JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of Heterocycle-Containing 9,9-Diarylfluorenes Using Superelectrophiles

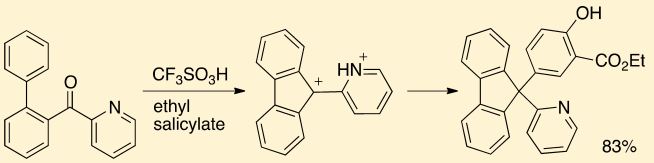
Makafui Gasonoo,[†] Akinari Sumita,[‡] Kenneth N. Boblak,[†] Kristen Giuffre,[†] Tomohiko Ohwada,*[,‡] and Douglas A Klumpp*[,†]

[†]Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115, United States

[‡]Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-8654, Japan

Supporting Information

ABSTRACT: A superacid-promoted method for the synthesis of 9,9-diarylfluorenes is described. The chemistry involves cyclizations and arylations with biphenyl-substituted heterocyclic ketones and a mechanism is proposed involving superelectrophilic intermediates. The key reactive intermediates—dicationic and trication fluorenyl cations have been observed by low-temperature NMR and the mechanism has been further studied using DFT calculations.

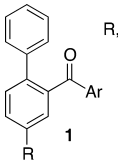


INTRODUCTION

9,9-Diarylfluorenes are an important class of aromatic compounds. Examples of these compounds have found use in electroluminescent devices and other applications.[1] Spirocyclic fluorenes have likewise been extensively studied, as their unusual π-systems have been used in organic light emitting diodes, light harvesting arrays, and organic-based electronics.[2] Due to their value in electronic devices, several useful synthetic methods have been developed for their synthesis. The most common method involves a Friedel—Crafts-type reaction with a 9-aryl fluorenyl cation, often generated from the corresponding fluoren-9-ol.[3] Electrophilic reactions at the fluorenyl cation provide the desired 9,9-diaryl fluorenes, including some spirocyclic products.[2] In the following manuscript, we describe a convenient route to heterocycle-containing 9,9-diarylfluorenes by the superacid promoted condensation of biaryl ketones. A mechanism is proposed involving superelectrophilic, di- and tricationic intermediates and the species have been further studied by DFT calculations.

RESULTS AND DISCUSSION

Dicationic carboxonium ions have been shown to be highly reactive electrophiles in Friedel—Crafts type reactions.[4] Both inter- and intramolecular transformations have been demonstrated. Heterocycle-substituted carbonyl compounds are particularly useful in Friedel—Crafts condensation reactions and they have been utilized in several synthetic methodologies leading to condensed arenes.[5] We reasoned that the 9,9-diarylfluorenes may be prepared from heterocyclic ketones having a biphenyl group. These substrates could be prepared by a number of approaches,[6] but we found that the reaction between heterocyclic nitriles and a Grignard reagent was generally the most useful.[7] Thus, 2-biphenylmagnesium bromide is reacted with 2-pyridinecarbonitrile to provide the heterocyclic ketone (**1a**) in good yield upon aqueous workup. A complementary method was developed in which a metalated heterocycle is reacted with 2-biphenylcarboxaldehyde, followed by oxidation with PCC. This methodology provides ketone **1** with 2-benzothiazole (**1h**) and 1-methyl-2-benzimidazole (**1i**) substituents.



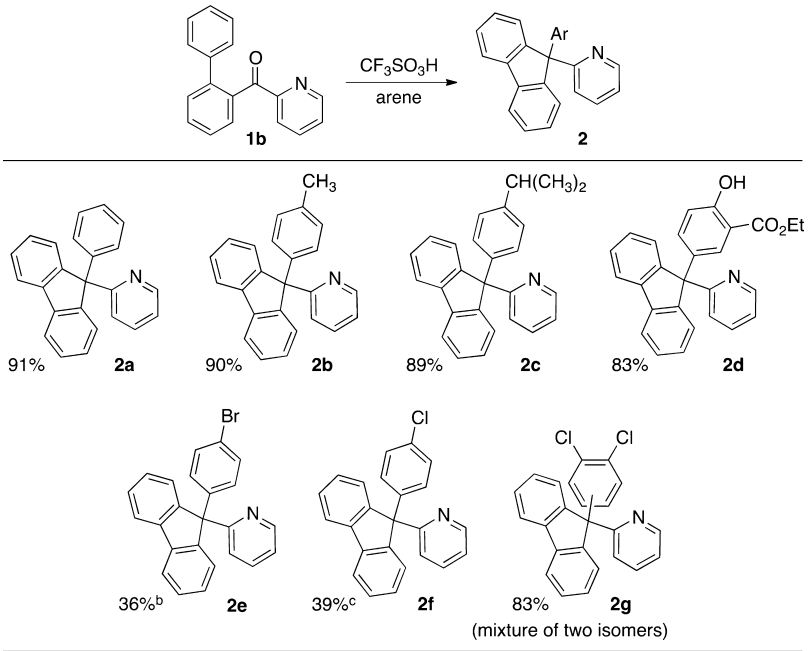
R, Ar:
1a, H, pyridin-2-yl
1b, H, pyrazin-2-yl
1c, H, pyrimidin-2-yl
1d, H, pyrimidin-5-yl
1e, H, pyridazin-3-yl
1f, CH_3, 1-butyl-1*H*-imidazol-2-yl
1g, CH_3, 1-methyl-1*H*-imidazol-2-yl
1h, H, benzo[*d*]thiazol-2-yl
1i, H, 1-methyl-1*H*-benzo[*d*]imidazol-2-yl
1j, H, phenyl

When compounds **1a** is reacted with arenes in the Brønsted superacid, CF_3SO_3H (triflic acid), the condensation products (**2a—g**) are formed in generally good yields (Table 1). For example, reaction with benzene in triflic acid gives the 9-phenyl-9-(2-pyridyl)fluorene (**2a**) in 91% yield. Compound **2a** itself has been used in electroluminescent devices.[8] Substituted arenes likewise provide the condensation products (**2b—g**) in fair to good yields. Alkyl-substituted benzenes give products **2b** and **2c** in good yields and regioselectivities. There is no evidence of transalkylation products when alkyl-substituted benzenes are utilized as nucleophiles. The condensation chemistry also produces a single regioisomer (**2d**) from ethylsalicylate. For the bromo-, chloro-, and 1,2-dichlorobenzene, the condensations occur in good yields, however the chemistry gives mixtures of regioisomers. Low yields of pure regioisomers are isolated by column chromatograpy. 1,2-Dichlorobenzene is a moderately deactivated arene, and with the good yield of product(s) **2g**, this indicates a fairly reactive electrophile is involved in the chemistry. The condensation chemistry has also been shown to be efficient with a variety of *N*-heterocyclic substrates (Table 2). Thus, diazinyl groups, such as pyrazinyl, pyrimidyl, pyridazinyl-substrates, provide good

Received: February 9, 2017
Published: May 30, 2017

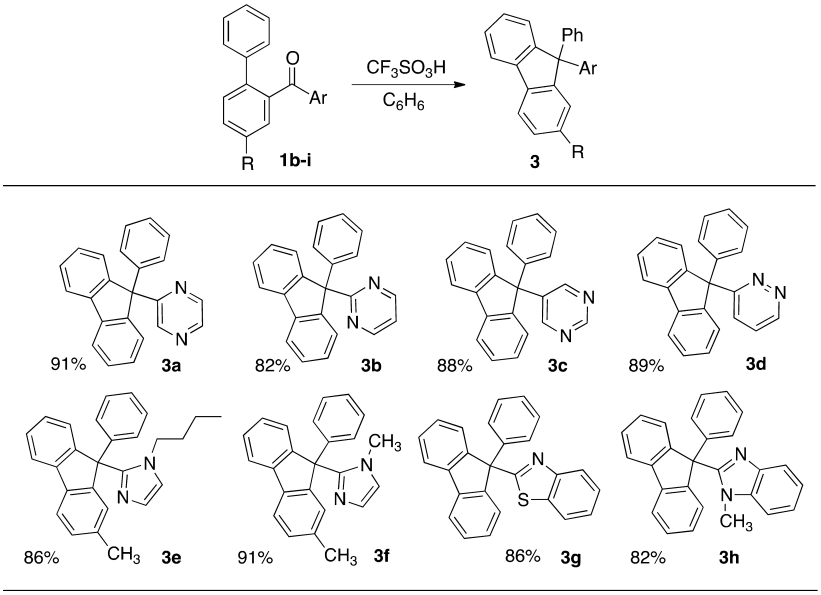
DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044−6053

Table 1. Products and Yields for the Reactions of Arenes with Ketone 1b[a]



[a]Isolated yields. [b]Mixture of regioisomers also isolated in 57% yield. [c]Mixture of regioisomers also isolated in 55% yield.

Table 2. Products and Yields for the Reactions of C_6H_6 with Ketones 1b–i[a]



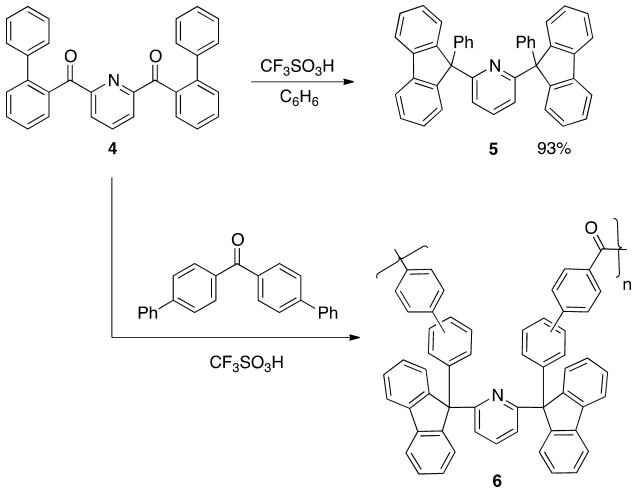
[a]Isolated yields.

