.[20a] A 20 mL scintillation vial was charged with fused pyrrolidine **5a** (0.102 mmol, 1.00 equiv), $NaBH_3CN$ (0.510 mmol, 5.00 equiv), and 2 mL of MeCN to form a 0.05 M solution. A solution of HCl in MeOH (2.00 mL, 1.00 M) was added dropwise, and the reaction mixture was allowed to stir at 25 °C for ∼16 h and monitored by TLC (TLC eluent, 30% EtOAc/hexanes; R_f of **5a** = 0.63, and R_f of **11a** = 0.59; UV_{254} lamp). A second portion of $NaBH_3CN$ (0.150 mmol, 1.50 equiv) was added at 16 h, and the reaction mixture was allowed to stir for an additional 6 h. Once fused pyrrolidine **5a** was fully consumed, the reaction was quenched with saturated $NaHCO_3$ (∼10 mL) and the mixture extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (∼25 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The resulting crude residue was wet-loaded onto silica gel using CH_2Cl_2 (0.5−1.0 mL) and purified by medium-pressure chromatography (6% EtOAc/hexanes) to afford **11a** as a beige solid (0.034 g, 78%, dr >20:1): ^1H NMR (500 MHz, $CDCl_3$) δ 8.03−8.02 (m, 2H), 7.63−7.58 (m, 3H), 7.52−7.49 (m, 2H), 7.44−7.41 (m, 2H), 7.35−7.31 (m, 5H), 7.26−7.23 (m, 1H), 4.26 (d, J = 7.4 Hz, 1H), 3.66 (d, J = 2.7 Hz, 1H), 3.44−3.33 (m, 2H), 2.66 (d, J = 7.4 Hz, 1H), 2.14 (s, 3H), 1.51 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.5, 199.0, 173.7, 143.1, 138.3, 136.9, 133.6, 131.4, 129.4, 128.8, 128.4, 128.3, 128.1, 127.8, 127.2, 127.0, 66.6, 62.2, 60.2, 54.6, 41.5, 19.8, 14.3; IR (thin film) 2919, 1738, 1696, 1678, 1631, 1597, 1579, 1491, 1446, 1401 cm^{-1}; HRMS (ESI) m/z calcd for $C_{29}H_{28}NO_2$ $(M + H)^+$ 422.2120, found 422.2111; mp 109−112 °C.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01976.

Experimental details for starting materials made by known procedures, mechanistic experiments, spectral data, and crystallographic data (PDF)

Accession Codes

Deposition Numbers 2370375 and 2390522 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge

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J. Org. Chem. 2024, 89, 17804−17812

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Notes

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