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A Cascade Reaction of Cinnamyl Azides with Acrylates Directly Generates Tetrahydro-Pyrrolo-Pyrazole Heterocycles

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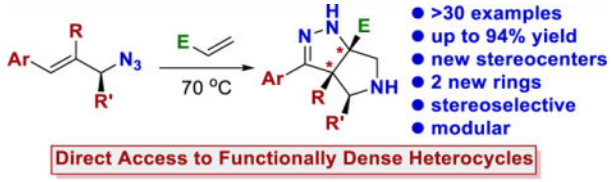
Abstract

Developing reactions to generate complex and modular building blocks in a concise and direct fashion remains a contemporary synthetic challenge. This work describes a stereo-selective cascade reaction between allylic azides and acrylates that directly generates tetrahydro-pyrrolo-pyrazole ring systems. These products contain up to four contiguous stereocenters, two of which may be tetrasubstituted carbon atoms attached to a nitrogen atom. Over 30 examples are provided with an average isolated yield of 71% (ranging from 40% to 94%). The reaction was easily scaled to use more than one gram of starting material, and the products can be readily diversified.

Graphical Abstract



INTRODUCTION

Nitrogen-containing heterocycles are ubiquitous in pharmaceuticals, agrochemicals, and natural products.[1,2] Often, saturated heterocycles provide particularly advantageous properties.[3–7] Specifically, substituted tetrahydro-pyrrolo-pyrazole heterocycles are known to be biologically active with a variety of potential applications (Figure 1).[8–12] A direct and efficient synthesis of these functionally dense heterocycles from simple starting materials would be empowering.[13,14] Classically, tetrahydro-pyrrolo-pyrazole heterocycles are generated through cycloaddition of a diazo species with activated maleimide derivatives.[8,10]

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Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00535.
Crystallographic data for compound **2hh** (CIF)
Crystallographic data for compound **5a** (CIF)
Crystallographic data for compound **5bb** (CIF)
Crystallographic data for compound **5v·HCl** (CIF)
Optimization procedures and tables; NMR spectra of all new compounds; HPLC traces; X-ray data (PDF)

The authors declare no competing financial interest.

More recently, Zard demonstrated that hydrazones with pendant alkenes can be oxidized to the corresponding diazo species, which subsequently undergoes an intramolecular cycloaddition (Scheme 1a).[15] Jahn demonstrated that a domino *aza*-Michael reaction can afford similar heterocycles using *n*-BuLi and NfN_3.[16,17]

Recently, our lab has been developing synthetic methods that leverage the unique properties of allylic azides. We showed that allylic azides can react selectively at either the alkene[18–20] or azide[21] functional group. These results led us to ask if a reaction could synergistically utilize both functional groups. We were encouraged to find an example of such a reaction. Yang reported a cycloaddition cascade with cinnamyl azide and methyl acrylate to form tetrahydro-pyrrolo-pyrazole hetero-cycles (Scheme 1b).[22,23] We were excited to build upon these reports. Unfortunately, neither report provided full experimental details. Our attempts to replicate the procedure using cinnamyl azide afforded a low yield (82% reported, less than 15% obtained). We speculated that this cascade could be a powerful tool if a more reproducible procedure could be developed and if the scope of this reaction was expanded.

This report provides a reoptimized and fully documented procedure that affords tetrahydro-pyrrolo-pyrazole hetero-cycles in high yields from simple cinnamyl azides. The substrate scope of Yang's reaction is expanded to include (i) secondary and tertiary azides, (ii) cinnamyl azides substituted at the α or β carbon, (iii) the use of an enantioenriched azide, (iv) additional Michael acceptors, and (v) derivatization of the products (Scheme 1c).

RESULTS AND DISCUSSION

This study began by examining the thermally promoted cascade sequence between methyl acrylate and cinnamyl azide using the conditions originally reported by Yang (Table 1).[22,23] Yang's experimental procedure states that cinnamyl azide (5M in THF) was mixed with methyl acrylate (1 or 2 equiv) at room temperature for a time ranging between several hours to a few days.[23] In our hands, the room-temperature reaction with 1 equiv of methyl acrylate did not fully consume the azide after 3 days (Table 1). Several intermediates and byproducts could be identified and quantified (**2a**–**4a**). A yield below 25% was observed, even if both observable tautomers of the desired product (**3a** and **5a**) are combined. The reaction with cinnamyl azide **1a** was extensively screened, and in no case did we observe a yield exceeding 70% (see Supporting Information, Tables S1−S3). These observations prompted a reoptimization of this cascade reaction.

Qualitatively, the cascade reaction appeared to proceed more efficiently with a cinnamyl azide featuring a polarizing aryl substituent. This was true regardless of if the substituent is commonly thought of as an electron-donating (e.g., OMe) or -withdrawing (e.g., NO_2) group (*vide infra*). The substrate 2-nitrocinnamyl azide (**1b**) was selected for optimization along with methyl acrylate due to the availability of 2-nitrocinnamaldehyde (Table 2). Solvents with a range of polarities were examined (entries 1–5). Polar solvents promoted the conjugate addition that formed product **4b** (entries 1 and 2), while less polar solvents suppressed the conjugate addition (entries 4 and 5). The observation that the formation of product **4b** could be suppressed in less polar media is consistent with the need to form ionic intermediates during conjugate addition. When hexane was used, a significant amount of the

conjugate addition was observed because the product was insoluble in hexane, resulting in a reaction that was pseudoneat in methyl acrylate (entry 3).

Having identified THF and benzene as the optimal solvents, several additives were examined. The addition of acetic acid or HFIP promoted the conjugate addition (entries 6 and 7). Prior work from L'abbe indicated that the triazoline to diazo-ester equilibrium could be facilitated by the addition of an amine base (*vide infra*).[24,25] Thus, the addition of an amine base proved most effective at converting triazoline intermediate **2b** to the desired product (entries 8–14). Given the complications associated with conjugate addition (e.g., polymerization of acrylate and over addition), it is perhaps unsurprising that DMAP and pyridine provided poor results and that less nucleophilic amine bases were preferred. Ultimately, conditions utilizing DIPEA in benzene (entry 11) were chosen as the optimal conditions. Toluene and THF were suitable alternative solvents (entries 12–14). It is worth noting that, at the end of the reaction, the desired product typically existed as a mixture of the two tautomers **3b** and **5b**. TFA was added during the workup to convert the mixture into the more stable conjugated tautomer **5b**. In some instances, silica gel and DBU were also able to promote tautomerization (see Table 7 in Experimental Section). When compared to Yang's original conditions, this reoptimization reflects a change in the (i) solvent, (ii) concentration, (iii) temperature, (iv) equivalents of acrylate, (v) time, and (vi) addition of DIPEA. The optimized reaction conditions work well with a variety of cinnamyl azides (Table 3). Compound **5b** was isolated in 94% yield under the reoptimized conditions. The product from cinnamyl azide (**5a**) was crystalline, and diffraction analysis confirmed the structure (see Supporting Information). While the 64% yield of product **5a** observed was a significant improvement over the data shown in Table 1, it was still lower than the yield originally reported by Yang.[22,23] Other cinnamyl azides containing electron-donating groups (**5c**, **5d**, and **5h**) and electron-withdrawing groups (**5f**, **5g**, and **5i**) were tolerated. Substrates with *ortho* substitution were tolerated (**5b**, **5h**, and **5i**). Lastly, products with an electron-rich heteroarene (**5j** and **5k**) or an electron-deficient heteroarene (**5l**−**5n**) were isolated in good yields. As previously noted, substrates with polarizing groups on the arene appeared to be better suited for this cascade, with some of the highest yields observed for products **5b** and **5h** as well as 5k and 5l. Recent attention has been focused on developing reactions that are effective with heterocycles,[26,27] and the ability of this cascade to generate products **5j**−**5n** under identical conditions should be considered an attribute.

The substrate scope was further expanded (Table 4). A methyl or a phenyl group could be incorporated adjacent to the azide (**5o** and **5p**). For product **5o**, a minor diastereomer was observed that could arise from the *Z*-alkene isomer. An *E/Z* alkene isomerization could be occurring under the reaction conditions via the Winstein rearangement.[28−30] The relative configuration of product **5p** was assigned based on a crystal structure (see Supporting Information), and that of product **5o** was assigned by analogy to product **5p**. A minor diastereomer was not detected for compound **5p**. Tertiary azide 1q afforded product **5q**. A methyl group could be incorporated at the α or β position relative to the arene, affording compounds **5r** and **5s**. In both cases, a minor diastereomer was not detected. The relative configuration of compound **5s** was assigned by 2D NMR and is consistent with the alkene geometry of the starting material as would be expected for a cycloaddition. The trans

relationship between the methyl and hydrogen on starting azide **1s** should be maintained in the product if the reaction proceeds through a concerted cycloaddition. A branched allylic azide was suitable and afforded product **5t**, which demonstrated that a cinnamyl azide was not necessary. Product **5t** is noteworthy because significant eclipsing interactions likely exist between the bridgehead substituents. Furthermore, a cyclic azide afforded tricyclic products (**5u**− **5w**). A proximal arene was not required for the reaction to proceed, and product **5w** was derived from unsaturated ester **1w**.

A single enantiomer of azide **1v** (>99:1 er) was utilized (Scheme 2).[30] Product **5v** could be isolated as a single diastereomer with no loss in enantiomeric purity (>99:1 er). A crystal structure of (±)−**5v·HCl** was obtained to confirm its identity and relative stereochemistry (see Supporting Information). This represents a tremendous amplification of stereochemical complexity. Azide **1v** contains only a single stereocenter. Product **5v** contains four contiguous stereo-centers, three of which are generated from this cascade reaction. Two stereocenters are formed at tetrasubstituted carbon atoms that bear a nitrogen substituent, which are known to be particularly challenging stereocenters to establish.[13,31]

The reaction was investigated with other Michael acceptors (Table 5). Simple acrylates provided high yields, and ethyl (**5x**), *tert*-butyl (**5y**), and benzyl (**5z**) esters were isolated. The selective formation of cinnamate 5aa is interesting because the putative α-diazoester intermediate selectively engaged one of the two pendant alkenes. The use of methyl or benzyl crotonate afforded products **5bb** and **5cc** in high yields and modest dr's. The relative configuration of compound **5bb** was determined by X-ray diffraction analysis, and the relative configuration of product **5cc** was assigned by analogy to product **5bb**. The use of methyl vinyl ketone afforded exclusively the product of conjugate addition (**4dd**, see Experimental Section). To prevent this, TsCl and DMAP were added to trap the initial adduct prior to conjugate addition, which allowed the isolation of product 5dd. Other Michael acceptors including acrylamide (**5ee**), acrylonitrile (**5ff**), and diethyl vinyl phosphonate (**5gg**) were also effective as partners in this cascade reaction. This provides access to a diverse array of functional groups via this cascade.

A plausible mechanism for this cascade reaction and side product formation is shown in Scheme 3. This proposal is based on the work of L'abbe[24,25] and Yang.[22,23] The cascade is thought to proceed via an initial Huisgen cycloaddition to afford triazoline **2**.[24,25,32−36] This cycloaddition generally proceeds with good selectivity, but the regioisomeric triazoline **2′** was frequently observed (~5%).[24] When diethyl vinyl phosphonate was used as the Michael acceptor, triazoline **2gg′** was a significant byproduct (ca. 1:1). In some cases, the triazoline was stable to isomerization with a base and could be isolated. A crystal structure of one triazoline, derived from *N*-phenylmaleimide, was obtained to verify the structure (see Supporting Information).

Triazoline **2** can equilibrate to achiral diazo species **6**.[24,37] Amine bases facilitate this equilibrium.[24,25] The role of the amine is most likely to deprotonate at the α position of the ester. The resulting ammonium salt then can facilitate proton transfer to the distal nitrogen, leading to fragmentation and forming diazo compound **6**. Intermediate **6** can undergo an intramolecular cycloaddition between the diazo and alkene to afford compound **3**.[22,23]

Alternatively, in the presence of excess acrylate, diazo **6** can intercept a second equivalent of acrylate to form product **7**.[22,23,38,39] To mitigate this side product, a second procedure was developed for products where the intramolecular cyclization was slow (Table 4). The triazoline was preformed by mixing the azide and acrylate neat at room temperature. Excess acrylate was removed in vacuo. Then, the triazoline was heated in the presence of DIPEA in C_6H_6, which triggered the remainder of the cascade.

When compound **3** contains a hydrogen atom at the benzylic position, it can tautomerize to generate conjugated product **5.**[22,23] This tautomerization was readily accomplished with TFA or DBU during workup (see Experimental Section for details). When the benzylic position was tetrasubstituted, product **3** was isolated. Cyclopropane **8** was observed as a side product in a low yield for substrate **1j**. This product likely arises from intermediate **3** via the loss of nitrogen.[22,40] Lastly, products **3** and **5** are sufficiently nucleophilic to engage excess acrylate in a conjugate addition, affording compound **4**.[22,23] As shown in the optimization above (Table 2), less polar solvents generally minimized the conjugate addition by destabilizing ionic intermediates.

Conducting the cascade reaction in the presence of various electrophiles was a productive means to extend the cascade process (Table 6). The addition of Boc_2O (**9a**), TsCl (**9b**), TrCl (**9c**), and CbzCl (**9d**) all afforded derivatized products directly in good yields. When TrCl was used, the product was initially isolated as a mixture of tautomers. Tautomerization of this mixture was slower than for other substrates, and it was promoted by exposure to 0.5 equiv of DBU, after which only the conjugated isomer was observed by ^{1}H NMR.

The cascade cyclization could be conducted on a gram scale without any decrease in efficiency (Scheme 4). Each of the functional groups present in product **5b** could be selectively derivatized. The nitro group could be selectively reduced to afford aniline **10**. The ester present in product **5** could be reduced to afford alcohol **11** or hydrolyzed to acid **12**. The pyrrolidine nitrogen could be alkylated, arylated, or acylated to afford products **9d**, **13**, and **14**, respectively. Lastly, the hydrazine motif could be acylated, yielding compound **15**. These results clearly highlight how the dense functionality present on the tetrahydro-pyrrolo-pyrazole core can be selectively elaborated and diversified.

CONCLUSION

In conclusion, cinnamyl azides and Michael acceptors can engage in a modular cascade cyclization to directly generate fused tetrahydro-pyrrolo-pyrazole heterocycles. The reaction proceeds on an array of coupling partners. Furthermore, the products can be derivatized *in situ*. This reaction rapidly amplifies the complexity of two trivial starting materials and directly affords functionally dense bicyclic amine building blocks. This cascade is modular and amenable to diversification.

EXPERIMENTAL SECTION

Azide Safety.

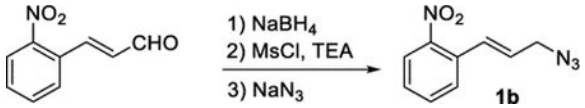
Azides are known to be high-energy materials, and explosions have been reported when working with azides. In the course of this work, no issues were encountered. The majority of the azides synthesized in this report have C/N ratios equal to or above the recommended guideline of 3. Those with C/N ratios below 3 were prepaired on a small scale and extra precution was used when handeling them. Precautionary safety shields were used for all reactions using or producing more than 1 mmol of azide. Safety shields were used both in the fume hood and during rotary evaporation. All waste and aqueous solution that could be contaminated with azide anin were kept in individually labeled containers and were kept STRICTLY free of acid to avoid the accidental production on HN_3: DO NOT use aqueous HCl during the workup in any of reaction that could result in HN_3 formation. Further reading on azide safety is available.[41–43]

Methods and Reagents.

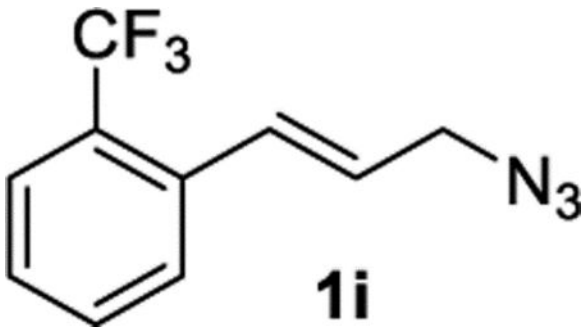
All reactions conducted at the elevated temperature used aluminum heating blocks with magnetic stirring bars (200 rpm). Reported temperatures were based on an external thermal couple. All commercially available chemicals were used without further purification. Dry tetrahydrofuran (THF), toluene, and methylene chloride were obtained from a commercial solvent system utilizing activated alumina columns under a positive pressure of argon. Thin-layer chromatography (TLC) was used for monitoring reaction progress. Visualization was conducted by using UV light, $KMnO_4$, or PMA stains. Organic solutions were concentrated using a rotary evaporator under reduced pressure at or below 40 °C. Flash chromatography was performed on a Teledyne Isco CombiFlash R_f system utilizing normal phase precolumn load cartridges and gold high-performance columns. Structural assignments were made with additional information from COSY, HSQC, and HMBC experiments. All proton (^{1}H) nuclear magnetic resonance spectra were recorded at 400 or 500 MHz. All carbon (^{13}C) nuclear magnetic resonance spectra were recorded at 101 or 126 MHz. The fluorine (^{19}F) nuclear magnetic resonance spectra were recorded at 376 MHz with proton decoupling. Chemical shifts are expressed in parts per million and are referenced to residual solvent ($CDCl_3$: 7.26 ppm), to the central carbon in the NMR solvent ($CDCl_3$: 77.2 ppm). Data is presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, and m = multiplet), integration, and coupling constant in hertz (Hz). Infrared (IR) spectra were taken in a Nicolet Nexus 670 FT-IR with salt plates. IR spectra were reported in cm^{-1}. Enantiomeric excesses were determined using a Shimadzu HPLC with a PDA detector and RegisPack 5 Micron column or Regis Reflect column (C-Amylose A; 3 μ, 250 mm × 4.6 mm).

Azide Synthesis.

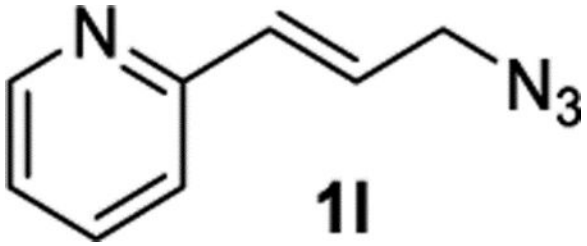
The following cinnamyl azides were prepared through known procedures and have been previously characterized: **1a**,[44,45] **1c–1d,**[44,45] **1e–1f**,[44,46] **1g**,[44,47] **1h**,[18,44] **1j–1k**,[44,47] **1o**,[44,45] **1p–1q**,[44] **1t**,[46,48,49] **1u–1v**,[30] **1w**,[49–51] and **1hh**.[18,44]



2-Nitrocinnamylazide (1b).—To a solution of 2-nitrocinnamalde-hyde (1.02 g, 5.77 mmol) in MeOH (13 mL) in an ice bath was added slowly $NaBH_4$ (257 mg, 6.80 mmol). After 45 min, the reaction was quenched by the addition of H_2O (25 mL), and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude material (1.20 g) was used without further purification. Characterization data for 2-nitrocinnamyl alcohol has been reported.[52] The crude oil was reconstituted in DCM (20 mL) and cooled in an ice bath, and TEA (1.6 mL, 12 mmol) was added, followed by the dropwise addition of MsCl (0.67 mL, 8.7 mmol). After 1.5 h, the reaction was quenched by the addition of water and extracted with DCM (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was dissolved in acetone (5 mL) at rt, and an aqueous solution of NaN_3 (5 mL, 1.9 M, 9.4 mmol) was added. After 18 h, the reaction was diluted with water and extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Final purification by column chromatography (EtOAc in hexanes, gradient elution 0–5%) afforded compound **1b** (962 mg, 82% over three steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.4 Hz, 1H), 7.68–7.57 (m, 2H), 7.51–7.41 (m, 1H), 7.18 (d, J = 15.6 Hz, 1H), 6.22 (dt, J = 15.6, 6.4 Hz, 1H), 4.04 (d, J = 6.3 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.8, 133.3, 132.0, 129.9, 129.0, 128.7, 127.9, 124.7, 52.6. IR (NaCl, thin film, cm^{-1}): 3072, 2927, 2850, 2094, 1524, 1344, 964. HRMS (CITOF): *m/z* [M + NH_4]$^+$ calcd for $C_9H_{12}N_5O_2^+$, 222.0986; found, 222.0978.

