Highly Diastereoselective Convergent Synthesis of Polycyclic Pyrroles with Consecutive Quaternary Stereocenters: Cascade Construction of Multiple C−C and C−Hetero Bonds

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Ⓢ *Supporting Information*

ABSTRACT: A three-component strategy for the efficient and diastereoselective synthesis of unprecedented polycyclic pyrroles (**4**) bearing four consecutive quaternary stereocenters has been developed. The reaction was performed with three readily available starting materials: heterocyclic ketene aminals (HKAs) (**1**), acenaphthylene-1,2-dione (**2**), and ethyl trifluoroacetylacetate (**3**). In the one-step cascade reaction, two C−C bonds, two C−Hetero bonds, four consecutive quaternary stereocenters, and two heterocycles were constructed. The established protocol presented outstanding diastereoselectivity (up to 99:1) and provided a valuable route to access highly functionalized polycyclic pyrroles with conciseness, rapidness, and practicability. The reaction is particularly attractive due to the following advantages: atom economy, optimum convergence, high bond-forming efficiency, and operational simplicity.

KEYWORDS: *Cascade reaction, C−C bonds, C−Hetero bonds, Diastereoselective, Heterocyclic ketene aminals, Multicomponent reaction, Pyrrole, Quaternary stereocenters*
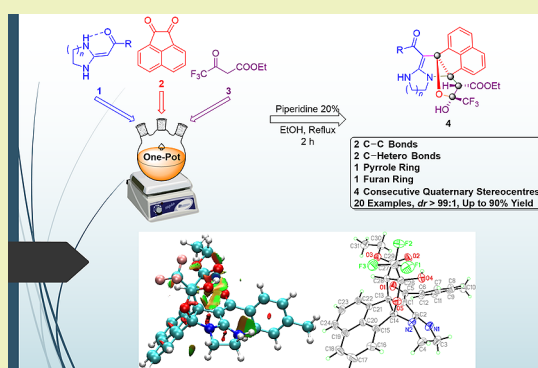
■ INTRODUCTION

One of the most important aspects of modern organic synthesis is necessary to develop methods with a low environmental impact.[1] In recent years, the pivotal areas in green chemistry have been in searching for environmentally benign reaction media to replace the commonly used toxic organic solvents in chemical processes[2] or through one-pot reactions to avoid the usage of stoichiometric catalysts and precious metals.

The formation of C−C bonds or C−Hetero bonds is a key goal in synthetic organic chemistry[3−7] due to their unique roles in assembling the diverse and complex carbon backbones. Particularly, the efficient and stereoselective introduction of quaternary stereocenters into organic compounds represents a continuing challenge to organic chemists. On the other hand, quaternary stereocenters are prevalent in many naturally occurring and biologically active secondary metabolites and some pharmaceutical agents. Actually, the construction of consecutive quaternary stereocenters is usually seriously impeded by steric hindrance, and methods for preparing such architectures in one-step are few and far between. Therefore, it is highly desirable to develop alternative methods for construction of such compounds that could be advantageous for functional group tolerance and operational simplicity, as well as the use of readily available and stable starting materials.

Recently, several methods for construction of quaternary stereocenters have been reported,[8−18] for example, the Michael addition of active methylene compounds,[19,20] Morita−Baylis−Hillman reaction of electron-poor alkenes,[21] intramolecular acylcyanation of α-substituted activated alkenes,[22] conjugate addition of arylboronic acids to α,β-unsaturated ketones,[23] addition of highly substituted allylic organometallics to carbonyl derivatives[24,25] and transition metal-catalyzed allylic alkylation[17] or substitution,[26] as well as cross-coupling reaction,[27−30] C−H bonds' arylation[31,32] etc.[33−42] The construction of target compounds with four consecutive quaternary stereocenters in one-step is rare. In fact, only a few reactions can make multiple quaternary stereocenters, such as the intramolecular [3 + 2] cross cycloaddition (IMCC),[43] Diels−Alder reaction,[44] and cyclopropane ring-opening followed by an intramolecular Friedel−Crafts alkylation of nucleophiles.[45] In addition, most of the methods described above suffer from common limitations for the use of toxic solvents and hazardous and costly catalysts, and they often require rigorous reaction conditions.

