JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

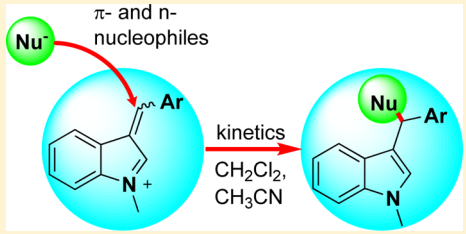
Structure and Reactivity of Indolylmethylium Ions: Scope and Limitations in Synthetic Applications

Elsa Follet, Guillaume Berionni, Peter Mayer, and Herbert Mayr*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13, Haus F, 81377 München, Germany

Supporting Information

ABSTRACT: Eight substituted aryl(indol-3-yl)methylium tetrafluoroborates **3(a–h)-BF$_4$** and three bis(indol-3-yl)methylium tetrafluoroborates **3(i–k)-BF$_4$** have been synthesized and characterized by NMR spectroscopy and X-ray crystallography. Their reactions with π-nucleophiles **8(a–j)** (silylated enol ethers and ketene acetals) were studied kinetically using photometric monitoring at 20 °C. The resulting second-order rate constants were found to follow the correlation log k(20 °C) = $s_N(N + E)$, in which nucleophiles are characterized by the two solvent-dependent parameters N and s_N, and electrophiles are characterized by one parameter, E. From the previously reported N and s_N parameters of the employed nucleophiles and the measured rate constants, the electrophilicities of the indol-3-ylmethylium ions **3(a–k)** were derived and used to predict potential nucleophilic reaction partners. A discrepancy between published rate constants for the reactions of morpholine and piperidine with the (2-methylindol-3-yl)phenylmethylium ion **3h** and those calculated from E, N, and s_N was analyzed and demonstrated to be due to a mistake of the value reported in the literature.

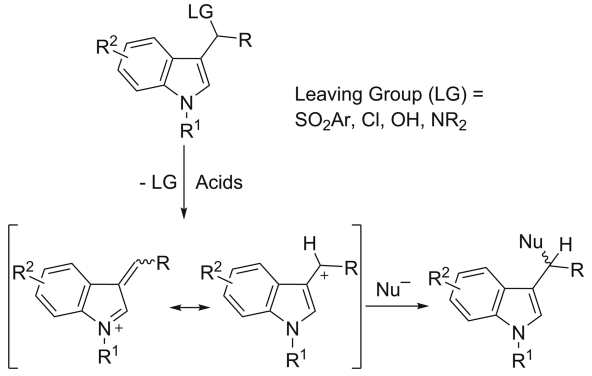


INTRODUCTION

Indolyl-substituted carbenium ions have recently been employed as prochiral intermediates in asymmetric Diels–Alder reactions,[1] Friedel–Crafts reactions,[2,3a] additions to aliphatic π-systems,[3] α-alkylations of aldehydes and other CH acidic compounds,[4] hydrogenation reactions,[5] and several asymmetric syntheses.[6] They are commonly generated by treatment of readily available precursors with Brønsted or Lewis acids (Scheme 1) and subsequently trapped by hydride donors, organometallic reagents, and other nucleophiles to give a wide variety of functionalized indole derivatives.[1−6]

While some electron-donor substituted aryl(indol-3-yl)-methylium ions (Scheme 1, R = Ar) have previously been characterized in solution and in the solid state[7] and have been used as dyes,[7c−g] quantitative information about their electrophilic reactivity is rare. Apart from investigations of their Lewis acidities (pK_{R^+}),[8a−c] we are aware of only one kinetic investigation of their reactions with amines and hydride nucleophiles.[8d]

Scheme 1. *In Situ* Generation and Trapping of Aryl(indol-3-yl)methylium Ions with Nucleophiles



In order to evaluate the scope and limitations of their reactions with nucleophiles we have now quantified the electrophilicities of aryl(indol-3-yl)methylium ions using a method analogous to that which we have used previously for quantifying the electrophilicity of a large number of iminium and carbenium ions. These results have then been integrated into a comprehensive electrophilicity scale.[9a−f,10]

RESULTS AND DISCUSSION

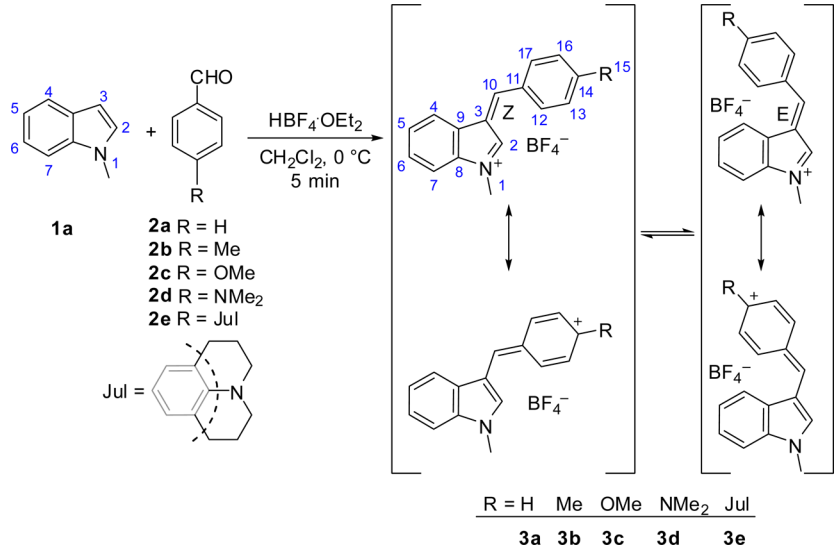
Synthesis of Aryl(indol-3-yl)methylium Ions. Substituted aryl(indol-3-yl)methylium tetrafluoroborates **3(a–e)-BF$_4$** were obtained in good yields in a one-pot procedure by adding 1.5 equiv of HBF$_4$·OEt$_2$ to 1:1 mixtures of *N*-methylindole **1a** and one of the benzaldehydes **2a–e** in CH_2Cl_2 solution (Table 1). An optimization of these reaction conditions has recently been reported and used to synthesize a large variety of diarylmethylium tetrafluoroborates, including several indolyl-substituted systems.[7b] The mechanism of the formation of **3** has been reported previously.[6c] Whereas the less stabilized aryl-(indol-3-yl)methylium tetrafluoroborates **3(a–c)-BF$_4$** decomposed within a few hours at ambient temperature, **3(d–e)-BF$_4$** did not change when stored in an ordinary atmosphere for a year.

Most known aryl(indol-3-yl)methylium ions are substituted at C2; because of the steric repulsion between the C2 substituent and the aryl ring, they generally adopted the (*E*)-configuration as

Received: June 9, 2015
Published: July 28, 2015

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643–8656

Table 1. Syntheses, Structures, Yields, Visible-Absorption Maxima λ_{max}, and Molar Absorbances ε of the Aryl(*N*-methylindol-3-yl)methylium Tetrafluoroborates 3(a–e)-BF_4



						Z/E ratio in CD_2Cl_2	
R	aldehyde	indolylmethylium ions	isolated yields (%)	λ_{max} (nm) in CH_2Cl_2	ε (M^{-1} cm^{-1}) in CH_2Cl_2	expt[a]	calcd[b]
H	**2a**	**3a**	36	425	2.34×10^4	75:25[c]	73:27
Me	**2b**	**3b**	79	431	2.81×10^4	77:23[c]	82:18
OMe	**2c**	**3c**	60	492	2.84×10^4	78:22[c]	88:12
NMe_2	**2d**	**3d**	57	580	8.88×10^4	>99:1	97:3
Jul	**2e**	**3e**	68	589	9.22×10^4	>99:1	99.8:0.2

[a]Determined by ^{1}H NMR at 27 °C. [b]Calculated at the B3LYP/6-31G(d) DFT level in CH_2Cl_2 for the tetrafluoroborate salts; see details in the Supporting Information. [c]The Z/E ratios in CD_3CN: for **3a**, 83/17; for **3b**, 85/15; for **3c**, 87/13.

revealed by NMR spectroscopy and X-ray crystallography.[7a,b,d,e] In contrast, the carbenium ions **3a–c**, which are unsubstituted at C2, give an ~3:1 (*Z*):(*E*) diastereomeric mixture in CD_2Cl_2 and an ~5:1 mixture in CD_3CN at 27 °C. The predominant (*Z*)-configuration of **3c** was derived from an NOE effect observed between 2-H and 12-H and 17-H (Table 1). The (*Z*):(*E*) ratio of **3c** is almost independent of temperature. Between +27 °C and −80 °C in CD_2Cl_2, the (*Z*):(*E*) ratio changes from 78:22 to 86:14, and between +27 °C to +60 °C in CD_3CN, the (*Z*):(*E*) ratio changes from 87:13 to 83:17 (see Supporting Information pp S39–S41).

DFT calculations of the tetrafluoroborate salts showed that the (*Z*)-isomers have smaller dipole moments than the (*E*)-isomers and are more stable by several kJ mol^{-1} (see Supporting Information p S33). As the (*Z*):(*E*) ratio increases with increasingly electron-donating substituents in the phenyl ring (Table 1), only the (*Z*)-isomers of **3d–e** were observed by ^{1}H NMR in CD_2Cl_2. The (*Z*)-isomers crystallized preferentially as shown by the X-ray structures of the aryl(indol-3-yl)methylium ions **3b**, **3c**, and **3e** (Figure 1).[11]

According to the X-ray structures shown in Figure 1, the molecules are almost planar, with dihedral angles between the aryl ring and the indole ring of less than 10 degrees. The considerably shorter bond length C3–C10 (1.37 Å) compared to C10–C11 (1.43–1.44 Å) shows that the positive charge is more stabilized by the indole ring than the aryl ring in the case of **3b** and **3c**, as represented by the upper resonance structures in Table 1. However, in the case of the -Jul substituted indolylmethylium ion **3e**, the increasing stabilizing effect of the anilino ring is indicated by the similar C3–C10 and C10–C11 bond lengths (1.400 ± 0.005 Å) (Figure 1). As a consequence of the increased double-bond character between C10 and C11, the rotation around this bond is restricted, as revealed by distinct resonances for 12-H and 17-H in the 400 MHz ^{1}H NMR spectra below −20 °C (**3d**) and +25 °C (**3e**) (see Supporting Information pp S40 and S43). Analogous dynamic effects were not observed in the ^{1}H NMR spectra of **3a–c**, and there was no evidence for the interconversion of the (*Z*)- and (*E*)-isomers on the NMR time scale.

In agreement with a recently published X-ray structure by Barbero et al.,[7a,b] and subsequent NMR investigations of related compounds,[7b] the aryl(indol-3-yl)methylium ions **3f–h** with a methyl group at C2 of the indole ring were formed exclusively as the (*E*)-isomers (Table 2) from the 2-methyl substituted indoles **1b–c**. DFT calculations showed that even in the case of the julolidyl substituted analogue (2-methyl derivative of **3e**) the (*E*)-isomer is more stable than the (*Z*)-isomer by 18.7 kJ mol^{-1}; i.e., the steric repulsion by the 2-methyl group is so large that now the isomer with the larger dipole moment is preferred.

The bis(indol-3-yl)methylium tetrafluoroborates **3(i–k)-BF_4** were synthesized, as shown in Table 3, from the indoles **1** and triethyl orthoformate **4** following the procedure of Pindur et al.[12]

The X-ray structures of the bis(indol-3-yl)methylium ions **3i** and **3k** depicted in Figure 2 illustrate that a methyl group at C2 of the indole rings induces a change of configuration. Whereas the 2-unsubstituted indole-derivative **3i** is almost planar with a twist angle of 7.21° between the two indole planes and adopts the (*Z*,*Z*)-configuration, the bis-methylated derivative **3k** adopts the (*E*,*E*)-configuration and has an indole–indole twist angle of 42.57°.[11]

We also attempted to synthesize the *p*-anisyl(indol-2-yl)-methylium ion **3l** from the alcohol **5**, as shown in Scheme 2.