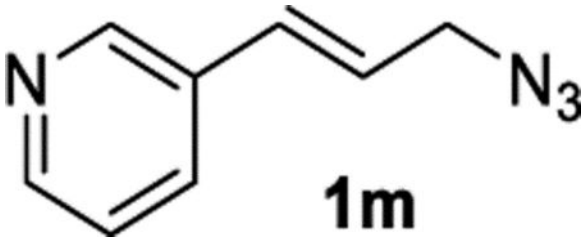


2-Trifluoromethylcinnamyl Azide (1i).—The preparation of compound **1i** was adapted from a known procedure.[44] Purification by column chromatography (gradient EtOAc/hexane from 0–40%) afforded compound **1i** in 53% yield (603 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.08 (d, J = 15.6 Hz, 1H), 6.24 (dt, J = 15.6, 6.5 Hz, 1H), 4.00 (d, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 135.2 (q, J_{C-F} = 1.8 Hz), 132.0, 130.4 (q, J_{C-F} = 2.1 Hz), 127.8, 127.64, 127.63 (q, J_{C-F} = 30.1 Hz), 126.9, 125.8 (q, J_{C-F} = 5.7 Hz), 124.2 (q, J_{C-F} = 274.9 Hz), 52.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −59.4. IR (NaCl, thin film, cm^{-1}): 3063, 2198, 2104, 1314, 1160, 1125, 765. HRMS (CI-TOF): *m/z* [M + NH_4]$^+$ calcd for $C_{10}H_{12}F_3N_4^+$, 245.1009; found, 245.1000.



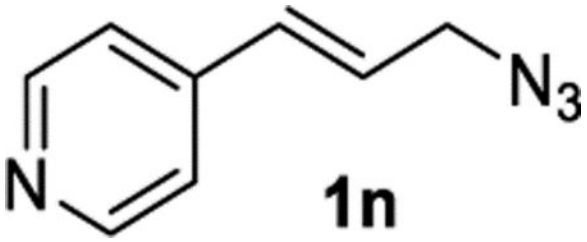
1l

(E)-2-(3-Azidoprop-1-en-1-yl)pyridine (1l).—The preparation of compound **1l** was adapted from a known procedure.[44] Purification by column chromatography (gradient EtOAc/hexane from 0–50%) afforded compound **1l** in 46% yield (369 mg) as a yellow oil. Note that cinnamyl azide **1l** is not stable in storage at an ambient temperature and should be used immediately or stored in a freezer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 4.8 Hz, 1H), 7.67 (td, J = 7.7, 1.8 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.19 (dd, J = 7.4, 4.9 Hz, 1H), 6.84–6.70 (m, 2H), 4.03 (d, J = 5.0 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.4, 149.7, 136.6, 133.4, 127.1, 122.7, 122.0, 52.5. IR (NaCl, thin film, cm^{-1}): 3000, 2918, 2209, 1585, 1470, 1431, 975. HRMS (CI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_8H_9N_4^{+}$, 161.0822; found, 161.0821.



1m

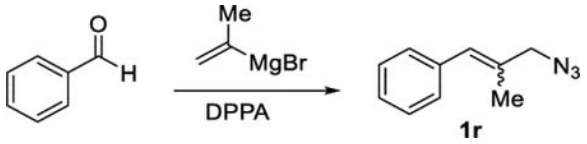
(E)-3-(3-Azidoprop-1-en-1-yl)pyridine (1m).—The preparation of compound **1m** was adapted from a known procedure.[44] Purification by column chromatography (gradient EtOAc/hexane from 0–70%) afforded compound **1m** in 34% yield (272 mg) as a yellow oil. Note that cinnamyl azide **1m** is not stable in storage at ambient temperature and should be used immediately or stored in a freezer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.56–8.50 (m, 1H), 7.77–7.71 (m, 1H), 7.32–7.25 (m, 1H), 6.67 (d, J = 15.8 Hz, 1H), 6.33 (dtd J = 15.4, 6.3 Hz, 1H), 4.01 (d, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.2, 148.5, 133.1, 131.7, 130.7, 125.0, 123.5, 52.8. IR (NaCl, thin film, cm^{-1}): 3031, 2102, 1416, 1243, 971. HRMS (CI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_8H_9N_4^{+}$, 161.0822; found, 161.0821.



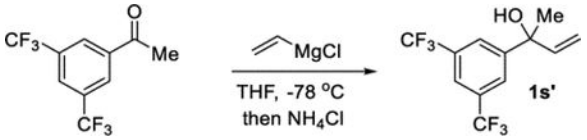
1n

(E)-4-(3-Azidoprop-1-en-1-yl)pyridine (1n).—The preparation of compound **1n** was adapted from a known procedure.[44] Purification by column chromatography (DCM in

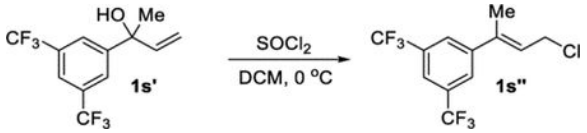
hexanes, gradient elution 0–70%) afforded compound **1n** in 62% yield (498 mg) as a yellow oil. Note that cinnamyl azide **1n** is not stable in storage at ambient temperature and should be used immediately or stored in a freezer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 6.2 Hz, 2H), 7.28 (d, J = 6.2 Hz, 2H), 6.63 (d, J = 15.9 Hz, 1H), 6.46 (dt, J = 15.9, 6.1 Hz, 1H), 4.03 (d, J = 6.1, 1.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 150.3, 143.3, 131.5, 127.6, 121.0, 52.5. IR (NaCl, thin film, cm^{-1}): 3029, 2106, 1596, 1415, 974. HRMS (CI-TOF): m/z [M + H]$^{+}$ calcd for $C_8H_9N_4^{+}$, 161.0822; found, 161.0821.



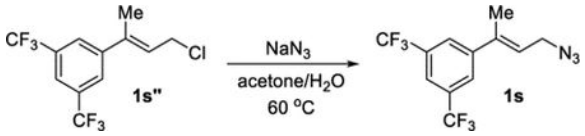
(3-Azido-2-methylprop-1-en-1-yl)benzene (1r).—The preparation of compound **1r** was adapted from a known procedure.[44] Purification by column chromatography (gradient EtOAc/hexane from 0–20%) afforded compound **1r** in 60% yield (519 mg) as a colorless oil with an *E/Z* ratio of 85:15. The major product of the obtained material provided an identical ^{1}H NMR spectrum.



2-(3,5-Bis(trifluoromethyl)phenyl)but-3-en-2-ol (1s′).—An oven-dried flask was equipped with a stir bar, fitted with a septum, sealed under argon, charged with THF (20 mL), and vinyl magnesium chloride (3.80 mL, 1.6 M in THF, 6.1 mmol). The solution was cooled in an acetone/dry ice bath. Dropwise addition of 3′,5′-bis(trifluoromethyl)acetophenone (0.90 mL, 5.0 mmol) to the flask was conducted over 5 min. The reaction was gradually warmed to an ambient temperature. After 16 h, the reaction was quenched by the addition of water (20 mL). The resulting solution was diluted with water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (EtOAc in hexanes, gradient elution 0– 40%) afforded target compound **1s′** as a colorless oil (360 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 2H), 7.80 (s, 1H), 6.17 (dd, J = 17.3, 10.6 Hz, 1H), 5.79 (d, J = 17.3 Hz, 1H), 5.28 (d, J = 10.6 Hz, 1H), 2.15 (br, 1H), 1.72 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.1, 143.3, 131.5 (q, J_{C-F} = 33.4 Hz), 125.6 (m), 123.4 (q, J_{C-F} = 273.9 Hz), 121.0 (sept, J_{C-F} = 4.0 Hz), 114.3, 74.4, 29.5. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): −62.8. IR (NaCl, thin film, cm^{-1}): 3406, 2917, 1374, 1278, 1174, 1134. HRMS (ESI-TOF): *m/z* [M]$^{+}$ calcd for $C_{12}H_{10}F_6O^{+}$, 284.0630; found, 284.0629.

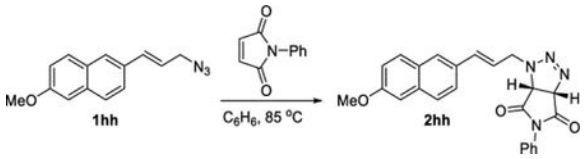


(E)-1-(4-Chlorobut-2-en-2-yl)-3,5-bis(trifluoromethyl)benzene (1s″).—The synthesis of compound **1s″** was adapted from a known method with slight modification.[53] An oven-dried flask was equipped with a stir bar, fitted with a septum, sealed under argon, and charged with compound **1s′** (281 mg, 1.00 mmol) and DCM (5 mL). The solution was cooled in an ice bath. The dropwise addition of thionyl chloride (0.29 mL, 4.0 mmol) to the flask was conducted over 5 min. The reaction was gradually warmed to an ambient temperature. After 16 h, the reaction was quenched by the addition of water (5 mL). The resulting solution was diluted with water (10 mL) and extracted with DCM (3 × 15 mL). The combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (hexanes as eluant) afforded target compound **1s″** as a colorless oil (107 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 2H), 7.82 (s, 1H), 6.12 (tq, J = 7.9, 1.4 Hz, 1H), 4.30 (d, J = 7.9 Hz, 2H), 2.21 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.3, 138.2, 131.8 (q, $J_{C–F}$ = 33.3 Hz), 126.2, 126.0 (m), 123.3 (q, $J_{C–F}$ = 273.7 Hz), 121.3 (sept, $J_{C–F}$ = 3.8 Hz), 40.1, 15.8. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): −62.9. IR (NaCl, thin film, cm^{-1}): 2950, 1380, 1280, 1182, 1132, 898. HRMS (EITOF): *m/z* [M − Cl]$^+$ calcd for $C_{12}H_9F_6^+$, 267.0603; found, 267.0598.



(E)-1-(4-Azidobut-2-en-2-yl)-3,5-bis(trifluoromethyl)benzene (1s).—A flask was charged with compound **1s″** (171 mg, 0.592 mmol) and acetone (1 mL) and equipped with a stir bar. An aqueous solution of sodium azide (1.0 mL, 0.96 M, 0.96 mmol) was added to the reaction at an ambient temperature. The flask was equipped with a condenser, and the reaction was heated to 60 °C. After 3 h, the reaction was cooled and diluted with water (5 mL). The resulting solution was extracted with EtOAc (3 × 15 mL). The combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (EtOAc in hexanes, gradient elution 0–40%) afforded target compound 1s as a colorless oil (148 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 2H), 7.83 (s, 1H), 6.01 (tq, J = 7.2, 1.4 Hz, 1H), 4.01 (d, J = 7.1 Hz, 2H), 2.19 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.4, 138.5, 131.8 (q, $J_{C–F}$ = 33.4 Hz), 126.0, 124.0, 123.3 (q, $J_{C–F}$ = 273.8 Hz), 121.3 (sept, $J_{C–F}$ = 3.8 Hz), 48.5, 16.3. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): −62.9. IR (NaCl, thin film, cm^{-1}): 2292, 2103, 1380, 1280, 1179, 1132. HRMS (CI-TOF): *m/z* [M − N_2 + H]$^+$ calcd for $C_{12}H_{10}F_6N^+$, 282.0712; found, 282.0705.

Formation of Triazoline 2b.



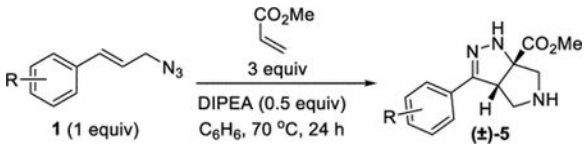
(3aS,6aR)-1-((E)-3-(6-Methoxynaphthalen-2-yl)allyl)-5-phenyl-3a,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(1H,5H)-dione (2hh).—A 4 mL vial was charged with azide **1hh** (119.4 mg, 0.500 mmol), N-phenylmaleimide (86.6 mg, 0.500 mmol), and benzene (0.5 mL). The vial was sealed and heated to 85°C. After 24 h, the reaction was cooled. The crude solid was collected using a Hirsch funnel and washed with hexanes (3 × 2 mL). This afforded compound 2hh as a white solid (179.5 mg, 81%). ^{1}H NMR (400 MHz, CDCl3): δ 7.78–7.67 (m, 3H), 7.59 (dd, J = 8.6, 1.8 Hz, 1H), 7.53–7.41 (m, 3H), 7.32–7.26 (m, 2H), 7.21–7.12 (m, 2H), 6.91 (d, J = 15.8 Hz, 1H), 6.31 (ddd, J = 15.7, 8.6, 5.4 Hz, 1H), 5.69 (d, J = 10.9 Hz, 1H), 5.02 (dd, J = 15.1, 5.4 Hz, 1H), 4.56 (d, J = 11.0 Hz, 1H), 4.52 (dd, J = 15.2, 8.6 Hz, 1H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CD3CN): δ 171.9, 170.7, 158.0, 134.5, 134.3, 131.82, 131.79, 129.5, 129.2, 129.0, 128.9, 127.2, 126.9, 126.4, 124.1, 122.7, 119.0, 106.0, 82.4, 58.2, 55.0, 51.2. IR (NaCl, thin film, cm^{-1}): 2935, 1723, 1600, 1477, 1378, 1178. HRMS (ESI-TOF): m/z [M − N2 + H]$^{+}$ calcd for $C_{24}H_{20}N_4NaO_3^{+}$, 435.1428; found, 435.1433.

Reaction Optimization.

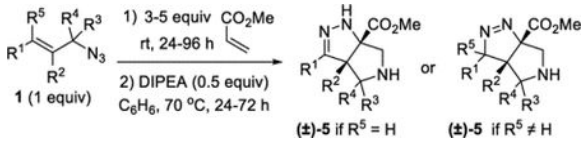
Procedure for Table 1.—A stock solution of azide 1a (87.8 mg, 0.552 mmol) and naphthalene (18.8 mg, 0.147 mmol, internal standard) was prepared in THF (0.10 mL). Individual 4 mL vials were charged with 30 μL portions of this solution and methyl acrylate (10 or 20 μL). The vials were sealed under air at rt. After 72 h, the reactions were concentrated under reduced pressure and analyzed by ^{1}H NMR. All of the reactions were run in duplicate, and the average values are reported.

Procedure for Table 2 (Solvent Screening Procedure).—A stock solution of azide **1b** (197 mg, 0.964 mmol) and naphthalene (54.9 mg, 0.429 mmol, internal standard) was prepared in DCM (455 μL). Individual 4 mL vials were charged with 50 μL portions of this solution, and the DCM was evaporated. The respective solvent (370 μL) was added to each vial, followed by methyl acrylate (20 μL, 0.22 mmol). The vials were sealed under air and heated to 70 °C. After 24 h, the reactions were cooled to ambient temperature, and TFA (28 μL) was added. After 10 min, each reaction was diluted with K_2CO_3 (sat. aq 1 mL) and EtOAc (1 mL). The phases were separated, and the organic layer was analyzed by GC-FID to determine the yield. All of the reactions were run in duplicate, and the average values are reported.

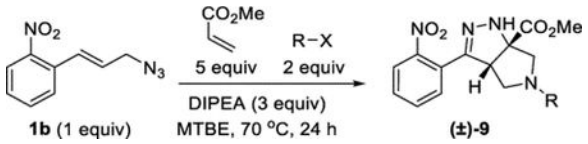
Procedure for Table 2 (Additive Screening Procedure).—A stock solution of azide **1b** (263 mg, 1.29 mmol), methyl acrylate (0.35 mL, 3.9 mmol), and naphthalene (166 mg, 1.30 mmol, internal standard) was prepared in benzene (6.5 mL). Individual 4 mL vials were charged with 380 μL portions of this solution. One additive (0.5 equiv) was added individually to each vial. The vials were sealed under air and heated to 70 °C. After 24 h, the reactions were cooled to an ambient temperature, and TFA (28 μL) was added. After 10 min, each reaction was diluted with a saturated K_2CO_3 aqueous solution (1 mL) and EtOAc (1 mL). The phases were separated, and the organic layer was analyzed by GC-FID to determine percent yields. All of the reactions were run in duplicate, and the average values are reported.



General Procedure I.—Procedure for the single-step synthesis of tetrahydro-pyrrolo-pyrazoles, example given for R = 2-NO_2. A 20 mL vial was sequentially charged with azide **1b** (81.7 mg, 0.400 mmol, 1 equiv), benzene (2.0 mL), methyl acrylate (0.11 mL, 1.2 mmol, 3 equiv), and DIPEA (35 μL, 0.20 mmol, 0.5 equiv). The vial was sealed with a Teflon-lined cap and heated to 70 °C. After 24 h, the reaction was cooled to an ambient temperature, and the solvent was removed under reduced pressure. The reaction was reconstituted in DCM (2 mL), and TFA (0.15 mL, 2.0 mmol, 5 equiv) was added. (Note that the treatment with TFA helped promote the tautomerization to the hydrazone. This step was not necessary; however, skipping it resulted in a mixture of tautomers.) After 5 min, the solvent was removed under reduced pressure. Final purification by column chromatography (IPA in DCM with 1% TEA, gradient elution 0–10%) afforded compound **5b** (109 mg, 93%) as an orange oil.

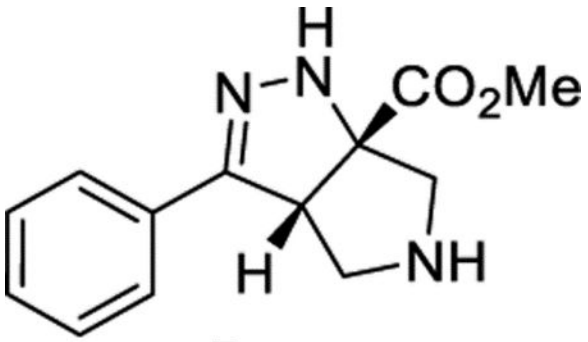


General Procedure II.—Procedure for the two operation synthesis of tetrahydro-pyrrolo-pyrazoles, example given for R^1 = Ph, R^2 = Me, R^3 = R^4 = R^5 = H. A 4 mL vial was charged with azide **1r** (86.8 mg, 0.501 mmol, 1 equiv) and methyl acrylate (0.23 mL, 2.5 mmol, 5 equiv). The vial was sealed with a Teflon-lined cap, and the reaction was stirred at an ambient temperature. After 48 h, the reaction was transferred to a 20 mL vial and then concentrated under reduced pressure at an ambient temperature. The residual methyl acrylate was removed under a high vacuum for 15 min. The crude triazoline was reconstituted in benzene (2.0 mL), and DIPEA (44 μL, 0.25 mmol, 0.5 equiv) was added. The vial was sealed with a Teflon-lined cap and heated to 70 °C. After 24 h, the reaction was cooled, and the solvent was removed under reduced pressure. Final purification by column chromatography (IPA in DCM with 1% TEA, gradient elution 0– 10%) afforded compound 5r (91.0 mg, 70%) as a colorless oil.



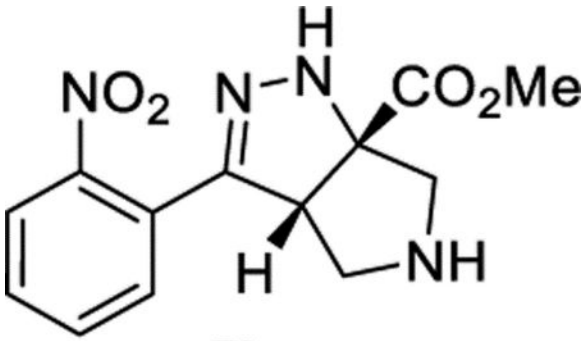
General Procedure III.—Procedure for the single-step synthesis of the N-protected tetrahydro-pyrrolo-pyrazoles, example given for R–X = Boc_2O and R = Boc. A 20 mL vial was charged with azide **1b** (61.0 mg, 0.30 mmol, 1 equiv) and MTBE (1.5 mL). Di-*tert*-butyl dicarbonate (0.14 mL, 0.61 mmol, 2 equiv) was added to the reaction, followed by methyl acrylate (0.14 mL, 1.5 mmol, 5 equiv) and DIPEA (0.16 mL, 0.92 mmol, 3 equiv). The vial was sealed with a Teflon-lined cap, and the reaction was heated to 70 °C. After 24 h, the

reaction was cooled to an ambient temperature, and the mixture was diluted with water (5 mL). The resulting solution was extracted with DCM (3 × 20 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (EtOAc in hexanes, gradient elution 0–100%) afforded target compound 9a as a yellow solid (92.9 mg, 80%).