Molecularly diverse and complex heterocycles play important roles as leading compounds in discovery of new pharmaceutical reagents.[46−49] Notwithstanding, creating these compounds from common and readily available substrates and forming various C−C, C−O, and C−N bonds and rings in a single operation continues to be challenging. Multicomponent cascade reactions[50−58] combine three or more reagents in a one-pot process to form a product that incorporates the structural features of each reagent. Such reactions have many advantages, including high atom economy, step efficiency, diversity, and operational simplicity. In the past decade, a lot of multicomponent reactions have been reported,[59−63] yet developing novel MCRs that meet almost all of advantages above is still in the burgeoning phase.

HKAs (**1**) are readily available synthons in organic synthesis.[64−66] They have been widely used for the synthesis of a large variety of heterocyclic and fused heterocyclic compounds.[67−79] As a continuation of our research interest in the construction of new heterocyclic compounds, we describe herein a cascade double [3 + 2] strategy for the diastereoselective convergent synthesis of a series of unexpected polycyclic pyrroles (**4**) bearing four consecutive quaternary stereocenters and two heterocycles (Scheme 1). To

Scheme 1. General Strategy for Diastereoselective Synthesis of Polycyclic Pyrroles 4 via a Double [3 + 2] Cascade Reaction
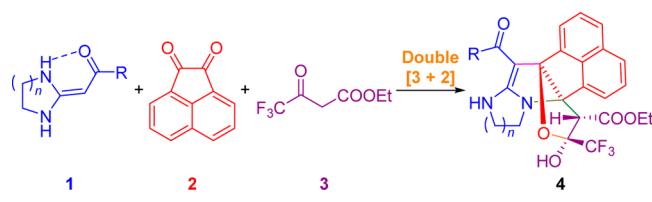
the best of our knowledge, the synthesis of the polycyclic pyrrole derivatives (**4**) has not been reported. Hence, we design the first methodology to synthesize desirable targets via a tandem multicomponent reaction of enamines (**1**), 1,2-biacceptor (**2**), and active methylene compound (**3**).

EXPERIMENTAL SECTION

General Methods. All chemicals and solvents were used as received without further purification unless otherwise stated. Materials **2** and **3** were purchased from Adamas Reagent Co., Ltd. Column chromatography was performed on silica gel (200−300 mesh). All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) or Bruker AVIII-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz). Chemical shifts (δ) are expressed in ppm, and J values are given in Hz. DMSO-d_6 was used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using a KBr pellet. The reactions were monitored by thin-layer chromatography (TLC) using silica gel GF254. The melting points were determined on a XT-4A melting point apparatus and are uncorrected. HRMS was performed on an Agilent LC/Msd TOF and monoisotopic mMass instrument.

Noncommercially Available Compounds. Synthesis of HKAs **1**. This series of compounds was prepared according to a procedure described in the literature.[71] The identity of the materials was confirmed by ^{1}H and ^{13}C NMR, and by the MS spectra.

General Procedure for the Synthesis of Compound 4. A mixture of HKAs **1** (1.0 mmol), acenaphthylene-1,2-dione **2** (1.1 mmol), and ethyl trifluoroacetylacetate **3** (1.1 mmol) with piperidine (0.2 mmol) was dissolved, in succession, in ethanol (15 mL) and stirred at reflux for 2 h. Upon completion, monitored by TLC, the