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643–8656

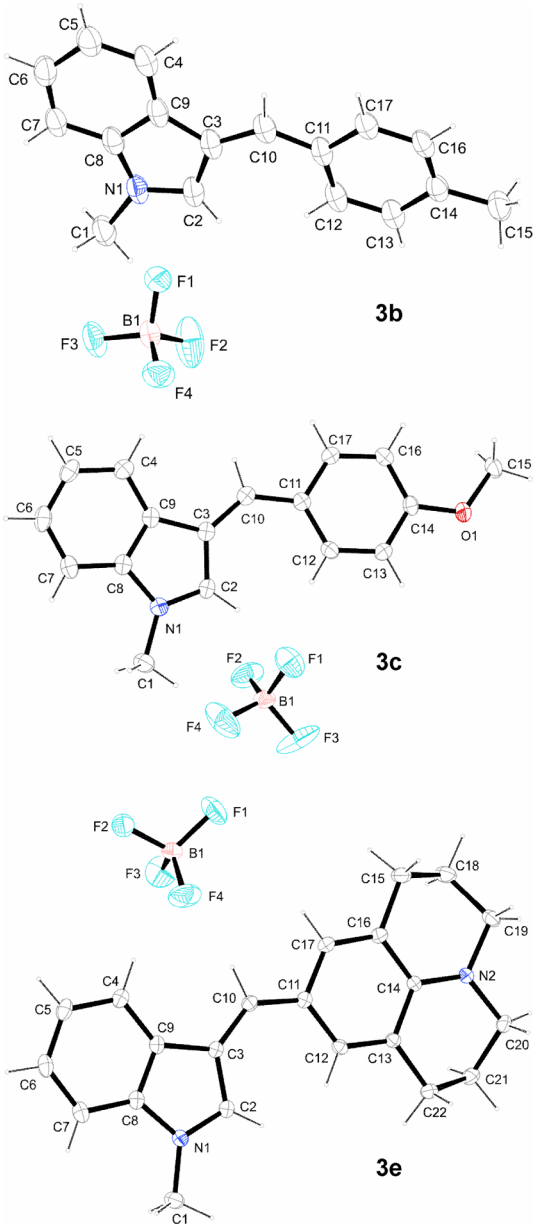
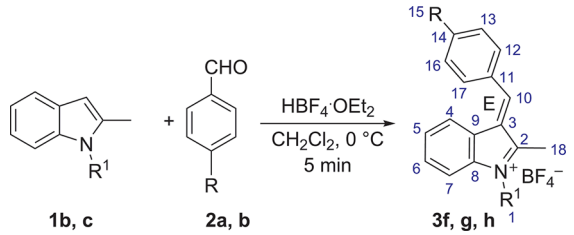


Figure 1. ORTEP drawings (50% probability ellipsoids) of the (*Z*)-aryl(indol-3-yl)methylium tetrafluoroborates **3b**-BF_4, **3c**-BF_4 and **3e**-BF_4. Selected interatomic distances (Å) and angles (deg) for **3b**: N1−C2 = 1.311(3), C2−C3 = 1.432(3), C3−C10 = 1.365(3), C10−C11 = 1.439(3) and N1−C2−C3 = 110.0(2), C2−C3−C10 = 130.7(2), C3−C10−C11 = 133.2(2), C2−C3−C10−C11 = 2.9(4), C3−C10−C11−C12 = 5.7(3). For **3c**: N1−C2 = 1.319(3), C2−C3 = 1.430(3), C3−C10 = 1.373(3), C10−C11 = 1.430(3), N1−C2−C3 = 110.19(18), C2−C3−C10 = 130.64(19), C3−C10−C11 = 132.8(2), C2−C3−C10−C11 = −3.1(4), C3−C10−C11−C12 = −6.2(4). For **3e**: N1−C2 = 1.339(3), C2−C3 = 1.408(3), C3−C10 = 1.395(3), C10−C11 = 1.404(3), N1−C2−C3 = 110.53(17), C2−C3−C10 = 130.58(18), C3−C10−C11 = 132.77(19), C2−C3−C10−C11 = 1.0(4), C3−C10−C11−C17 = −179.7(2).[11]

Dropwise addition of $HBF_4{\cdot}OEt_2$ to a solution of the *p*-anisyl(indol-2-yl)methanol **5** in CH_2Cl_2 at 0 °C produced a deep violet solution, attributed to **3l**, which faded spontaneously. After 5 min the pentacyclic compound **6** precipitated as a colorless solid. The inverse addition of a CH_2Cl_2 solution of **5** to an equimolar amount of $HBF_4{\cdot}OEt_2$ dissolved in CH_2Cl_2 also produced a transient violet species which yielded **6**, and we did not succeed in isolating **3l**.

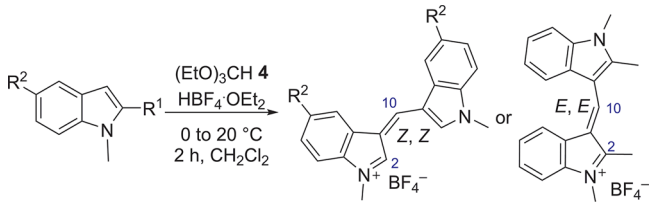
Table 2. Syntheses, Structures, Yields, Visible-Absorption Maxima λ_{max}, and Molar Absorbances ε of the Aryl(2-methyl-indol-3-yl)methylium Tetrafluoroborates 3(f–h)-BF_4



1b, c **2a, b** **3f, g, h**

indole (R^1)	aldehyde (R)	salt	isolated yields (%)	λ_{max} (nm) in CH_2Cl_2	ε (M^{-1} cm^{-1}) in CH_2Cl_2
1b (H)	**2b** (Me)	**3f**-BF_4	71	417	2.15×10^4
1c (Me)	**2b** (Me)	**3g**-BF_4	88	425	2.28×10^4
1c (Me)	**2a** (H)	**3h**-BF_4	84	405	–

Table 3. Syntheses, Structures, Yields, Visible-Absorption Maxima λ_{max}, and Molar Absorbances ε of the Symmetrical Bis(indol-3-yl)methylium Tetrafluoroborates 3(i–k)-BF_4



1a, c, d **3 i, j** **3k**

indole (R^1, R^2)	salt	isolated yields (%)	λ_{max} (nm) in CH_2Cl_2	ε (M^{-1} cm^{-1}) in CH_2Cl_2
1a (H, H)	**3i**-BF_4	86	540[a]	4.87×10^4[a]
1d (H, OMe)	**3j**-BF_4	69	540[a]	2.39×10^4[a]
1c (Me, H)	**3k**-BF_4	74	497	5.33×10^4

[a]5% (v/v) of CH_3CN was added for full solubilization of **3i** and **3j**.

Only one diastereoisomer of **6** was formed and we were not able to assign its configuration. The acid-catalyzed cyclization of aryl(indol-2-yl)methanols has been previously reported by Santoso et al.[13] to give pentacyclic dihydro-indolo[3,2-*b*]-carbazoles with cis configuration (X-ray analysis). We, therefore, assume that the phenyl groups in our analogous product **6** are also in cis configuration.

Product Studies. For the quantification of the electrophilic reactivities of indolylmethylium ions **3a–k** we have studied their reactions with representative π-nucleophiles of known nucleophilicity (Table 4).

As depicted in Scheme 3 for a series of representative combinations of aryl(indol-3-yl)methylium ions **3** with π-nucleophiles **8**, all reactions occurred regioselectively at the 10 position of **3**, but were not diastereoselective when prochiral π-nucleophiles **8b,h** were used.[14] Reactions of aryl(indol-3-yl)methylium ions **3** with electron-rich dienes, such as Danishefsky's diene **8d** and 1-(trimethylsiloxy)buta-1,3-diene **8i**, yielded the α,β-unsaturated compounds **11** and **12**, respectively.

The reactions of π-nucleophiles with the bis(indol-3-yl)-methylium ions **3i,k** sometimes followed a different pattern, as shown for the silyl enol ethers **8a–c** (Scheme 4).[12]

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656

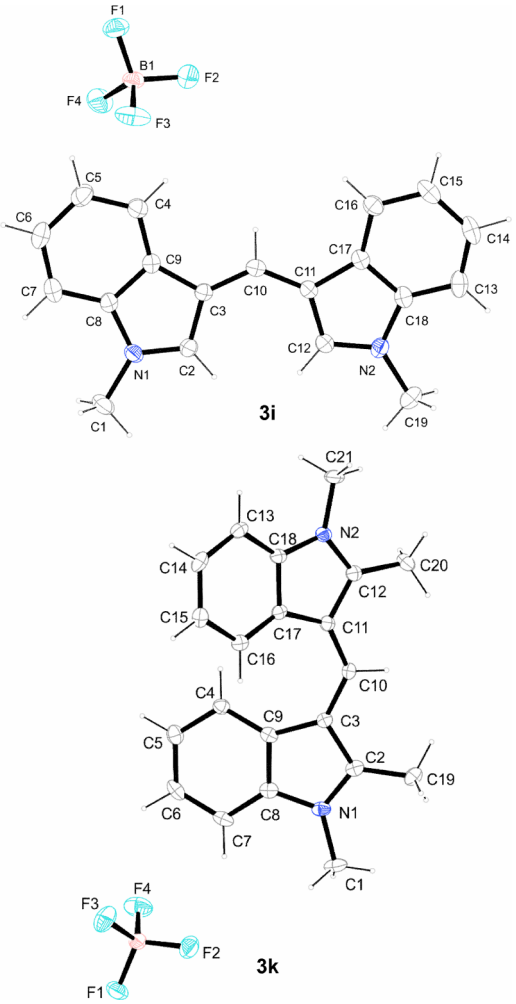


Figure 2. ORTEP drawing (50% probability ellipsoids) of the bis(indol-3-yl)methylium tetrafluoroborates **3i**-BF_4 and **3k**-BF_4.[11] Selected interatomic distances (Å) and angles (deg) for **3i**: N1−C2 = 1.329(2), C2−C3 = 1.410(2), C3−C10 = 1.391(2), C10−C11 = 1.392(2), N1−C2−C3 = 110.39(13), C2−C3−C10 = 130.09(14), C3−C10−C11 = 131.49(14), C2−C3−C10−C11 = 2.6(3), C3−C10−C11−C12 = 2.1(3). For **3k**: N1−C2 = 1.343(2), C2−C3 = 1.425(2), C3−C10 = 1.397(2), C10−C11 = 1.394(2), N1−C2−C3 = 109.02(14), C2−C3−C10 = 121.82(15), C3−C10−C11 = 130.37(14), C2−C3−C10−C11 = −162.78(16), C3−C10−C11−C12 = −160.44(16).

Whereas the reaction of the bis(indol-3-yl)methylium ion **3i** with the ketene acetal **8c** gave the expected product **15** in high yield, the reactions of **3i**,**k** with the cyclic ketene acetals **8a**−**b** gave a mixture of the analogously formed products (**16**−**19**)**a**, accompanied by the alkylidene lactones (**16**−**19**)**b** and the indoles **1a**,**c**. Single crystals of **19b** were obtained, and the X-ray diffraction analysis confirmed its (*E*)-configuration in the solid state with dihedral angle C3−C10−C11−C12 = 178.8° (Figure 3).[11]

The formation of (**16**−**19**)**b** may occur via two different pathways. As shown in Scheme 5 for the reaction of **3i**,**k** with **8a**−**b**, the cleavage of one indole ring may in principle occur before or after desilylation. As fragmentation of the isolated compound **17a** observed by ^{1}H NMR takes days in $CDCl_3$ solution, we can conclude that the elimination of an indole ring occurs before desilylation (left pathway in Scheme 5) or via BF_3 induced cleavage of the initial adducts (**16**−**19**)**a**. This type of *β*-elimination of indole was previously observed in other cases.[15]

Scheme 2. Attempted Synthesis of the *p*-Anisyl(indol-2-yl)methylium Tetrafluoroborate 3l-BF_4 and Formation of the Dihydro-indolo[3,2-*b*]carbazole 6

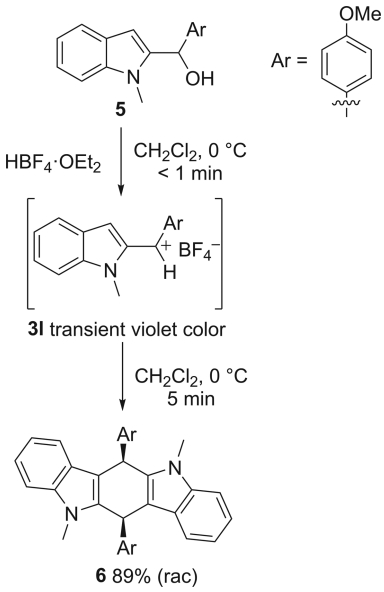
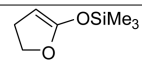
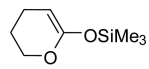
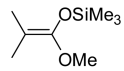
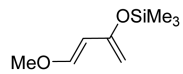
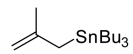
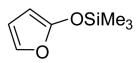
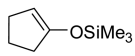
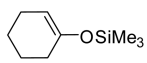
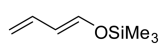
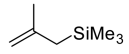
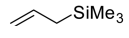


Table 4. *π*-Nucleophiles 8 Employed as Reference Compounds for the Determination of the Electrophilicity of the Indolylmethylium Ions 3a−k

Nu	Structure	*N* (s_N)[a]
8a		12.56 (0.70)
8b		10.61 (0.86) 10.52 (0.78)[b]
8c		9.00 (0.98) 9.11 (0.88)[b]
8d		8.57 (0.84)
8e		7.48 (0.89)
8f		7.22 (1.00)
8g		6.57 (0.93)
8h		5.21 (1.00)
8i		4.60 (0.90)
8j		4.41 (0.96)
8k		1.68 (1.00)