5a

Methyl (3aS,6aS)-3-Phenyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]-pyrazole-6a(1H)-carboxylate (5a).—General Procedure I was used, and the product was isolated in 66% (83.3 mg) and 61% (77.9 mg) yields in duplicate trials. An average of 64% is reported. The material provided similar ^{1}H NMR as previously reported.[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.58 (m, 2H), 7.40–7.30 (m, 3H), 6.57 (br, 1H), 4.20 (dd, J = 7.0, 3.6 Hz, 1H), 3.80 (s, 3H), 3.34–3.26 (m, 3H), 3.17 (d, J = 12.1 Hz, 1H), 2.50 (br, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.2, 153.5, 131.5, 129.2, 128.9, 126.3, 81.5, 61.6, 58.6, 54.8, 53.1. IR (NaCl, thin film, cm^{-1}): 3317, 2951, 1732, 1679, 1446, 1272, 1219. HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{13}H_{15}N_3NaO_2^+$, 268.1056; found, 268.1059.

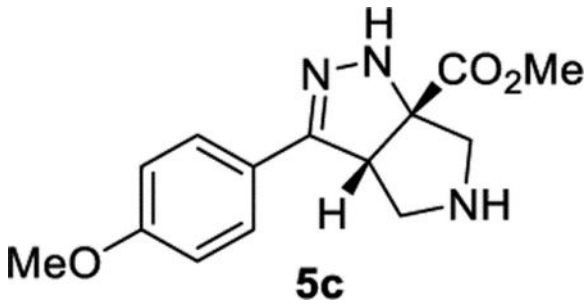


5b

Methyl (3aS,6aS)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo-[3,4-c]pyrazole-6a(1H)-carboxylate (5b).—General Procedure I was used, and the product was isolated in 93% (109 mg) and 94% (108 mg) yields in duplicate trials. The average of 94% is reported. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.81–7.72 (m, 1H), 7.69–7.60 (m, 1H), 7.57–7.47 (m, 2H), 6.78 (br, 1H), 4.21 (dd, J = 7.9, 2.1 Hz, 1H), 3.85 (s, 3H), 3.29 (d, J = 12.1 Hz, 1H), 3.24 (dt, J = 12.5, 1.9 Hz, 1H), 3.18–3.10 (m, 2H), 2.25 (br, 1H). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ 173.5, 149.1, 149.0, 132.2, 129.7, 129.4, 126.2, 124.1, 81.2,

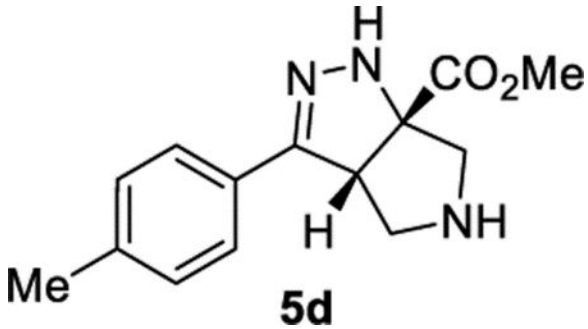
61.4, 60.0, 53.9, 52.9. IR (NaCl, thin film, cm^{-1}): 3338, 2950, 1736, 1729, 1528, 1273. HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{13}H_{15}N_4O_4^+$, 291.1088; found, 291.1089.

Gram-Scale Synthesis of 5b.—A 100 mL round-bottom flask was equipped with a stir bar and charged with azide **1b** (1.02 g, 5.00 mmol), methyl acrylate (1.36 mL, 15.0 mmol, 3 equiv), and benzene (25 mL). DIPEA (0.44 mL, 2.5 mmol, 0.5 equiv) was added to the flask, and the flask was sealed with a glass stopper. The reaction was heated to 70 °C. After 24 h, the reaction was cooled, and TFA (1.9 mL, 25 mmol) was added to the flask. After 5 min, the solvent was removed under reduced pressure. Final purification by column chromatography (IPA in DCM with 1% TEA, gradient elution 0– 10%) afforded compound **5b** (1.41 g, 97%) as an orange oil. A duplicate trial afforded compound **5b** (1.06 g, 92%). The average of 95% is reported.



5c

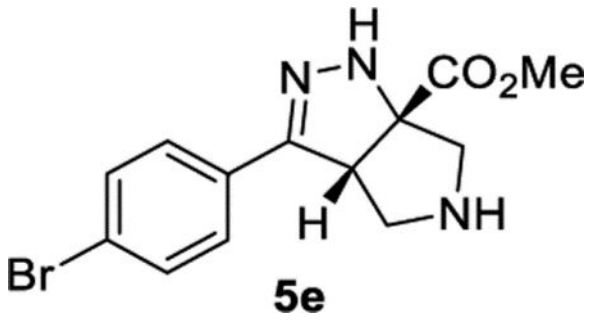
Methyl (3aS, 6aS)-3-(4-Methoxyphenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5c).—General Procedure I was used, and the product was isolated in 79% (112 mg) and 84% (118 mg) yields in duplicate trials. The average of 82% is reported. ^{1}H NMR (500 MHz, C_6D_6): δ 7.58 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.55 (br, 1H), 3.97 (apparent t, J = 5.3 Hz, 1H), 3.26 (s, 3H), 3.18 (s, 3H), 3.07 (br, 2H), 3.04–3.00 (m, 2H), 1.74 (br, 1H). ^{13}C{^{1}H} NMR (126 MHz, C_6D_6): δ 173.8, 160.2, 152.2, 128.0, 125.0, 114.0, 81.5, 61.5, 58.7, 54.6, 54.5, 51.8. IR (NaCl, thin film, cm^{-1}): 3323, 2953, 2840, 1731, 1672, 1608, 1516, 1253, 1220, 1176, 1037. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{17}N_3NaO_3^+$, 298.1162; found, 298.1161.



5d

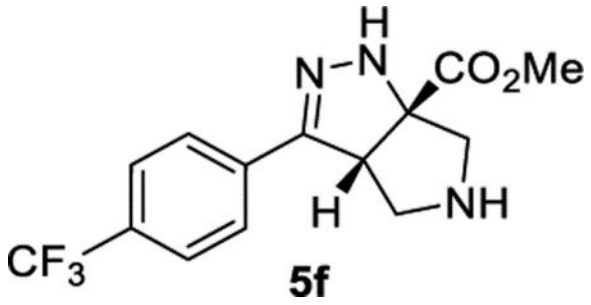
Methyl (3aS,6aS)-3-(p-Tolyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]-pyrazole-6a(1H)-carboxylate (5d).—General Procedure I was used, and the product was isolated in 72% (103 mg) and 74% (116 mg) yields in duplicate trials. The average of 73% is reported. ^{1}H NMR (500 MHz, C_6D_6): δ 7.57 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 7.9 Hz, 2H), 6.59 (br, 1H),

3.98 (apparent t, J = 5.3 Hz, 1H), 3.18 (s, 3H), 3.05 (br, 2H), 3.00 (d, J = 5.3 Hz, 2H), 2.07 (s, 3H), 1.67 (br, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 174.1, 153.6, 139.2, 129.4, 128.6, 126.2, 81.2, 61.4, 58.5, 54.6, 53.0, 21.4. IR (NaCl, thin film, cm^{-1}): 3324, 2952, 2873, 1731, 1436, 1272, 1220, 1039. HRMS (ESITOF): *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}N_3O_2^+$, 260.1394; found, 260.1397.



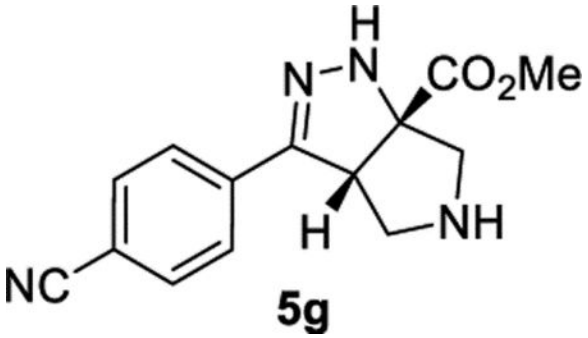
5e

Methyl (3aS,6aS)-3-(4-Bromophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5e).—General Procedure I was used, and the product was isolated in 67% (86.9 mg) and 71% (90.4 mg) yields in duplicate trials. The average of 69% is reported. ^{1}H NMR (500 MHz, C_6D_6): δ 7.25–7.19 (m, 4H), 6.58 (br, 1H), 3.79 (dd, J = 8.1, 2.4 Hz, 1H), 3.19 (s, 3H), 3.02 (br, 2H), 2.90 (dd, J = 12.3, 8.0 Hz, 1H), 2.82 (dd, J = 12.4, 2.5 Hz, 1H), 2.09 (br, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, C_6D_6): δ 173.4, 151.0, 131.6 (tentatively assigned as 2C), 131.0, 122.5, 81.6, 61.3, 57.9, 54.3, 51.8. IR (NaCl, thin film, cm^{-1}): 3324, 2951, 1730, 1491, 1399, 1271, 1220, 1070. HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{13}H_{15}BrN_3O_2^+$, 324.0342; found, 324.0342.



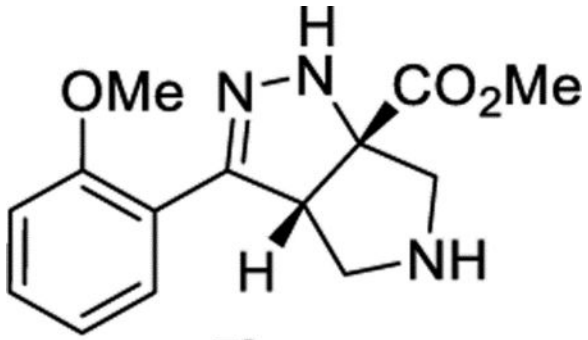
5f

Methyl (3aS,6aS)-3-(4-(Trifluoromethyl)phenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5f).—General Procedure I was used, and the product was isolated in 78% (103 mg) and 80% (98.6 mg) yields in duplicate trials. The average of 79% is reported. ^{1}H NMR (400 MHz, C_6D_6): δ 7.39 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.63 (br, 1H), 3.81 (dd, J = 8.0, 2.4 Hz, 1H), 3.21 (s, 3H), 3.01 (br, 2H), 2.92 (dd, J = 12.3, 8.0 Hz, 1H), 2.81 (dd, J = 12.3, 2.5 Hz, 1H), 1.70 (br, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, C_6D_6): δ 173.3, 150.4, 135.5, 131.2 (q, J_{C-F} = 271.8 Hz), 129.7 (q, J_{C-F} = 32.5 Hz), 126.0, 125.3 (q, J_{C-F} = 3.8 Hz), 81.9, 61.4, 57.8, 54.3, 51.9. $^{19}F\{^{1}H\}$ NMR (471 MHz, $CDCl_3$): δ −62.72. IR (NaCl, thin film, cm^{-1}): 3305, 2955, 1732, 1327, 1274, 1220, 1165, 1120, 1068. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{14}H_{14}F_3N_3NaO_2^+$,336.0930; found, 336.0927.



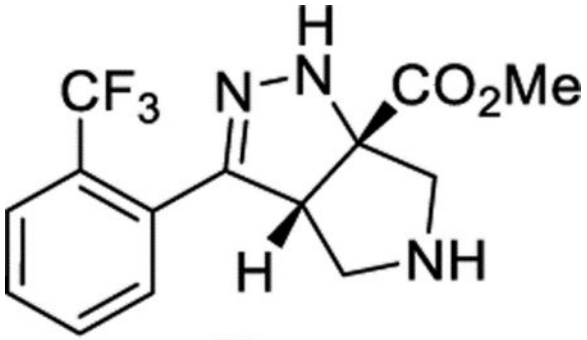
5g

Methyl (3aS,6aS)-3-(4-Cyanophenyl)-3a,4,5,6-tetrahydropyrrolo-[3,4-c]pyrazole-6a(1H)-carboxylate (5g).—General Procedure I was used, and the product was isolated in 76% (104 mg) and 77% (103 mg) yields in duplicate trials. The average of 77% is reported. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.75–7.69 (m, 2H), 7.69–7.65 (m, 2H), 6.82 (br, 1H), 4.20 (dd, J = 8.0, 2.5 Hz, 1H), 3.82 (s, 3H), 3.38–3.22 (m, 3H), 3.20 (d, J = 12.1 Hz, 1H), 2.19 (br, 1H). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ 173.6, 150.8, 136.1, 132.4, 126.2, 118.7, 111.6, 82.0, 61.3, 57.8 54.4, 52.8. IR (NaCl, thin film, cm^{-1}): 3331, 3050, 2954, 2226, 1728, 1606, 1579, 1435, 1274, 1220. HRMS (ESI-TOF): *m/z* [M + Na]$^{+}$ calcd for $C_{14}H_{14}N_4NaO_2^{+}$, 293.1009; found, 293.1010.



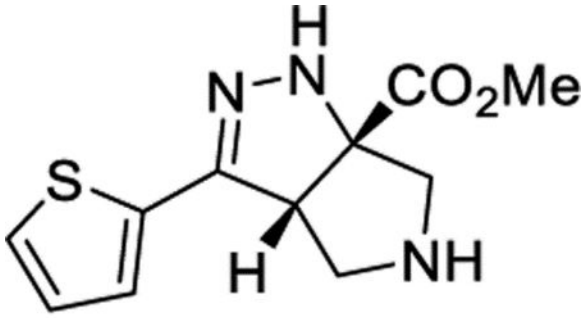
5h

Methyl (3aS,6aS)-3-(2-Methoxyphenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5h).—General Procedure I was used, and the product was isolated in 88% (121 mg) and 79% (109 mg) yields in duplicate trials. The average of 84% is reported. ^{1}H NMR (500 MHz, C_6D_6): δ 8.26 (dd, J = 7.9, 1.7 Hz, 1H), 7.02 (td, J = 7.8, 1.7 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.72 (br, 1H), 6.44 (d, J = 8.3 Hz, 1H), 4.50 (dd, J = 8.5, 2.6 Hz, 1H), 3.93 (br, 1H), 3.30–3.19 (m, 3H), 3.23 (s, 3H), 3.18–3.09 (m, 1H), 3.14 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, C_6D_6): δ 173.7, 156.6, 151.1, 129.9, 129.3, 121.0, 120.9, 111.4, 80.3, 60.5, 60.0, 54.5, 54.4, 51.9. IR (NaCl, thin film, cm^{-1}): 3318, 2950, 1737, 1688, 1680, 1599, 1245, 1200, 1130. HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{14}H_{18}N_3O_3^{+}$, 276.1343; found, 276.1340.



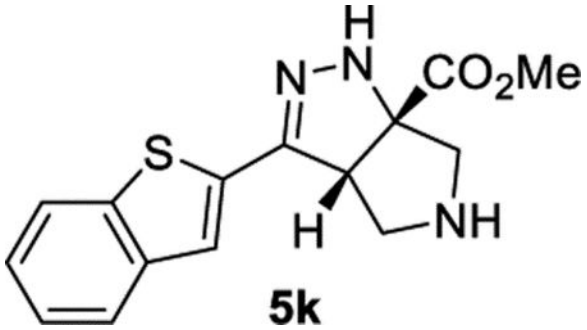
5i

Methyl (3aS,6aS)-3-(2-(Trifluoromethyl)phenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5i).—General Procedure I was used, and the product was isolated in 76% (95 mg), 56% (70 mg), and 56% (74 mg) yields in triplicate trials. The average of 63% is reported. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.77 (d, J = 7.2 Hz, 1H), 7.63 (t, J = 7.1 Hz, 1H), 7.57–7.50 (m, 2H), 6.74 (br, 1H), 4.25 (dd, J = 7.6, 2.6 Hz, 1H), 3.86 (s, 3H), 3.29 (d, J = 12.0 Hz, 1H), 3.20–3.05 (m, 3H), 2.21 (br, 1H). 13C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ 173.8, 151.4, 131.9, 131.6 (q, J_{C-F} = 2.1 Hz), 130.5, 128.8, 128.1 (q, J_{C-F} = 30.8 Hz), 126.8 (q, J_{C-F} = 5.6 Hz), 124.1 (q, J_{C-F} = 274.4 Hz), 81.0, 62.0, 61.4, 53.6, 52.8. ^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ −58.7. IR (NaCl, thin film, cm^{-1}): 3329, 2956, 2877, 1729, 1601, 1436, 1312, 1274, 1217, 1170, 1127, 1035, 766. HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{14}H_{15}F_3N_3O_2^{+}$, 314.1111; found, 314.1112.



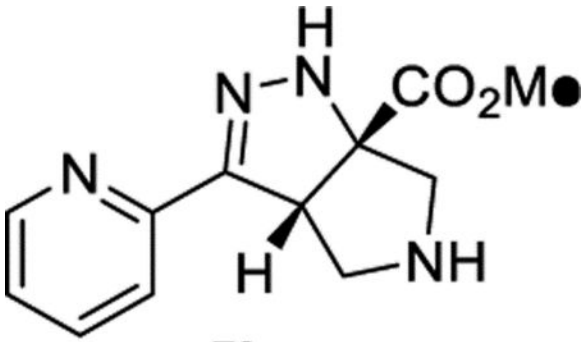
5j

Methyl (3aS,6aS)-3-(Thiophen-2-yl)-3a,4,5,6-tetrahydropyrrolo-[3,4-c]pyrazole-6a(1H)-carboxylate (5j).—General Procedure I was used, and the product was isolated in 70% (88.7 mg) and 77% (95.8 mg) yields in duplicate trials. The average of 74% is reported. ^{1}H NMR (400 MHz, CD_3CN): δ 7.38 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 3.5 Hz, 1H), 7.04 (dd, J = 4.9, 3.8 Hz, 1H), 6.61 (br, 1H), 4.17 (dd, J = 7.5, 3.0 Hz, 1H), 3.76 (s, 3H), 3.30–3.20 (m, 2H), 3.18 (d, J = 11.9 Hz, 1H), 3.13 (d, J = 12.1 Hz, 1H).1.30 (br, 1H). ^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 173.4, 148.3, 136.0, 127.6, 126.6, 126.5, 80.9, 60.3, 58.9, 53.6, 52.4. IR (NaCl, thin film, cm^{-1}): 3277, 2952, 1731, 1659, 1433, 1413, 1271, 1220. HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{11}H_{14}N_3O_2S^{+}$, 252.0801; found, 252.0805.



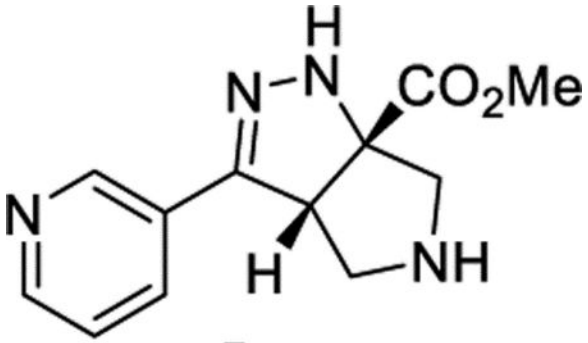
5k

Methyl (3aS,6aS)-3-(Benzo[b]thiophen-2-yl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5k).—General Procedure I was used, and the product was isolated in 74% (89.4 mg) and 85% (103 mg) yields in duplicate trials. The average of 80% is reported. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.86–7.72 (m, 2H), 7.44–7.32 (m, 2H), 7.28 (s, 1H), 6.67 (br, 1H), 4.26 (dd, J = 8.0, 2.2 Hz, 1H), 3.84 (s, 3H), 3.46 (d, J = 12.2 Hz, 1H), 3.41–3.28 (m, 2H), 3.21 (d, J = 12.1 Hz, 1H), 2.28 (br, 1H). ^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2): δ 173.6, 149.2, 139.8, 139.7, 136.0, 125.3, 124.6, 123.8, 122.8, 122.2, 82.0, 61.4, 59.0, 54.6, 52.8. IR (NaCl, thin film, cm^{-1}): 3304, 2936, 1725, 1414, 1266, 1210, 836. HRMS (ESI-TOF): m/z [M + H]$^{+}$ calcd for $C_{15}H_{16}N_3O_2S^{+}$, 302.0958; found, 302.0956.