reaction mixture was quenched with a saturated NH$_4$Cl solution (2 mL) and extracted with ethyl acetate (20 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by flash chromatography with petroleum ether−ethyl acetate (3:1, v/v) giving a white pure solid **4**.
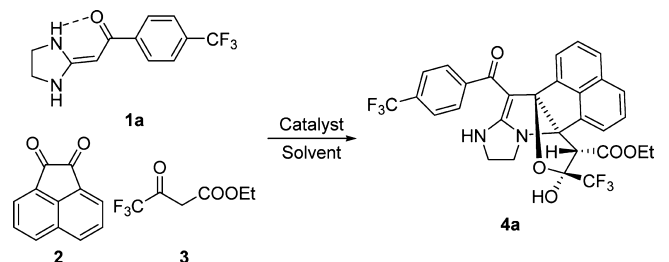
Representative Characterization Data. Ethyl (6bR,11aR,13S,14S)-13-hydroxy-13-(trifluoromethyl)-11-(4-(trifluoromethyl)benzoyl)-9,10-dihydro-8H-11a,6b-(epoxyethano)-acenaphtho[1′,2′:4,5]pyrrolo[1,2-a]imidazole-14-carboxylate (**4a**). White solid, mp. 217−219 °C; IR (KBr) (ν_{max}, cm^{-1}): 3453, 3219, 1701, 1557, 1190, 1027, 853. ^{1}H NMR (400 MHz, CDCl$_3$) (δ, ppm): 8.39 (d, J = 7.0 Hz, 1H, ArH), 7.87 (d, J = 8.0 Hz, 1H, ArH), 7.81 (d, J = 8.2 Hz, 1H, ArH), 7.63−7.68 (m, 2H, ArH), 7.49−7.60 (m, 5H, ArH), 4.36−4.46 (m, 2H, COCH_2), 3.95−3.99 (m, 1H, NCH_2), 3.83−3.90 (m, 1H, NCH_2), 3.70 (br, s, 1H, OH), 3.54−3.66 (m, 2H, NCH_2), 3.46 (s, 1H, CH), 1.44 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl$_3$) (δ, ppm): 183.2, 172.7, 163.6, 146.6, 143.0, 135.6 (d, J = 19.0 Hz), 132.1, 131.2 (d, $^2J_{C−F}$ = 32.0 Hz), 129.6, 127.6, 126.9, 126.5, 125.8, 124.5, 123.1, 122.8, 122.5, 118.8, 109.3, 105.3 (q, J = 34.0 Hz), 87.2, 77.7, 63.2, 52.8, 48.4, 40.4, 13.9. HRMS (ESI-TOF, [M + H]$^+$): calcd for C$_{30}$H$_{23}$F$_6$N$_2$O$_5$, 605.1506; found, 605.1505.

Computational Methods. All calculations were performed with the Gaussian 03 program.[80] Geometry optimizations were carried out with the M06-2X hybrid meta-GGA density functional[81] and 6-311+G(d,p) basis set.[82] The default self-consistent reaction field (SCRF) SMD model[83] was used with ethanol as solvent (dielectric constant, ε = 24.852). Frequency calculations were also employed to evaluate the structures as minimum points (no imaginary frequencies) in energy and to achieve the relevant zero-point and thermal corrections to the electronic energies in the liquid phase. The grid data for reduced density gradient (RDG) analysis[84] was generated via the Multiwfn program[85] and visualized with VMD software.[86]

RESULTS AND DISCUSSION

On the basis of our recent work, we examined the cascade reaction which employed **1a**, **2**, and **3** as the substrates in ethanol at reflux. Initially, the three-component reaction was carried out at room temperature. Whether the catalyst was added or not, the target compound **4a** was not obtained after 6 h (Table 1, entries 1 and 2). However, when the reaction was refluxed and the piperidine was added, we found that the reaction completed quickly and obtained the desirable product **4a** in an isolated yield of 83% with more than 99:1 diastereoselectivity within 2 h (Table 1, entry 3). Next, different types of organic bases such as Et$_3$N, DBU, DABCO, DMAP, and PPh$_3$ were employed as the catalysts, but no transformation was observed (Table 1, entries 3−8). The performance of inorganic bases was not satisfying either (Table 1, entries 9−12). Then, for comparison, numerous organic acidic catalysts were tested, and no desired product **4a** was obtained (Table 1, entries 13−15). Subsequently, we optimized the reaction conditions by screening several solvents or mixed solvents (Table 1, entries 16−22). Ethanol was found to be the most suitable candidate. Therefore, the best reaction conditions were achieved by employing **1** (1.0 mmol), **2** (1.1 mmol), and **3** (1.1 mmol) with piperidine (0.2 mmol) in ethanol (15 mL) under reflux for 2 h (Table 1, entry 3).