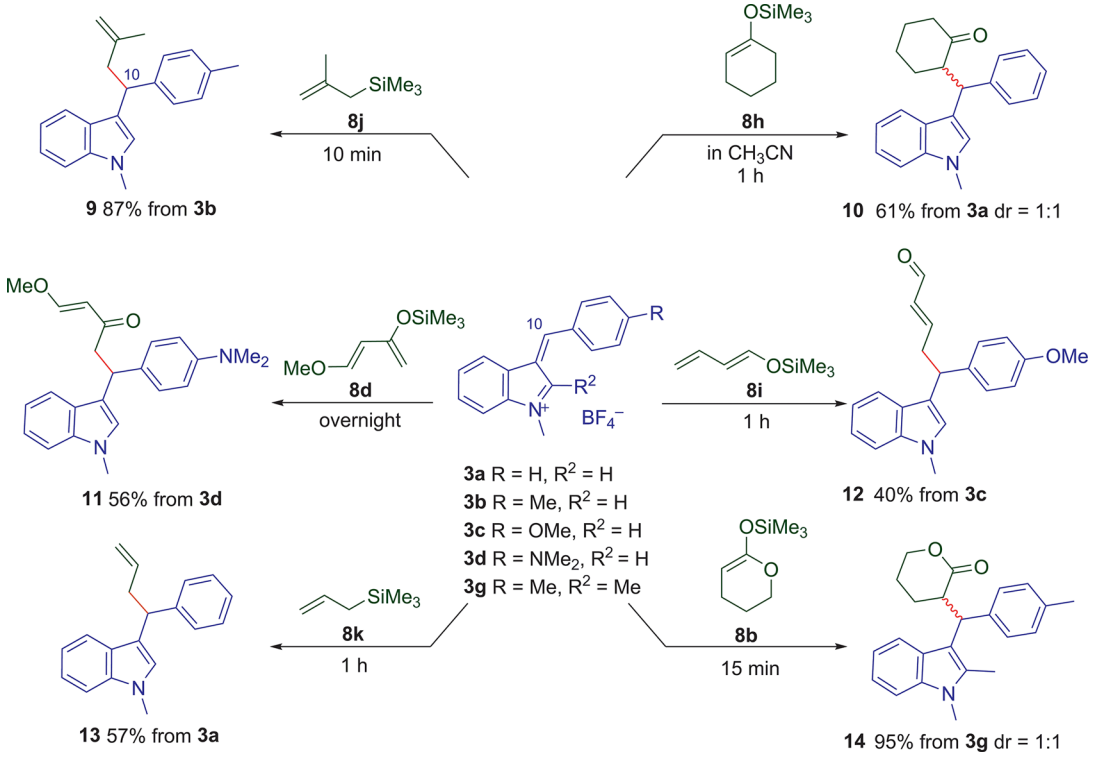
[a]Nucleophilicity parameters *N* and nucleophile-specific sensitivity parameters s_N for **8a**−**k** in CH_2Cl_2 from ref 9f. [b]In CH_3CN.

Compound **15**, obtained by the reaction with **8c**, cannot undergo this cleavage because there are no hydrogens in the *β*-position which are needed for the 1,2-elimination of indole.

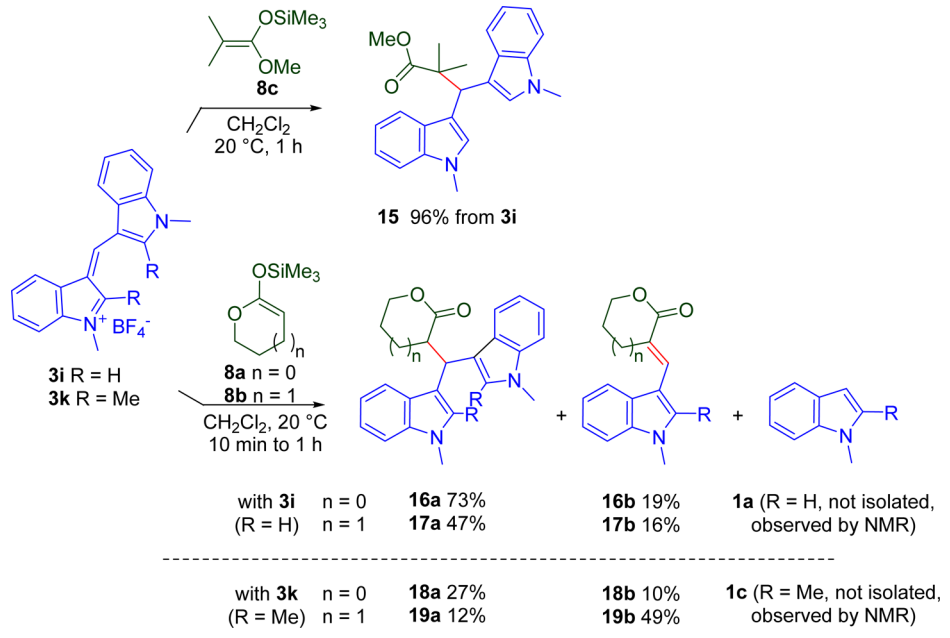
Kinetic Investigations. The kinetics of the reactions of the carbocations **3** with the nucleophiles **8** were determined in

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656

Scheme 3. Reactions of Representative π-Nucleophiles 8 with Aryl(indol-3-yl)-methylium Tetrafluoroborates 3-BF_4 (in CH_2Cl_2 at 20 °C)



Scheme 4. Reactions of Bis(indol-3-yl)methylium Ions 3i,k with Silyl Enol Ethers 8a–c



CH_2Cl_2 by following the disappearance of the absorbances of **3a–k** at their maximum wavelengths λ_{max} (Tables 1–3). In the presence of an excess (10–200 equiv) of the nucleophiles **8a–j** (Table 4), pseudo-first-order conditions were achieved, as indicated by the monoexponential decays of the absorbances of **3a–k**, which is illustrated in Figure 4 for the reaction of the ketene acetal **8j** with the indolylmethylium ion **3b**. Plots of k_{obs} (s^{-1}) against the concentrations of the nucleophiles were linear with negligible intercepts as illustrated in Figure 4. The second-order rate constants k_2 for the reactions of **3a–k** with the nucleophiles **8a–j** were derived from the slopes of these linear plots (see Supporting Information pp S2–S14) and are reported in Table 5.

As shown in Table 5, the second-order rate-constants k_2 for the reactions of the ketene acetals **8b** and **8c** with the aryl(indol-3-yl)methylium ion **3e** differ by less than a factor of 2 in CH_3CN and in CH_2Cl_2, illustrating that the solvent has little effect on the reaction kinetics, as previously reported for analogous reactions

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643–8656

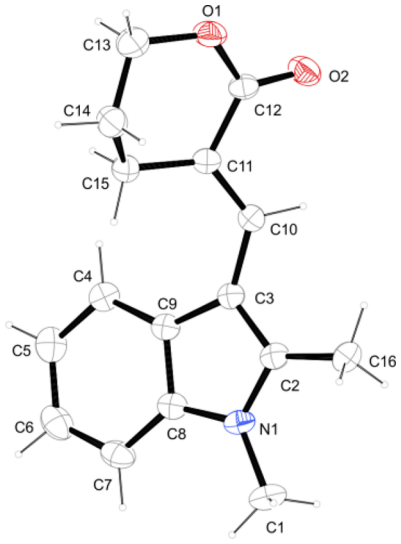
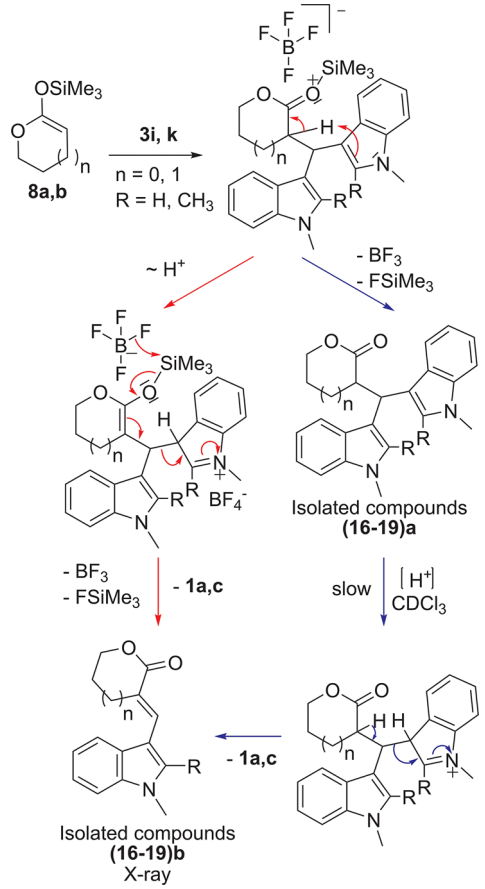


Figure 3. ORTEP drawing (50% probability ellipsoids) of the alkylidene lactone **19b**.[11] Selected interatomic distances (Å) and angles (deg): N1−C2 = 1.375(2), C2−C3 = 1.383(2), C3−C10 = 1.452(2), C10−C11 = 1.347(2), C11−C12 = 1.488(2), C12−O2 = 1.209(2), N1−C2−C3 = 109.64(13), C2−C3−C10 = 123.78(14), C3−C10−C11 = 128.00(14), C10−C11−C12 = 116.08(14), C11−C12−O2 = 124.11(14), C2−C3−C10−C11 = −139.90(17), C3−C10−C11−C12 = 178.80(14).

Scheme 5. Possible Mechanisms for the Formation of the Products (16−19)a−b



of benzhydrylium and iminium ions with neutral π-nucleophiles.[9] Variation of the counterion (BF_4^- vs PF_6^-) of aryl(indol-3-yl)methylium ion **3e** affected the second-order rate constants in CH_2Cl_2 by less than 5% indicating that the counterion effects on the kinetics of these reactions are negligible.[16]

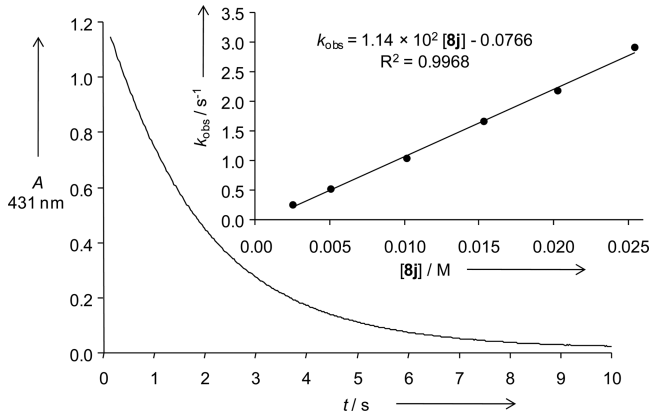


Figure 4. Exponential decay of the absorption of **3b** (9.28×10^{-5} M) during the reaction with **8j** (5.09×10^{-3} M) ($k_{obs} = 5.23 \times 10^{-1}$ s^{-1}) in CH_2Cl_2. Inset: plot of the first-order rate constants k_{obs} versus the nucleophile concentrations [**8j**] ($k_2 = 1.14 \times 10^2$ M^{-1} s^{-1}).

Determination of the Electrophilicity of 3a−k. Since the pioneering work of Swain and Scott[10a] numerous attempts have been made to quantify the nucleo- and electrophilicity,[10b−j] among which Ritchie's constant selectivity relationship[10h,i] and its extensions by Kane-Maguire and Sweigart[10j] are the most prominent ones. In 1994 we have introduced eq 1 which characterizes electrophiles by one parameter, E, and nucleophiles by the solvent-dependent nucleophilicity parameter N and the sensitivity parameter s_N.[9d]

$$\log k_2(20\ ^\circ\mathrm{C}) = s_N(N + E) \quad (1)$$

Figure 5 shows that plots of $(\log k_2)/s_N$ vs the nucleophilicity N of **8a−j** are linear with slopes close to 1, which indicates the applicability of eq 1. By enforcing a slope of 1.0 for the least-squares minimization it was possible to evaluate the electrophilicities E of **3a−k** which are listed in Table 5. Only the correlation lines for cations **3e**, **3i**, and **3j**, which include reactions with the sterically most demanding π-nucleophile **8c**, showed some scatter presumably because the steric crowding at the disubstituted nucleophilic site of **8c** affected the transition states of the reactions with **3e,i,j** more than those of the reactions with benzhydrylium ions, which were used for the calibration of the nucleophile-specific parameters N and s_N for **8a−k**.