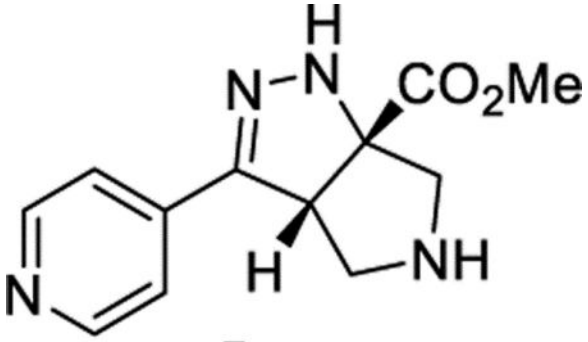
5l

Methyl (3aS,6aS)-3-(Pyridin-2-yl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5l).—General Procedure I was used, and the product was isolated in 93% (115 mg) and 84% (104 mg) yields in duplicate trials. The average of 89% is reported. ^{1}H NMR (500 MHz, C_6D_6): δ 8.34 (d, J = 4.8 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.02 (td, J = 7.8, 1.7 Hz, 1H), 6.77 (br, 1H), 6.60–6.52 (m, 1H), 4.52 (dd, J = 7.9, 2.6 Hz, 1H), 3.44–3.31 (m, 2H), 3.14 (s, 3H), 3.09 (d, J = 12.0 Hz, 1H), 3.05 (d, J = 12.0 Hz, 1H), 1.98 (br, 1H). ^{13}C{^{1}H} NMR (126 MHz, C_6D_6): δ 173.7, 153.6, 151.9, 148.8, 135.4, 122.3, 120.6, 81.0, 61.3, 58.8, 552, 51.7. IR (NaCl, thin film, cm^{-1}): 3272, 2950, 1743, 1680, 1437, 1284, 1202, 1133. HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{12}H_{15}N_4O_2^{+}$, 247.1190; found, 247.1197.



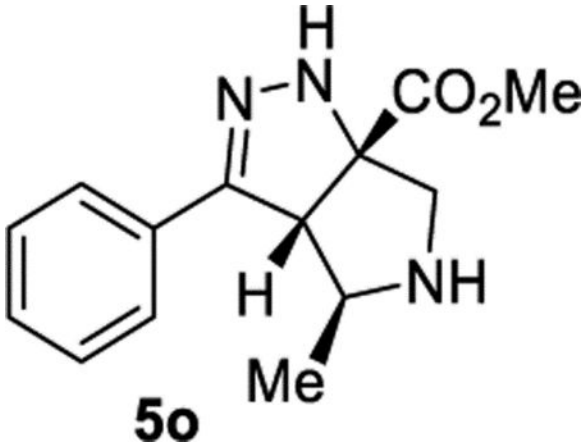
5m

Methyl (3aS,6aS)-3-(Pyridin-3-yl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5m).—General Procedure I was used, and the product was isolated in 72% (88.0 mg) and 63% (76.4 mg) yields in duplicate trials. The average of 68% is reported. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.80 (dd, J = 2.3, 0.9 Hz, 1H), 8.54 (dd, J = 4.8, 1.7 Hz, 1H), 7.96 (ddd, J = 8.0, 2.3, 1.7 Hz, 1H), 7.31 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 6.78 (br, 1H), 4.22 (dd, J = 7.9, 2.6 Hz, 1H), 3.81 (s, 3H), 3.38–3.23 (m, 3H), 3.19 (d, J = 12.2 Hz, 1H), 2.42 (br, 1H). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ 173.8, 150.1, 149.5, 147.3, 132.9, 127.7, 123.4, 81.5, 61.2, 58.0, 54.3, 52.8. IR (NaCl, thin film, cm^{-1}): 3308, 2953, 1730, 1591, 1434, 1274, 1221. HRMS (ESITOF): m/z [M + H]$^{+}$ calcd for $C_{12}H_{15}N_4O_2^{+}$, 247.1190; found, 247.1189.



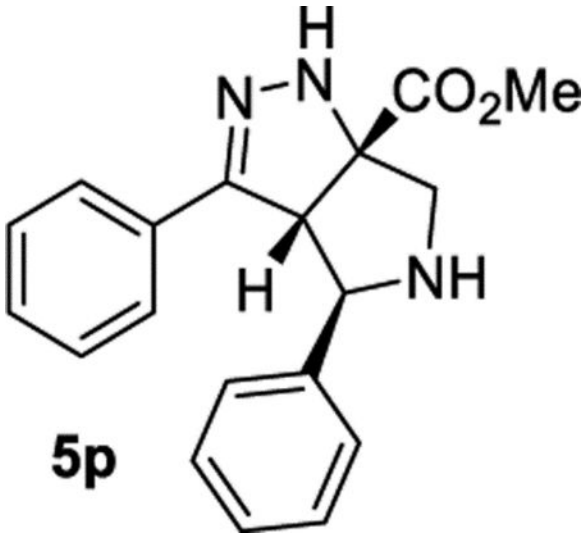
5n

Methyl (3aS,6aS)-3-(Pyridin-4-yl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5n).—General Procedure I was used, and the product was isolated in 70% (86.7 mg), 49% (61.1 mg), and 61% (74.7 mg) yields in triplicate trials. The average of 60% is reported. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.59 (d, J = 6.2 Hz, 2H), 7.46 (d, J = 6.2 Hz, 2H), 6.88 (br, 1H), 4.19 (dd, J = 7.9, 2.6 Hz, 1H), 3.82 (s, 3H), 3.37–3.23 (m, 3H), 3.20 (d, J = 12.1 Hz, 1H), 2.52 (br, 1H). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ 173.5, 150.2, 150.1, 138.9, 119.9, 81.9, 61.3, 57.6, 54.3, 52.8. IR (NaCl, thin film, cm^{-1}): 3295, 2954, 2923, 1732, 1599, 1434, 1415, 1275, 1219. HRMS (ESITOF): m/z [M + H]$^{+}$ calcd for $C_{12}H_{15}N_4O_2^{+}$, 247.1190; found, 247.1189.



5o

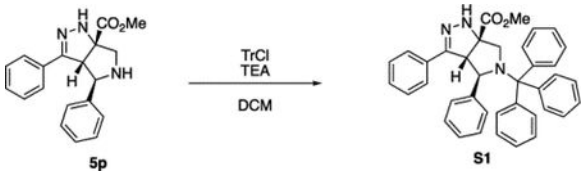
Methyl (3aS,4S,6aS)-4-Methyl-3-phenyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5o).—General Procedure II was used, and the product was isolated in 63% and 46% yields. The average of 55% is reported. The dr was determined by crude ^{1}H NMR to be 8.81:1 and 8.71:1 in duplicate trials. The average dr of 8.8:1 was reported. Final purification by column chromatography (gradient IPA/acetone from 0 to 40%) afforded the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.60 (m, 2H), 7.43–7.33 (m, 3H), 6.58 (br, 1H), 3.86 (d, J = 2.6 Hz, 1H), 3.84 (s, 3H), 3.57 (qd, J = 6.9, 2.6 Hz, 1H), 3.46 (d, J = 12.3 Hz, 1H), 3.26 (d, J = 12.3 Hz, 1H), 2.45 (br, 1H), 1.42 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.1, 153.1, 131.6, 129.1, 128.7, 126.1, 82.3, 65.0, 61.7, 58.6, 53.1, 21.1. IR (NaCl, thin film, cm^{-1}): 3319, 2961, 1731, 1445, 1271, 1227. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{17}N_3NaO_2^+$, 282.1213; found, 282.1202.



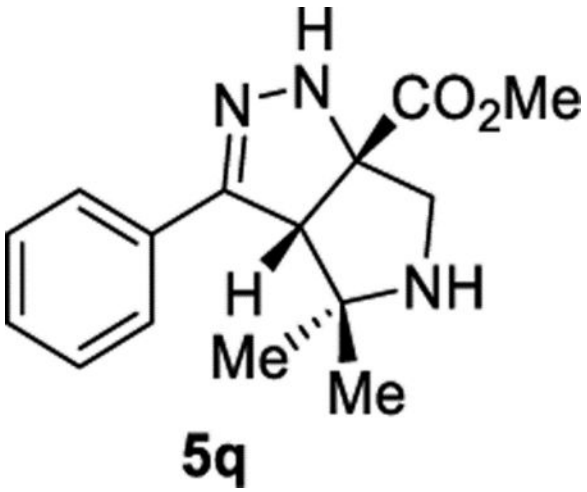
5p

Methyl (3aS,4R,6aS)-3,4-Diphenyl-3a,4,5,6-tetrahydropyrrolo-[3,4-c]pyrazole-6a(1H)-carboxylate (5p).—General Procedure I was used, and the reaction time was 48 h. Final purification by column chromatography (IPA in hexanes with 1% TEA, gradient elution 10– 40%) afforded product 5p in 48% (59.2 mg) and 48% (58.5 mg) yields

in duplicate trials. The average of 48% is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54–7.49 (m, 4H), 7.42 (apparent t, J = 7.5 Hz, 2H), 7.39–7.34 (m, 1H), 7.33–7.26 (m, 3H), 6.66 (br, 1H), 4.52 (d, J = 4.0 Hz, 1H), 4.40 (d, J = 4.0 Hz, 1H), 3.87 (s, 3H), 3.59 (d, J = 12.1 Hz, 1H), 3.31 (d, J = 12.1 Hz, 1H) 2.77 (br, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.0, 153.0, 142.2, 131.4, 129.1, 128.9, 128.6, 127.7, 127.3, 126.5, 82.5, 69.7, 64.2, 59.5, 53.1. IR (NaCl, thin film, cm^{-1}): 3333, 3031, 2953, 1732, 1446, 1274, 1225. HRMS (ESITOF): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{19}N_3NaO_2^+$, 344.1369; found, 344.1364.



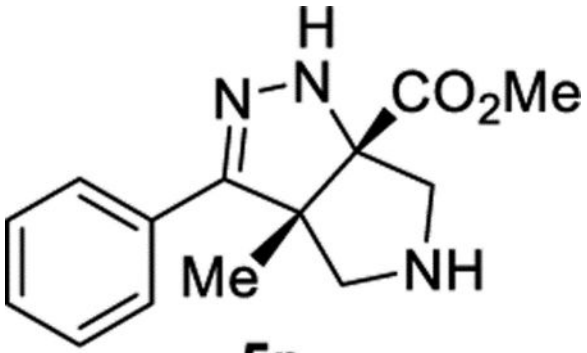
Methyl (3aS,4R,6aS)-3,4-Diphenyl-5-trityl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (S1).—To a solution of compound 5p (160 mg, 0.498 mmol) in DCM (3 mL) was added TEA (0.14 mL, 1.0 mmol) and TrCl (168 mg, 0.602 mmol) at rt. After 6 h, the reaction was quenched by the addition of H_2O and extracted with DCM. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Final purification by recrystallization in EtOAc/hexanes (ca. 1:5) afforded compound S1 (194 mg, 69%) as a white solid. ^{1}H NMR (500 MHz, C_6D_6) δ 7.71 (d, J = 7.5 Hz, 2H), 7.39 (d, J = 7.8 Hz, 6H), 7.04–6.98 (m, 4H), 6.98–6.94 (m, 3H), 6.94–6.90 (m, 7H), 6.88–6.83 (m, 3H), 5.31 (s, 1H), 4.46 (s, 1H), 3.62 (d, J = 10.5 Hz, 1H), 3.46 (d, J = 10.6 Hz, 1H), 3.07 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, C_6D_6) δ 172.7, 151.9, 144.0, 143.6, 132.3, 129.8, 129.2, 128.5, 128.4, 128.3, 127.3, 127.1, 126.5, 125.8, 77.1, 73.9, 67.3, 64.1, 58.4, 51.9. IR (NaCl, thin film, cm^{-1}): 3058, 3031, 2952, 1727, 1690, 1597, 1491, 1448, 1265, 1221. HRMS (ESI-TOF): m/z $[M - CH_3]^+$ calcd for $C_{37}H_{30}N_3O_2^+$, 548.2333; found, 548.2297.



5q

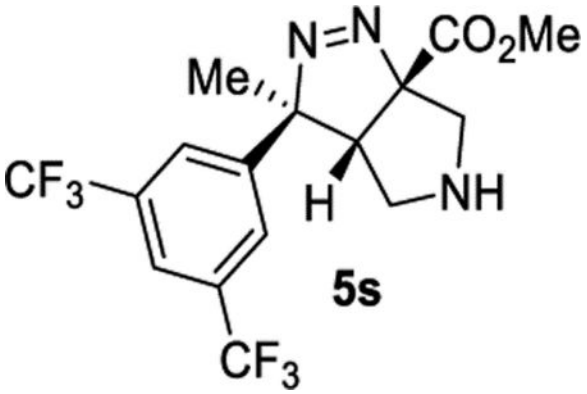
Methyl (3aS,6aS)-4,4-Dimethyl-3-phenyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5q).—General Procedure I was used and the reaction time was 72 h. The product was isolated in 82% (113 mg) and 70% (95.4 mg) yields in

duplicate trials. The average of 76% is reported. ^{1}H NMR (400 MHz, CD_3CN): δ 7.69–7.61 (m, 2H), 7.44–7.32 (m, 3H), 6.79 (br, 1H), 3.91 (s, 1H), 3.76 (s, 3H), 3.37 (d, J = 12.5 Hz, 1H), 3.12 (d, J = 12.5 Hz, 1H), 2.33 (br, 1H), 1.35 (s, 3H), 0.94 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 174.2, 151.9, 133.4, 128.5, 128.4, 126.1, 84.9, 66.1, 66.0, 56.0, 52.4, 28.3, 25.2. IR (NaCl, thin film, cm^{-1}): 3331, 2962, 1730, 1446, 1270, 1241. HRMS (ESI-TOF): *m/z* [M + Na]$^{+}$ calcd for $C_{15}H_{19}N_3NaO^{+}_2$, 296.1369; found, 296.1366.



5r

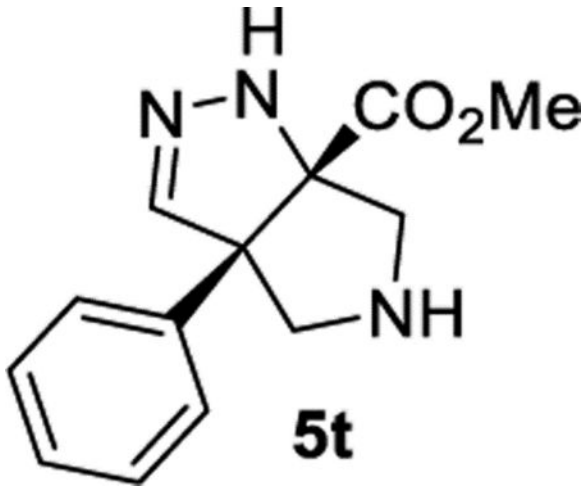
Methyl (3aS,6aS)-3a-Methyl-3-phenyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5r).—General Procedure II was used, and the product was isolated in 70% (91.0 mg) and 57% (73.1 mg) yields in duplicate trials. The average of 64% is reported. ^{1}H NMR (400 MHz, CD_2Cl_2): **δ** 7.75–7.61 (m, 2H), 7.49–7.29 (m, 3H), 6.35 (br, 1H), 3.81 (s, 3H), 3.74 (d, J = 12.3 Hz, 1H), 3.50 (d, J = 12.3 Hz, 1H), 3.15 (d, J = 12.3 Hz, 1H), 2.98 (d, J = 12.3 Hz, 1H), 2.50 (br, 1H), 1.41 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ 172.7, 154.5, 131.5, 128.5, 128.4, 126.6, 84.7, 66.8, 61.5, 60.0, 52.5, 19.6. IR (NaCl, thin film, cm^{-1}): 3322, 2951, 1727, 1444, 1263. HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{14}H_{18}N_3O_2^{+}$, 260.1394; found, 260.1399.



5s

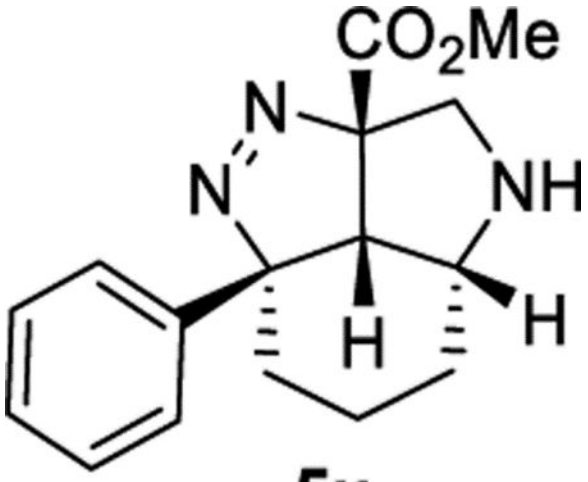
Methyl (3S,3aR,6aS)-3-(3,5-Bis(trifluoromethyl)phenyl)-3-methyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(3H)-carboxylate (5s).—General Procedure II was used, and the product was isolated in 64% (72.3 mg) and 45% (51.0 mg) yields in duplicate trials. The average of 55% is reported. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.66 (s, 2H), 3.83 (d, J = 12.1 Hz, 1H), 3.67 (s, 3H), 3.41 (d, J = 12.1 Hz, 1H), 3.28 (d, J = 12.0 Hz, 1H), 2.99 (dd, J = 12.0, 7.1 Hz, 1H), 2.64 (d, J = 7.0 Hz, 1H), 1.88 (s, 3H), 1.58

(br, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 169.2, 147.0, 131.9 (q, J_{C-F} = 33.5 Hz), 125.5 (m), 123.1 (q, J_{C-F} = 273.9 Hz), 121.4 (sept, J_{C-F} = 3.9 Hz), 109.3, 97.1, 55.1, 52.9, 51.2, 50.2, 22.2. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): −62.9. IR (NaCl, thin film, cm^{-1}): 3323, 2957, 2848, 1739, 1375, 1279, 1182, 1135. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{16}H_{15}F_6N_3NaO_2^+$, 418.0961; found, 418.0949.



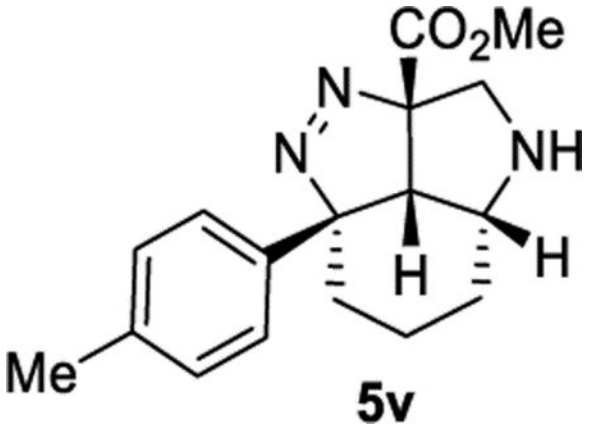
5t

Methyl (3aS,6aS)-3a-Phenyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]-pyrazole-6a(1H)-carboxylate (5t).—General Procedure II was used, and the product was isolated in 67% (80.6 mg) and 60% (79.7 mg) yields in duplicate trials. The average of 64% is reported. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.37 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 6.57 (s, 1H), 6.35 (br, 1H), 3.70 (d, J = 12.6 Hz, 1H), 3.55 (d, J = 12.2 Hz, 1H), 3.45 (d, J = 12.6 Hz, 1H), 3.25 (d, J = 12.2 Hz, 1H), 3.17 (s, 3H), 2.32 (br, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, CD_2Cl_2): δ 171.8, 147.2, 137.2, 128.3, 127.6, 127.3, 83.9, 75.8, 61.5, 57.3, 51.9. IR (NaCl, thin film, cm^{-1}): 3315, 2948, 1728, 1446, 1434, 1259, 1069. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{13}H_{15}N_3NaO_2^+$, 268.1056; found, 268.1063.



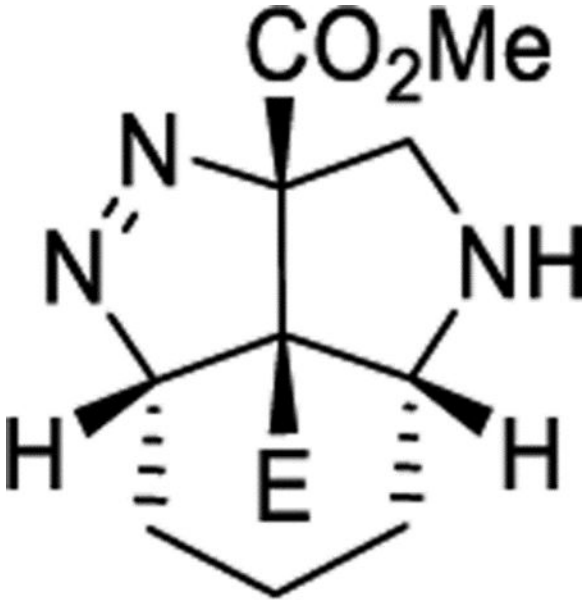
5u

Methyl (2aS,2a1R,5aR,7aS)-2a-Phenyl-2a,2a1,3,4,5,5a,6,7-octa-hydro-7aH-pyrrolo[4,3,2-cd]indazole-7a-carboxylate (5u).—General Procedure II was used, and the product was isolated in 67% (76.2 mg) and 69% (78.3 mg) yields in duplicate trials. The average of 68% is reported. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.36–7.28 (m, 2H), 7.28–7.19 (m, 3H), 4.00 (d, J = 11.8 Hz, 1H), 3.49–3.41 (m, 1H), 3.44 (s, 3H), 3.29 (d, J = 11.8 Hz, 1H), 3.18–3.09 (m, 1H), 2.86 (d, J = 8.2 Hz, 1H), 1.97 (ddd, J = 14.6, 13.6, 3.6 Hz, 1H), 1.91–1.83 (m, 1H), 1.71–1.56 (m, 2H), 1.49–1.40 (m, 1H), 1.35–1.21 (m, 1H). ^{3}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ 169.0, 145.3, 128.2, 126.8, 125.0, 108.8, 96.2, 57.1, 53.6, 52.1, 47.1, 36.8, 26.1, 16.0. IR (NaCl, thin film, cm^{-1}): 3336, 2934, 2861, 1735, 1445, 1433, 1286, 1212. HRMS (ESI-TOF): m/z [M + Na]$^{+}$ calcd for $C_{16}H_{19}N_3NaO_2^{+}$, 308.1369; found, 308.1370.