With the optimal reaction conditions, we then investigated the use of different starting materials in order to determine the reactivity domain of the cascade reaction (Table 2, entries 1−20). For HKAs **1**, the substituents, whether with electron-withdrawing (CF$_3$, F, Cl, and Br) or electron-donating (Me, Et, OCF$_3$, OMe) groups on the aromatic ring, afforded corresponding products in good to excellent yields with reasonable regioselectivity. Additionally, thiophene substituted HKA was also tolerant to the reaction (Table 2, entry 6). Also,

Table 1. Screening Optimum Reaction Conditions for the Model Reaction[a]

entry	catalyst[b]	solvent	yield[c] (%)	dr[d]
1[e]	–	EtOH	–	–
2[e]	piperidine	EtOH	–	–
3	piperidine	EtOH	83	>99:1
4	Et$_3$N	EtOH	–	–
5	DBU	EtOH	–	–
6	DABCO	EtOH	–	–
7	DMAP	EtOH	–	–
8	PPh$_3$	EtOH	–	–
9	K$_2$CO$_3$	EtOH	–	–
10	Na$_2$CO$_3$	EtOH	–	–
11	KOH	EtOH	–	–
12	NaOH	EtOH	–	–
13	HAc	EtOH	–	–
14	p-TSA	EtOH	–	–
15	L-proline	EtOH	–	–
16	piperidine	1,4-dioxane	67	>99:1
17	piperidine	toluene	77	>99:1
18	piperidine	CH$_3$CN	79	>99:1
19	piperidine	H$_2$O	trace	–
20	piperidine	H$_2$O/EtOH (1:1, v-v)	trace	–
21	piperidine	H$_2$O/EtOH (1:2, v-v)	trace	–
22	piperidine	H$_2$O/EtOH (1:3, v-v)	trace	–

[a]Reactions were performed with **1a** (1.0 mmol), **2** (1.1 mmol), **3** (1.1 mmol), and the solvent (15 mL) under reflux for 2 h. [b]Catalyst (0.2 mmol). [c]Isolated yields based on HKA **1a**. [d]Determined by ^{1}H NMR spectroscopy of the crude mixture. [e]Reactions in these entries were performed at room temperature for 6 h.
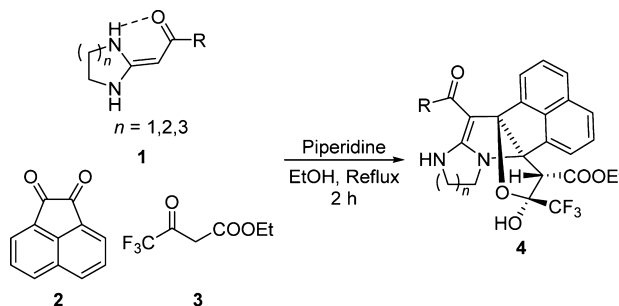
aromatic groups on substrates **1** with diverse substitution patterns (*para*, *ortho*, and *meta*) could form the target products **4** in good yields. To our delight, most of the products were generated with superior diastereoselectivity (*dr* > 99:1). However, the presence of Cl at C2 of the HKA **1n**'s aromatic ring led to moderate diastereoselectivity for unknown reasons (Table 2, entry 14).

It is worth noting that the electronic nature of the aryl group in substrate **1** has a significant impact on the yield of the reaction (e.g., Table 2, entries 1, 2, 7, and 10). A substrate with a more electron-deficient aryl afforded a much higher yield than a more electron-rich one. In addition, the **1** with substituents at the *para*-position afforded higher yields than the counterparts at the *ortho*- or *meta*-positions (e.g., Table 2, entries 2, 12, and 13).