Figure 6 shows a linear correlation of the electrophilicity E of the four para-substituted aryl(indol-3-yl)methylium ions **3a−d** with Hammett's σ_p constants of the substituents of the phenyl ring, which is of higher quality than the corresponding correlation with σ_p^+. The slope of this correlation (5.59) corresponds to the Hammett reaction constant ρ for reactions with nucleophiles of $s_N = 1$. It is considerably larger than the corresponding slopes of E vs σ_p correlations for substituted benzylidene malonates (3.45), quinone methides (1.79), and *trans*-β-nitrostyrenes (2.08), comparable to that of aryl-*para*-methoxyphenylmethylium ions (7.38), which can be explained by the more efficient ground-state effects of the substituents in the more electron-deficient aryl-indolyl and benzhydryl cations.

From the electrophilicity parameter of **3h** given in Table 5 (E = −4.96) and the previously reported reactivity parameters for the Hantzsch ester **8o** (N = 9.00, s_N = 0.90 in CH_2Cl_2),[9g] one can calculate the rate constant for hydride transfer of 4.33×10^3 M^{-1}

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656

Table 5. Second-Order Rate Constants k_2 for the Reactions of the Nucleophiles 8a−j with the Indolylmethylium Tetrafluoroborates 3(a−k)-BF_4 in CH_2Cl_2 at 20 °C

electrophile	nucleophile	k_2/M^{-1} s^{-1}	k_{calcd}[a]/M^{-1} s^{-1}	E[b]
3a	**8g**	3.07×10^4	2.73×10^4	−1.80
(R = H)	**8h**	2.22×10^3	2.57×10^3	
	8j	3.42×10^2	3.20×10^2	
3b	**8g**	1.35×10^4	1.18×10^4	−2.19
(R = Me)	**8h**	1.08×10^3	1.05×10^3	
	8j	1.14×10^2	1.35×10^2	
3c	**8g**	1.91×10^3	2.00×10^3	−3.02
(R = OMe)	**8h**	1.48×10^2	1.55×10^2	
	8j	2.34×10^1	2.16×10^1	
3d	**8d**	1.36×10^2	8.72×10^1	−6.26
($R = NMe_2$)	**8e**	9.19	1.22×10^1	
	8g	1.71	1.94	
3e	**8b**	3.62×10^2	2.66×10^2	−7.79
(R = Jul)		3.65×10^2[c]	2.66×10^2	
		1.78×10^2[d]	1.35×10^2	
	8c	9.35	1.53×10^1	
		9.02[c]	1.53×10^1	
		6.70[d]	1.45×10^1	
	8e	8.78×10^{-1}	5.30×10^{-1}	
	8g	5.56×10^{-2}	7.33×10^{-2}	
3f	**8d**	6.32×10^2	7.46×10^2	−5.15
	8e	1.67×10^2	1.18×10^2	
	8g	1.72×10^1	2.09×10^1	
	8h	1.13	1.15	
3g	**8b**	3.50×10^4	6.05×10^4	−5.05
	8d	1.43×10^3	9.05×10^2	
	8g	2.62×10^1	2.59×10^1	
	8h	1.54	1.45	
3h	**8g**	3.30×10^1	3.14×10^1	−4.96
	8h	1.70	1.78	
3i	**8b**	1.32×10^4	9.40×10^3	−5.99
	8c	5.21×10^2	8.91×10^2	
	8f	2.39×10^1	1.70×10^1	
	8g	3.07	3.46	
3j	**8b**	2.23×10^3	1.55×10^3	−6.90
	8c	5.92×10^1	1.14×10^2	
	8g	7.15×10^{-1}	4.93×10^{-1}	
3k	**8a**	2.96×10^1	4.28×10^1	−10.23
	8b	1.57	2.12	
	8d	7.49×10^{-2}	4.03×10^{-2}	

[a]Calculated by using eq 1, N and s_N from Table 4, and E from this table. [b]For the determination of E, see Figure 5 and accompanying text. [c]Counterion PF_6^-. [d]In CH_3CN.

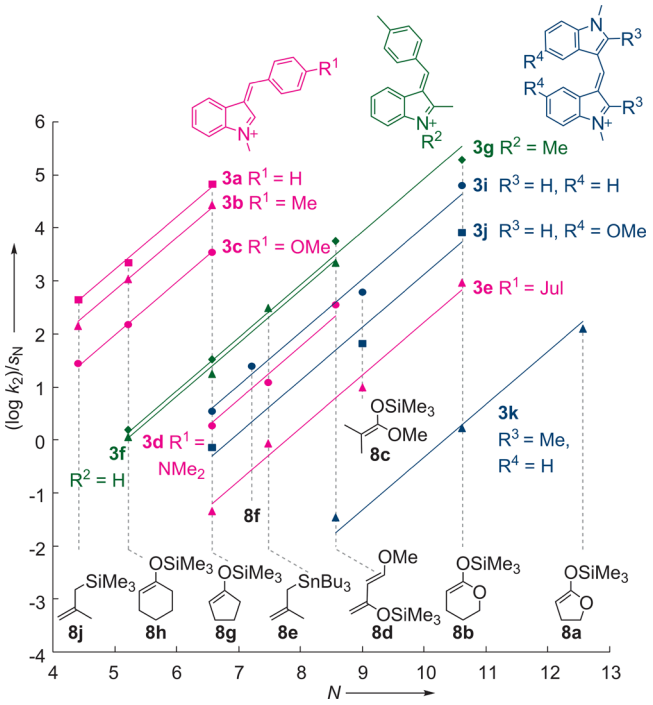


Figure 5. Plots of $(\log k_2)/s_N$ vs N for the reactions of indolylmethylium ions **3a−g,i−k** with the nucleophiles **8a−j** in CH_2Cl_2 at 20 °C. k_2 values from Table 5 and N and s_N values for **8a−j** from Table 4.

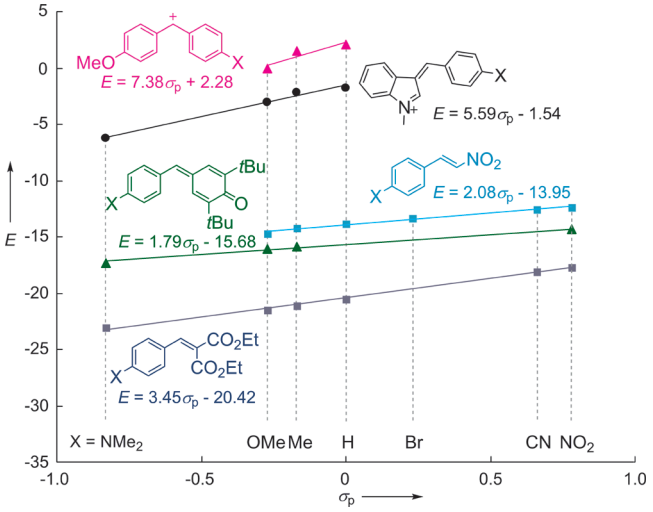


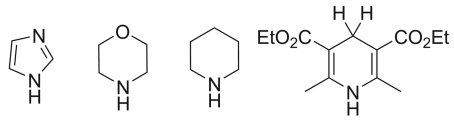
Figure 6. Correlation of the E values of aryl(indol-3-yl)methylium ions **3a−d**, benzhydrylium ions, benzylidene malonates, quinone methides, and *trans*-β-nitrostyrenes with Hammett's σ_p constants (σ_p = 0.78 (NO_2), 0.66 (CN), 0.23 (Br), −0.17 (Me), −0.27 (OMe), −0.83 (NMe_2)).[17]

s^{-1} (CH_2Cl_2, 20 °C) by eq 1. This value agrees within the confidence limit of eq 1 (factor 10−100) with the experimental rate constant of 1.32×10^4 M^{-1} s^{-1} (CH_3CN, 30 °C) for this reaction reported by Huffman et al.[8d] (Table 6, entry 5). While calculated (eq 1) and reported experimental rate constants also agree nicely for the reaction of **3h** with imidazole (**8l**, Table 6, entry 1), the calculated values for the reactions of the indolylmethylium ion **3h** with morpholine (**8m**) and piperidine (**8n**) were approximately 3 orders of magnitude larger than those reported by Huffman et al.[8d] (Table 6, entries 2 and 4). Apart from the discrepancy with the rate constants predicted by eq 1, Huffman's report that morpholine (**8m**) and piperidine (**8n**) reacted more slowly than imidazole (**8l**) appeared surprising to us, since in all reactions of carbocations and Michael acceptors studied so far, the reactivity order was always the other way around. In order to clarify the origin of this discrepancy, we have repeated the reactions of the n-nucleophiles **8l−n** with the aryl(indol-3-yl)methylium ion **3h** using different counterions.

The kinetic investigations, which were performed under pseudo-first-order conditions as described above, gave a rate constant of 2.65×10^5 M^{-1} s^{-1} for the reaction of imidazole (**8l**) with **3h**, close to Huffman's value[8d] and to the rate constant calculated by eq 1. As expected from the calculations based on eq 1, the reactions of **3h** with morpholine (**8m**) and piperidine (**8n**)

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656

Table 6. Experimental and Calculated Second-Order Rate-Constants k_2 (M^{-1} s^{-1}) for the Reactions of the Nucleophiles 8l–o with the Indolylmethylium Ions 3h,k in CH_3CN



	8l	8m	8n	8o
N^a	11.47	15.65	17.35	9.00 (CH_2Cl_2)
$s_N{}^a$	0.79	0.74	0.68	0.90 (CH_2Cl_2)
$pK_{aH}{}^b$	6.9	8.4	11.2	

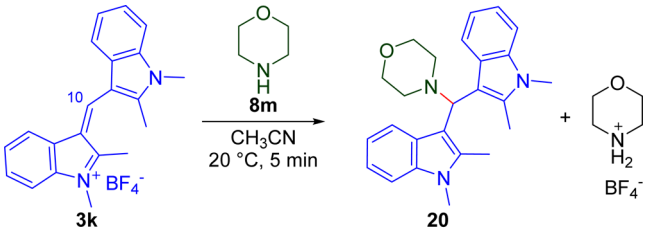
entry	nucleophiles	cations 3 (E)	$k_2{}^{exp}$ Huffman[c]	$k_2{}^{exp}$ this work[d]	$k_2{}^{calcd}$ from eq 1[e]
1	**8l**	**3h** (−4.96)	4.26×10^5[f]	2.65×10^5	1.39×10^5
2	**8m**	**3h** (−4.96)	1.15×10^5	$\gg 10^6$	8.14×10^7
3	**8m**	**3k** (−10.23)	n.d.[g]	2.90×10^4	1.03×10^4
4	**8n**	**3h** (−4.96)	2.30×10^5	$\gg 10^6$	2.66×10^8
5	**8o**	**3h** (−4.96)	1.32×10^4	n.d.[g]	4.33×10^3[h]

[a]From ref 9. [b]In H_2O from ref 18a. [c]At 30 °C, with HSO_4^- as counteranion, from ref 8d. [d]At 20 °C, with BF_4^- as counteranion. [e]At 20 °C. [f]Averaged from two second-order rate constants in ref 8d. [g]Not determined. [h]In CH_2Cl_2.

were much faster than those reported by Huffman and were too fast to be followed with our stopped-flow equipment.

For that reason, we measured the rate constant for the reaction of morpholine (**8m**) with the less electrophilic bis(indol-3-yl)methylium ion **3k**, which proceeded selectively at C10 according to NMR of the crude material (Scheme 6, the poor

Scheme 6. Reaction of Bis(indol-3-yl)methylium Tetrafluoroborate 3k-BF_4 with Morpholine (8m)



yield of isolated adduct **20** is due to losses during recrystallization). Because the measured rate constant is in accord with that calculated by eq 1, we can conclude that eq 1 is also applicable to reactions of the carbenium ions **3** with amines and that the rate constants for the reactions of **3h** with **8m** and **8n** reported by Huffman cannot refer to the attack of the amines at the carbenium ions. Unfortunately, the experimental part of Huffman's article does not give detailed information about the concentrations used for the different kinetic experiments. Possibly the amines **8m** and **8n** were not used in high excess over the indolylmethylium hydrogen sulfate with the consequence that protonation of the amines by the HSO_4^- counterion may account for the incorrect rate constants reported for these reactions.