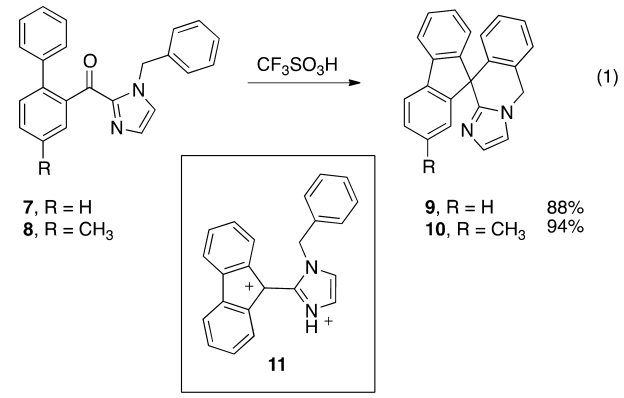
yields of products (**3a–d**). Likewise, imidazole-substrates give condensation products **3e–f**. Ring-fused *N*-heterocycles may be incorporated into the substrates, providing compounds such as **3g** and **3h**. In addition to these diarylfluorene condensation products, reaction of the diketone **4** provides the bis(fluorenyl)-pyridine **5** in excellent yield (Scheme 1). Thus, each carbonyl group undergoes condensation leading to the two 9-fluorenyl groups. As a substance with two reactive functional groups, diketone **4** has the potential to form macromolecular products in A_2B_2 polymerizations. To explore this possibility, compounds **4** was also reacted with 4,4′diphenylbenzophenone in superacid. The resulting product (**6**) precipitated from solution upon quenching of the reaction mixture with ice water. The high-molecular weight product exhibited low solubility in organic solvents and a melting point/glass transition temperature in excess of 200 °C. The material remains a solid even at 350 °C, though the sample begins to darken. The infrared spectrum of the polymeric material shows a carbonyl group stretch at 1640 cm^{-1}, which is in the expected range of biaryl ketones, ca. 1660 cm^{-1}, and 4,4′diphenylbenzophenone, 1638 cm^{-1}.

In an effort to prepare spirocyclic structures, the benzyl-substituted imidazoles **7** and **8** were prepared (eq 1). This synthetic approach is reminiscent of the work done by Zhou and co-workers in their preparation of 9,9′spirobifluorene-1,1′-diol.[9] The desired precursors were synthesized in three steps

DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044–6053

Scheme 1. Condensation Reactions with Diketone 4



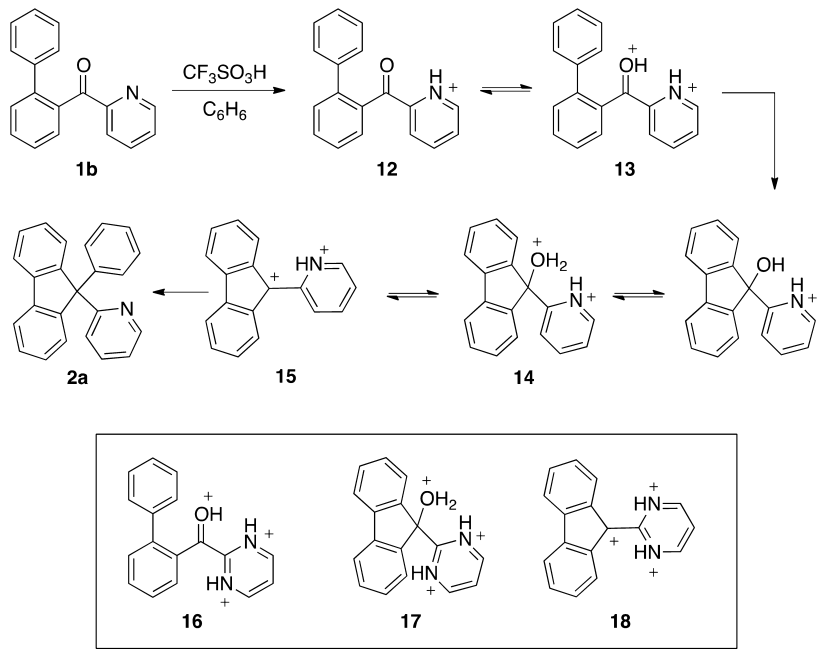


from 1-benzylimidazole. For example, **7** is prepared from 2-biphenyl carboxaldehyde by reaction with the 2-lithiated 1-benzylimidazole, followed by PCC oxidation. When substrate **7** is reacted with superacid, the spirocyclic fluorene derivative **9** is formed in 88% yield. The chemistry is assumed to involve formation of the dicationic species **11** by reaction at the carbonyl group. Cyclization of the benzyl group then leads to product **9**.

In a similar respect, the condensation reactions of the other systems involve superelectrophilic di- and tricationic species. Compound **1b** leads to the dicationic carboxonium ion (**13**), oxonium ion (**14**), and carbenium ion (**15**) intermediates (Scheme 2). It is assumed that cyclization is rapid, so formation of **13**–**15** precludes reaction with benzene. Low temperature (−40 °C) NMR studies were done using compound **1b**, and upon solvation in FSO_3H–SO_2ClF, the dication **15** is directly observed. The spectrum of **15** matches the reported spectral data obtained from ionization of **1b** in magic acid solution, FSO_3H–SbF_5–SO_2ClF.[10,11] The intensely colored (blue) ion **15** is formed almost instantaneously in the superacid—neither the carboxonium **13** or oxonium ions were **14** detected in the NMR spectrum. Fluorosulfonic acid has an acidity (H_o −15.1) similar to triflic acid (H_o −14.1),[12] so it is likely that ions **13** and **14** are transient species in the triflic acid-promoted condensations. The dicationic carbenium ion **15** gives the final product **2a** by Friedel–Crafts reaction with benzene. In the cases where diazine substrates are used, tricationic intermediates are likely involved. For example with the pyrimidine derivative **1c**, the tricationic species **16**, **17**, and **18**, are involved in the conversion to the condensation product **4a** (Scheme 2). The tricationic carbenium ion **18** may be directly observed by low temperature NMR with ionization of the pyrimidyl ketone (**1c**) in FSO_3H–SbF_5–SO_2ClF.[10] In a similar respect, ionization of the diketone **4** under stable ion conditions leads to the tricationic structure **19** (Figure 1). The 14 signals from compounds **4** simplify to 9 ^{13}C signals observed from trication **19** (two peaks overlap). With ionization of compound **4**, the carbonyl signal at δ 197.5 disappears and the fluorenyl cation resonance arises at δ 187.2.

In order to compare the reactivities of the di- and tricationic electrophiles with a monocationic homologue, 2-phenyl

Scheme 2. Proposed Mechanism for the Condensation of 1b and the Intermediates Arising from 1c



DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044–6053

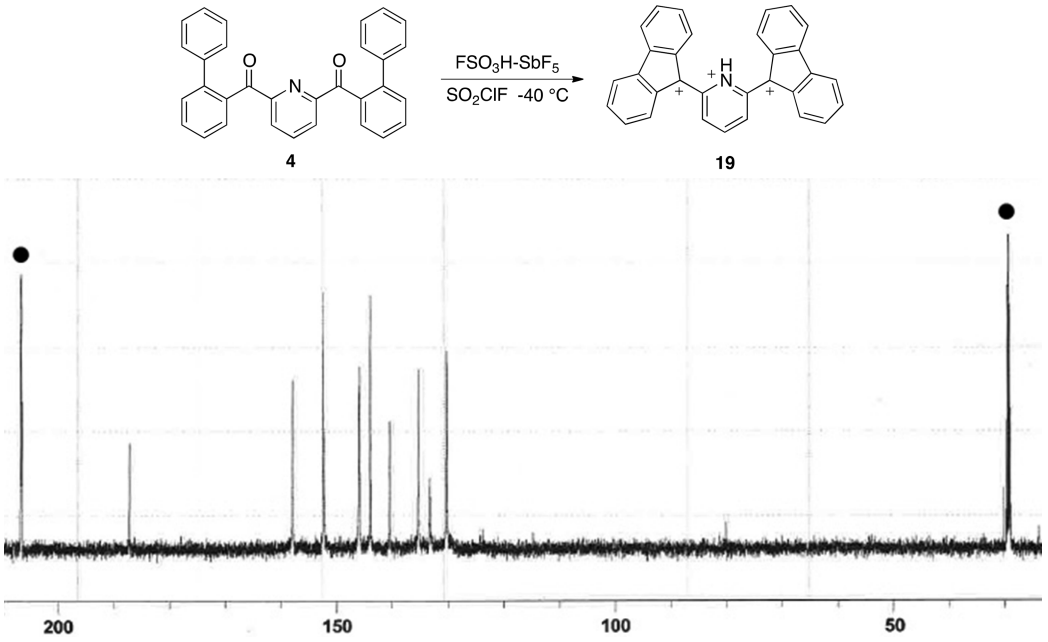
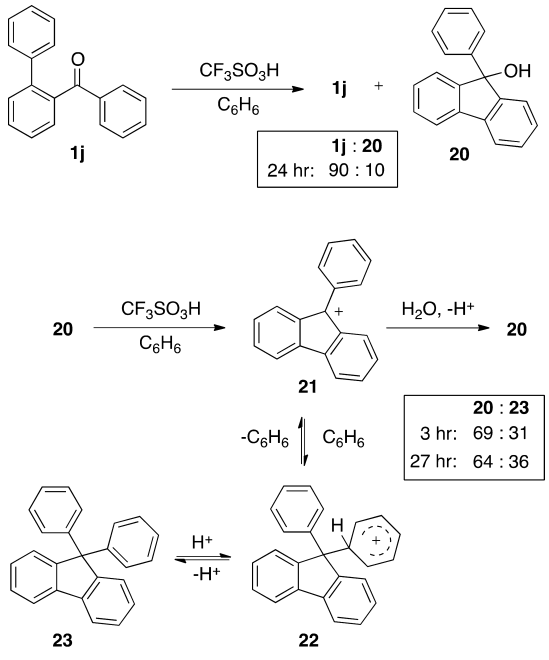


Figure 1. ^{13}C NMR of trication **19** from ionization of diketone **4** in $FSO_3H-SbF_5-SO_2ClF$ at −40 °C (● denotes signals from d_6-acetone external standard).

benzophenone (**1j**) was also reacted with benzene and triflic acid. After 24 h of reaction time (25 °C), more than 90% of the mixture was found to be unreacted ketone (**1j**) with some (<10%) 9-phenyl-fluoren-9-ol (**20**) also present (Scheme 3).

Scheme 3. Reactions of Ketone 1j, Alcohol 20, and the Relative Yields of Products



This suggests that the corresponding monocationic carboxonium ion (*vide infra*) exhibits low electrophilic reactivity compared to analogous superelectrophilic carboxonium ions (**13** and **16**).