To further broaden the scope of the title reaction, the six- and seven-membered HKAs were also employed (Table 2, entries 15–20). As expected, both reactions proceeded well and produced the related heterocyclic derivatives **4o–4t** with excellent diastereoselectivity. Compared to the five-membered HKAs, the six- or seven-membered HKAs gave lower yields because a certain amount of side-product **4'** was obtained (Scheme 2). Under the optimal reaction conditions, no products of **4** were observed for other 1,2-biacceptors (**2**) (e.g., phenanthrene-9,10-dione, indoline-2,3-dione, and benzyl)

or active methylene compounds (**3**) (e.g., ethyl 3-oxobutanoate, diethyl malonate, hexafluoropentane-2,4-dione, and ethyl 2-cyanoacetate). In order to probe the reactivity of the synthons and estimate their reaction sequence, some additional experiments were performed. First, we began our investigation by testing the reaction of **2** and **3** in ethanol that was catalyzed by piperidine. The expected Knoevenagel condensation intermediate (**Int 1'**) was not observed, yet a product (**Int 1**) was formed by the reaction of **2** and piperidine. Afterward, **1a** was added to the resulting mixture, while no target molecule was obtained (Scheme 3). Thus, it can be concluded that the HKAs **1** are more reactive than synthon **3** in the formation of C–C bond.

In addition, we depicted the reduced density gradient (RDG) isosurface of three model compounds **4g**, **4r**, and **4t** in Figure 1. It was shown that when the size of the diazaheterocycle (ring **A**) increased the ring strains between rings **A** and **B** decreased. By rule, the six- or seven-membered products (**4r** or **4t**) should be more stable than the five-membered (**4g**). Interestingly, the yield of **4r** or **4t** is less than that of **4g**. This phenomenon can be explained by two aspects: (i) The release of the ring strains cannot counteract the effects of the side reaction. (ii) The six- or seven-membered HKA is more reactive than the five-membered one.

Table 2. Substrate Scope and Synthesis of Target Materials 4[a]

| entry	1 (n/R)	4	yield[b] (%)	dr[c]
1	1a (1/4-CF$_3$Ph)	4a	83	>99:1
2	1b (1/4-FPh)	4b	83	>99:1
3	1c (1/4-ClPh)	4c	85	>99:1
4	1d (1/4-BrPh)	4d	84	>99:1
5	1e (1/Ph)	4e	86	>99:1
6	1f (1/C$_4$H$_3$S)	4f	81	>99:1
7	1g (1/4-CH$_3$Ph)	4g	89	>99:1
8	1h (1/4-EtPh)	4h	88	>99:1
9	1i (1/4-OCF$_3$Ph)	4i	81	>99:1
10	1j (1/4-OCH$_3$Ph)	4j	90	>99:1
11	1k (1/3,4-diFPh)	4k	82	>99:1
12	1l (1/2-FPh)	4l	79	>99:1
13	1m (1/3-FPh)	4m	80	>99:1
14	1n (1/2-ClPh)	4n	81	9:5
15	1o (2/4-FPh)	4o	57	>99:1
16	1p (2/4-ClPh)	4p	54	>99:1
17	1q (2/Ph)	4q	60	>99:1
18	1r (2/4-CH$_3$Ph)	4r	62	>99:1
19	1s (3/Ph)	4s	54	>99:1
20	1t (3/4-CH$_3$Ph)	4t	56	>99:1

[a]Reactions were performed with 1 (1.0 mmol), 2 (1.1 mmol), and 3 (1.1 mmol) with piperidine (0.2 mmol) in ethanol (15 mL) under reflux for 2 h. [b]Isolated yields based on HKAs 1. [c]Determined by ^{1}H NMR spectroscopy of the crude mixture.