Structure–Reactivity Relationships. The right column of Figure 7 compares the reactivities of the aryl(indol-3-yl)-methylium ions **3a–k** with those of structurally related benzhydrylium ions. One can see that replacement of the NH group of the aryl(*N*-methylindol-3-yl)methylium ion **3f** (E = −5.15) by NMe to give **3g** (E = −5.05) has a negligible effect on electrophilicity, analogous to the small *N*-methyl effect on the relative nucleophilicities of indole and *N*-methylindole.[19] The indol-3-ylmethylium ion **3d** (E = −6.26) has a similar electrophilicity as the bis(*p*-dimethylamino)benzhydrylium ion (E = −7.02) and the bis(*N*-methylindol-3-yl)methylium ion **3i** (E = −5.99), indicating that the *N*,*N*-dimethylaminophenyl group and the *N*-methyl-indole ring stabilize carbenium ions to a similar extent, in agreement with the similar magnitudes of the Hammett σ^+ constants for the *N*,*N*-dimethylamino group ($\sigma_p{}^+$ = −1.70)[20a] and *N*-methylindole ($\sigma^+{}_{arene}$ = −1.93).[20b]

In order to demonstrate the practical use of the electrophilicity parameters of the indolylmethylium ions determined in this work, we have complemented the electrophilicity scale on the right of Figure 7 with a nucleophilicity scale on the left side. By arranging the reactivities of electrophiles and nucleophiles in opposite order, electrophiles and nucleophiles shown in Figure 7 which are placed on the same level react with a rate constant of 1 M^{-1} s^{-1}. Using the rule of thumb[9b] that electrophile–nucleophile combinations may take place at room temperature if $E + N > -5$, one can derive that the indolylmethylium ions will react with those nucleophiles which are positioned below them or not more than 5 units above them in Figure 7.

One can, thus, expect that indoles, furans, thiophenes, and pyrroles which have *N* parameters from 1 to 8 undergo Friedel–Crafts reactions with most aryl(indol-3-yl)methylium ions to give tris(heteroaryl)methanes. Organocatalytic reactions of indolylmethylium ions with enamines and enamides, which are good nucleophiles ($5 < N < 19$),[9f] have been reported to proceed smoothly even at low temperature.[4a–c,6a] Trialkylsilanes $HSiR_3$ are not sufficiently nucleophilic to react with the least reactive indolylmethylium ions **3e,k** ($E + N < -5$), but stronger hydride donors such as the Hantzsch ester (**8o**, N = 9.00) can be used to reduce all **3a–k** with formation of bis-indolyl-methanes or aryl(indolyl)methanes. Allyl-silane, -stannane, and organoboron nucleophiles, which have been calibrated in our scale,[9f] are also suitable reaction partners for indolylmethylium ions.[2c,3a] The data reported in this work can thus be employed for designing syntheses of bis(indol-3-yl)methane derivatives, which have been identified as building blocks of several alkaloids.[21]

CONCLUSION

The second-order rate constants for the reactions of the indolylmethylium ions **3**(**a–k**) with π-nucleophiles follow eq 1, which allowed us to derive the electrophilicitiy parameters −10.2 < E < −1.8 for these substituted indolylmethylium ions and to predict potential nucleophilic reaction partners. In line with the similar values of $\sigma_p{}^+$ (NMe_2) and $\sigma^+{}_{arene}$ (1-methylindol-3-yl), the bis(4-dimethylamino)-substituted benzhydrylium ion and the substituted indol-3-ylmethylium ions **3d** and **3i** were found to have similar electrophilic reactivities (Figure 7).

Earlier attempts in our group to generate benzhydrylium ions in the reactivity range −6 < E < −2 by combining strong (NMe_2) and weak (Me, OMe) electron-donating substituents at the two phenyl rings failed, because electrophilic attack at the NMe_2 group (protonation?) could not be avoided. Since 1-methylindole is a considerably weaker Bronsted base (pK_{aH} = −2.32 in H_2O)[18b] than *N*,*N*-dimethylaniline (pK_{aH} = 5.15 in H_2O),[18c] the strong electron-donating indolyl group can be combined with weaker electron donating groups, such as phenyl, tolyl, and anisyl, to give the stable diarylcarbenium ions **3**(**a–c**), which may be used as readily accessible reference electrophiles in future mechanistic investigations.

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643–8656

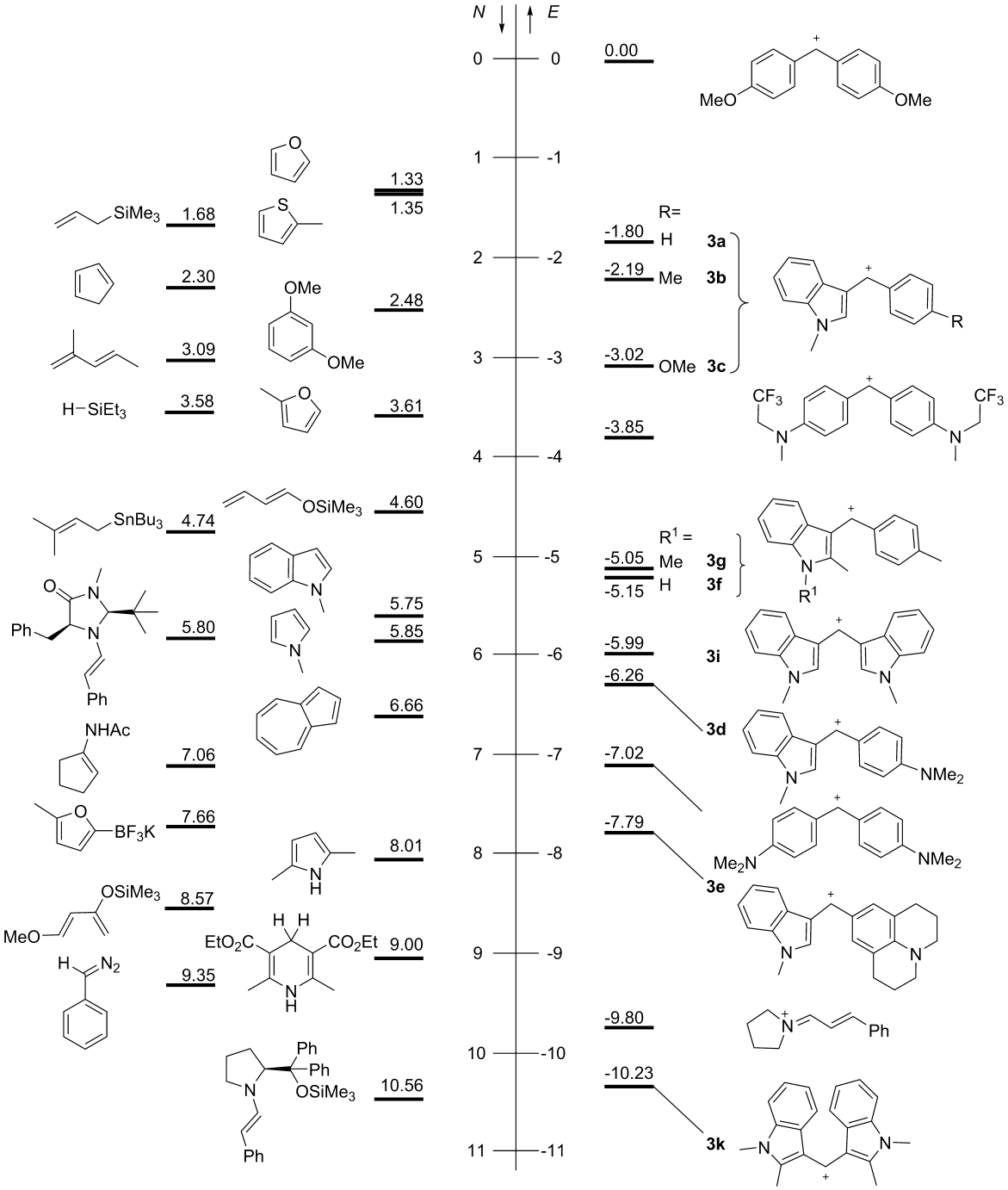


Figure 7. Ranking of the indolylmethylium ions **3a−g,i,k** in the electrophilicity scale and scope of their reactions with nucleophiles.

EXPERIMENTAL SECTION

Materials. Dichloromethane was freshly distilled over CaH_2 prior to use, and Et_2O was distilled over sodium/benzophenone. Commercially available acetonitrile (99.9%, extra dry) and dimethyl sulfoxide (99.7%, extra dry) were used as received. Indoles (**1**), 4-(dimethylamino)-benzaldehyde (**2d**), $HBF_4{\cdot}OEt_2$, HPF_6 (65 wt % in H_2O), triethyl orthoformate (**4**), and nucleophiles (**8c−e, g−i, k−l, n**) were purchased and used without further purification. Aldehydes (**2a−c**) and nucleophile **8m** were purchased and distilled prior to use. 1,2,3,5,6,7-Hexahydropyrido[3,2,1-*ij*]quinoline-9-carbaldehyde (**2e**)[9a] and nucleophiles (**8a**,[22] **8b**,[22] **8f**,[23] **8j**[24]) were synthesized as described in the literature.

Analytics. The ^1H, ^{13}C, ^{19}F, and ^{31}P NMR chemical shifts are in ppm and recorded in $CDCl_3$ ($\delta_H = 7.26$, $\delta_C = 77.16$), CD_3CN ($\delta_H = 1.94$, $\delta_C = 118.69$), $(CD_3)_2SO$ ($\delta_H = 2.50$, $\delta_C = 39.52$), and CD_2Cl_2 ($\delta_H = 5.32$, $\delta_C = 53.84$). The following abbreviations were used for signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, sept = septet. NMR signal assignments were based on additional 2D-NMR experiments (COSY, HSQC, HMBC, and NOESY). HRMS in EI and ESI mode were performed on an LTQ mass spectrometer. Melting points were determined in capillary tubes with a standard melting point device and were not corrected. An IR spectrometer with an ATR unit (attenuated total reflection) was used to record the IR spectra of neat compounds. The composition of the compounds was determined with a conventional C-, H-, N-, S- elemental analyzer. All yields refer to nonoptimized procedures.

Synthesis of Aryl(indol-3-yl)methylium Tetrafluoroborates 3(a−g)-BF_4. *General Procedure.* Benzaldehyde **2** was dissolved in a mixture of CH_2Cl_2 (5 mL) and Et_2O (5 mL) in a flame-dried Schlenk-

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656

flask, flushed with nitrogen. Then an indole **1** (1.00 g, 1.00 equiv) was added to the mixture, and the solution was stirred until complete homogenization (2 min). The solution was cooled to 0 °C, and $HBF_4{\cdot}OEt_2$ (1.50 equiv) was added dropwise at this temperature. After 10 min, the solution was allowed to warm at room temperature while a strongly colored solid precipitated (see Tables 1 and 2). After 10 min the solid was filtered, washed thoroughly with Et_2O (4 × 25 mL), and crystallized in CH_3CN/Et_2O (1/1) to give the aryl(indol-3-yl)methylium tetrafluoroborates **3-BF$_4$** as colored crystals of high purity.

*(1-Methyl-1H-indol-3-yl)phenylmethylium Tetrafluoroborate (**3a-BF$_4$**).* From **1a** (1.00 g, 7.62 mmol), **2a** (809 mg, 7.62 mmol), and $HBF_4{\cdot}OEt_2$ complex (1.85 g, 11.4 mmol): 850 mg (2.77 mmol, 36%), bright yellow-orange solid, mp 137−139 °C (dec.). Major isomer ((*Z*)-isomer): ^{1}H NMR (CD_3CN, 400 MHz) δ 9.20 (s, 1H, H-2), 9.06 (s, 1H, H-10), 8.18−8.11 (m, 1H, H-4), 8.00 (d, 2H, *J* = 8.0 Hz, H-12 and H-17), 7.83−7.76 (m, 2H, H-7 and H-14), 7.75−7.66 (m, 4H, H-5, H-6, H-13 and H-16), 4.15 (s, 3H, H-1); ^{13}C NMR (CD_3CN, 101 MHz) δ 159.3 (C-10), 158.0 (C-2), 142.7 (C-8), 136.7 (C-14), 135.3 (C-11), 134.9 (C-12 and C-17), 131.5 (C-13 and C-16), 131.1 (C-6), 130.9 (C-5), 130.1 (C-3), 129.1 (C-9), 122.9 (C-4), 116.1 (C-7), 38.4 (C-1); ^{19}F NMR (CD_3CN, 376 MHz) δ −151.7. HRMS (ESI) *m*/*z*: $[M - BF_4^-]^+$ Calcd for $C_{16}H_{14}N^+$ 220.1121; Found 220.1119. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1621, 1608, 1588, 1570, 1548, 1457, 1414, 1348, 1293, 1253, 1214, 1129, 1105, 1049, 1037, 759, 678, 620.