The superacid-promoted reaction was also attempted with 9-phenyl-9*H*-fluoren-9-ol (**20**, Scheme 3). Thus, ionization of **20** in superacid with benzene provides the Friedel−Crafts product **22** in low conversion (30%), along with recovered starting material **20** (product ratio determined by GC-FID). With extended reaction time, the ratio of **20** and **23** still favors the starting alcohol, indicating that an equilibrium ratio is obtained (ca. 65:35, **20:23**). With formation of the 9-fluorenyl cation **21**, the Friedel−Crafts reaction leads to the σ-complex **22** and then the product **23**. However, the superacid is capable of *ipso*-protonation of the phenyl group on **23**,[13] reversing the reaction path, and leading to the carbocation **21** and then **20** upon aqueous workup. This equilibrium is likely a consequence of the stability, and relatively low electrophilicity, of the monocation **21**. These data are in accord with the observations of Huang and co-workers, where ion **21** is only found to react with electron-rich or activated arenes and heteroarenes.[3a] In contrast, the di- and tricationic fluorenyl cations (i.e., **15** and **18**) provide complete conversions to the respective phenylation products. It is suggested that the di- and tricationic fluorenyl cations exhibit superelectrophilic character, leading to equilibria favoring the Friedel−Crafts product.

In order to further characterize the reactivities of the cationic intermediates, DFT calculations were done.[14] The calculations sought to compare the energetics of cyclization and phenylation of the monocationic, dicationic, and tricationic electrophiles. Starting from the proposed carboxonium ion intermediates, the reaction pathways were divided into three steps: the cyclization step, the dehydration step, and the S_EAr step (Figures 2−4). The structures of the intermediates and transition states were optimized at the CPCM-M062*X*/6-311++G(d,p) level (solvent = CF_3SO_3H) and the energies of the optimized structures were then calculated at the CPCM-B3LYP/6-31+G(d) (solvent = CF_3SO_3H) level.[14]

The first reaction step examined involves cyclization of the carboxonium ions at the neighboring phenyl group. Thus, C−C bond formation occurs with monocation **24** to give the cyclization intermediate **25** (Figure 2), with a calculated Gibbs activation energy of 24.1 kcal/mol (**TS1**). The cyclization intermediate **25** is estimated to be less stable (19.1 kcal/mol) than the carboxonium ion **24**.

DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044−6053

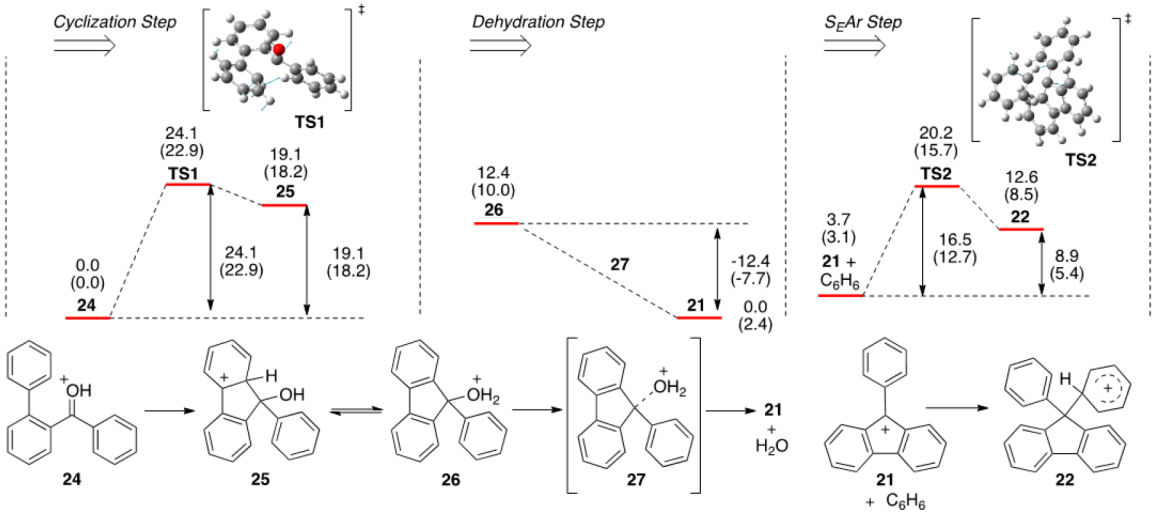


Figure 2. Calculated structures and energies, ΔG kcal/mol (at 298.15K), for Friedel–Crafts reaction of monocationic species (ΔH values in parentheses). **26** cannot be defined as a local minimum, as it spontaneously collapses into monocation **21** and water without an apparent transition state. The frequency and energy of cation **26** was calculated using a structure modeled from the stable oxonium ion **14** (see Figure 3).

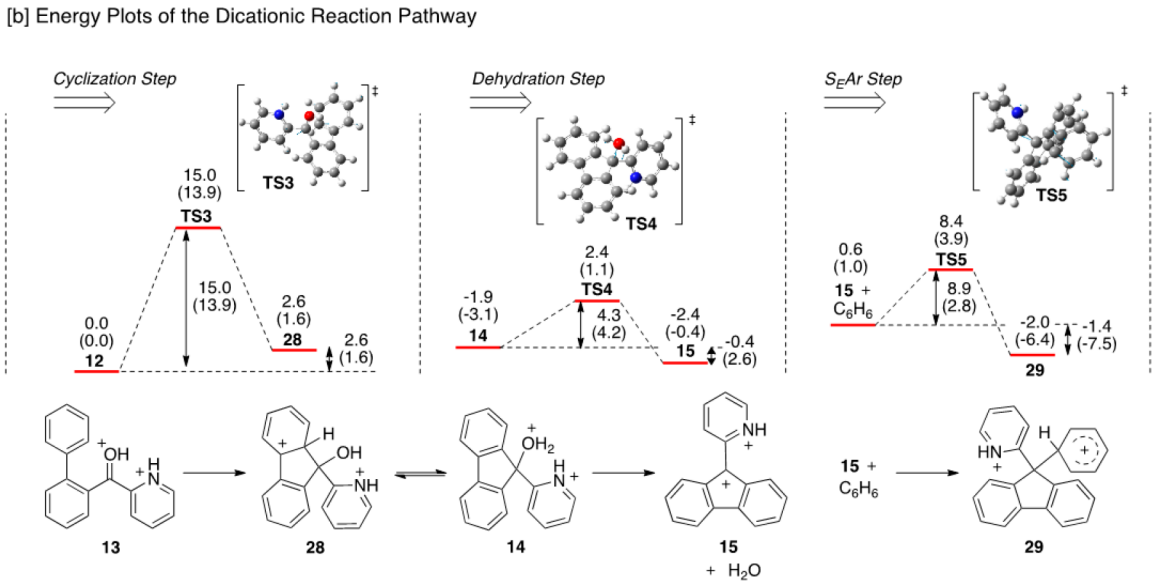


Figure 3. Calculated structures and energies, ΔG kcal/mol (at 298.15K), for Friedel–Crafts reactions of dicationic species (ΔH values in parentheses).

Increasing the charge on the carboxonium ion leads to significant changes in the energetics of cyclization. In the case of the dication **13**, the Gibbs activation energy is reduced (compared to the monocation) to 15.0 kcal/mol (Figure 3). This represents a 9.1 kcal/mol lowering of the activation energies for cyclization. This change may be understood to be a consequence of the high electrophilic reactivity of **13** and the effective separation of positive charge during the bond-forming step. Previous studies have shown that charge separation is a strong driving force in the chemistry of multiply charged carbocations.[15] In addition to the lower barrier to cyclization, the cyclization intermediate **27** is only slightly less stable (+2.6 kcal/mol) than the carboxonium ion **13**. This is in contrast to the monocationic system, where the cyclization intermediate is considerably less stable (+19.1 kcal/mol) than the carboxonium ion. The same trends are observed with the tricationic cyclization (Figure 4), where the activation barrier is further lowered to 12.2 kcal/mol and the cyclization intermediate (**29**) is found to be 9.2 kcal/mol more stable than the carboxonium ion (**16**). As the charge on the substituent (heterocyclic) ring increases, the cyclization becomes increasingly favored, as seen with lowered energy barriers and stabilized cyclization intermediates relative to the carboxonium ions.

The dehydration step involves formation of the appropriate oxonium ion which undergoes loss of water to give a fluorenyl cation. In the case of the monocationic system, the oxonium ion **26** could not be located as a minimum on the potential energy surface (when the scanning procedure is conducted about the C–O bond length in **26**, the total energy is monotonously decreased without a transition state as the bond length becomes longer. See footnote in Figure 2, and in detail, see the Supporting Information). However, the transformation from the cyclization intermediate **25** to the fluorenyl cation **21** is calculated to be exergonic by more than 19 kcal/mol. Both the dicationic and tricationic oxonium ions (**14** and **17**) were characterized as intermediates, protected only by a small energy

DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044–6053

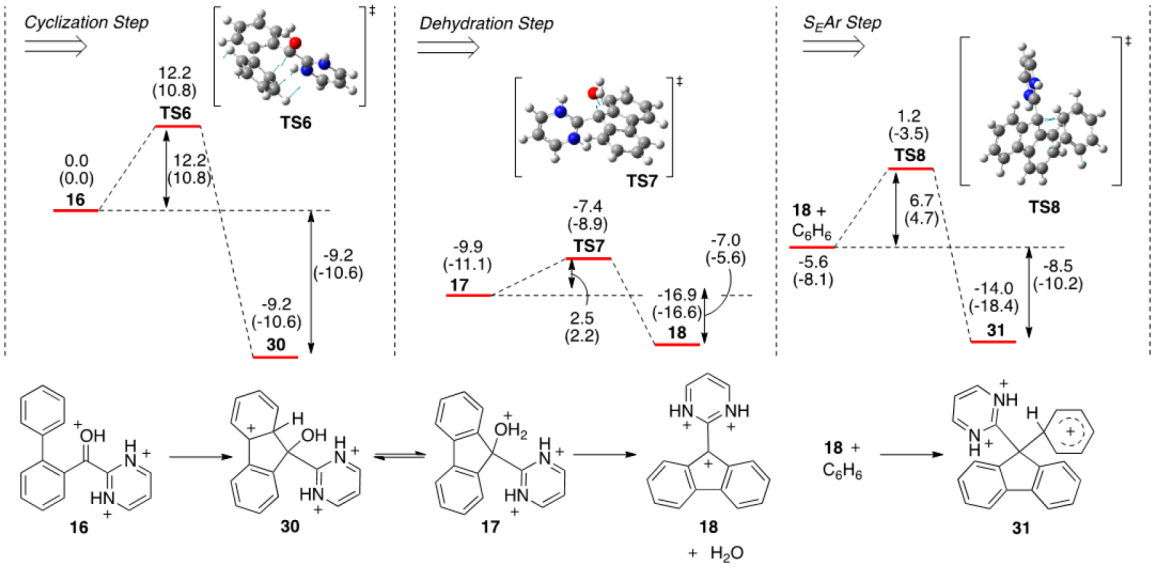


Figure 4. Calculated structures and energies, ΔG kcal/mol (at 298.15K), for Friedel–Crafts reactions of tricationic species (ΔH values in parentheses).

barrier leading to the respective fluorenyl cations (**15** and **18**). Oxonium ion **14** provides the fluorenyl dication (**15**) through transition state **TS4**, which is calculated to be just 4.3 kcal/mol less stable than **14** (Figure 3). The barrier to cleave oxonium ion **17** to the fluorenyl trication **18** is only 2.5 kcal/mol (**TS7**, Figure 4). These calculations are consistent with the experiment observations that no oxonium ions could be observed by low temperature NMR. Evidently, the oxonium ions cleave almost instantly to the fluorenyl cations.