Scheme 2. Side-Product 4′ Was Observed during the Reaction
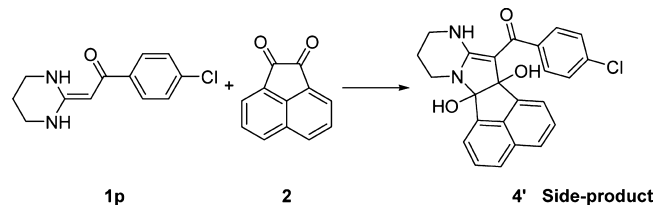
Scheme 3. Competition Reaction between Synthon 3 and Piperidine
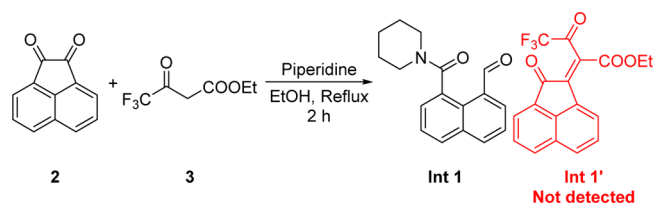
The chemical structures of polycyclic pyrroles 4 were identified by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra and further confirmed by X-ray diffraction analysis of the single crystal of 4g (Figure 2).

On the basis of experimental results above, a tentative reaction mechanism for the three-component cascade reaction is postulated (Scheme 4). With a strong electron-withdrawing keto-carbonyl group at the α-position and electron-donating diamino groups on the diazaheterocycle of HKAs, HKA 1 can serve as a nucleophilic component to react with the electrophilic acenaphthylene-1,2-dione 2, which was mediated by piperidine. First, the aza-ene addition of HKA 1 to acenaphthylene-1,2-dione 2 leads to intermediate [A], which undergoes a rapid imine−enamine tautomerization to give intermediate [B]. Then, the piperidine catalyzes ethyl trifluoroacetylacetate 3 and intermediate [B] to form the Knoevenagel intermediate [C]. Subsequently, the NH group of intermediate [C] attacks the intramolecular C−C bond via a Michael addition to form intermediate [D]. Eventually, an intramolecular Hemiketal reaction of intermediate [D] leads to the formation of target molecule 4. It is necessary to rationalize the role of the base. We propose that as a protonic base, piperidine favors the formation of an intermolecular hydrogen bond (N−H···O ↔ O−H···N) with 3 so that it could stabilize the active species 3′, which ensured that the further Knoevenagel reaction proceeded timely.[87]