*(1-Methyl-1H-indol-3-yl)(p-tolyl)methylium Tetrafluoroborate (**3b-BF$_4$**).* From **1a** (1.00 g, 7.62 mmol), **2b** (917 mg, 7.63 mmol), and $HBF_4{\cdot}OEt_2$ complex (1.85 g, 11.4 mmol): 1.93 g (6.01 mmol, 79%), bright orange solid, mp 162−169 °C (dec.). Major isomer ((*Z*)-isomer): ^{1}H NMR (CD_3CN, 400 MHz) δ 9.19 (s, 1H, H-2), 8.99 (s, 1H, H-10), 8.16−8.09 (m, 1H, H-4), 7.94 (d, 2H, *J* = 8.3 Hz, H-12 and H-17), 7.80−7.74 (m, 1H, H-7), 7.73−7.66 (m, 2H, H-5 and H-6), 7.53 (d, 2H, *J* = 8.2 Hz, H-13 and H-16), 4.15 (s, 3H, H-1), 2.51 (s, 3H, H-15); ^{13}C NMR (CD_3CN, 101 MHz) δ 159.6 (C-10), 156.9 (C-2), 149.8 (C-14), 142.3 (C-8), 135.5 (C-12 and C-17), 132.8 (C-11), 132.4 (C-13 and C-16), 130.7 (C-6), 130.6 (C-5), 129.4 (C-9), 128.7 (C-3), 122.6 (C-4), 115.9 (C-7), 38.2 (C-1), 22.6 (C-15); ^{19}F NMR (CD_3CN, 376 MHz) δ −151.7. HRMS (ESI) *m*/*z*: $[M - BF_4^-]^+$ Calcd for $C_{17}H_{16}N^+$ 234.1277; Found 234.1281. Anal. Calcd for $C_{17}H_{16}BF_4N$: C, 63.58; H, 5.02; N, 4.36. Found: C, 63.53; H, 5.10; N, 4.38. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1619, 1584, 1540, 1457, 1409, 1344, 1259, 1188, 1130, 1103, 1047, 1032, 1009, 984, 951, 901, 821, 770, 751, 625.

*(4-Methoxyphenyl)(1-methyl-1H-indol-3-yl)methylium Tetrafluoroborate (**3c-BF$_4$**).* From **1a** (500 mg, 3.81 mmol), **2c** (520 mg, 3.82 mmol), and $HBF_4{\cdot}OEt_2$ complex (928 mg, 5.73 mmol): 770 mg (2.28 mmol, 60%), bright red solid, mp 198−208 °C (dec.). Major isomer ((*Z*)-isomer): ^{1}H NMR (CD_3CN, 400 MHz) δ 9.13 (d, 1H, *J* = 0.9 Hz, H-2), 8.91 (s, 1H, H-10), 8.12−8.05 (m, 3H, H-4, H-12 and H-17), 7.78−7.71 (m, 1H, H-7), 7.70−7.61 (m, 2H, H-5 and H-6), 7.22 (d, 2H, *J* = 8.9 Hz, H-13 and H-16), 4.12 (d, 3H, *J* = 0.9 Hz, H-1), 3.99 (s, 3H, H-15). ^{13}C NMR (CD_3CN, 101 MHz) δ 168.9 (C-14), 159.3 (C-10), 154.8 (C-2), 141.7 (C-8), 139.1 (C-12 and C-17), 130.0 (C-6), 129.9 (C-5), 129.8 (C-9), 128.5 (C-11), 125.9 (C-3), 122.1 (C-4), 117.7 (C-13 and C-16), 115.5 (C-7), 57.7 (C-15), 37.9 (C-1); ^{19}F NMR (CD_3CN, 376 MHz) δ −151.7. HRMS (ESI) *m*/*z*: $[M - BF_4^-]^+$ Calcd for $C_{17}H_{16}NO^+$ 250.1226; Found 250.1228. Anal. Calcd for $C_{17}H_{16}BF_4NO$: C, 60.57; H, 4.78; N, 4.15. Found: C, 60.46; H, 4.69; N, 4.14. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1577, 1555, 1528, 1455, 1438, 1411, 1351, 1328, 1275, 1259, 1218, 1179, 1165, 1134, 1093, 1047, 1037, 1014, 1001, 883, 859, 838, 804, 765, 757.

*(4-(Dimethylamino)phenyl)(1-methyl-1H-indol-3-yl)methylium Tetrafluoroborate (**3d-BF$_4$**).* From **1a** (1.12 g, 8.54 mmol), **2d** (1.28 g, 8.58 mmol), and $HBF_4{\cdot}OEt_2$ complex (1.67 g, 10.3 mmol): 1.70 g (4.85 mmol, 57%), dark blue solid, mp 204−206 °C (dec.). ^{1}H NMR (CD_3CN, 400 MHz) δ 8.60 (s, 1H, H-2), 8.42 (s, 1H, H-10), 8.11−7.86 (m, 3H, H-4, H-12 and H-17), 7.64−7.60 (m, 1H, H-7), 7.53−7.46 (m, 2H, H-5, H-6), 6.99 (d, 2H, *J* = 9.1 Hz, H-13 and H-16), 4.01 (s, 3H, H-1), 3.33 (s, 6H, H-15). ^{13}C NMR (CD_3CN, 101 MHz) δ 159.5 (C-14), 154.6 (C-10), 145.4 (C-2), 139.9 (C-8), 129.9 (C-9), 127.1 (C-6), 126.6 (C-5), 125.4 (C-11), 120.8 (C-4), 118.0 (C-3), 116.2 (C-13 and C-16), 113.7 (C-7), 42.1 (C-1), 36.1 (C-15), C12 and C17 not detected, probably overlapped with CD_3CN resonances at 118.7 ppm. ^{19}F NMR (CD_3CN, 376 MHz) δ −151.8. HRMS (ESI) *m*/*z*: $[M - BF_4^-]^+$ Calcd for $C_{18}H_{19}N_2^+$ 263.1543; Found 263.1544. Anal. Calcd for $C_{18}H_{19}BF_4N_2$: C, 61.74; H, 5.47; N, 8.00. Found: C, 61.54; H, 5.41; N, 8.00. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1607, 1577, 1531, 1509, 1469, 1388, 1365, 1340, 1314, 1268, 1202, 1182, 1161, 1130, 1093, 1048, 982, 938, 825, 764, 757, 753, 723, 679.

*(Julolidin-9-yl)(1-methyl-1H-indol-3-yl)methylium Tetrafluoroborate (**3e-BF$_4$**).* From **1a** (316 mg, 2.41 mmol), **2e** (485 mg, 2.41 mmol), and $HBF_4{\cdot}OEt_2$ complex (468 mg, 2.89 mmol): 662 mg (1.65 mmol, 68%), dark violet solid, mp 159−161 °C (dec.). ^{1}H NMR (CD_3CN, 400 MHz) δ 8.42 (s, 1H, H-2), 8.05 (br s, 1H, H-10), 7.93−7.89 (m, 1H, H-4), 7.85 (br s, 1H, H-12 or H-17), 7.59−7.53 (m, 1H, H-7), 7.47−7.39 (m, 2H, H-5 and H-6), 7.27 (br s, 1H, H-12 or H-17), 3.96 (s, 3H, H-1), 3.60 (t, 4H, *J* = 5.7 Hz, H-15 and H-22), 2.80 (2 × br s, 4H, H-19 and H-20), 2.03−1.96 (m, 4H, H-18 and H-21). ^{13}C NMR (CD_3CN, 101 MHz) δ 156.1 (C-14), 149.9 (C-10), 141.7 (C-2 and C-12 or C-17), 139.3 (C-8), 133.6 (C-12 or C-17), 129.9 (C-9), 128.7 (C-13 or C-16), 126.3 (C-6), 126.1 (C-11), 125.4 (C-5 and C-13 or C-16), 120.4 (C-4), 116.2 (C-3), 113.1 (C-7), 53.3 (C-15 and C-22), 35.5 (C-1), 28.1 (C-19 or C-20), 27.6 (C-19 or C-20), 21.5 (C-18 and C-21). ^{19}F NMR (CD_3CN, 376 MHz) δ −151.7. HRMS (ESI) *m*/*z*: $[M - BF_4^-]^+$ Calcd for $C_{22}H_{23}N_2^+$ 315.1856; Found 315.1859. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1627, 1585, 1575, 1530, 1505, 1455, 1400, 1370, 1354, 1313, 1263, 1212, 1187, 1133, 1110, 1047, 1032, 975, 953, 912, 766, 749, 681.

*(Julolidin-9-yl)(1-methyl-1H-indol-3-yl)methylium Hexafluorophosphate(V) (**3e-PF$_6$**).* From **1a** (170 mg, 1.30 mmol), **2e** (262 mg, 1.30 mmol), and HPF_6 (190 mg, 1.30 mmol): 52 mg (0.11 mmol, 8%), dark violet solid, mp 135−142 °C (dec.). ^{1}H NMR (CD_3CN, 400 MHz) δ 8.42 (s, 1H, H-2), 8.08 (s, 1H, H-10), 7.92 (dd, 1H, *J* = 1.6, 6.7 Hz, H-4), 7.87 (s, 1H, H-12 or H-17), 7.58 (dd, 1H, *J* = 1.3, 6.8 Hz, H-7), 7.49−7.37 (m, 2H, H-5 and H-6), 7.29 (s, 1H, H-12 or H-17), 3.98 (s, 3H, H-1), 3.61 (t, 4H, *J* = 5.7 Hz, H-15 and H-22), 2.81 (2 × br s, 4H, H-19 and H-20), 2.07−1.96 (m, 4H, H-18 and H-21). ^{19}F NMR (CD_3CN, 376 MHz) δ −72.9 (d, $J_{F,P}$ = 706 Hz). ^{31}P NMR (CD_3CN, 162 MHz) δ −144.64 (sept, $J_{P,F}$ = 706 Hz). HRMS (ESI) *m*/*z*: $[M - BF_4^-]^+$ Calcd for $C_{22}H_{23}N_2^+$ 315.1856; Found 315.1856. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1608, 1533, 1507, 1464, 1369, 1357, 1314, 1264, 1229, 1216, 1113, 1074, 1011, 828, 762, 744, 736, 688.

*(2-Methyl-1H-indol-3-yl)(p-tolyl)methylium Tetrafluoroborate (**3f-BF$_4$**).* From **1b** (1.08 g, 8.23 mmol), **2b** (989 mg, 8.23 mmol) and $HBF_4{\cdot}OEt_2$ complex (2.00 g, 12.3 mmol): 1.88 g (5.85 mmol, 71%), bright orange solid, mp 180−183 °C (dec.). ^{1}H NMR (CD_3CN, 400 MHz) δ 12.38 (br s, 1H, H-1), 8.68 (s, 1H, H-10), 8.17 (d, 1H, *J* = 7.9 Hz, H-4), 7.95 (d, 2H, *J* = 8.2 Hz, H-12 and H-17), 7.63 (d, 1H, *J* = 7.5 Hz, H-7), 7.60−7.55 (m, 1H, H-6), 7.51 (d, 2H, *J* = 8.1 Hz, H-13 and H-16), 7.48−7.43 (m, 1H, H-5), 2.92 (s, 3H, H-18), 2.51 (s, 3H, H-15). ^{13}C NMR (CD_3CN, 101 MHz) δ 175.2 (C-2), 160.5 (C-10), 148.3 (C-14), 141.9 (C-8), 134.1 (C-12 and C-17), 131.9 (C-11), 131.7 (C-13 and C-16), 131.6 (C-6), 131.5 (C-3), 129.6 (C-5), 125.7 (C-9), 124.7 (C-4), 116.6 (C-7), 22.6 (C-15), 15.2 (C-18). ^{19}F NMR (CD_3CN, 376 MHz) δ −151.0. HRMS (ESI) *m*/*z*: $[M - BF_4^-]^+$ Calcd for $C_{17}H_{16}N^+$ 234.1277; Found 234.1279. Anal. Calcd for $C_{17}H_{16}BF_4N$: C, 63.59; H, 5.02; N, 4.36. Found: C, 63.51; H, 4.93; N, 4.30. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1579, 1551, 1456, 1406, 1383, 1334, 1321, 1295, 1211, 1181, 1125, 1077, 1024, 993, 913, 865, 812, 765.

*(1,2-Dimethyl-1H-indol-3-yl)(p-tolyl)methylium Tetrafluoroborate (**3g-BF$_4$**).* From **1c** (1.01 g, 6.96 mmol), **2b** (840 mg, 6.99 mmol), and $HBF_4{\cdot}OEt_2$ complex (1.70 g, 10.5 mmol): 2.04 g (6.09 mmol, 88%), bright yellow solid, mp 190−195 °C (dec.). ^{1}H NMR (CD_3CN, 400 MHz) δ 8.68 (s, 1H, H-10), 8.16 (d, 1H, *J* = 7.9 Hz, H-4), 7.91 (d, 2H, *J* = 8.2 Hz, H-12 and H-17), 7.70 (d, 1H, *J* = 8.0 Hz, H-7), 7.64 (td, 1H, *J* = 0.9, 7.8 Hz, H-6), 7.54−7.46 (m, 3H, H-5, H-13 and H-16), 3.94 (s, 3H, H-1), 2.89 (s, 3H, H-18), 2.51 (s, 3H, H-15). ^{13}C NMR (CD_3CN, 101 MHz) δ 174.0 (C-2), 158.7 (C-10), 147.6 (C-14), 144.6 (C-8), 133.8 (C-12 and C-17), 131.9 (C-11), 131.6 (C-13 and C-16), 131.5 (C-6), 131.4 (C-3), 130.0 (C-5), 125.5 (C-9), 124.6 (C-4), 115.4 (C-7), 34.9 (C-1), 22.5 (C-15), 13.9 (C-18). ^{19}F NMR (CD_3CN, 376 MHz) δ −151.8. HRMS (ESI) *m*/*z*: $[M - BF_4^-]^+$ Calcd for $C_{18}H_{18}N^+$ 248.1434; Found 248.1436. Anal. Calcd for $C_{18}H_{18}BF_4N$: C, 64.51; H,

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656

5.41; N, 4.18. Found: C, 64.39; H, 5.42; N, 4.11. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1613, 1591, 1566, 1554, 1458, 1360, 1222, 1210, 1185, 1031, 907, 827, 792, 754, 748.