As a measure of the electrophilic reactivities of the fluorenyl cations, the S_EAr step was also examined computationally, specifically comparing the energies of the fluorenyl cations (with added benzene) and the resulting σ-complexes. It was hypothesized that increasing electrophilic reactivities should be evident by decreasing barriers to the transition states and increasing relative stabilities of the σ-complexes. The results from the calculations confirm this hypothesis. Thus, the monocationic system involves formation of transition state **TS2** from benzene the fluorenyl monocation (**21**), wherein the Gibbs activation energy is calculated to be 16.5 kcal/mol for this transformation (Figure 2). Continuation of the reaction step leads to the σ-complex **22** which is 8.9 kcal/mol less stable than the fluorenyl monocation **21** with benzene (Figure 2). In contrast, the Gibbs activation energy decreases to 8.9 kcal/mol for the dicationic transition state (**TS5**, Figure 3) and further decreases to 6.7 kcal/mol for the tricationic transition state (**TS8**, Figure 4). Both the dicationic and trication σ-complexes (**29** and **31**) are found to be more stable than the respective fluorenyl cations and benzene. In the case of the dication, σ-complex **29** is found to be 1.4 kcal/mol more stable than the fluorenyl dication **15** with benzene (Figure 3). The tricationic system is even more exergonic, with the σ-complex **31** found to be 14.0 kcal/mol more stable than the fluorenyl trication **18** with benzene (Figure 4). These data are consistent with the observations from the synthetic reactions, that is, the *N*-heterocyclic systems provide highly reactive electrophiles, or superelectrophiles, which give the 9,9-diarylfluorenes in good to excellent yields. When the less reactive phenyl-substituted fluorenyl monocation is generated, only low yields of the 9,9-diphenylfluorene is obtained (Scheme 3).

CONCLUSIONS

With *N*-heterocyclic substituents, biphenyl ketones undergo efficient condensation reactions with arene nucleophiles to give 9,9-diarylfluorenes in good yields. The chemistry may be used to prepare spirocyclic products, as well as macromolecules by condensation polymerization. A mechanism is proposed involving initial formation of 9-fluorenyl cation electrophiles. With protonated *N*-heterocyclic substituents, these 9-fluorenyl cations are part of di- and tricationic superelectrophilic systems. Theoretical calculations show that the more highly charged 9-fluorenyl cations exhibit greater reactivity toward cyclization and S_EAr reactions.

EXPERIMENTAL SECTION

General. All reactions were performed using oven–dried glassware under an argon atmosphere. Trifluoromethanesulfonic acid (triflic acid) was freshly distilled prior to use. All purchased compounds and solvents were used as received. ^{1}H and ^{13}C NMR were done using either a 300 or 500 MHz NMR spectrometer. Low–temperature NMR spectra were done using acetone-d_6 as the external standard. Low-resolution mass spectra were obtained from a gas chromatography instrument equipped with a mass-selective detector, whereas high-resolution mass spectra were obtained from a commercial analytical laboratory (electron impact ionization; sector instrument analyzer type). Compounds **1a**, **1b**, **1c**, and **1j** were prepared by published methods.[10,16]

Safety Considerations. In the procedures described below, flammable solvents and air-sensitive reagents are used, such as ethers and organolithium and Grignard reagents. Triflic acid, fluorosulfonic acid, and antimony pentafluoride are considered superacids, and as such, these materials are extremely corrosive. These substances pose significant risk and should only be used by properly trained individuals having all necessary personal protective equipment. The toxicities of the substances reported are not fully known, so it is imperative that all procedures are done in an efficient fume hood. No direct skin contact should be made with any chemical reagents or products. The use of thick rubber gloves is strongly advised.

Preparation of Heterocyclic Ketones, 1, General Method A. Magnesium turnings (72 mg, 3.0 mmol) are combined with 10 mL of THF and a crystal of iodine. The solution is then heated to 60–65 °C and 2-bromobiphenyl (0.52 mL, 3.0 mmol) is added. After stirring for 3–4 h, the mixture is cooled to 0 °C after which a solution of the

DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044–6053

nitrile (2.0 mmol in 5 mL of THF) is added slowly. The solution is then allowed to warm to room temperature and stirred for an additional 14 h. Following this period, 15 mL of 6.0 M HCl is added directly to the product mixture and stirring is continued for and additional 2 h. The resulting solution is made basic (ca. pH 8) by addition of 10 M NaOH, and the mixture partitioned between chloroform and water. The aqueous layer is further extracted (2×), after which the organic extracts are combined, washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent is then removed and the resulting product purified by column chromatography (1:1, hexanes:ethyl acetate).

Preparation of Heterocyclic Ketones, 1, General Method B. The heterocyclic derivative (2.24 mmol) is dissolved in 10 mL of THF and the solution is cooled to −78°·C. *n*-BuLi solution (0.89 mL, 2.24 mmol in hexanes) is added and the mixture 1 h, after which 2-biphenyl carboxaldehyde (0.30 mL, 1.0 mmol dissolved in 5 mL THF) is added. The solution is allowed to warm to 25 °C and stirred for 4 h. Saturated ammonium chloride solution (5 mL) is added to the mixture and the products are partitioned between ether and water. The aqueous layer is further extracted (2×) after which the organic extracts are combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The solvent is then removed under reduced pressure. The crude alcohol product is the dissolved in CH_2Cl_2 and then pyridinium chlorochromate (1.20 g, 5.57 mmol) is added. The solution is stirred at 25 °C for at least 6 h, after which it is diluted with 15 mL of CH_2Cl_2 and filtered through a pad of Celite. Following removal of the solvent, the product is purified by column chromatography (1:1, hexanes:ethyl acetate).

[1,1′-Biphenyl]-2-yl(pyrimidin-5-yl)methanone, ***1d.*** Using General Method A, compound **1d** is isolated (0.39 g, 1.5 mmol, 75%) as solid, mp 79−81 °C. R_f = 0.35 (hexane: ethyl acetate, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 7.12−7.21 (m, 5 H), 7.51 (t, J = 9.8 Hz, 2 H), 7.63 (d, J = 5.0 Hz, 2 H), 8.71 (s, 2 H), 9.03 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 127.9, 128.0, 128.7, 129.1, 129.3, 130.1, 130.6, 131.9, 137.0, 139.5, 141.4, 157.1, 160.3, 195.7 Low resolution MS (EI): 260 (M^+), 231, 204, 181, 152, 127, 107, 76, 52. High-resolution MS (EI), calcd for $C_{17}H_{12}N_2O$, 260.0950, found 260.0948.

[1,1′-Biphenyl]-2-yl(pyridazin-3-yl)methanone, ***1e.*** Using General Method A, compound **1e** is isolated (0.41 g, 1.58 mmol, 79%) as oil. R_f = 0.39 (hexane: ethyl acetate, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ, 7.08−7.16 (m, 3 H), 7.19−7.22 (m, 2 H), 7.36−7.40 (m, 1 H), 7.46−7.55 (m, 2 H), 7.60−7.66 (m, 1 H), 7.75−7.78 (m, 1 H), 7.81−7.85 (m, 1 H), 9.01 (d, J = 6.39 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 126.0, 126.4, 127.3, 127.4, 128.2, 129.2, 129.6, 129.9, 131.6, 137.6, 140.3, 142.2, 152.0, 157.9, 197.3. Low resolution MS (EI): 260 (M^+), 231, 204, 181, 152, 127, 101, 76, 51. High-resolution MS (EI), calcd for $C_{17}H_{12}N_2O$, 260.0950, found 260.0946.

(1-Butyl-1H-imidazol-4-yl)(4-methyl-[1,1′-biphenyl]-2-yl)-methanone, ***1f.*** 1-Butyl-1*H*-imidazole (0.26 mL, 2.0 mmol) is dissolved in 5 mL THF and the solution is cooled to −78 °C. To this is solution is slowly added *n*-BuLi solution (2.2 mmol). The mixture is stirred for 2 h and then 4′-methyl-2-cyanobiphenyl 4′-methyl-2-cyanobiphenyl (0.386 g, 2.0 mmol, dissolved in 10 mL THF) is added. The solution is stirred for 30 min at −78 °C and then allowed to warm to 25 °C. After stirring an additional 4 h, the reaction is quenched with 15 mL of 6.0 M HCl. This solution is stirred for 2 h and neutralized (to pH ∼ 8) by addition of 10 M NaOH. The mixture is partitioned between ether and water, with the aqueous layer further extracted twice with ether. The organic fractions are combined, washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent is then removed and the resulting product purified by column chromatography (hexane: ethyl acetate, 5:1). Compound **1f** is isolated as a yellow resin (0.5897 g, 1.8 mmol, 93% yield). R_f = 0.15 (hexane: ethyl acetate, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.40 Hz, 3 H), 1.31 (septet, J = 7.70 Hz, 2 H), 1.70−1.76 (m, 2 H), 2.32 (s, 3 H), 4.36 (t, J = 7.30 Hz, 2 H), 7.00 (d, J = 0.80 Hz, 1 H), 7.08 (d, J = 0.80 Hz, 2 H), 7.10 (s, 1 H), 7.22 (d, J = 4.60 Hz, 2 H), 7.43−7.64 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 19.7, 21.1, 33.0, 48.3, 125.4, 126.6, 128.3, 128.8, 128.9, 129.6, 130.2, 130.5, 136.6, 138.0, 139.0, 141.4, 143.2, 188.0. Low resolution MS (EI): 318 (M+), 289, 275, 261, 165, 152. High-resolution MS (ESI-TOF) m/z: [M+H]+ calcd for $C_{21}H_{23}N_2O$, 319.1810, found 319.1811.