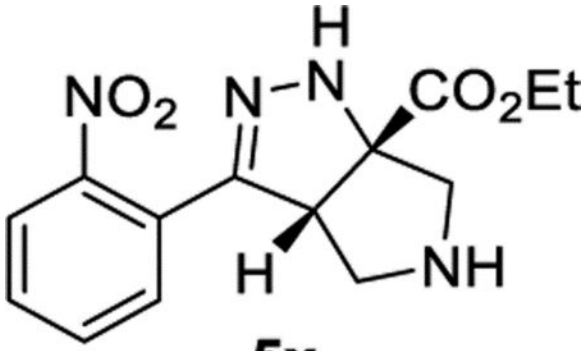
5v

Methyl (2aS,2a1R,5aR,7aS)-2a-(p-Tolyl)-2a,2a1,3,4,5,5a,6,7-octahydro-7aH-pyrrolo[4,3,2-cd]indazole-7a-carboxylate (5v).—General Procedure II was used, and the product was isolated in 62% (74.3 mg) and 47% (58.1 mg) yields in duplicate trials. The average of 55% is reported. ^{1}H NMR (400 MHz, CD_3CN): δ 7.13 (br, 4H), 3.90 (d, J = 11.4 Hz, 1H), 3.44 (s, 3H), 3.44–3.36 (m, 1H), 3.21 (d, J = 11.5 Hz, 1H), 3.05–2.96 (m, 1H), 2.85 (d, J = 8.2 Hz, 1H), 2.30 (s, 3H), 2.17 (br, 1H), 2.01–1.89 (m, 1H), 1.81–1.70 (m, 1H), 1.63 (tt, J = 14.0, 4.0 Hz, 1H), 1.58–1.47 (m, 1H), 1.38–1.25 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 169.1, 142.5, 136.5, 128.8, 125.0, 108.4, 95.9, 56.8, 53.3, 51.8, 46.4, 36.5, 25.9, 20.0, 15.9. IR (NaCl, thin film, cm^{-1}): 2931, 2861, 1736, 1433, 1287, 1212. HRMS (ESITOF): *m/z* [M + Na]$^{+}$ calcd for $C_{17}H_{21}N_3NaO^{+}{}_2$, 322.1526; found, 322.1528.



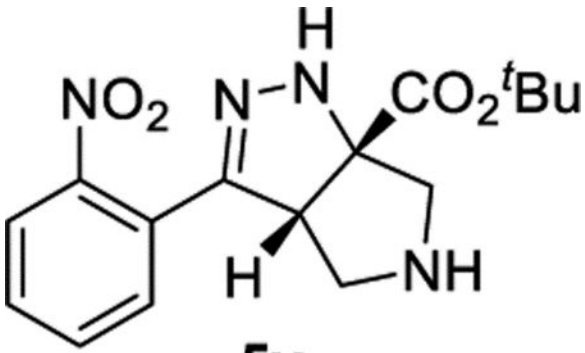
5w

2a1-Ethyl 7a-Methyl (2aS,2a1S,5aR,7aS)-3,4,5,5a,6,7-Hexahydro-2a1H-pyrrolo[4,3,2-cd]indazole-2a1,7a(2aH)-dicarboxylate (5w).—General Procedure I was used with a minor modifications. The reaction time was 48 h and column chromatography was performed with IPA in hexanes with 1% TEA, gradient elution 10–60%. The product was isolated in 45% (60.2 mg) and 39% (51.9 mg) yields in duplicate trials. The average of 42% is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.91 (dd, J = 6.2, 2.1 Hz, 1H), 4.15–4.08 (m, 2H), 3.90 (d, J = 12.7 Hz, 1H), 3.69 (s, 3H), 3.52 (d, J = 12.7 Hz, 1H), 3.46 (d, J = 4.1 Hz, 1H), 3.00 (d, J = 14.5 Hz, 1H), 1.93 (tdd, J = 14.3, 6.2, 3.7 Hz, 1H), 1.86 (d, J = 14.1 Hz, 1H), 1.61–1.49 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H), 1.19–1.07 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.6, 166.4, 111.7, 89.5, 62.3, 61.9, 57.7, 52.8, 52.4, 25.4, 25.1, 14.8, 14.1. IR (NaCl, thin film, cm^{-1}): 2939, 2854, 1733, 1446, 1269, 1245, 1106, 1050. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{13}H_{19}N_3NaO_4^+$, 304.1268, found, 304.1273.



5x

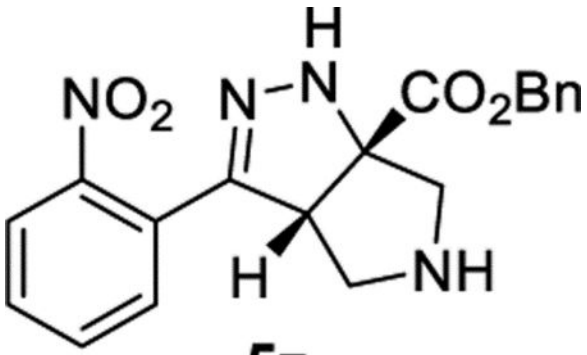
Ethyl (3aS,6aS)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo-[3,4-c]pyrazole-6a(1H)-carboxylate (5x).—General Procedure I was used with a minor modifications. The reaction was concentrated and purified directly (no TFA equilibration was necessary). The product was isolated in 93% (98.0 mg) and 95% (109 mg) yields in duplicate trials. The average of 94% is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8.1 Hz, 1H), 7.60 (apparent t, J = 7.6 Hz, 1H), 7.53– 7.45 (m, 2H), 6.72 (br, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.16 (dd, J = 8.1, 2.2 Hz, 1H), 3.31 (d, J = 12.1 Hz, 1H), 3.23 (d, J = 12.5 Hz, 1H), 3.16–3.08 (m, 2H), 2.21 (br, 1H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 173.1, 149.8, 149.0, 132.5, 130.0, 129.6, 126.8, 124.4, 81.6, 62.3, 61.5, 60.1, 54.1, 14.3. IR (NaCl, thin film, cm^{-1}): 3329, 2982, 2873, 1726, 1529, 1349, 1267, 1214. HRMS (ESITOF): m/z [M + Na]$^{+}$ calcd for $C_{14}H_{16}N_4NaO_4^{+}$, 327.1064; found, 327.1071.



5y

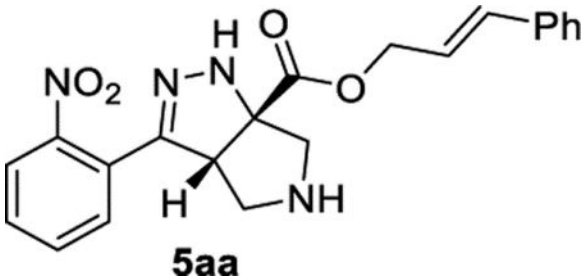
tert- Butyl (3aS,6aS)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5y).—General Procedure I was used with a minor modifications. The reaction was concentrated and purified directly (no TFA equilibration was necessary). The product was isolated in 85% (90.6 mg) and 89% (95.2 mg) yields in duplicate trials. The average of 87% is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 1H), 7.59 (apparent t, J = 7.6 Hz, 1H), 7.51–7.45 (m, 2H), 6.66 (br, 1H), 4.08 (dd, J = 8.1, 2.2 Hz, 1H), 3.27 (d, J = 12.0 Hz, 1H), 3.18 (d, J = 12.4 Hz, 1H), 3.12–3.05 (m, 2H), 2.16 (br, 1H), 1.52 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.2, 150.1, 148.9, 132.6, 130.2, 129.6, 127.1, 124.5, 83.3, 82.2, 61.4, 60.1, 54.1, 28.1. IR (NaCl, thin film, cm^{-1}):

3329, 2979, 2934, 2873, 1722, 1530, 1369, 1347, 1284, 1259, 1159. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{16}H_{20}N_4NaO_4^+$, 355.1377; found, 355.1372.



5z

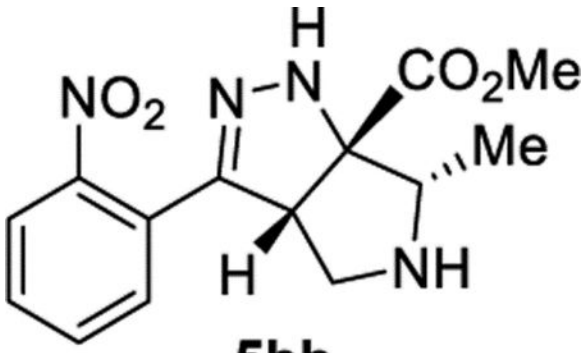
Benzyl (3aS,6aS)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo-[3,4-c]pyrazole-6a(1H)-carboxylate (5z).—General Procedure I was used with a minor modifications. The reaction was concentrated and purified directly (no TFA equilibration was necessary). The product was isolated in 91% (123 mg) and 96% (124 mg) yields in duplicate trials. The average of 94% is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 1H), 7.60 (apparent t, J = 7.6 Hz, 1H), 7.49 (apparent t, J = 8.7 Hz, 2H), 7.43–7.34 (m, 5H), 6.75 (br, 1H), 5.28 (s, 2H), 4.20 (dd, J = 8.1, 2.1 Hz, 1H), 3.32 (d, J = 12.1 Hz, 1H), 3.23 (d, J = 12.5 Hz, 1H), 3.17 (d, J = 12.1 Hz, 1H), 3.12 (dd, J = 12.5, 8.0 Hz, 1H), 2.24 (br, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 173.0, 149.6, 149.0, 135.1, 132.4, 130.0, 129.6, 128.84, 128.75, 128.4, 126.7, 124.4, 81.5, 67.9, 61.5, 60.2, 54.1. IR (NaCl, thin film, cm^{-1}): 3329, 2936, 2874, 1729, 1530, 1347, 1267, 1213. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{18}N_4NaO_4^+$, 389.1220; found, 389.1228.



5aa

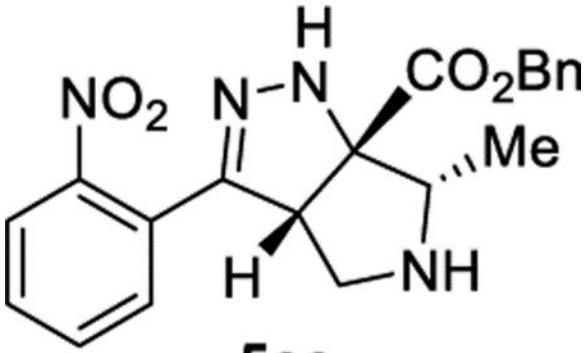
Cinnamyl (3aS,6aS)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5aa).—General Procedure I was used with a minor modifications. The reaction was concentrated and purified directly (no TFA equilibration was necessary). The product was isolated in 83% (75.3 mg) and 72% (59.6 mg) yields in duplicate trials. The average of 78% is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 1H), 7.61 (apparent t, J = 7.6 Hz, 1H), 7.54–7.48 (m, 2H), 7.44 (d, J = 7.7 Hz, 2H), 7.36 (apparent t, J = 7.5 Hz, 2H), 7.32–7.27 (m, 1H), 6.76– 6.70 (m, 2H), 6.34 (dt, J = 15.9, 6.6 Hz, 1H), 4.92 (d, J = 6.6 Hz, 2H), 4.22 (d, J = 7.6 Hz, 1H), 3.36 (d, J = 12.1 Hz, 1H), 3.26 (d, J = 12.5 Hz, 1H), 3.23–3.12 (m, 2H), 2.23 (br, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.9, 149.7, 148.9, 135.9, 135.5, 132.4, 129.9, 129.5, 128.7, 128.4, 126.8, 126.7,

124.4, 122.1, 81.5, 66.8, 61.5, 60.1, 54.0. IR (NaCl, thin film, cm^{-1}): 3339, 3027, 2937, 2874, 1728, 1529, 1346, 1264, 1209. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{21}H_{20}N_4NaO_4^+$, 415.1377; found, 415.1380.



5bb

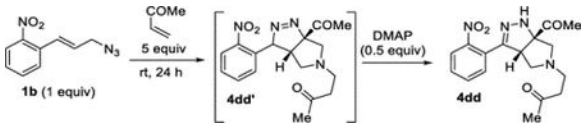
Methyl (3aS,6S,6aS)-6-Methyl-3-(2-nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5bb).—General Procedure I was used with a minor modifications. The reaction time was 5 days, and the reaction was concentrated and purified directly (no TFA equilibration was necessary). The product was isolated in 83% (53.1 mg) and 90% (79.9 mg) yields in duplicate trials with a 3.2:1 dr. The average of 87% is reported. ^1H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 8.3 Hz, 1H), 7.61 (apparent t, J = 7.6 Hz, 1H), 7.54–7.48 (m, 2H), 6.47 (br, 1H), 4.21 (t, J = 5.1 Hz, 1H), 3.87 (s, 3H), 3.40 (q, J = 6.5 Hz, 1H), 3.18 (d, J = 5.1 Hz, 2H), 2.02 (br, 1H), 1.23 (d, J = 6.4 Hz, 3H). ^1H NMR (500 MHz, $CDCl_3$) minor diastereomer: δ 7.80 (d, J = 8.0 Hz, 1H), 7.61 (apparent t, J = 7.6 Hz, 1H), 7.55–7.48 (m, 2H), 6.67 (br, 1H), 4.32 (dd, J = 8.5, 4.1 Hz, 1H), 3.86 (s, 3H), 3.47–3.38 (m, 2H), 3.05 (dd, J = 12.5, 4.2 Hz, 1H), 1.16 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ173.7, 150.3, 148.8, 132.3, 129.9, 129.5, 126.5, 124.3, 83.4, 65.8, 60.4, 53.1, 52.7, 13.3. IR (NaCl, thin film, cm^{-1}): 3348, 2955, 2882, 1731, 1531, 1435, 1378, 1355, 1274, 1208. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{16}N_4NaO^+_4$, 327.1064; found, 327.1068.



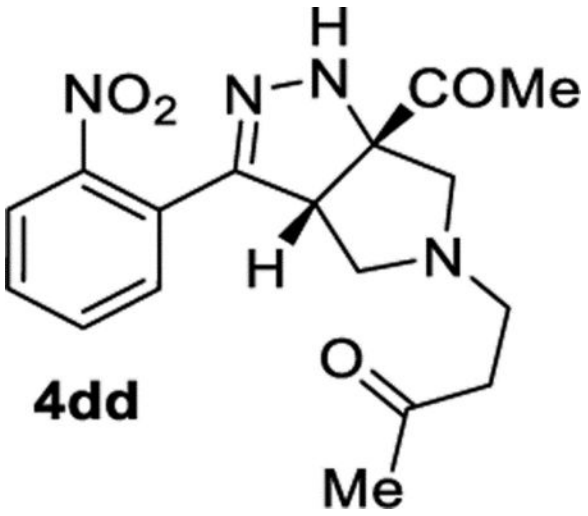
5cc

Benzyl (3aS,6S,6aS)-6-Methyl-3-(2-nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (5cc).—General Procedure I was used with a minor modifications. The reaction time was 5 days, and the reaction was concentrated and purified

directly (no TFA equilibration was necessary). The product was isolated in 83% (70.6 mg) and 76% (66.6 mg) yields in duplicate trials with a 3.8:1 dr. The average of 80% is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 1H), 7.61 (apparent t, J = 7.6 Hz, 1H), 7.53–7.47 (m, 2H), 7.45–7.35 (m, 5H), 6.49 (br, 1H), 5.29 (s, 2H), 4.23 (t, J = 5.1 Hz, 1H), 3.41 (q, J = 6.4 Hz, 1H), 3.17 (d, J = 5.1 Hz, 2H), 2.06 (br, 1H), 1.20 (d, J = 6.8 Hz, 3H). ^{1}H{^{1}H} NMR (400 MHz, $CDCl_3$) minor diastereomer: δ 7.79 (d, J = 7.9 Hz, 1H), 7.64–7.56 (m, 1H), 7.54–7.48 (m, 2H), 7.43–7.36 (m, 5H), 6.69 (br, 1H), 5.27 (d, J = 12.0 Hz, 1H), 5.26 (d, J = 12.0 Hz, 1H), 4.33 (dd, J = 8.4, 4.1 Hz, 1H), 3.47–3.35 (m, 2H), 3.03 (dd, J = 12.5, 4.1 Hz, 1H), 1.08 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1, 150.3, 148.8, 135.1, 132.4, 129.9, 129.5, 128.8, 128.7, 128.3, 126.5, 124.4, 83.4, 67.8, 65.8, 60.4, 52.6, 13.3. IR (NaCl, thin film, cm^{-1}): 3342, 2970, 2878, 1727, 1533, 1377, 1353, 1266, 1203. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{20}H_{20}N_4NaO^+_4$, 403.1377; found, 403.1375.

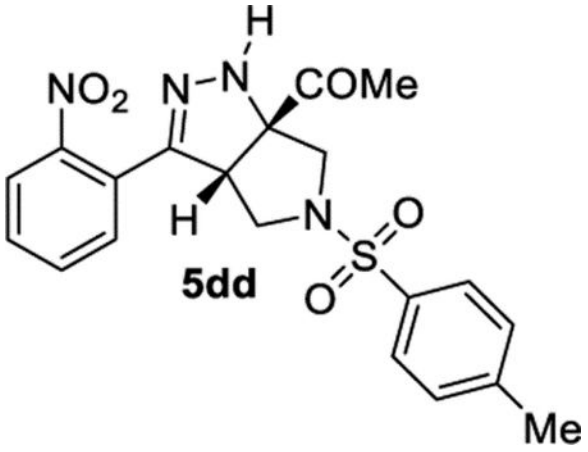


4-((3aS,6aS)-6a-Acetyl-3-(2-nitrophenyl)-3a,4,6,6atetrahydropyrrolo[3,4-c]pyrazol-5(1H)-yl)butan-2-one (4dd).—A 4 mL vial was charged with azide 1b (61.3 mg, 0.300 mmol) and methyl vinyl ketone (0.13 mL, 1.6 mmol). The vial was sealed with a Teflon-lined cap, and the reaction was stirred at an ambient temperature. After 24 h, excess methyl vinyl ketone was removed under reduced pressure (<15 Torr). The resulting oil was directly purified by column chromatography (EtOAc in hexanes, gradient elution 0–80%), which afforded compound **4dd′** as a yellow oil. Compound 4dd′ was isolated in 95% (98.4 mg) and 79% (81.7 mg) in duplicate trials. The average of 87% is reported. Compound **4dd′** tends to gradually tautomerize to compound 4dd at an ambient temperature. Pure 4dd can be synthesized using the procedure above with minor modifications. The crude 4dd′ was reconstituted in a 20 mL vial with DCM (2 mL), and DMAP (18 mg, 0.15 mmol) was added. The vial was sealed with a Teflon-lined cap, and the reaction was stirred at an ambient temperature. After 16 h, the solvent was removed under reduced pressure. Purification by column chromatography (IPA in DCM with 1% TEA, gradient elution 0–10%) afforded 4dd as a yellow oil (37.7 mg, 38%), along with recovered unreacted **4dd′**.