*(1,2-Dimethyl-1H-indol-3-yl)phenylmethylium Tetrafluoroborate (**3h-BF$_4$**).* From **1c** (1.12 g, 7.71 mmol), **2a** (820 mg, 7.73 mmol) and $HBF_4{\cdot}OEt_2$ complex (1.50 g, 9.26 mmol): 2.09 g (6.51 mmol, 84%), bright yellow solid, mp 176−181 °C (dec.). ^{1}H NMR (CD_3CN, 400 MHz) δ 8.72 (s, 1H, H-10), 8.08 (d, 1H, J = 7.9 Hz, H-4), 7.99−7.91 (m, 2H, H-12 and H-17), 7.76−7.61 (m, 5H, H-6, H-7, H-13, H-14 and H-16), 7.48 (td, 1H, J = 1.1, 7.7 Hz, H-5), 3.96 (s, 3H, H-1), 2.91 (s, 3H, H-18).^{13}C NMR (CD_3CN, 101 MHz) δ 174.6 (C-2), 158.2 (C-10), 144.8 (C-8), 135.2 (C-14), 134.6 (C-11), 133.0 (C-12 and C-17), 132.5 (C-3), 131.8 (C-6), 130.8 (C-13 and C-16), 130.1 (C-5), 125.4 (C-9), 124.7 (C-4), 115.5 (C-7), 35.0 (C-1), 14.0 (C-18). ^{19}F NMR (CD_3CN, 376 MHz) δ −151.7. HRMS (ESI) m/z: $[M - BF_4^-]^+$ Calcd for $C_{17}H_{16}N^+$ 234.12773; Found 234.12745. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1606, 1589, 1556, 1453, 1366, 1307, 1221, 1183, 1093, 1047, 1034, 916, 780, 757, 693.

*General Procedure for the Synthesis of Bis(indol-3-yl)methylium Tetrafluoroborates **3(i-k)-BF$_4$**.* Analogous to ref 12, an indole **1a**, **c**, **d** (1.00 g, 2.00 equiv) was dissolved in 20 mL of CH_2Cl_2 and the solution was stirred until complete homogenization and cooled down at 0 °C. Then triethyl orthoformate **4** (1.00 equiv) was added followed by the dropwise addition of the $HBF_4{\cdot}OEt_2$ complex (1.00 equiv). After addition, the solution was allowed to warm at room temperature and was stirred for 2 h. The colored crystals which precipitated were filtered and washed with a mixture of Et_2O and then recrystallized in CH_3CN/Et_2O.

*Bis(1-methyl-1H-indol-3-yl)methylium Tetrafluoroborate (**3i-BF$_4$**).* From **1a** (1.03 g, 7.85 mmol), **4** (579 mg, 3.91 mmol), and $HBF_4{\cdot}OEt_2$ complex (633 mg, 3.91 mmol): 1.22 g (3.39 mmol, 86%), dark green solid, mp 235−240 °C (dec.). ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ 9.28 (br s, 3H, H-2, H-10, H-12), 8.30 (d, 2H, J = 8.2 Hz, H-4, H-16), 7.81−7.75 (m, 2H, H-7, H-13), 7.58−7.50 (m, 4H, H-5, H-15, H-6, H-14), 4.09 (s, 6H, H-1, H-19). ^{1}H NMR spectra agreed with literature data (ref 12b). ^{13}C NMR ($(CD_3)_2SO$, 101 MHz) δ 147.5 (C-10), 146.2 (C-2 and C-12), 138.8 (C-8 and C-18), 128.1 (C-9 and C-17), 126.0 (C-6 and C-14), 125.7 (C-5 and C-15), 120.1 (C-4 and C-16), 117.1 (C-3 and C-11), 113.1 (C-7 and C-13), 35.3 (C-1 and C-19). ^{19}F NMR ($(CD_3)_2SO$, 376 MHz) δ −148.2. HRMS (ESI) m/z: $[M - BF_4^-]^+$ Calcd for $C_{19}H_{17}N_2^+$ 273.1386; Found 273.1388. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1613, 1590, 1567, 1504, 1473, 1445, 1421, 1398, 1311, 1283, 1253, 1211, 1096, 1062, 1029, 959, 806, 748, 681, 657.

*Bis(5-methoxy-1-methyl-1H-indol-3-yl)methylium Tetrafluoroborate (**3j-BF$_4$**).* From **1d** (548 mg, 3.40 mmol), **4** (252 mg, 1.70 mmol), and $HBF_4{\cdot}OEt_2$ complex (275 mg, 1.70 mmol): 493 mg (1.17 mmol, 69%), dark brown solid, mp 256−258 °C (dec.). ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ 9.23 (s, 1H, H-10), 9.18 (br s, 2H, H-2 and H-13), 7.87 (s, 2H, H-4 and H-17), 7.69 (d, 2H, J = 8.9 Hz, H-7 and H-14), 7.11 (dd, 2H, J = 2.4, 8.9 Hz, H-6 and H-15), 4.06 (s, 6H, H-1 and H-20), 3.92 (s, 6H, H-11 and H-21). ^{13}C NMR ($(CD_3)_2SO$, 101 MHz) δ 158.4 (C-5 and C-16), 146.2 (C-10), 144.9 (C-2 and C-13), 133.1 (C-8 and C-19), 129.7 (C-9 and C-18), 116.6 (C-3 and C-12), 114.0 (C-6, C-7, C-14 and C-15), 103.4 (C-4 and C-17), 55.9 (C-11 and C-21), 35.4 (C-1 and C-20).^{19}F NMR (CD_3CN, 376 MHz) δ −151.9. HRMS (ESI) m/z: $[M - BF_4^-]^+$ Calcd for $C_{21}H_{21}O_2N_2^+$ 333.1598; Found 333.1596. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1617, 1579, 1550, 1511, 1473, 1439, 1400, 1306, 1243, 1219, 1184, 1135, 1049, 1036, 946, 917, 846, 799, 790, 769, 715.

*Bis(1,2-dimethyl-1H-indol-3-yl)methylium Tetrafluoroborate (**3k-BF$_4$**).* From **1c** (1.37 g, 9.43 mmol), **4** (699 mg, 4.72 mmol), and $HBF_4{\cdot}OEt_2$ complex (765 mg, 4.72 mmol): 1.36 g (3.50 mmol, 74%), bright red orange solid, mp 252 °C (dec.). ^{1}H NMR (CD_3CN, 400 MHz) δ 8.85 (s, 1H, H-10), 7.68 (dt, 2H, J = 0.8, 8.2 Hz, H-4 and H-16), 7.54−7.47 (m, 2H, H-5 and H-15), 7.34−7.27 (m, 2H, H-6 and H-14), 7.05 (dt, 2H, J = 0.8, 7.1 Hz, H-7 and H-13), 3.93 (s, 6H, H-1 and H-21), 2.83 (s, 6H, H-19 and H-20). ^{1}H NMR spectra agreed with literature data (ref 12b, in $(CD_3)_2SO/CDCl_3$: 1/1). ^{13}C NMR (CD_3CN, 101 MHz) δ 161.8 (C-2 and C-12), 148.1 (C-10), 141.8 (C-8 and C-18), 127.1 (C-5 and C-15), 126.1 (C-9 and C-17), 126.0 (C-6 and C-14), 124.9 (C-7 and C-13), 119.2 (C-3 and C-11), 113.5 (C-4 and C-16), 33.1 (C-1 and C-21), 13.3 (C-19 and C-20). ^{19}F NMR (CD_3CN, 376 MHz) δ −151.8. HRMS (ESI) m/z: $[M - BF_4^-]^+$ Calcd for $C_{21}H_{21}N_2^+$ 301.1699; Found 301.1703. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1563, 1496, 1480, 1387, 1356, 1322, 1290, 1229, 1177, 1094, 1049, 1035, 981, 896, 880, 813, 767, 759, 648, 613, 579.

Product Studies. *(4-Methoxyphenyl)(1-methyl-1H-indol-2-yl)-methanol (**5**).* To a solution of **1a** (1.00 g, 7.63 mmol) in tetrahydrofuran (25 mL) at −78 °C was added dropwise *n*-BuLi (2.50 M, 3.05 mL, 7.63 mmol). After 3 h at this temperature, **2c** (1.14 g, 8.38 mmol, 1.10 equiv) was added to the pale-yellow solution which was then allowed to warm at room temperature followed by stirring overnight. The reaction was quenched by addition of 30 mL of water and extracted with Et_2O (2 × 20 mL). Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, *n*-pentane/EtOAc = 80/20): 1.36 g (5.11 mmol, 67%), yellow oil, R_f (*n*-pentane/EtOAc = 80/20) = 0.15. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (dt, 1H, J = 0.9, 7.9 Hz), 7.34−7.25 (m, 3H), 7.20 (distorted ddd, 1H, J = 1.2, 7.0, 8.2 Hz), 7.08 (distorted ddd, 1H, J = 1.1, 7.0, 8.0 Hz), 6.91−6.86 (m, 2H), 6.30 (br s, 1H), 5.99 (d, 1H, J = 4.4 Hz), 3.80 (s, 3H), 3.63 (s, 3H), 2.27 (d, 1H, J = 4.7 Hz, OH). The decomposition of **5** in $CDCl_3$ is too fast to measure the ^{13}C NMR. HRMS (ESI) m/z: $[M + H^+]$ Calcd for $C_{17}H_{18}NO_2$ 268.1338; Found 268.1330.

*6,12-Bis(4-methoxyphenyl)-5,11-dimethyl-5,6,11,12-tetrahydro-indolo[3,2-b]carbazole (**6**).* To a CH_2Cl_2 (5 mL) solution of **5** (1.20 g, 4.49 mmol, 1 equiv) cooled at 0 °C was added dropwise $HBF_4{\cdot}Et_2O$ (728 mg, 4.49 mmol). Subsequently, the solution was allowed to warm at room temperature and Et_2O was added to give a brown precipitate. After filtration and washing of the solid with cold Et_2O, **6** (1.00 g, 2.01 mmol, 89%) was obtained as a brown solid, mp 335−346 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.46 (app d, 2H, J = 7.9 Hz), 7.24−7.21 (m, 4H), 7.16 (app d, 2H, J = 8.1 Hz), 7.09 (distorted ddd, 2H, J = 1.2, 7.0, 8.1 Hz), 6.96 (distorted ddd, 2H, J = 1.0, 7.0, 8.0 Hz), 6.77−6.73 (m, 4H), 5.70 (s, 2H), 3.71 (s, 6H), 3.42 (s, 6H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 158.3 (C), 138.3 (C), 136.6 (C), 136.1 (C), 130.0 (CH), 125.8 (C), 121.2 (CH), 119.3 (CH), 119.0 (CH), 114.1 (CH), 112.1 (C), 108.9 (CH), 55.4 (CH_3), 39.6 (CH), 30.6 (CH_3). HRMS (EI) m/z: [M] Calcd for $C_{34}H_{30}N_2O_2$ 498.2307; Found 498.2300. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1608, 1507, 1474, 1401, 1376, 1302, 1253, 1224, 1174, 1112, 1032, 828, 806, 759, 737, 613.

*1-Methyl-3-(3-methyl-1-(p-tolyl)but-3-en-1-yl)-1H-indole (**9**).* To a CH_2Cl_2 (5 mL) solution of **3b-BF$_4$** (301 mg, 0.937 mmol, 1.00 equiv) was added **8j** (143 mg, 1.12 mmol, 1.20 equiv), and the solution was stirred for 10 min at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, *n*-pentane/EtOAc = 95/5) to give **9** as a colorless oil (248 mg, 0.818 mmol, 87%), R_f (*n*-pentane/EtOAc = 95/5) = 0.62. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (app d, 1H, J = 8.0 Hz), 7.32−7.19 (m, 4H, superimposed with resonance of $CHCl_3$), 7.12 (app d, 2H, J = 7.9 Hz), 7.07 (distorted ddd, 1H, J = 1.1, 7.0, 8.0 Hz), 6.89 (s, 1H), 4.76 (br s, 1H), 4.71 (br s, 1H), 4.47 (app t, 1H, J = 7.8 Hz), 3.77 (s, 3H), 2.96 (dd, 1H, J = 6.9, 14.4 Hz), 2.78 (dd, 1H, J = 8.7, 14.5 Hz), 2.34 (s, 3H), 1.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 144.2 (C), 142.2 (C), 137.4 (C), 135.5 (C), 129.1 (2 × CH), 128.0 (2 × CH), 127.6 (C), 126.2 (CH), 121.6 (CH), 119.7 (CH), 118.9 (C), 118.8 (CH), 112.3 (CH_2), 109.3 (CH), 44.9 (CH_2), 40.8 (CH), 32.9 (CH_3), 22.8 (CH_3), 21.2 (CH_3). HRMS (EI) m/z: [M] Calcd for $C_{21}H_{23}N$ 289.1830; Found 289.1828.