(1-Methyl-1H-imidazol-2-yl)(4-methyl-[1,1′-biphenyl]-2-yl)-methanone, ***1g.*** 1-Methylimidazole (0.30 mL, 3.78 mmol) is dissolved in 5 mL THF and the solution is cooled to −78 °C. To this is solution is slowly added *n*-BuLi solution (3.8 mmol). The mixture is stirred for 2 h and then 4′-methyl-2-cyanobiphenyl 4′-methyl-2-cyanobiphenyl (487 mg, 2.52 mmol, dissolved in 10 mL THF) is added. The solution is stirred for 30 min at −78 °C and then allowed to warm to 25 °C. After stirring an additional 4 h, the reaction is quenched with 15 mL of 6.0 M HCl. This solution is stirred for 2 h and neutralized (to pH ∼ 8) by addition of 10 M NaOH. The mixture is partitioned between ether and water, with the aqueous layer further extracted twice with ether. The organic fractions are combined, washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent is then removed and the resulting product purified by column chromatography (hexane: ethyl acetate, 3:1). Compound **1g** is isolated (0.60 g, 2.2 mmol, 86%) as a yellow solid mp 77−80 °C, R_f = 0.20 (hexane: ethyl acetate, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 3.92 (s, 3 H), 6.91 (s, 1 H), 7.05 (s, 1 H), 7.11 (d, J = 7.90 Hz, 2 H), 7.24 (d, J = 8.05 Hz, 2 H), 7.43−7.47 (m, 2 H), 7.53−7.56 (m, 1H), 7.68−7.69 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 35.8, 126.5, 126.6, 128.7, 128.9, 129.2, 129.7, 130.3, 130.6, 136.7, 138.0, 138.7, 141.6, 143.9, 188.6 Low resolution MS (EI): 276 (M^+), 261, 247, 185, 165, 152. High-resolution MS (EI), calcd for $C_{18}H_{16}N_2O$, 276.1263, found 276.1264.

Benzo[d]thiazol-2-yl(4-methyl-[1,1′-biphenyl]-2-yl)methanone, ***1h.*** Using General Method B, compound **1h** is isolated (0.47 g, 1.5 mmol, 67%) as oil, R_f = 0.28 (hexane: ethyl acetate, 7:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 1.2 Hz, 1 H), 7.22−7.27 (m, 1H), 7.39 (d, J = 7.86 Hz, 2 H), 7.45−7.59 (m, 4 H), 7.67 (d, J = 8.34 Hz, 1 H), 7.90 (d, J = 7.05 Hz, 2 H), 8.08 (d, J = 7.29 Hz, 1 H).^{13} C NMR (75 MHz, $CDCl_3$) δ 122.2, 125.6, 126.8, 127.2, 127.3, 127.6, 128.3, 129.0, 130.5, 131.7, 136.8, 137.1, 140.7, 142.6, 153.5, 166.8, 190.9. Low resolution MS (EI): 315 (M^+), 286, 238, 181, 152, 127. High-resolution MS (EI), calcd for $C_{20}H_{13}NOS$, 315.0718, found 315.0719.

(1-Benzyl-1H-imidazol-2-yl)(4-methyl-[1,1′-biphenyl]-2-yl)-methanone, ***1i.*** Using General Method B, compound **1i** is isolated (0.51 g, 1.5 mmol, 65%) as an oil, R_f = 0.21 (hexane: ethyl acetate, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (s, 2 H), 6.97 (s, 1 H), 7.10 (s, 1 H), 7.19 (d, J = 7.6 Hz, 2 H), 7.26 (t, J = 2.45 Hz, 3 H), 7.35−7.39 (m, 5 H), 7.48−7.52 (m, 2 H), 7.57−7.60 (m, 1H), 7.71 (d, J = 7.30 Hz, 1 H).^{13} C NMR (125 MHz, $CDCl_3$) δ 51.5, 125.6, 126.9, 127.0, 127.9, 128.15, 128.23, 128.9, 129.0, 129.1, 130.3, 130.7, 136.5, 139.0, 141.0, 141.6, 143.3, 188.7. Low resolution MS (EI): 352 (M^+), 362, 212, 196, 195, 167, 165, 152. High-resolution MS (EI), calcd for $C_{24}H_{20}N_2O$, 352.1576, found 352.1575.

Preparation of 9,9-Diarylfluorenes, 2 and 4, General Method C. The ketone substrate **1** (0.1 g, ca. 0.4 mmol) is dissolved in 1 mL of CH_2Cl_2 with the arene nucleophile (0.5 mL or 6 mmol). To this solution is slowly added triflic acid (0.5 mL, 5.5 mmol) and the mixture is stirred for 4 h at 25 °C. The solution is then poured over about 10 g of ice, neutralized with 10 M NaOH (pH > 7), and partitioned between chloroform and water. The aqueous phase is extracted twice with chloroform and the combined organic extracts are washed with water and then brine. Following drying with sodium sulfate, the solvent is removed and the crude product subjected to column chromatography.

2-(9-Phenyl-9H-fluoren-9-yl)pyridine, ***2a.*** Compound **2a** has been previously reported in the patent literature.[17] Using General Method C, [1,1′-biphenyl]-2-yl(pyridin-2-yl)methanone, **1a** (0.102 g, 0.39 mmol) and benzene (0.5 mL, 5.6 mmol), provides compound **2a** (0.11 g, 0.35 mmol, 91%) as a white solid, mp 166−170 °C, R_f = 0.41 (hexane: ethyl acetate, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11−7.17 (m, 4 H), 7.24−7.29 (m, 3 H), 7.34−7.37 (m, 2 H), 7.44 (td, J = 7.50 Hz, J = 1.0 Hz, 2 H), 7.47−7.51(m, 1 H), 7.68 (d, J = 7.60 Hz, 2 H), 7.85 (d, J = 7.60 Hz, 2 H), 8.72−8.74 (m, 1 H). ^{13} C NMR (125 MHz, $CDCl_3$) δ 67.2, 120.2, 121.5, 121.8, 126.7, 127.8, 127.9, 128.4, 136.3, 140.5, 149.8, 149.9, 163.0. Low resolution MS (EI): 319 (M^+),

DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044−6053

241, 158. High-resolution MS (ESI-TOF) m/z: [M+H]+ calcd for $C_{24}H_{18}N$, 320.1439, found 320.1442.

2-(9-(p-Tolyl)-9H-fluoren-9-yl)pyridine, ***2b.*** Using General Method C, [1,1′-biphenyl]-2-yl(pyridin-2-yl)methanone, **1b** (0.05 g, 0.193 mmol) and toluene (0.5 mL, 4.70 mmol) provides compound **2b** (0.058 g, 0.17 mmol, 90%) as white solid, mp 169−169 °C. R_f = 0.18 (hexane: ethyl acetate, 19:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 7.06 (d, J = 8.25 Hz, 2 H), 7.11−7.17 (m, 4 H), 7.36−7.40 (m, 2 H), 7.44−7.51 (m, 3 H), 7.72 (d, J = 7.60 Hz, 2 H), 7.87 (d, J = 7.50 Hz, 2 H), 8.75−8.76 (m, 1 H).^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 67.0, 120.2, 121.4, 121.5, 121.7, 126.8, 127.0, 127.76, 127.77, 127.82, 129.1, 136.16, 136.23, 140.5, 143.1, 149.8, 150.1, 164.1. Low resolution MS (EI): 333 (M^+), 317, 255, 239, 159. High-resolution MS (ESI-TOF) m/z: [M+H]+ calcd for $C_{25}H_{20}N$, 334.1596, found 334.1597.

2-(9-(4-Isopropylphenyl)-9H-fluoren-9-yl)pyridine, ***2c.*** Using General Method C, [1,1′-biphenyl]-2-yl(pyridin-2-yl)methanone **1a** (0.05g, 0.19 mmol) and cumene (0.5 mL, 3.59 mmol) provides compound **2c** (0.061 g, 0.17 mmol, 89%) as oil. R_f = 0.59 (hexane: ethyl acetate, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, J = 6.95 Hz, 6 H), 2.86 (q, J = 6.90 Hz, 1 H), 7.00 (d, J = 8.35 Hz, 2 H), 7.08−7.15 (m, 4 H), 7.30−7.34 (m, 2 H), 7.39−7.43 (m, 2 H), 7.47−7.50 (m, 1 H), 7.64 (d, J = 7.60 Hz, 2 H), 7.81 (d, J = 7.55 Hz, 2 H), 8.70 (q, J = 3.75 Hz, 1 H).^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 33.6, 67.0, 120.1, 121.5, 121.6, 126.4, 126.8, 127.62, 127.65, 127.68, 136.2, 140.4, 143.1, 146.8, 149.7, 150.1, 164.0. Low resolution MS (EI): 361 (M^+), 344, 318, 283, 267, 252, 241, 165. High-resolution MS (ESI-TOF) m/z: [M+H]+ calcd for $C_{27}H_{24}N$, 362.1909, found 362.1907.

Ethyl 2-Hydroxy-5-(9-(pyridin-2-yl)-9H-fluoren-9-yl)benzoate, ***2d.*** Using General Method C, [1,1′-biphenyl]-2-yl(pyridin-2-yl)-methanone **1** (0.05 g, 0.19 mmol) and ethyl salicylate (0.5 mL, 3.40 mmol) provides compound **2d** (0.064 g, 0.16 mmol, 83%) as oil. R_f = 0.31 (hexane: ethyl acetate, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, J = 7.10 Hz, 3 H), 4.31 (quartet, J = 7.10 Hz, 2 H), 6.88 (d, J = 8.80 Hz, 1 H), 7.04 (d, J = 7.95 Hz, 1 H), 7.15−7.21 (m, 2 H), 7.34 (quartet, J = 7.60 Hz, 2 H), 7.41−7.44 (m, 2 H), 7.47−7.51 (m, 1 H), 7.60 (d, J = 8.15 Hz, 3 H), 7.82 (d, J = 7.65 Hz, 2 H), 10.8 (s, 1 H).^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 61.2, 66.3, 112.2, 117.7, 120.0, 120.3, 121.4, 121.8, 126.5, 127.0, 127.86, 127.90, 128.5, 135.6, 136.4, 136.5, 140.4, 149.8, 160.5, 163.5, 170.1. Low resolution MS (EI): 407 (M^+), 361, 332, 304, 283, 255, 241, 226, 207, 180, 166, 152. High-resolution MS (EI), calcd for $C_{27}H_{21}O_3N$, 407.1521, found 407.1526.