■ CONCLUSIONS

In conclusion, we have successfully developed an efficient, one-pot, three-component, piperidine-catalyzed cascade reaction for the construction of highly functionalized and rarely occurred polycyclic pyrroles, which contain four consecutive quaternary
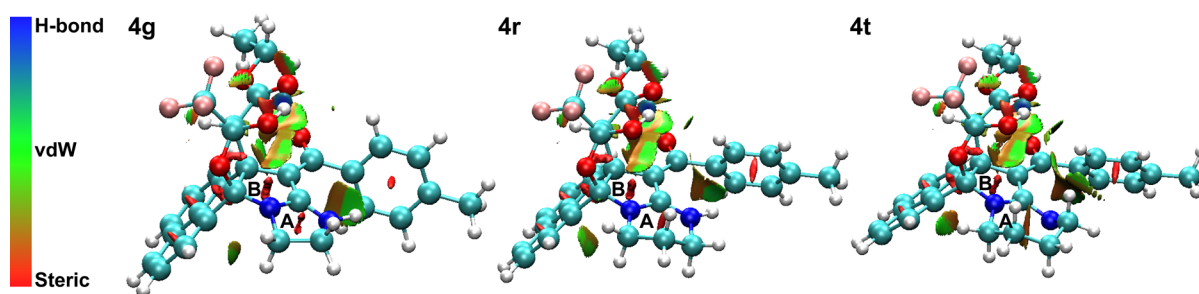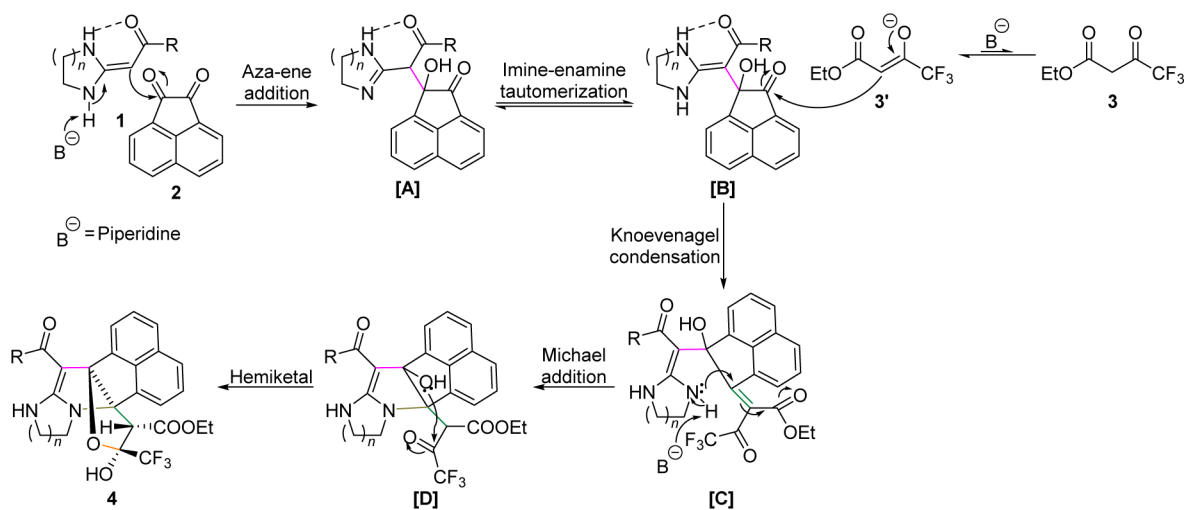
Figure 1. Reduced density gradient isosurface of compounds **4g**, **4r**, and **4t**. The color presented in the scale bar denotes the type of weak interaction (blue = hydrogen bond, green = van der Waals interaction, brown = weak steric effect, and red = strong steric effect).
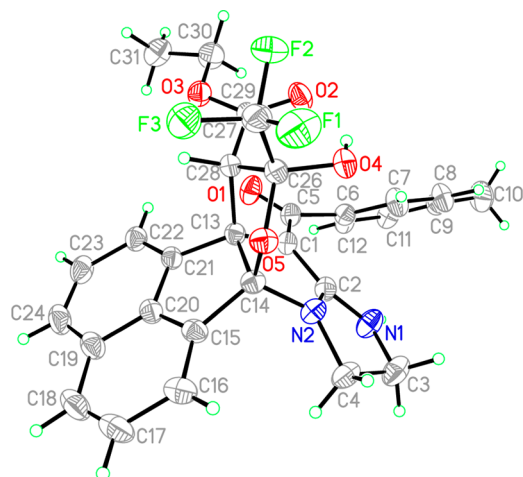
Figure 2. ORTEP view of the crystal structure of compound **4g**.

stereocenters. The outcome of the reaction is two C−C bonds, two C−Hetero bonds (C−N and C−O), and two heterocycles (pyrrole and furan rings). The reaction is particularly attractive due to the following advantages: atom economy, optimum convergence, high bond-forming efficiency, and operational simplicity. We therefore anticipate that this protocol will arouse wide interests and attention of the organic or medicinal chemistry communities. Further studies aimed at exploring the in vitro biological activities and discovering related medicinal targets of compound **4** are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic and analytical data. Original copies of ^{1}H and ^{13}C NMR spectra. Cartesian coordinates. Crystal X-ray structures (CCDC 988694) of compound **4g**. X-ray crystallographic data (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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X.-B. Chen and Z.-C. Liu contributed equally.

Notes
The authors declare no competing financial interest.

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Scheme 4. Proposed Mechanism for Construction of Polycyclic Pyrroles 4

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