4dd

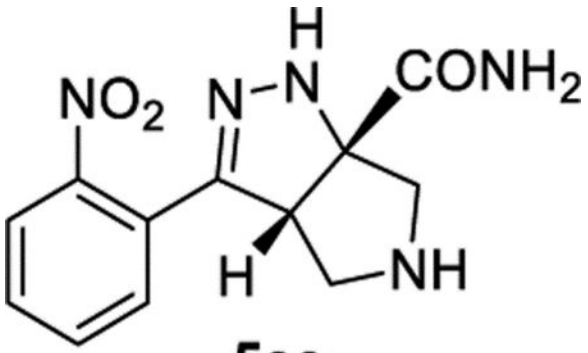
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.2 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.58–7.50 (m, 2H), 6.50 (br, 1H), 4.02 (dd, J = 7.5, 3.7 Hz, 1H), 3.02 (d, J = 10.0 Hz, 1H), 2.91 (d, J = 10.0 Hz, 1H), 2.86–2.70 (m, 3H), 2.70–2.64 (m, 1H), 2.60 (t, J = 7.1 Hz, 2H), 2.37 (s, 3H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 207.3, 206.2, 149.6, 148.1, 133.0, 131.2, 129.7, 127.2, 124.5, 82.2, 64.3, 57.6, 56.3, 49.0, 42.7, 29.9, 25.3. IR (NaCl, thin film, cm^{-1}): 3328, 2913, 2807, 1710, 1529, 1354. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{17}H_{20}N_4NaO_4^+$, 367.1377; found, 367.1374.



5dd

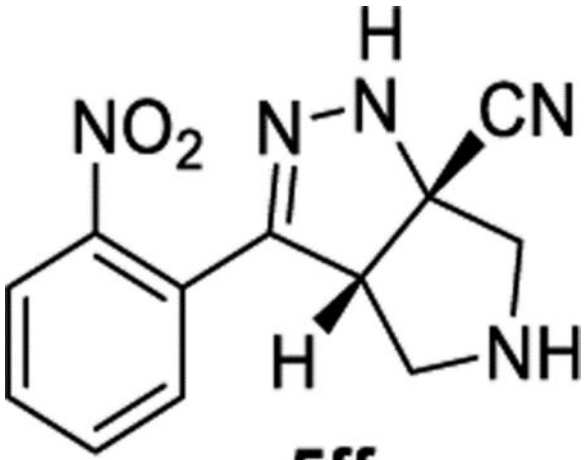
1-((3aS,6aS)-3-(2-Nitrophenyl)-5-tosyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-6a(1H)-yl)ethan-1-one (5dd).—General Procedure III was used with a minor modification. DMAP was used to replace DIPEA. The product was isolated in 49% (62.0 mg) and 66% (90.4 mg) yields in duplicate trials. The average of 58% is reported. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.2 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.63–7.55 (m, 2H), 7.36 (d, J = 8.0 Hz, 2H), 6.41 (br, 1H), 4.06 (dd, J = 7.8, 3.3 Hz, 1H), 3.62 (d, J = 10.6 Hz, 1H), 3.50 (d, J = 10.7 Hz, 1H), 3.32 (dd, J = 10.1, 3,4 Hz, 1H), 3.10 (dd, J = 10.1, 7.7 Hz, 1H), 2.46 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 205.0, 148.4, 147.8, 144.5, 133.7, 131.8, 131.5, 130.3, 130.0, 128.0, 126.7, 124.8, 81.7, 57.3, 56.7, 51.3, 25.5, 21.6. IR (NaCl, thin film, cm^{-1}): 3334, 2292, 2868, 1712, 1529,

1345, 1163. HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{20}H_{20}N_4NaO_5S^+$, 451.1047; found, 451.1036.



5ee

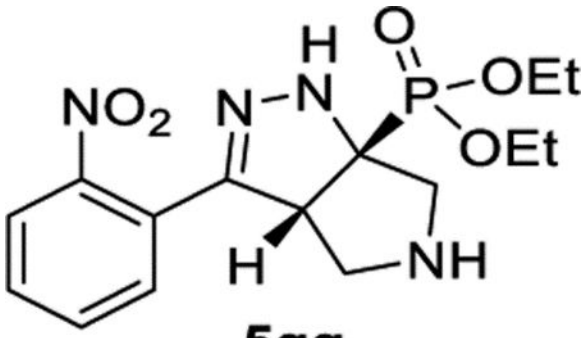
(3aS,6aS)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]-pyrazole-6a(1H)-carboxamide (5ee).—General Procedure I was used with a minor modifications. During the reaction, the product precipitated as a yellow solid. The solid was purified by recrystallization in MeOH/DCM/hexanes (1:2:10), and the product was isolated in 75% (82.5 mg) and 68% (69.6 mg) in duplicate trials. The average of 72% is reported. ^{1}H NMR (500 MHz, DMSO): δ 7.77 (d, J = 8.0 Hz, 1H), 7.68–7.65 (m, 2H), 7.62 (br, 1H), 7.57–7.51 (m, 1H), 7.41 (br, 2H), 4.03 (d, J = 7.4 Hz, 1H), 3.12 (d, J = 11.9 Hz, 1H), 3.07–2.98 (m, 2H), 2.88 (d, J = 11.9 Hz, 1H), 2.28 (br, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO): δ 175.4, 149.1, 145.8, 132.4, 129.9, 129.4, 125.5, 124.1, 79.9, 61.2, 59.8, 54.2. IR (NaCl, thin film, cm^{-1}): 3289, 3189, 1630, 1526, 1420, 1356. HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{12}H_{13}N_5NaO_3^+$, 298.0911; found, 298.0921.



5ff

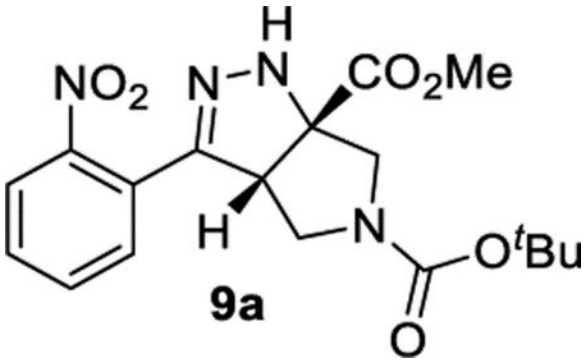
(3aS,6aS)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]-pyrazole-6a(1H)-carbonitrile (5ff).—General Procedure II was used with a minor modifications. Both parts of the reaction were heated at 40 °C for 24 h. The product was purified by recrystallization (EtOAc/hexanes). The product was isolated in 68% (66.3 mg) and 72% (64.4 mg) yields in duplicate trials. The average of 70% is reported. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.36 (br,

1H), 7.85 (d, J = 8.0 Hz, 1H), 7.75–7.66 (m, 2H), 7.62–7.56 (m, 1H), 4.48 (dd, J = 7.9, 2.5 Hz, 1H), 3.30 (d, J = 12.2 Hz, 1H), 3.18–3.07 (m, 2H), 2.96 (d, J = 12.1 Hz, 1H), 2.68 (br, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 148.9, 146.5, 132.7, 130.3, 130.1, 124.7, 124.3, 120.8, 67.7, 61.7, 61.4, 53.5. IR (NaCl, thin film, cm^{-1}): 3320, 2926, 2237, 1529, 1345. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{11}N_5NaO_2^+$, 280.0805; found, 280.0816.



5gg

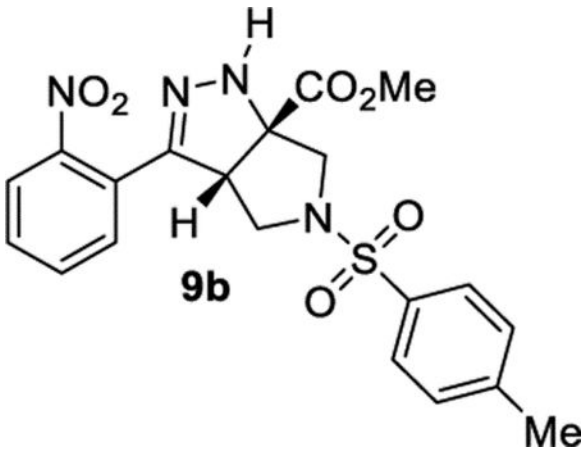
Diethyl ((3aR,6aR)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-6a(1H)-yl)phosphonate (5gg).—General Procedure I was used, and the product was isolated in 38% (56.4 mg) and 42% (62.0 mg) yields in duplicate trials. The average of 40% is reported. ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.1 Hz, 1H), 7.61 (apparent t, J = 7.6 Hz, 1H), 7.53–7.48 (m, 2H), 6.18 (d, J = 7.3 Hz, 1H), 4.34–4.17 (m, 5H), 3.31 (dd, J = 12.7, 6.0 Hz, 1H), 3.24 (dd, J = 12.6, 3.4 Hz, 1H), 3.16 (d, J = 12.4 Hz, 1H), 3.03 (dd, J = 12.5, 7.6 Hz, 1H), 2.09 (br, 1H), 1.36 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 149.1, 148.2 (d, J_{C-P} = 7.3 Hz), 132.2, 129.8, 129.4, 126.3, 124.3, 74.6 (d, J_{C-P} = 159.7 Hz), 63.4 (d, J_{C-P} = 7.0 Hz), 62.9 (d, J_{C-P} = 7.3 Hz), 59.4 (d, J_{C-P} = 13.8 Hz), 58.2, 53.7 (d, J_{C-P} = 13.6 Hz), 16.6 (d, J_{C-P} = 5.5 Hz), 16.5 (d, J_{C-P} = 5.6 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 23.3. IR (NaCl, thin film, cm^{-1}): 3245, 2979, 2928, 2873, 1532, 1236, 1048. HRMS (ESITOF): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{21}N_4NaO_5P^+$, 391.1142; found, 391.1141.



9a

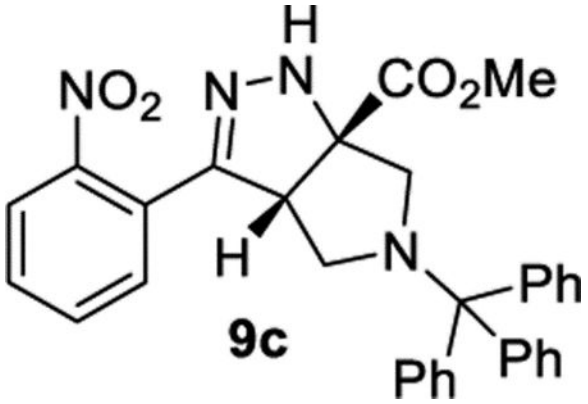
5-(tert-Butyl) 6a-Methyl (3aS,6aS)-3-(2-nitrophenyl)-3a,4-dihydropyrrolo[3,4-c]pyrazole-5,6a(1H,6H)-dicarboxylate (9a).—General Procedure III was used, and the product was isolated in 80% (92.9 mg) as a single tautomer. ^1H NMR (400 MHz, CD_3CN):

7.80 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.62–7.54 (m, 2H), 7.05 (br, 1H), 4.28 (dd, J = 8.9, 4.4 Hz, 1H), 3.88–3.78 (m, 2H), 3.80 (s, 3H), 3.72–3.65 (m, 1H), 3.60–3.52 (m, 1H), 1.43 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3CN): 171.8, 153.6, 148.8, 147.9, 132.4, 130.0, 129.7, 125.2, 124.0, 79.5, 55.9 (br, tentatively assigned as 2C), 52.7, 51.4, 49.3, 27.5. IR (NaCl, thin film, cm^{-1}): 3345, 2979, 2870, 1737, 1693, 1530, 1400, 1367. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{22}N_4NaO_6^+$, 413.1432; found, 413.1424.



9b

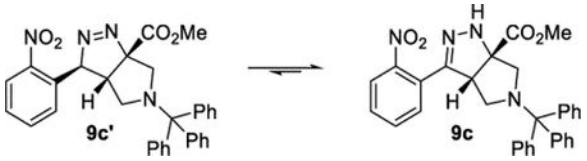
Methyl (3aS,6aS)-3-(2-Nitrophenyl)-5-tosyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (9b).—General Procedure III was used with R–X = 4-toluenesulfonyl chloride (TsCl). Product 9b was isolated in 74% (126.7 mg) and 69% (91.6 mg) yields in duplicate trials. An average of 72% is reported. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 6.64 (br, 1H), 4.21 (dd, J = 8.3, 3.9 Hz, 1H), 3.82 (s, 3H), 3.74 (d, J = 10.2 Hz, 1H), 3.46 (d, J = 10.3 Hz, 1H), 3.37 (dd, J = 10.0, 3.9 Hz, 1H), 3.29 (dd, J = 10.1, 8.3 Hz, 1H), 2.45 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 171.2, 148.8, 147.9, 144.3, 133.2, 132.2, 131.2, 130.1, 129.9, 127.9, 126.3, 124.6, 77.8, 58.7, 56.0, 53.6, 51.3, 21.6. IR (NaCl, thin film, cm^{-1}): 3332, 2956, 2857, 1738, 1530, 1346, 1164. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{20}N_4NaO_6S^+$, 467.0996; found, 467.1000.



9c

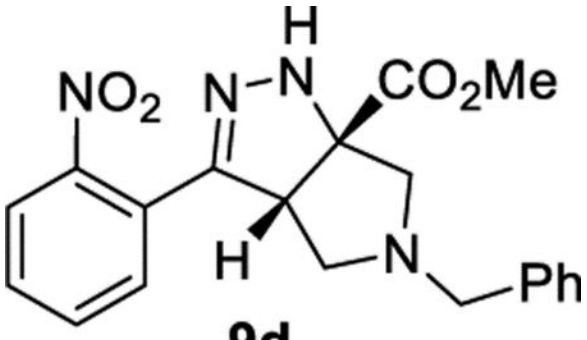
Methyl (3aS,6aS)-3-(2-Nitrophenyl)-5-trityl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (9c).—General Procedure III was used and with R–X = triphenylmethyl chloride (TrCl). Product 9c was isolated in 88% (140.7 mg) as a tautomeric mixture **9c′/9c** = 1.5:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.55– 7.46 (m, 7H), 7.28–7.21 (m, 6H), 7.19–7.14 (m, 3H), 6.76 (br, 1H), 4.02 (d, J = 7.2 Hz, 1H), 3.75 (s, 3H), 3.44 (d, J = 9.4 Hz, 1H), 3.05 (d, J = 9.6 Hz, 1H), 2.09–2.00 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.6, 149.3, 148.5, 132.3, 130.6, 129.3, 129.1, 127.9, 127.6, 126.8, 126.3, 124.3, 75.9, 73.4, 58.4, 54.2, 53.0, 50.4. IR (NaCl, thin film, cm^{-1}): 3349, 2057, 2952, 2831, 1736, 1595, 1530, 1448, 1264, 1071, 738. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{32}H_{28}N_4NaO_4^+$, 555.2003; found, 555.2018.

Note.—



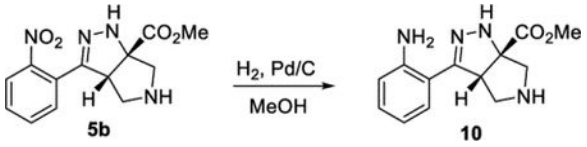
The trityl-protected product was isolated as a mixture of the unconjugated (**9c′**) and conjugated (**9c**) isomers. To determine how to convert the mixture into a single isomer, a stock solution of the 9c′/9c mixture (45.2 mg, 84.6 μmol) and 1,3,5-trimethoxybenzene (6.4 mg, 38 μmol) in CDCl3 (2.1 mL) was divided into three portions. TFA (6.5 μL, 38 μmol) was added to one portion, DBU (2.1 μL, 6.4 μmol) was added to the second portion, and the third was left with no additive. The three samples were analyzed by ^{1}H NMR after 0.5 and 18 h. After 18 h, the samples containing TFA or DBU had fully converted to the conjugated tautomer (**6d**).

Methyl (3aS,6aS)-5-Benzyl-3-(2-nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (9d).—

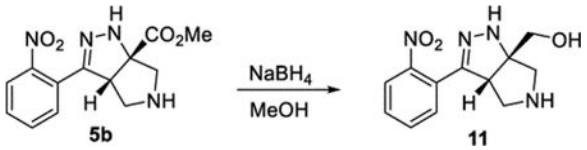


General Procedure III was used with R–X = benzyl chloroformate (CbzCl). Product **9d** was isolated in 81% (93.4 mg) as a single tautomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.1 Hz, 1H), 7.62–7.54 (m, 1H), 7.53–7.45 (m, 2H), 7.40–7.31 (m, 3H), 7.29 (d, J = 6.8 Hz, 1H), 7.27–7.21 (m, 1H), 6.61 (br, 1H), 4.22 (dd, J = 7.6, 2.5 Hz, 1H), 3.85 (s, 3H), 3.77 (d, J = 13.2 Hz, 1H), 3.59 (d, J = 13.2 Hz, 1H), 3.21 (d, J = 9.5 Hz, 1H), 2.91–2.81 (m, 2H), 2.62 (d, J = 9.5, 7.7 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.9, 150.0, 148.2, 138.2,

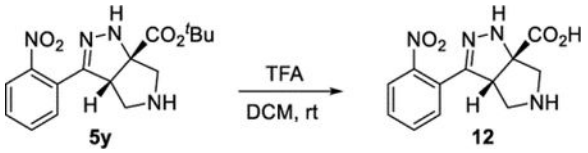
132.6, 130.9, 129.5, 128.5, 128.3, 127.2, 127.0, 124.3, 77.1, 65.9, 58.6, 57.0, 56.6, 53.1. IR (NaCl, thin film, cm^{-1}): 3345, 2956, 2804, 1734, 1532, 1347, 1275, 1227. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{20}N_4NaO_4^+$, 403.1377; found, 403.1373.



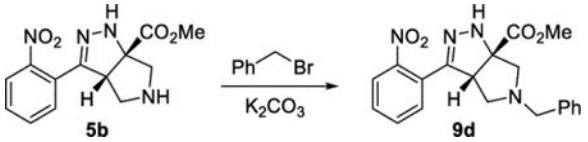
Methyl (3aS,6aS)-3-(2-Aminophenyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (10).—A vial was sequentially charged with compound **5b** (61 mg, 0.21 mmol), MeOH (1 mL), and Pd/C (6 mg, 10 wt % Pd). The vial was sealed with a septum and purged with hydrogen gas using a hydrogen balloon without stirring. After 10 min, the vial was equipped with 2 hydrogen balloons under ambient pressure. After 4 h, the reaction was filtered through a short plug of silica gel and rinsed with MeOH (5 mL). The solvent was removed under reduced pressure. This procedure afforded the product 10 in 100% (54 mg) as a yellow oil. ^1H NMR (500 MHz, CD_2Cl_2): δ 7.17–7.06 (m, 2H), 6.76–6.66 (m, 2H), 5.89 (br, 1H), 4.29 (d, J = 8.3 Hz, 1H), 3.81 (s, 3H), 3.43– 3.30 (m, 2H), 3.29 (d, J = 12.0 Hz, 1H), 3.22 (d, J = 12.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2): δ 174.2, 155.8, 147.3, 129.4, 128.8, 116.1, 115.6, 113.2, 79.6, 61.0, 59.8, 55.0, 52.8. IR (NaCl, thin film, cm^{-1}): 3449, 3314, 2948, 1730, 1613, 1495, 1453, 1267, 1124. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{16}N_4NaO^+_2$, 283.1165; found, 283.1149.



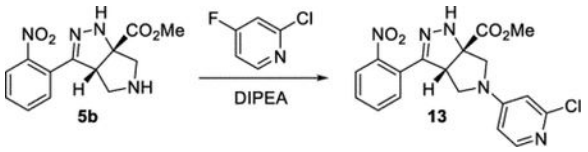
((3aS,6aS)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]-pyrazol-6a(1H)-yl)methanol (11).—To a solution of compound **5b** (48.6 mg, 0.168 mmol) in MeOH (2 mL) was added $NaBH_4$ (28.4 mg, 0.751 mmol). The reaction was sealed under air and heated to 60 °C. After 1 h, additional $NaBH_4$ (20.6 mg, 0.545 mmol) was added. After 1 h, the reaction was quenched by the addition of H_2O and brine. The reaction mixture was extracted with EtOAc (6 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to afford compound **11** (34.5 mg, 79%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8.1 Hz, 1H), 7.61 (apparent t, J = 7.6 Hz, 1H), 7.54–7.47 (m, 2H), 5.99 (br, 1H), 3.80 (s, 2H), 3.74 (d, J = 7.7 Hz, 1H), 3.19 (d, J = 12.3 Hz, 1H), 3.13 (d, J = 12.2 Hz, 1H), 3.04 (dd, J = 12.4, 7.7 Hz, 1H), 2.89 (d, J = 12.3 Hz, 1H), 2.57 (br, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, MeOD): δ 149.0, 148.8, 132.1, 129.8, 129.1, 126.8, 123.9, 79.4, 63.5, 57.0, 55.6, 51.6. IR (NaCl, thin film, cm^{-1}): 3290, 2921, 2868, 1528, 1347. HRMS (ESITOF): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{14}N_4NaO_3^+$, 285.0958; found, 285.0956.