2-(9-(4-Bromophenyl)-9H-fluoren-9-yl)pyridine, ***2e-para.*** Using General Method C, [1,1′-biphenyl]-2-yl(pyridin-2-yl)methanone, **1b** (0.100 g, 0.386 mmol), and chlorobenzene (0.5 mL, 5.6 mmol) provide compound **2e** as a mixture of regioisomers. Product **2e-*para*** is isolated (0.055 g, 0.139 mmol, 36%) by column chromatography (hexane: ethyl acetate, 1:1) as an off-white powder, mp 143−145 °C. [Along with this, isomeric products **2e** are obtained (0.087 g, 0.220 mmol, 57%)] R_f = 0.74, **2e-*para*** (hexane: ethyl acetate, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, J = 8.60 Hz, 2 H), 7.04 (d, J = 7.95 Hz, 1 H), 7.15−7.17 (m, 1 H), 7.31−7.36 (m, 4 H), 7.41−7.44 (m, 2 H), 7.47−7.50 (m, 1 H), 7.59 (d, J = 7.65 Hz, 2 H), 7.81 (d, J = 7.55 Hz, 2 H), 8.69 (t, J = 3.80 Hz, 1 H).^{13}C NMR (125 MHz, $CDCl_3$) δ 66.7, 120.3, 120.7, 121.3, 121.9, 126.6, 127.9, 128.0, 129.6, 131.4, 136.4, 140.4, 145.1, 149.4, 149.9, 163.2. Low resolution MS (EI): 397 (M^+), 319, 239, 213, 159, 145. High-resolution MS (EI), calcd for $C_{24}H_{16}NBr$, 397.0466, found 397.0471.

2-(9-(4-Chlorophenyl)-9H-fluoren-9-yl)pyridine, ***2f-para.*** Using General Method C, [1,1′-biphenyl]-2-yl(pyridin-2-yl)methanone, **1b** (0.100 g, 0.386 mmol), and chlorobenzene (0.5 mL, 4.53 mmol) provide compound **2f** as a mixture of regioisomers. Product **2f-*para*** is isolated (0.053 g, 0.151 mmol, 39% yield) by column chromatography (hexane: ethyl acetate, 3:1) as an off-white powder, mp 148−150 °C. [Along with this, isomeric products **2f** are obtained (0.084 g, 0.212 mmol, 55% yield) as an oil] R_f = 0.74, **2f-*para*** (hexane: ethyl acetate, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02−7.07 (m, 3 H), 7.15−7.18 (m, 1 H), 7.21−7.23 (m, 2 H), 7.33−7.36 (m, 2 H), 7.42−7.50 (m, 3 H), 7.62 (d, J = 7.60 Hz, 2 H), 7.83 (d, J = 7.55 Hz, 2 H), 8.72 (quartet, J = 3.75 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.6, 120.3, 121.3, 121.9, 126.6, 127.9, 128.0, 128.5, 129.3, 132.5, 136.4, 140.4, 144.6, 149.5, 149.9, 163.3 Low resolution MS (EI): 353 (M^+), 317, 275, 239, 213, 159. High-resolution MS (EI), calcd for $C_{24}H_{16}NCl$, 353.0971, found 353.0970.

2-(9-(3,4-Dichlorophenyl)-9H-fluoren-9-yl)pyridine and 2-(9-(2,3-dichlorophenyl)-9H-fluoren-9-yl)pyridine mixture, ***2g.*** Using General Method C, [1,1′-biphenyl]-2-yl(pyridin-2-yl)methanone, **1b** (0.050 g, 0.19 mmol) and 1,2-dichlorobenzene (0.5 mL, 4.42 mmol) provides compound **2g** is isolated as (inseparable) isomeric mixture (0.061 g, 0.158 mmol, 83%) as an oil. R_f = 0.44 (hexane: ethyl acetate, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91−6.93 (m, 1 H), 6.96−7.04 (m, 3 H), 7.10−7.12 (m, 2 H), 7.15 (quartet, J = 1.85 Hz, 1 H), 7.24−7.33 (m, 6 H), 7.37−7.50 (m, 7 H), 7.55 (t, J = 7.55 Hz, 3 H), 7.60 (d, J = 1.30 Hz, 1 H), 7.72 (d, J = 7.50 Hz, 1 H), 7.80 (t, J = 6.40 Hz, 2 H), 8.53 (d, J = 3.80 Hz, 1 H), 8.59 (d, J = 3.80 Hz, 1 H).^{13}C NMR (125 MHz, $CDCl_3$) δ 66.2, 67.4, 119.8, 120.2, 120.3, 120.4, 121.2, 121.4, 121.7, 121.9, 126.3, 126.52, 126.54, 126.6, 127.61, 127.63, 127.7, 127.79, 127.80, 127.88, 127.93, 128.2, 129.6, 130.1, 130.7, 132.3, 136.5, 138.8, 140.4, 140.5, 146.2, 146.4, 148.4, 148.6, 149.5, 149.6, 149.7, 163.0, 164.0. Low resolution MS (EI): 387 (M^+), 352, 309, 273, 239, 207, 176, 158.

2-(9-Phenyl-9H-fluoren-9-yl)pyrazine, ***3a.*** Using General Method C,, [1,1′-biphenyl]-2-yl(pyrazin-2-yl)methanone, **1b** (0.0984 g, 0.192 mmol), and benzene (0.5 mL, 5.6 mmol), compound **3a** is isolated (0.056 g, 0.175 mmol, 91%) as a yellow solid, mp 168−169 ° C. R_f = 0.33 (hexane: ethyl acetate, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07−7.29 (m, 5 H), 7.35 (dt, J = 1.0 Hz, J = 7.50 Hz, 2 H), 7.45 (dt, J = 0.90 Hz, J = 7.50 Hz, 2 H), 7.62 (d, J = 7.70 Hz, 2 H), 7.85 (d, J = 7.60 Hz, 2 H), 8.45 (d, J = 18.5 Hz, 2 H), 8.64 (s, 2 H).^{13}C NMR (125 MHz, $CDCl_3$) δ 65.5, 120.4, 16.6, 127.0, 127.7, 128.0, 128.2, 128.5, 140.5, 143.0, 144.3, 145.0, 148.7, 159.8. Low resolution MS (EI): 320 (M^+), 241, 160. High-resolution MS (ESI-TOF) m/z: [M+H]+ calcd for $C_{23}H_{17}N_2$, 321.1392, found 321.1392.

2-(9-Phenyl-9H-fluoren-9-yl)pyrimidine, ***3b.*** Using General Method C, [1,1′-biphenyl]-2-yl(pyrimidin-2-yl)methanone, **1c** (0.0453 mg, 0.174 mmol), and benzene (0.5 mL, 5.6 mmol) provides compound **3b** in (0.046 g, 0.143 mmol, 82%) as an off-white solid, mp 218−220 °C, R_f = 0.17 (hexane: ethyl acetate, 7:1).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04−7.08 (m, 2 H), 7.14 (t, J = 4.90 Hz, 1 H), 7.24−7.49 (m, 7 H), 7.79 (dd, J = 7.40 Hz, J = 19.1 Hz, 4 H), 8.72 (d, J = 4.90 Hz, 2 H).^{13}C NMR (125 MHz, $CDCl_3$) δ 68.5, 119.0, 120.0, 126.8, 127.4, 127.5, 127.9, 128.4, 140.7, 145.8, 148.9, 157.1, 172.6. Low resolution MS (EI): 320 (M^+), 291, 241, 159. High-resolution MS (ESI-TOF) m/z: [M+H]+ calcd for $C_{23}H_{17}N_2$, 321.1392, found 321.1396.

5-(9-Phenyl-9H-fluoren-9-yl)pyrimidine, ***3c.*** Using General Method C, [1,1′-biphenyl]-2-yl(pyrimidin-5-yl)methanone **1d** (0.050 g, 0.192 mmol) and benzene (0.5 mL, 5.6 mmol), provides compound **3c** (0.054 g, 0.169 mmol, 88%) as a white solid, mp 182−185 °C, R_f = 0.12 (hexane: ethyl acetate, 7:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17−7.19 (m, 2 H), 7.29−7.32 (m, 3 H), 7.33−7.39 (m, 2 H), 7.41 (d, J = 7.55 Hz, 2 H), 7.44 (q, J = 6.75 Hz, 2 H), 7.84 (d, J = 7.60 Hz, 2 H), 8.62 (s, 2 H), 9.11 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.9, 120.7, 125.8, 127.4, 127.7, 128.25, 128.31, 128.8, 139.8, 140.1, 143.5, 149.1, 156.3, 157.1 Low resolution MS (EI): 320 (M^+), 292, 241, 189. High-resolution MS (EI), calcd for $C_{23}H_{16}N_2$, 320.1314, found 320.1318.

2-(9-Phenyl-9H-fluoren-9-yl)pyridazine, ***3d.*** Using General Method C, [1,1′-biphenyl]-2-yl(pyridazin-3-yl)methanone, **1e** (0.0683 g, 0.26 mmol) and benzene (0.5 mL, 5.6 mmol) provides compound **3d** (0.074 g, 0.23 mmol, 89%) as a brown solid, mp 212−215 ° C. R_f = 0.10 (hexane: ethyl acetate, 3:1).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07−7.10 (m, 2 H), 7.22−7.24 (m, 5 H), 7.33 (t, J = 7.50 Hz, 2 H), 7.43 (t, J = 7.35 Hz, 2 H), 7.62 (d, J = 7.56 Hz, 2 H), 7.82 (d, J = 6.60 Hz, 2 H), 9.09 (s, 1 H).^{13}C NMR (75 MHz, $CDCl_3$) δ 66.0, 120.3, 124.9, 126.8, 127.7, 128.1, 128.2, 128.4, 140.5, 144.8, 149.0. Low resolution MS (EI): 320 (M^+), 291, 239, 213, 189, 159, 77. High-resolution MS (EI), calcd for $C_{23}H_{16}N_2$, 320.1314, found 320.1316.