(3aS,6aS)-3-(2-Nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]-pyrazole-6a(1H)-carboxylic acid (12).—To a solution of bicyclic amine 5y (38.7 mg, 0.117 mmol) in DCM (0.5 mL) was added TFA (0.5 mL) at an ambient temperature. After 4 h, the reaction mixture was concentrated under reduced pressure to afford the bis-TFA salt (59.7 mg) in a quantitative yield. ^{1}H NMR (500 MHz, MeOD:TFA 50:1): δ 7.96 (d, J = 8.0 Hz, 1H), 7.75 (apparent t, J = 7.6 Hz, 1H), 7.70–7.63 (m, 2H), 4.51 (dd, J = 9.8, 3.4 Hz, 1H), 3.88 (d, J = 12.0 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.71 (dd, J = 12.5, 9.6 Hz, 1H), 3.52 (dd, J = 12.4, 3.6 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, MeOD/TFA 50:1): δ 170.9, 148.5, 147.4, 132.7, 130.4, 130.0, 125.2, 124.2, 77.9, 54.8, 54.6, 49.4. IR (NaCl, thin film, cm^{-1}): 3323, 2917, 1779, 1721, 1659, 1519, 1344, 1204, 1160. HRMS (ESI-TOF): m/z [M + H]$^{+}$ calcd for $C_{12}H_{13}N_4O_4^{+}$, 277.0931; found, 277.0922.

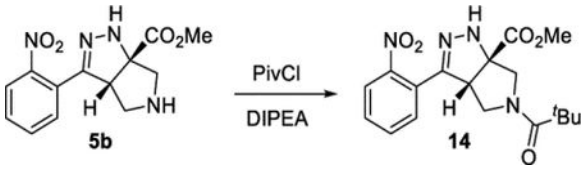


Methyl (3aS,6aS)-5-Benzyl-3-(2-nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (9d).—A 20 mL vial was charged with compound **5b** (112 mg, 0.384 mmol) and acetonitrile (9 mL). Potassium carbonate (160 mg, 1.16 mmol) and benzyl bromide (55 μL, 0.46 mmol) were added consecutively. The vial was sealed with a Teflon-lined cap, and the reaction was heated to 55°C. After 16 h, the reaction was diluted with water (5 mL). The resulting solution was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (EtOAc in hexanes, gradient elution 0–70%) afforded compound 9d as a yellow oil (104 mg, 72%). The material obtained provided an identical ^{1}H NMR spectra above.

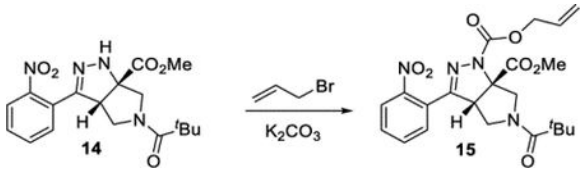


Methyl (3aS,6aS)-5-(2-Chloropyridin-4-yl)-3-(2-nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (13).—To a solution of compound **5b** (61.0 mg, 0.210 mmol) in DMF (0.5 mL) were added DIPEA (75 μL, 0.42 mmol) and 2-chloro-4-fluoropyridine (76.8 mg, 0.586 mmol). The reaction was sealed under air and heated to 80 °C. After 16 h, the reaction was cooled to rt and diluted with H_2O. The reaction mixture was extracted with Et_2O. The combined organic phases were washed with H_2O, brine, dried (Na_2SO_4), and concentrated under reduced pressure. Final purification by column chromatography (EtOAc in hexanes with 1% TEA, gradient elution 10–65%)

afforded compound 13 (65.9 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 5.9 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.68 (apparent t, J = 7.5 Hz, 1H), 7.61–7.55 (m, 2H), 6.94 (s, 1H), 6.38 (s, 1H), 6.30 (d, J = 5.9 Hz, 1H), 4.39 (dd, J = 9.5, 5.7 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 2H), 3.71 (t, J = 9.7 Hz, 1H), 3.47 (dd, J = 10.1, 5.7 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.8, 152.9, 152.2, 149.9, 149.3, 148.2, 133.2, 130.7, 130.3, 126.3, 124.7, 107.2, 106.9, 78.8, 57.4, 54.7, 53.7, 51.2. IR (NaCl, thin film, cm^{-1}): 3337, 2954, 2868, 1736, 1594, 1529, 1498. HRMS (ESITOF): *m/z* [M + Na]$^{+}$ calcd for $C_{18}H_{16}ClN_5NaO_4^{+}$, 424.0783; found, 424.0796.



Methyl (3aS,6aS)-3-(2-Nitrophenyl)-5-pivaloyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (14).—A 20 mL vial was charged with compound **5b** (67.1 mg, 0.231 mmol) and DCM (1 mL). Pivaloyl chloride (57 μL, 0.46 mmol) was added, followed by DIPEA (76 μL, 0.46 mmol). The vial was sealed with a Teflon-lined cap, and the reaction was stirred at an ambient temperature. After 16 h, the reaction was quenched by the addition of water (5 mL). The resulting solution was extracted with DCM (3 × 10 mL). The combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (EtOAc in hexanes, gradient elution 0–100%) afforded compound **14** as a yellow solid (75.7 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.2 Hz, 1H), 7.63 (apparent t, J = 7.6 Hz, 1H), 7.59–7.50 (m, 2H), 6.75 (br, 1H), 4.21–4.15 (m, 1H), 4.19 (d, J = 11.7 Hz, 1H), 3.97 (d, J = 11.8 Hz, 1H), 3.89 (s, 3H), 3.88–3.74 (m, 2H), 1.23 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 176.4, 171.9, 150.0 (br), 148.1, 133.1, 130.9, 130.0, 126.5, 124.6, 78.5 (br), 57.2, 54.6, 53.5, 50.6, 38.8, 27.5. IR (NaCl, thin film, cm^{-1}): 3331, 2529, 2959, 2868, 1738, 1624, 1533, 1141, 1365, 1348, 1276, 1233. HRMS (ESI-TOF): m/z [M + Na]$^{+}$ calcd for $C_{18}H_{22}N_4NaO_5^{+}$, 397.1482; found, 397.1464.



1-Allyl 6a-Methyl (3aS,6aS)-3-(2-Nitrophenyl)-5-pivaloyl-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-1,6a-dicarboxylate (15).—To a solution of compound **14** (52.1 mg, 0.139 mmol) in DMF (0.5 mL) were added K_2CO_3 (83.2 mg, 0.602 mmol) and allyl bromide (0.10 mL, 1.6 mmol). The reaction was sealed under air and heated to 60 °C. After 13 h, the reaction was cooled to rt and diluted with water. The reaction mixture was extracted with Et_2O. The combined organic phases were washed with water, brine, dried (Na_2SO_4), and concentrated under reduced pressure. Final purification by column chromatography (IPA in hexanes, gradient elution 0–15%) afforded compound 15 (44.5 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, J = 8.2 Hz, 1H), 7.75 (apparent t, J

= 7.5 Hz, 1H), 7.66 (apparent t, J = 7.9 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 6.01–5.91 (m, 1H), 5.38 (d, J = 17.2 Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 4.81 (dd, J = 13.3, 5.8 Hz, 1H), 4.77–4.67 (m, 2H), 4.37 (d, J = 12.7 Hz, 1H), 4.20 (d, J = 12.2 Hz, 1H), 4.13 (d, J = 8.5 Hz, 1H), 3.91 (s, 3H), 3.52–3.40 (m, 1H), 1.26 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 177.0, 168.8, 153.3, 152.2, 147.6, 134.2, 132.6, 131.8, 131.1, 125.9, 125.2, 119.1, 67.5, 57.2, 55.1, 54.2, 53.6, 49.4, 38.9, 27.6. IR (NaCl, thin film, cm^{-1}): 2974, 1747, 1704, 1633, 1531, 1435, 1415, 1346, 1277. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{22}H_{26}N_4NaO_7^+$, 481.1694; found, 481.1710.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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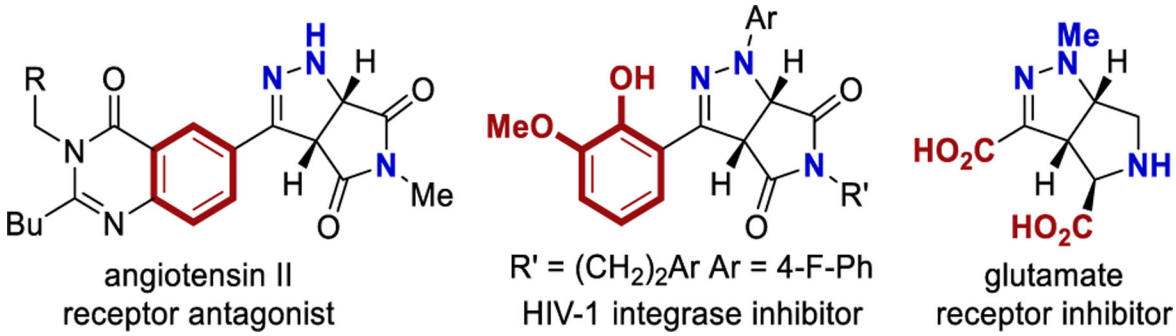
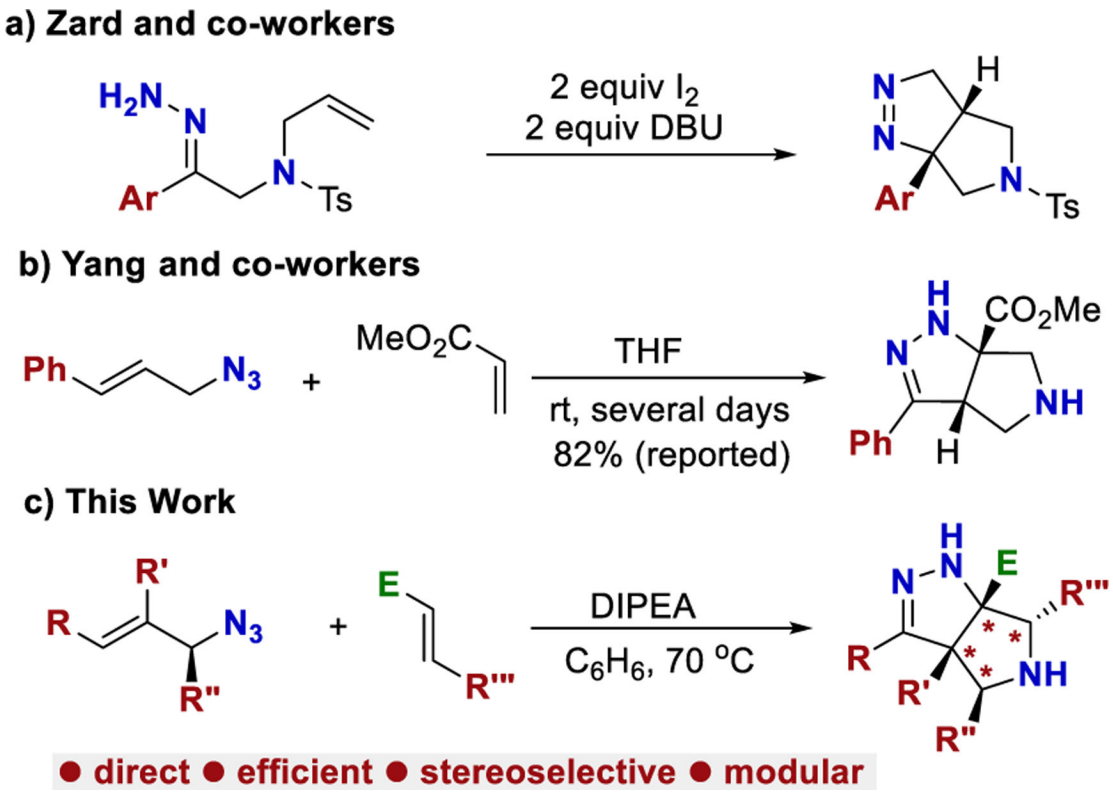
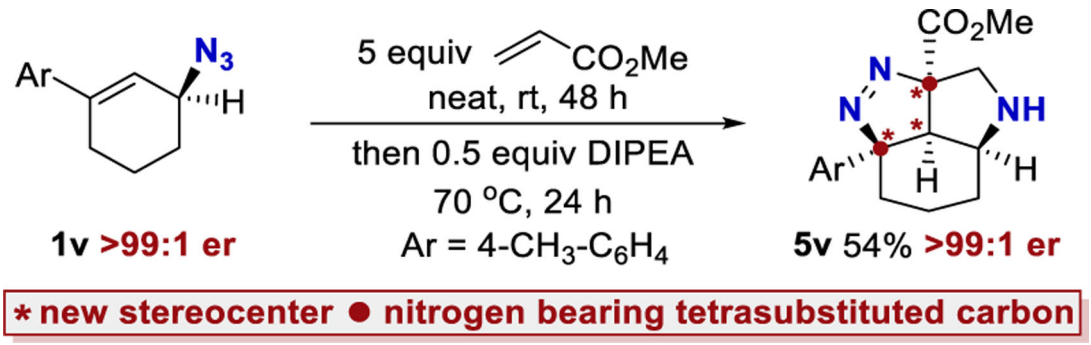


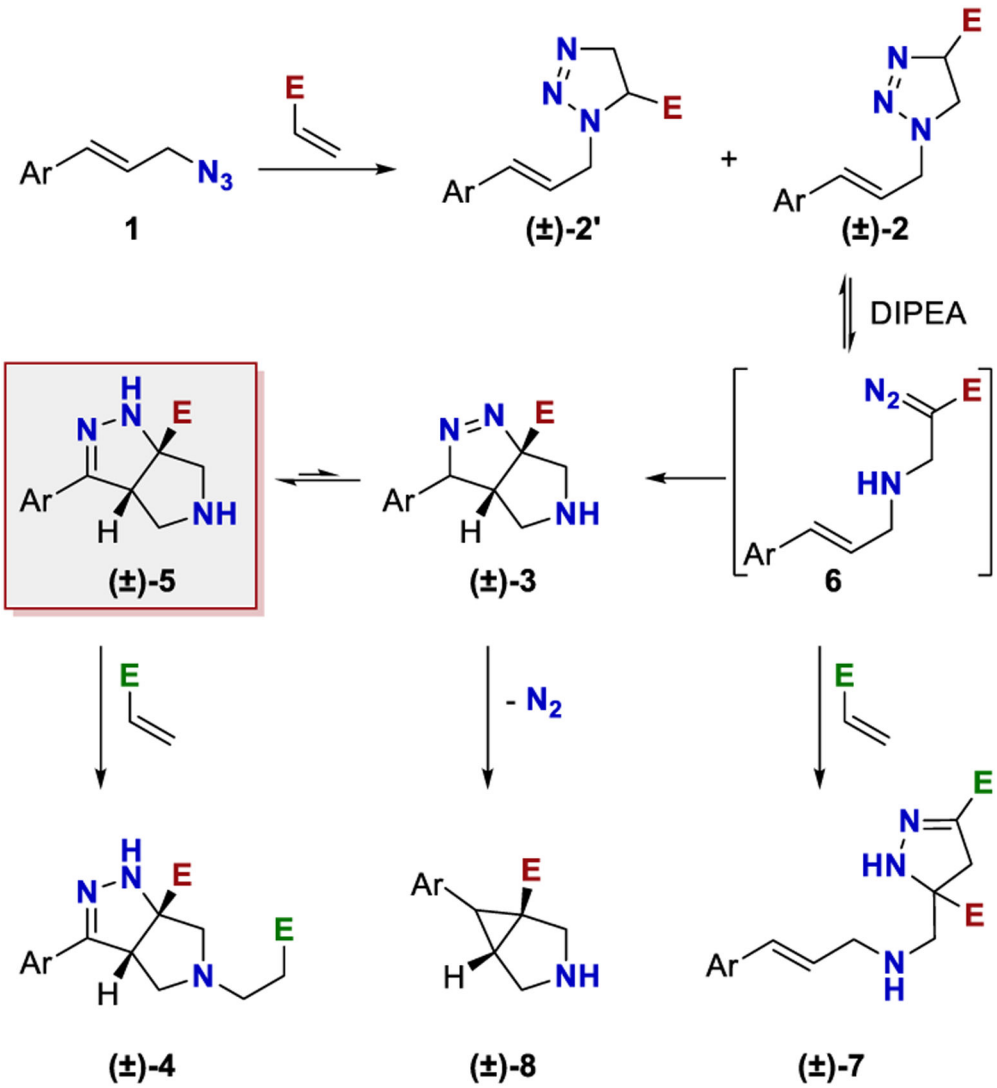
Figure 1.
Biologically active fused heterocycles.



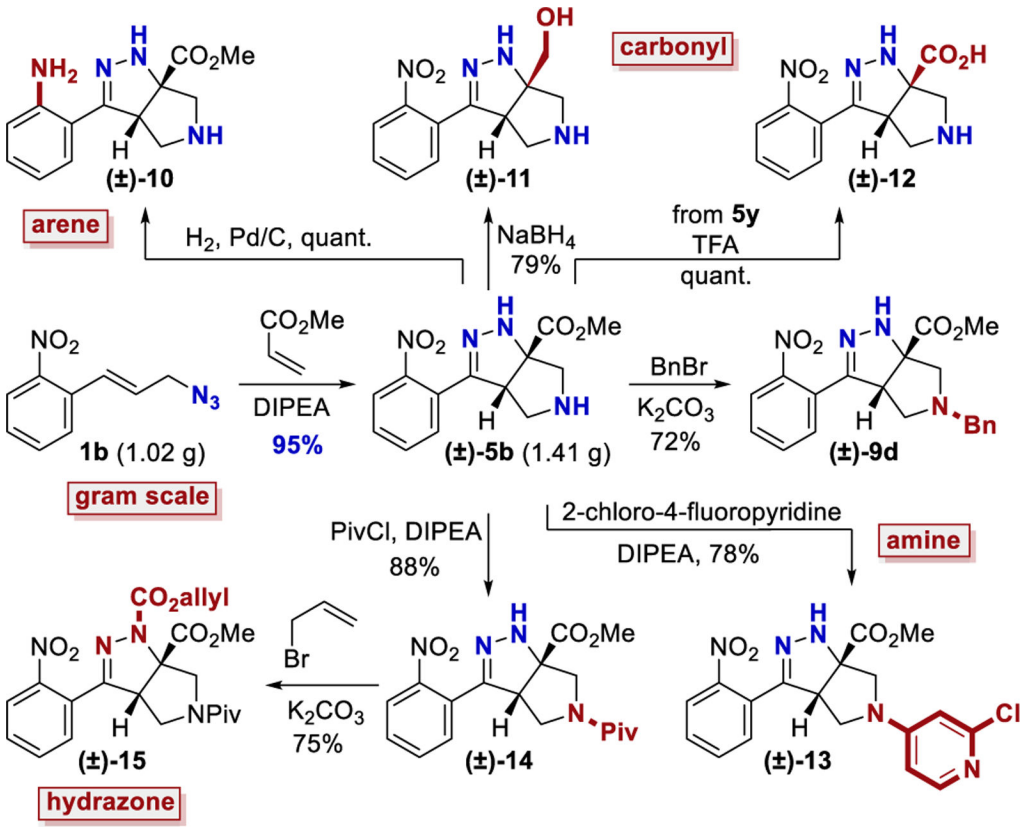
Scheme 1.
Synthesis of Tetrahydro-Pyrrolo-Pyrazoles



Scheme 2.
Stereospecific Cascade Reaction



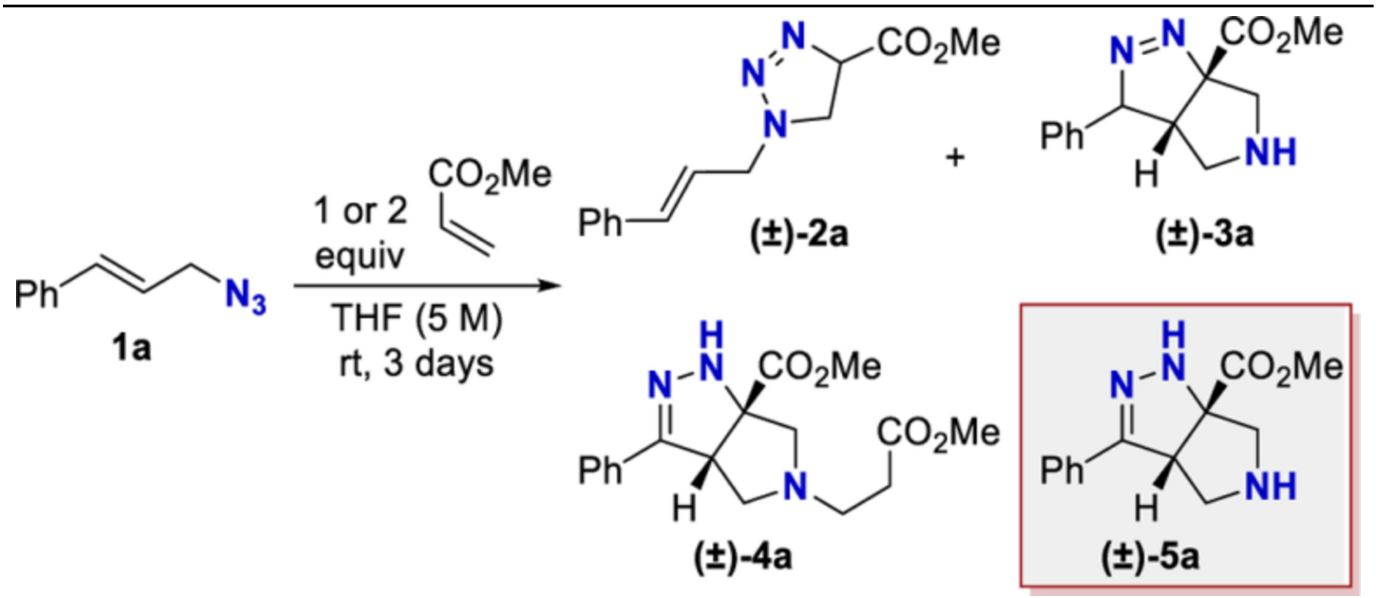
Scheme 3.
Mechanism of the Cascade Reaction



Scheme 4.
Gram-Scale Reaction and Product Derivatization

Table 1.