1-Butyl-2-(2-methyl-9-phenyl-9H-fluoren-9-yl)-1H-imidazole, ***3e.*** Using General Method C, (1-butyl-1H-imidazol-4-yl)(4-methyl-[1,1′-biphenyl]-2-yl)methanone, **1f** (0.108 g, 0.34 mmol) and benzene (0.5

DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044−6053

mL, 5.6 mmol) provides compound **3e** is isolated in 86% yield as solid, mp 136−142 °C, R_f = 0.08 (hexane: ethyl acetate, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.52−1.08 (m, 7 H), 2.38 (s, 3 H), 3.00 (t, J = 7.90 Hz, 2 H), 6.82 (d, J = 1.20 Hz, 1 H), 7.08 (d, J = 1.20 Hz, 1 H), 7.20−7.41 (m, 1 H), 7.46 (d, J = 7.70 Hz, 1 H), 7.68 (d, J = 7.70 Hz, 1 H), 7.75 (d, J = 7.50 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 32.5, 46.2, 61.4, 120.1, 120.2, 126.1, 126.7, 126.9, 127.2, 127.5, 127.9, 128.0, 128.4, 129.0, 137.5, 140.2, 143.7, 148.0, 148.7, 149.0. Low resolution MS (EI): 378 (M+), 377, 363, 349, 335, 321, 245. High-resolution MS (EI), calcd for $C_{27}H_{26}N_2$, 378.2098, found 378.2096.

1-Methyl-2-(2-methyl-9-phenyl-9H-fluoren-9-yl)-1H-imidazole, ***3f***. Using General Method C, (1-methyl-1H-imidazol-2-yl)(4-methyl-[1,1′-biphenyl]-2-yl)methanone, **1g** (0.0892 g, 0.323 mmol) and benzene (0.5 mL, 5.60 mmol) provides compound **3f** (0.099 g, 0.294 mmol, 91%) as an oil. R_f = 0.16 (hexane: ethyl acetate, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3 H), 2.74 (s, 3 H), 6.73 (d, J = 1 Hz, 1 H), 7.04 (d, J = 1.05 Hz, 1 H), 7.23−7.31 (m, 6 H), 7.39−7.42 (m, 3 H), 7.47 (d, J = 7.60 Hz, 1 H), 7.70 (d, J = 7.75 Hz, 1 H), 7.77 (d, J = 7.55 Hz, 1 H).^{13} C NMR (125 MHz, $CDCl_3$) δ 21.8, 33.9, 61.3, 120.1, 120.2, 122.9, 126.0, 126.6, 126.8, 127.0, 127.6, 127.8, 128.08, 128.12, 129.1, 137.7, 138.1, 140.4, 143.3, 148.3, 148.6. Low resolution MS (EI): 336 (M^+), 268, 245, 160. High-resolution MS (EI), calcd for $C_{24}H_{20}N_2$, 336.1627, found 336.1626.

2-(9-Phenyl-9H-fluoren-9-yl)benzo[d]thiazole, ***3g***. Using General Method C, benzo[d]thiazol-2-yl(4-methyl-[1,1′-biphenyl]-2-yl)-methanone, **1h** (0.180 g, 0.57 mmol) and benzene (0.5 mL, 5.60 mmol), provides compound **3g** (0.183 g, 0.49 mmol, 86%) as a light yellow solid, mp 197−199 °C. R_f = 0.38 (hexane:ethyl acetate, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, J = 6.00 Hz, 5 H), 7.35−7.42 (m, 3 H), 7.50 (t, J = 5.85 Hz, 3 H), 7.78 (d, J = 7.95 Hz, 1 H), 7.82 (d, J = 7.65 Hz, 2 H), 7.86 (d, J = 7.85 Hz, 2 H), 8.13 (d, J = 8.20 Hz, 1 H).^{13} C NMR (125 MHz, $CDCl_3$) δ 65.0, 120.3, 121.3, 123.2, 125.0, 126.0, 126.9, 127.3, 127.6, 128.1, 128.6, 128.7, 134.9, 140.4, 143.7, 149.1, 154.2, 174.6 Low resolution MS (EI): 375 (M^+), 341, 298, 239, 187, 171. High-resolution MS (EI), calcd for $C_{26}H_{17}NS$, 375.1082, found 375.1084.

1-Methyl-2-(9-phenyl-9H-fluoren-9-yl)-1H-benzo[d]imidazole, ***3h***. Using General Method C, biphenyl-2-yl(1-methyl-1H-benzo[d]-imidazol-2-yl)methanone, **1i** (0.0514 g, 0.164 mmol) and benzene (0.5 mL, 5.60 mmol), provides compound **3h** (0.050 g, 0.134 mmol, 82%) as an oil. R_f = 0.52 (hexane: ethyl acetate, 3:1).^{1} H NMR (500 MHz, $CDCl_3$) δ 2.92 (s, 3 H), 7.20 (q, J = 3.10 Hz, 1 H), 7.28 (t, J = 6.05 Hz, 5 H), 7.33 (t, J = 7.55 Hz, 2 H), 7.41 (d, J = 7.65 Hz, 2 H), 7.46 (t, J = 7.35 Hz, 2 H), 7.52 (d, J = 7.50 Hz, 2 H), 7.86 (d, J = 7.45 Hz, 2 H).^{13} C NMR (125 MHz, $CDCl_3$) δ 30.9, 62.1, 108.9, 110.1, 120.2, 120.4, 120.6, 121.8, 122.5, 122.9, 124.0, 126.2, 127.4, 127.8, 128.3, 128.4, 137.0, 140.4, 142.9, 148.0, 155.3. Low resolution MS (EI): 372 (M+), 355, 295, 281, 253, 239, 186. High-resolution MS (EI), calcd for $C_{27}H_{20}N_2$, 372.1626, found 372.1626.

Pyridine-2,6-diylbis([1,1′-biphenyl]-2-ylmethanone), ***4***. Using General Method A (4 mmol 2-biphenylmagnesium bromide), compound **4** is isolated compound as a light yellow solid, mp 111−114 °C. R_f = 0.44 (hexane: ethyl acetate, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71−6.74 (m, 4 H), 6.99−7.02 (m, 6 H), 7.21 (dd, J = 1.1 Hz, 7.6 Hz, 2 H), 7.48−7.51 (m, 2 H), 7.54−7.57 (m, 2 H), 7.59 (d, J = 1.4 Hz, 1 H), 7.61 (d, J = 1.4 Hz, 1 H), 7.66 (t, J = 7.7 Hz, 1 H), 7.85 (s, 1 H), 7.87 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.1, 126.6, 127.0, 127.8, 128.9, 129.1, 129.5, 130.6, 137.0, 140.8, 142.2, 152.4, 197.5. Low resolution MS (CI): 440 (M+1), 422, 368, 338, 232. High-resolution MS (CI), calcd for $C_{31}H_{22}NO_2$, 440.1651, found 440.1648.

2,6-Bis(9-phenyl-9H-fluoren-9-yl)pyridine, ***5***. Using General Method C and substrate **4** (0.10 g, 2.3 mmol) compound **5** is isolated (0.12 g, 2.1 mmol, 93%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 4H), 7.42−7.31 (m, 9H), 7.23−7.16 (m, 10H), 6.98 (d, J = 7.8 Hz, 2H), 6.90−6.87 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 149.5, 146.3, 140.5, 128.4, 128.1, 128.0, 127.6, 127.6, 127.5, 126.0, 119.8, 118.9, 66.9. Low resolution MS (CI): 560 (M+1), 415, 260, 187. High-resolution MS (CI), calcd for $C_{43}H_{30}N$, 560.2378, found 560.2381.

Polymer ***6***. 4,4-Diphenylbenzophenone (0.074 g, 0.22 mmol) and compound **4** (0.0971 g, 0.22 mmol) are dissolved in 2 mL of chloroform and triflic acid (0.5 mL, 5.7 mmol) is added. The solution is stirred at 25 °C for 24 h and then poured over ice. The solids were filtered and rinsed thoroughly with 1 M NaOH, then water, then methanol, and finally with ether. After drying in vacuum, a light brown solid is isolated (ca. 0.1 g). No melting point is observed, though the material darkens between 200 and 300 °C. The substance is insoluble in all organic solvents, but it does dissolve in pure H_2SO_4 or pure CF_3SO_3H. ^{1}H NMR (500 MHz, CF_3SO_3H) δ broad peaks between 5.9 and 7.0, 7.0−7.1, 7.1−7.2, 7.3−7.4. IR (KBr, cm^{-1}) 1640, 1601, 1275, 1224, 1025, 746, 633.

[1,1′-Biphenyl]-2-yl(1-benzyl-1H-imidazol-2-yl)methanone, ***7***. Using General Method B and 1-benzylimidazole (0.35 g, 2.24 mmol), compound **7** is isolated (0.49 g, 0.145 mmol, 65%) as an oil. R_f = 0.21 (hexane: ethyl acetate, 3:1). ^{1} H NMR (500 MHz, $CDCl_3$) δ 5.60 (s, 2 H), 6.97 (s, 1 H), 7.10 (s, 1 H), 7.19 (d, J = 7.6 Hz, 2 H), 7.26 (t, J = 2.45 Hz, 3 H), 7.35−7.39 (m, 5 H), 7.48−7.52 (m, 2 H), 7.57−7.60 (m, 1H), 7.71 (d, J = 7.30 Hz, 1 H).^{13} C NMR (125 MHz, $CDCl_3$) δ 51.5, 125.6, 126.9, 127.0, 127.9, 128.15, 128.23, 128.9, 129.0, 129.1, 130.3, 130.7, 136.5, 139.0, 141.0, 141.6, 143.3, 188.7. Low resolution MS (EI): 338 (M^+), 321, 309, 261, 247, 232, 181, 165, 152, 91, 65. High-resolution MS (EI), calcd for $C_{23}H_{18}N_2O$, 338.1419, found 338.1419.

(1-Benzyl-1H-imidazol-2-yl)(4-methyl-[1,1′-biphenyl]-2-yl)-methanone, ***8***. Using General Method B with 1-benzylimidazole (0.25 g, 1.58 mmol) and 4′-methyl-2-cyanobiphenyl (0.204 g, 1.10 mmol), compound **10** is isolated (0.325 g, 0.924 mmol, 84%) as an oil. R_f = 0.21 (hexane: ethyl acetate, 1:1). ^{1} H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 5.61 (s, 2 H), 6.98 (s, 1 H), 7.04 (d, J = 7.80 Hz, 1 H), 7.10 (s, 1 H), 7.17−7.21 (m, 4 H), 7.35−7.38 (m, 3 H), 7.44−7.48 (m, 2 H), 7.55−7.58 (m, 1 H), 7.64 (d, J = 6.95 Hz, 1 H). ^{13} C NMR (125 MHz, $CDCl_3$) δ 21.2, 51.5, 125.4, 126.6, 127.9, 128.1, 128.8, 128.9, 130.2, 130.6, 136.4, 136.5, 138.0, 138.9, 141.5, 143.4, 188.9. Low resolution MS (EI): 352 (M^+), 323, 261, 179, 165, 152, 91. High-resolution MS (EI), calcd for $C_{24}H_{20}N_2O$, 352.1576, found 352.1575.