Replicating Yang's Reported Conditions

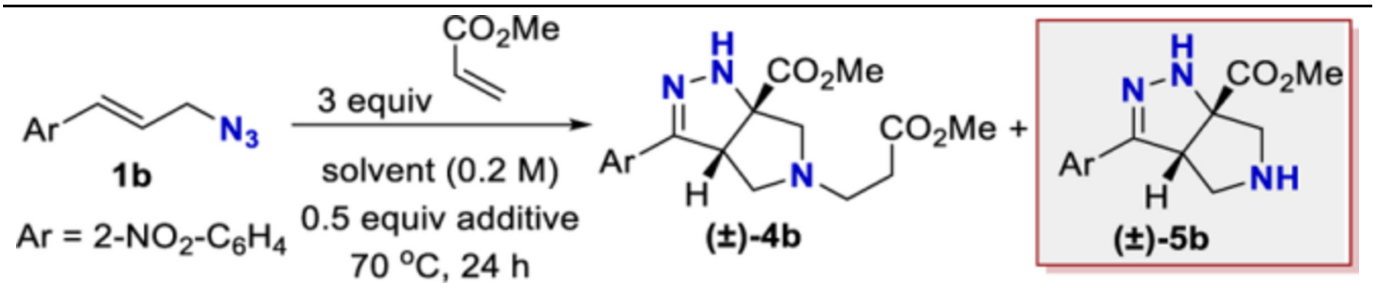


entry	equiv MA	% 1[a]	% 2[a]	% 3[a]	% 4[a]	% 5[a]
1	1	31	13	8	6	13
2	2	4	24	13	9	9

[a]Reactions were conducted with azide **1a** (90 μmol) and methyl acrylate (90 or 180 μmol) in THF (5 M) at rt. Conversion and yield were determined by ^{1}H NMR. Reactions were run in duplicate, and the average value is reported. MA = methyl acrylate

Table 2.

Cascade Optimization with Methyl Acrylate

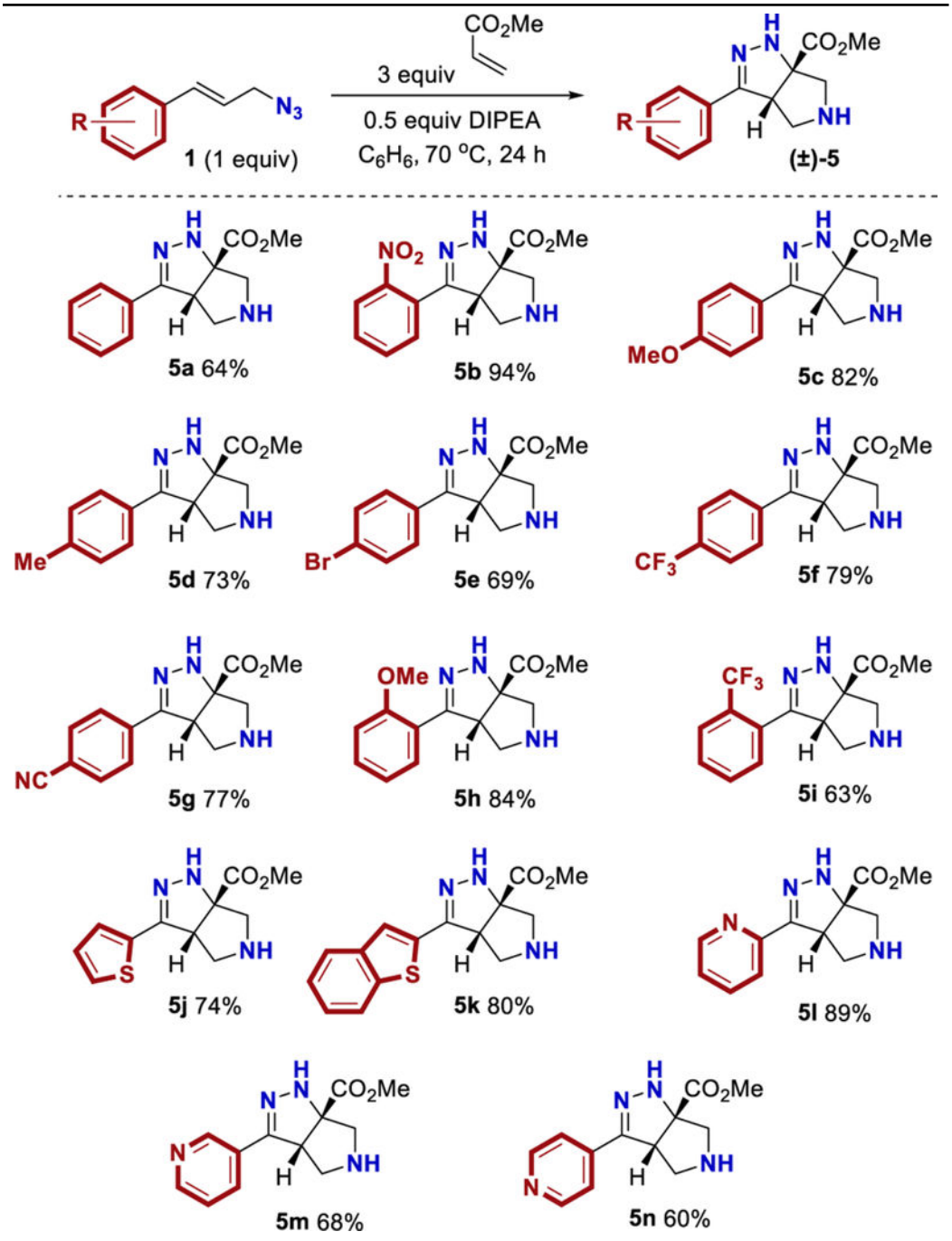


entry	solvent	additive	% 2b[a]	% 4b[a]	% 5b[a]
1	DMSO		nd	14	77
2	MeOH		nd	95	n.d.
3	hexane		nd	54	35
4	THF		34	nd	46
5	C_6H_6		37	nd	11
6	C_6H_6	AcOH	nd	67	nd
7	C_6H_6	HFIP	nd	55	17
8	C_6H_6	DMAP	nd	8	80
9	C_6H_6	pyridine	5	nd	41
10	C_6H_6	TEA	nd	nd	85
11	C_6H_6	DIPEA	nd	nd	91
12	PhMe	DIPEA	nd	nd	83
13	THF	TEA	nd	nd	72
14	THF	DIPEA	nd	nd	78

[a]Reactions were conducted with azide **1b** (70 μmol), methyl acrylate (210 μmol), and an additive (35 μmol) in solvent (0.2 M) at 70 °C. Conversion and yield were determined by calibrated GC-FID analysis. Reactions were run in duplicate, and the average value is reported. Not detected = nd.

Table 3.

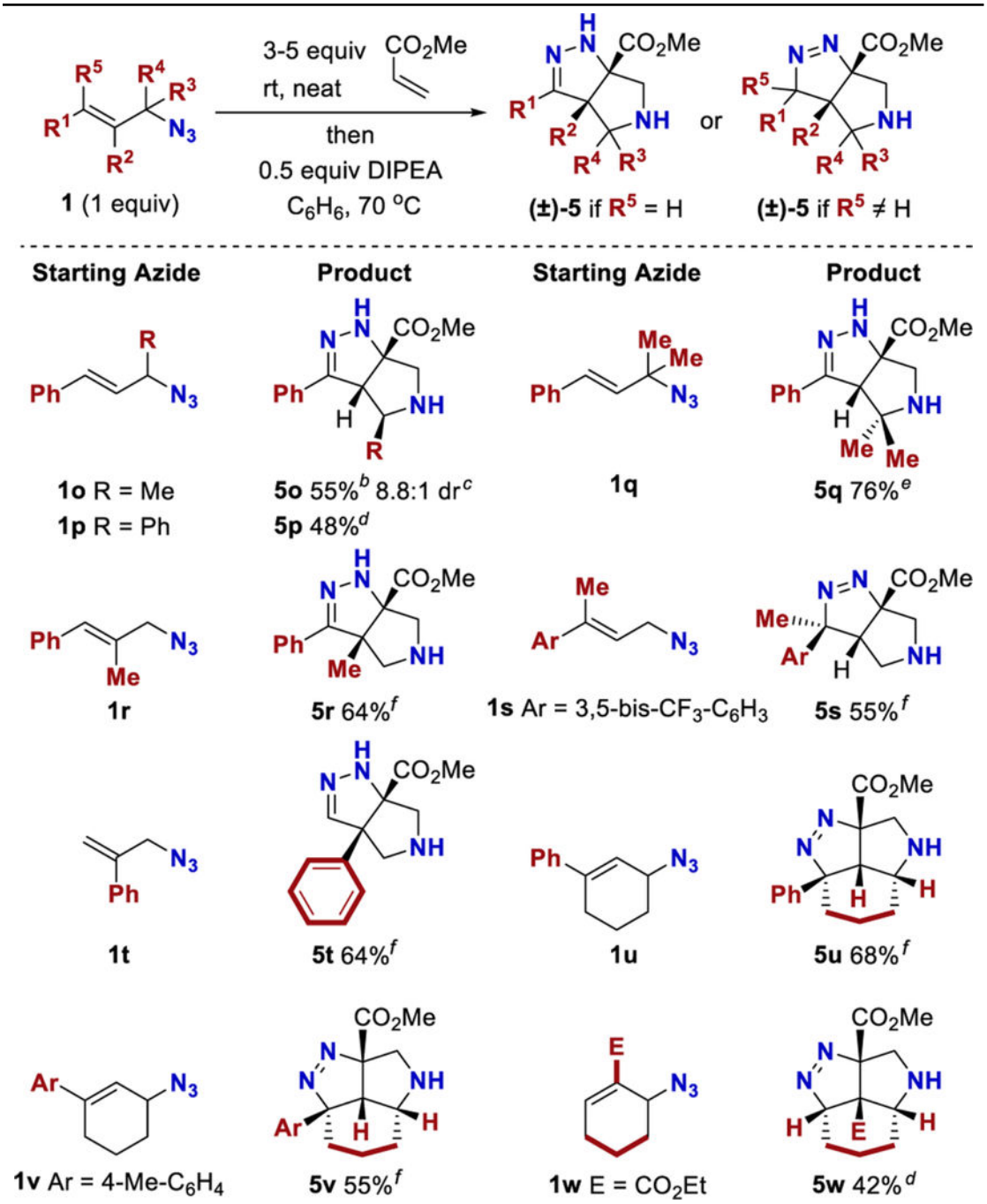
Scope of the Cascade Reaction with Cinnamyl Azides[a]



[a]Yields are reported for isolated and purified products. Yield values reflect the average of duplicate trials.

Table 4.

Reaction Scope with Substituted Allylic Azides[a]



[a]Yields are reported for isolated and purified products. Yield values reflect the average of duplicate trials.

[b]Initial 72 h incubation at rt with an additional 24 h at 70 °C.

[c] Diastereomeric ratio determined by crude ^{1}H NMR spectroscopy.

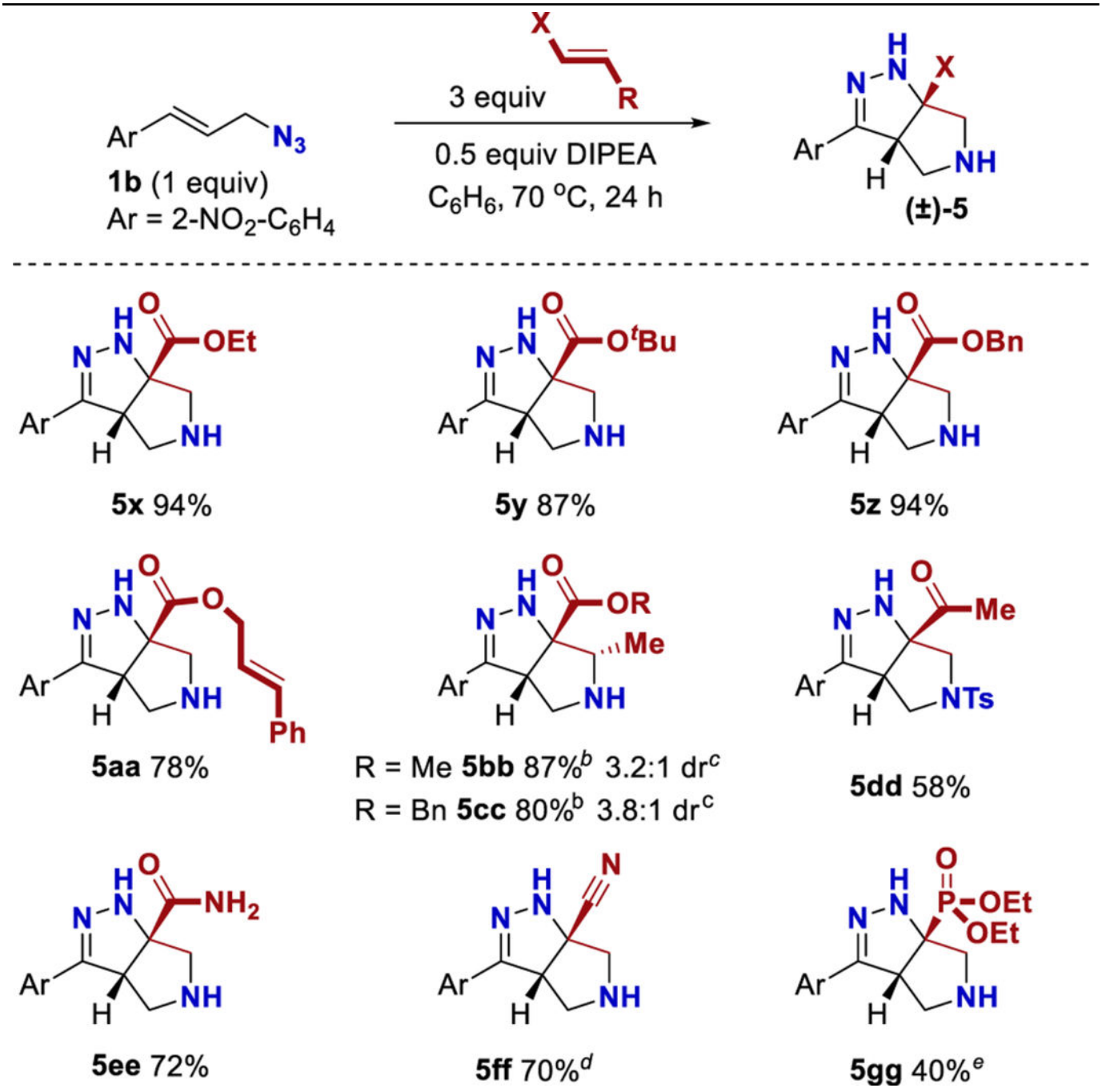
[d] Reaction for 48 h at 70 °C.

[e] Reaction for 72 h at 70 °C.

[f] Initial 48 h incubation at rt with an additional 24 h at 70 °C.

Table 5.

Reaction Scope with Different Michael Acceptors[a]



[a]Yields are reported for isolated and purified products. Yield values reflect the average of duplicate trials.

[b]Reaction for 5 days at 70 °C.

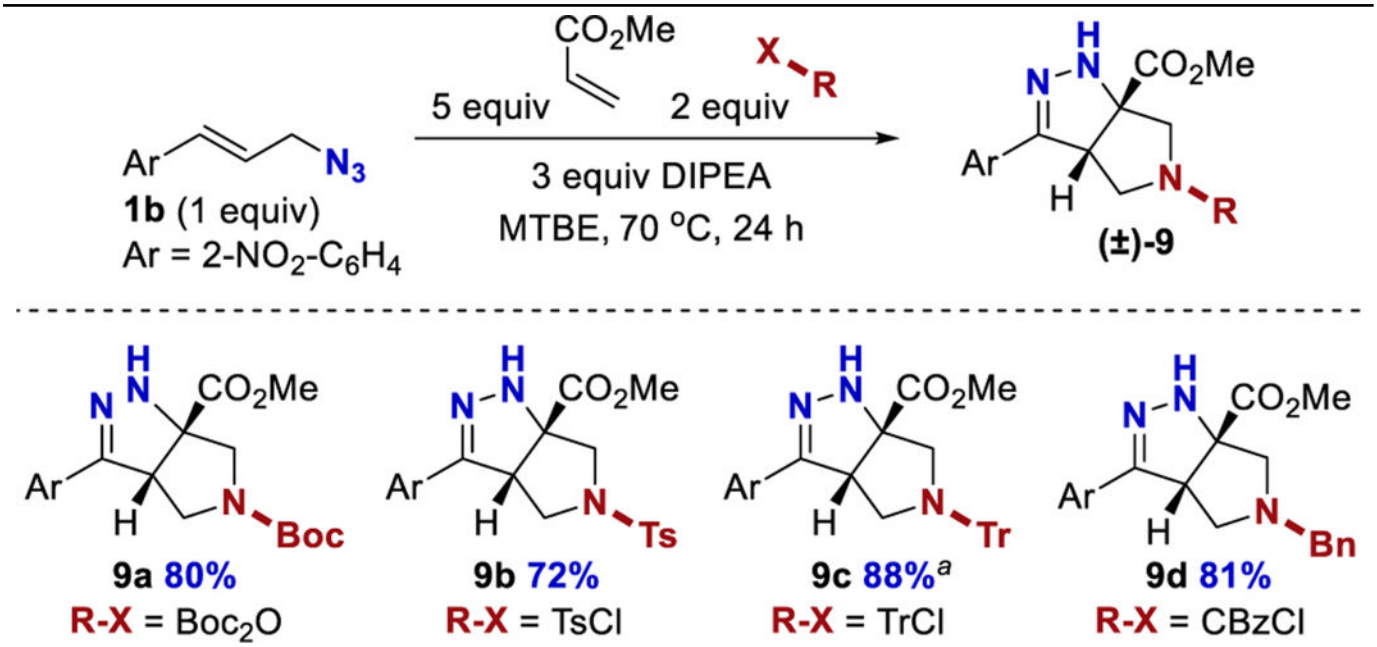
[c] Diastereomeric ratio determined by crude ^{1}H NMR spectroscopy.

[d] Initial 24 h incubation neat at 40 °C. Then C_6H_6 and DIPEA were added for an additional 24 h at 40 °C.

[e] The reaction was heated to 90 °C.

Table 6.

Product Functionalization *in Situ* to Expand Cascade[a]



[a]Yield reflects the sum of both tautomers. Yields are reported for isolated and purified products.

Table 7.

Tautomerization with TFA and DBU

additive (equiv)	time (h)	9c′/9c
none	0.5	55:45
none	18	55:45
TFA (3)	0.5	43:57
TFA (3)	18	0:100
DBU (0.5)	0.5	22:78
DBU (0.5)	18	0:100

Methyl (3aS,6aS)-5-Benzyl-3-(2-nitrophenyl)-3a,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-6a(1H)-carboxylate (9d).