5′H-Spiro[fluorene-9,10′-imidazo[1,2-b]isoquinoline], ***9***. Compound **7** (0.237 g, 0.70 mmol) is dissolved in 1 mL of CH_2Cl_2 and triflic acid (1.0 mL, 11 mmol) is slowly added. The mixture is stirred for 4 h at 25 °C, after which the solution is then poured over about 10 g of ice, neutralized with 10 M NaOH (pH > 7), and partitioned between chloroform and water. The aqueous phase is extracted twice with chloroform and the combined organic extracts are washed with water and then brine. Following drying with sodium sulfate, the solvent is removed and the crude product subjected to column chromatography (hexane: ethyl acetate, 1:1). Compound **9** is isolated (0.197 g, 0.62 mmol, 88%) as a yellow solid, mp 225−228 °C. R_f = 0.25 (hexane:ethyl acetate, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (s, 2 H), 6.62 (d, J = 7.50 Hz, 1 H), 7.05−7.10 (m, 5 H), 7.24 (dt, J = 1.00 Hz, 6.50 Hz, 2 H), 7.30 (t, J = 6.05 Hz, 1 H), 7.38−7.44 (m, 3 H), 7.87 (d, J = 7.60 Hz, 2 H).^{13} C NMR (125 MHz, $CDCl_3$) δ 47.6, 55.0, 117.9, 120.6, 124.6, 126.2, 127.3, 127.9, 128.1, 128.2, 128.3, 129.5, 129.8, 137.1, 140.6, 146.1, 151.6 Low resolution MS (EI): 320 (M^+), 292, 280, 263, 252, 159. High-resolution MS (EI), calcd for $C_{23}H_{16}N_2$, 320.1313, found 320.1312.

2-Methyl-5′H-spiro[fluorene-9,10′-imidazo[1,2-b]isoquinoline], ***10***. Compound **9** (0.078 g, 0.222 mmol) is dissolved in 1 mL of CH_2Cl_2 and triflic acid (1.0 mL, 11 mmol) is slowly added. The mixture is stirred for 4 h at 25 °C, after which the solution is then poured over about 10 g of ice, neutralized with 10 M NaOH (pH > 7), and partitioned between chloroform and water. The aqueous phase is extracted twice with chloroform and the combined organic extracts are washed with water and then brine. Following drying with sodium sulfate, the solvent is removed and the crude product subjected to column chromatography (hexane: ethyl acetate, 5:1). Compound **11** is isolated (0.070 g, 0.21 mmol, 94%) as an oil. R_f = 0.29 (hexane:ethyl acetate, 5:1). ^{1} H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3 H), 5.63 (s, 2 H), 6.60 (dd, J = 0.65 Hz, 0.60 Hz, 1 H), 6.82 (s, 1 H), 7.00 (d, J = 7.55 Hz, 1 H), 7.06−7.11 (m, 2 H), 7.16−7.21 (m, 2 H), 7.28−7.30 (m, 2 H), 7.38 (t, J = 6.75 Hz, 2 H), 7.73 (d, J = 7.80 Hz, 1 H), 7.80

DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044−6053

(d, J = 7.60 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 47.6, 55.8, 117.8, 120.19, 120.28, 124.5, 125.2, 126.1, 127.2, 127.7, 128.0, 128.1, 128.2, 129.1, 129.3, 129.8, 137.2, 138.0, 138.1, 140.7, 146.3, 151.5, 151.8. Low resolution MS (EI): 334 (M^+), 306, 266, 159. High-resolution MS (EI), calcd for $C_{24}H_{18}N_2$, 334.1470, found 334.1481.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00311.

NMR spectra for compounds **1**−**5**, polymer **6**, and **7**−**10**, and computational methods and results (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ohwada@mol.f.u-tokyo.ac.jp
*E-mail: dklumpp@niu.edu

ORCID

Tomohiko Ohwada: 0000-0001-5390-0203
Douglas A Klumpp: 0000-0001-5271-699X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support from the U.S. National Science Foundation is gratefully acknowledged (1300878). A.S. thanks Japan Society for the Promotion of Science for Research Fellowship for Young Scientists (16J08260). The computations were performed at the Research Center for Computational Science, Okazaki, Aichi, Japan. We thank the computational facility for generous allotments of computer time.

■ REFERENCES

(1) (a) Dong, Q.; Lian, H.; Gao, Z.; Guo, Z.; Xiang, N.; Zhong, Z.; Guo, H.; Huang, J.; Wong, W.-Y. *Dyes Pigm.* **2017**, *137*, 84. (b) Gruenberg, M. F.; Jia, F.; Rivas-Nass, A.; Goossen, L. J. *Adv. Synth. Catal.* **2016**, *358*, 1589. (c) Zhang, Z.; Zhang, Z.; Ding, D.; Wei, Y.; Xu, H.; Jia, J.; Zhao, Y.; Pan, K.; Huang, W. *J. Phys. Chem. C* **2014**, *118*, 20559. (d) Ren, B.-Y.; Ou, C.-J.; Zhang, C.; Chang, Y.-Z.; Yi, M.-D.; Liu, J.-Q.; Xie, L.-H.; Zhang, G.-W.; Deng, X.-Y.; Li, S.-B.; Wei, W.; Huang, W. *J. Phys. Chem. C* **2012**, *116*, 8881. (e) Miyatake, K.; Bae, B.; Watanabe, M. *Polym. Chem.* **2011**, *2*, 1919. (f) Xie, L.-H.; Yin, C.-R.; Lai, W.-Y.; Fan, Q.-L.; Huang, W. *Prog. Polym. Sci.* **2012**, *37*, 1192.

(2) (a) Saragi, T. P. I.; Spehr, T.; Siebert, A.; Fuhrmann-Lieker, T.; Salbeck, J. *Chem. Rev.* **2007**, *107*, 1011. (b) Xie, L.-H.; Liang, J.; Song, J.; Yin, C.-R.; Huang, W. *Curr. Org. Chem.* **2010**, *14* (18), 2169.

(3) (a) Yin, C.-R.; Han, Y.; Li, L.; Ye, S.-H.; Mao, W.-W.; Yi, M.-D.; Ling, H.-F.; Xie, L.-H.; Zhang, G.-W.; Huang, W. *Polym. Chem.* **2013**, *4*, 2540. (b) Zou, J.; Wu, H.; Lam, C.-S.; Wang, C.; Zhu, J.; Zhong, C.; Hu, S.; Ho, C.-L.; Zhou, G.-J.; Wu, H.; Choy, W. C. H.; Peng, J.; Cao, Y.; Wong, W.-Y. *Adv. Mater.* **2011**, *23*, 2976. (c) Xie, L.-H.; Hou, X.-Y.; Hua, Y.-R.; Tang, C.; Liu, F.; Fan, Q.-L.; Huang, W. *Org. Lett.* **2006**, *8*, 3701.

(4) (a) Boblak, K. N.; Klumpp, D. A. *J. Org. Chem.* **2014**, *79*, 5852. (b) Martin-Mingot, A.; Compain, G.; Liu, F.; Jouannetaud, M.-P.; Bachmann, C.; Frapper, G.; Thibaudeau, S. *J. Fluorine Chem.* **2012**, *134*, 56.

(5) (a) Lin, D.; Wei, Y.; Ou, C.; Huang, H.; Xie, L.; Tang, L.; Huang, W. *Org. Lett.* **2016**, *18*, 6220. (b) Boblak, K. N.; Klumpp, D. A. *J. Org. Chem.* **2014**, *79*, 5852. (c) Prakash, G. K. S.; Paknia, F.; Chacko, S.; Mathew, T.; Olah, G. A. *Heterocycles* **2008**, *76*, 783. (d) Klumpp, D. A.; Garza, G.; Sanchez, G. V.; Lau, S.; DeLeon, S. *J. Org. Chem.* **2000**, *65*, 8997.

(6) (a) Meng, G.; Szostak, M. *Org. Lett.* **2016**, *18*, 796. (b) Li, B.; Darcel, C.; Dixneuf, P. H. *ChemCatChem* **2014**, *6*, 127. (c) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136.

(7) Boblak, K. N.; Gasonoo, M.; Zhang, Y.; Klumpp, D. A. *J. Org. Chem.* **2015**, *80*, 11948.

(8) Xie, L.; Huang, W.; Zhao, X.; Yi, M.; Zhang, G.; Chang, Y.; Zhang, X. Chinese patent no. 102977006, 2013, CAN158:503935.

(9) Cheng, X.; Hou, G.-H.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2004**, *6*, 2381.

(10) Sumita, A.; Ohwada, T.; Boblak, K.; Gasonoo, M.; Klumpp, D. A. *Chem. - Eur. J.* **2017**, *23*, 2566.

(11) Dication **15**, ^{13}C NMR (−40 °C, FSO_3H-SO_2ClF): δ, 129.2, 130.3, 132.6, 134.6, 136.3, 142.6, 144.6, 144.9, 149.4, 151.9, 156.2, 189.8.

(12) Olah, G. A.; Prakash, G. K. S.; Molnar, A.; Sommer, J. *Superacids*, 2nd ed.; Wiley: NY, NY, 2009; Chap 2.

(13) (a) Koltunov, K. Yu.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *Heterocycles* **2004**, *62*, 757. (b) Necula, A.; Racoveanu-Schiketanz, A.; Gheorghiu, M. D.; Scott, L. T. *J. Org. Chem.* **1995**, *60*, 3448. (c) Li, A.; Gilbert, T. M.; Klumpp, D. A. *J. Org. Chem.* **2008**, *73*, 3654.

(14) Frisch, M. J.; et al. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2013. See the Supporting Information section for full details of the computations.

(15) Klumpp, D. A. *Chem. - Eur. J.* **2008**, *14*, 2004.

(16) Zhao, Z.; He, B.; Nie, H.; Chen, B.; Lu, P.; Qin, A.; Tang, B. Z. *Chem. Commun.* **2014**, *50*, 1131.

(17) Xie, L.; Huang, W.; Zhao, X.; Yi, M.; Zhang, G.; Chang, Y.; Zhang, X. Chinese Patent CN 2012−10560714, 2012.

DOI: 10.1021/acs.joc.7b00311
J. Org. Chem. 2017, 82, 6044−6053