*2-((1-Methyl-1H-indol-3-yl)phenylmethyl)cyclohexanone (**10**).* To a CH_3CN solution (5 mL) of **3a-BF$_4$** (175 mg, 0.570 mmol, 1.00 equiv) was added neat **8h** (100 mg, 0.588 mmol, 1.05 equiv), and the solution was stirred for 1 h at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, *n*-pentane/EtOAc = 90/10) to give **10** as a yellow oil (108 mg, 0.34 mmol, 61%) as a 1:1 mixture of diastereoisomers. ^{1}H NMR spectra agreed with literature data in ref 25. HRMS (EI) m/z: [M] Calcd for $C_{22}H_{23}ON$ 317.1780; Found 317.1780.

*(E)-5-(4-(Dimethylamino)phenyl)-1-methoxy-5-(1-methyl-1H-indol-3-yl)pent-1-en-3-one (**11**).* To a CH_2Cl_2 solution (5 mL) of **3d-BF$_4$** (266 mg, 0.759 mmol, 1.00 equiv) was added **8d** (157 mg, 0.912 mmol, 1.20 equiv), and the solution was stirred overnight at 20 °C. Solvent and volatile compounds were evaporated under reduced

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656

pressure. The crude product was purified by column chromatography (silica gel, gradient eluent: *n*-pentane/EtOAc = 90/10 to 80/20) to give **11** as a yellow oil (154 mg, 0.425 mmol, 56%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.50 (d, 1H, J = 12.6 Hz), 7.43 (app d, 1H, J = 7.9 Hz), 7.22 (app d, 1H, J = 8.2 Hz), 7.18 (br d, 2H, J = 7.2 Hz), 7.14 (app t, 1H, J = 7.6 Hz), 6.98 (app t, 1H, J = 7.5 Hz), 6.80 (s, 1H), 6.68 (br s, 2H), 5.54 (d, 1H, J = 12.6 Hz), 4.78 (t, 1H, J = 7.5 Hz), 3.70 (s, 3H), 3.59 (s, 3H), 3.23 (dd, 1H, J = 7.1, 15.4 Hz), 3.13 (dd, 1H, J = 7.9, 15.4 Hz), 2.88 (s, 6H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 198.4 (C), 162.8 (CH), 137.5 (C), 128.6 (2 × CH), 127.3 (C), 126.4 (3 × CH), 121.7 (CH), 120.0 (CH), 118.9 (CH), 118.5 (2 × C), 113.1 (C), 109.3 (CH), 105.9 (CH), 57.7 (CH_3), 48.6 (CH_2), 41.0 (2 × CH_3), 37.9 (CH), 32.9 (CH_3). HRMS (EI) m/z: [M] Calcd for $C_{23}H_{26}O_2N_2$ 362.1994; Found 362.1998. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2962, 1673, 1612, 1589, 1517, 1471, 1444, 1414, 1326, 1258, 1083, 1012, 944, 864, 792, 738, 702, 661.

*(E)-5-(4-Methoxyphenyl)-5-(1-methyl-1H-indol-3-yl)pent-2-enal (**12**).* To a CH_2Cl_2 (10 mL) solution of **3c-BF$_4$** (337 mg, 1.00 mmol, 1.00 equiv) was added **8i** (142 mg, 1.00 mmol, 1.00 equiv), and the mixture was stirred for 1 h at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: *n*-pentane/EtOAc = 90/10) to give **12** as a yellow oil (128 mg, 0.401 mmol, 40%), R_f (*n*-pentane/EtOAc = 90/10) = 0.22. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.39 (d, 1H, J = 7.9 Hz), 7.40 (app d, 1H, J = 8.0 Hz), 7.27 (app d, 1H, J = 8.2 Hz), 7.22−7.16 (m, 3H), 7.02 (distorted ddd, 1H, J = 0.9, 7.1, 8.0 Hz), 6.82−6.76 (m, 4H), 6.13 (app ddt, 1H, J = 1.3, 7.9, 15.6 Hz), 4.35 (t, 1H, J = 7.7 Hz), 3.76 (s, 3H), 3.74 (s, 3H), 3.17 (m, 1H), 3.01 (m, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 194.2 (CH), 158.4 (C), 157.3 (CH), 137.5 (C), 136.0 (C), 134.2 (CH), 128.9 (CH), 127.2 (C), 126.3 (CH), 122.1 (CH), 119.6 (CH), 119.2 (CH), 117.7 (C), 114.1 (CH), 109.5 (CH), 55.4 (CH_3), 41.5 (CH), 39.7 (CH_2), 33.0 (CH_3). HRMS (EI) m/z: [M] Calcd for $C_{21}H_{21}O_2N$ 319.1572; Found 319.1572. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2922, 2852, 1683, 1609, 1509, 1465, 1422, 1372, 1327, 1301, 1244, 1174, 1110, 1029, 974, 829, 740.

*1-Methyl-3-(1-phenylbut-3-enyl)-1H-indole (**13**).* To a CH_2Cl_2 solution (10 mL) of **3a-BF$_4$** (200 mg, 0.651 mmol, 1.00 equiv) was added **8k** (84.5 mg, 0.741 mmol, 1.14 equiv), and the solution was stirred for 1 h at 20 °C. Then the reaction was treated with 10 mL of water, and the organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, *n*-pentane/EtOAc = 90/10) to give **13** as a colorless oil (98 mg, 0.37 mmol, 57%), R_f (*n*-pentane/EtOAc = 90/10) = 0.60. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62−7.55 (m, 1H), 7.52−7.24 (m, 7H), 7.21−7.09 (m, 1H), 6.98 (app s, 1H), 6.08−5.84 (m, 1H), 5.27−5.15 (m, 1H), 5.14−5.05 (m, 1H), 4.41 (app t, 1H, J = 7.6 Hz), 3.80 (s, 3H), 3.17−3.03 (m, 1H), 3.00−2.86 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.1 (C), 137.6 (CH), 137.4 (C), 128.4 (2 × CH), 128.2 (2 × CH), 127.6 (C), 126.3 (CH), 126.2 (CH), 121.7 (CH), 119.7 (CH), 118.9 (CH), 118.4 (C), 116.1 (CH_2), 109.3 (CH), 43.2 (CH), 40.8 (CH_2), 32.8 (CH_3). HRMS (EI) m/z: [M] Calcd for $C_{19}H_{19}N^+$ 261.1517; Found 261.1511.

*3-((1,2-Dimethyl-1H-indol-3-yl)(p-tolyl)methyl)tetrahydro-2H-pyran-2-one (**14**).* To a bright orange CH_2Cl_2 solution (10 mL) of **3g-BF$_4$** (261 mg, 0.779 mmol, 1.00 equiv) was added **8b** (230 mg, 1.33 mmol, 1.71 equiv), and the mixture was stirred for 15 min at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, gradient eluent: *n*-pentane/EtOAc = 95/5 to 70/30) to give **14** (1:1 mixture of diastereoisomers) as a colorless solid (258 mg, 0.743 mmol, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (app d, 1H, J = 7.9 Hz), 7.35 (app d, 1H, J = 7.9 Hz), 7.24−7.14 (m, 6H), 7.14−7.06 (m, 2H), 7.06−6.90 (m, 5H), 5.01 (d, 1H, J = 7.0 Hz), 4.77 (d, 1H, J = 8.6 Hz), 4.41−4.28 (m, 3H), 4.25−4.14 (m, 1H), 3.80−3.68 (m, 1H), 3.63 (s, 6H), 3.49−3.32 (m, 1H), 2.43 (s, 3H), 2.37 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H), 2.08−1.71 (m, 6H), 1.65−1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.6 (C), 174.0 (C), 140.5 (C), 138.5 (C), 137.1 (C), 137.0 (C), 135.6 (C), 135.4 (C), 134.6 (C), 134.3 (C), 129.2 (CH), 129.1 (CH), 128.5 (CH), 127.5 (CH), 126.9 (2 × CH), 120.6 (CH), 120.3 (CH), 119.7 (CH), 119.5 (CH), 119.0 (CH), 118.9 (CH), 112.9 (C), 111.6 (C), 109.1 (CH), 108.9 (CH), 68.3 (CH_2), 67.9 (CH_2), 44.2 (CH), 42.7 (CH), 42.6 (CH), 42.5 (CH), 29.8 (2 × CH_3), 23.6 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 22.2 (CH_2), 21.1 (2 × CH_3), 11.1 (CH_3), 11.0 (CH_3). HRMS (EI) m/z: [M] Calcd for $C_{23}H_{25}O_2N$ 347.1885; Found 347.1880.

*Methyl 2,2-Dimethyl-3,3-bis(1-methyl-1H-indol-3-yl)propanoate (**15**).* To a CH_2Cl_2 solution (10 mL) of **3i-BF$_4$** (312 mg, 0.866 mmol, 1.00 equiv) was added **8c** (227 mg, 1.30 mmol, 1.50 equiv) and stirred for 1 h at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, gradient eluent: *n*-pentane/EtOAc = 90/10 to 80/20) to give **15** as a colorless solid (310 mg, 0.828 mmol, 96%), mp 130−133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (app d, 2H, J = 8.0 Hz), 7.21 (app d, 2H, J = 8.2 Hz), 7.16−7.11 (distorted ddd, 2H, J = 1.0, 7.0, 8.1 Hz), 7.03−6.97 (m, 4H), 5.11 (s, 1H), 3.71 (s, 6H), 3.46 (s, 3H), 1.37 (s, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 179.0 (C), 136.5 (C), 129.0 (C), 127.6 (CH), 121.4 (CH), 119.9 (CH), 118.8 (CH), 115.9 (C), 109.0 (CH), 52.0 (CH_3), 47.4 (C), 40.4 (CH), 33.0 (2 × CH_3), 24.4 (2 × CH_3). HRMS (EI) m/z: [M] Calcd for $C_{24}H_{26}O_2N_2$ 374.1994; Found 374.1979. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3050, 2946, 1728, 1613, 1537, 1465, 1430, 1373, 1330, 1251, 1205, 1183, 1152, 1123, 1112, 1060, 1014, 984, 938, 870, 818, 792, 739, 726, 709, 659, 569.

*3-(Bis(1-methyl-1H-indol-3-yl)methyl)dihydrofuran-2(3H)-one (**16a**).* To a CH_2Cl_2 solution (10 mL) of **3i-BF$_4$** (306 mg, 0.850 mmol, 1.00 equiv) was added **8a** (180 mg, 1.14 mmol, 1.34 equiv), and the solution was stirred for 10 min at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, gradient eluent: *n*-pentane/EtOAc = 80/20 to 50/50) to give **16b** as a yellow oil (37 mg, 0.16 mmol, 19%) and **16a** as a colorless solid (222 mg, 0.619 mmol, 73%), mp 90−100 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) of **16a** δ 7.41 (app t, 2H, J = 7.2 Hz), 7.27 (app d, 1H, J = 8.2 Hz), 7.25−7.22 (m, 1H), 7.18 (app t, 1H, J = 7.6 Hz), 7.14 (app t, 1H, J = 7.6 Hz), 7.05 (br s, 1H), 7.00−6.93 (m, 3H), 5.20 (d, 1H, J = 3.3 Hz), 4.14−4.06 (m, 1H), 3.84 (app td, 1H, J = 4.3, 8.7 Hz), 3.75 (s, 3H), 3.71 (s, 3H), 3.51 (app td, 1H, J = 3.4, 9.2 Hz), 2.49−2.42 (m, 1H), 2.42−2.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 178.9 (C), 137.2 (2 × C), 128.5 (CH), 127.9 (C), 127.8 (C), 126.8 (CH), 121.9 (CH), 121.6 (CH), 120.1 (CH), 119.6 (CH), 119.1 (2 × CH), 116.0 (C), 114.3 (C), 109.3 (2 × CH), 66.8 (CH_2), 45.0 (CH), 34.4 (CH), 33.0 (2 × CH_3), 26.6 (CH_2). HRMS (EI) m/z: [M] Calcd for $C_{23}H_{22}O_2N_2$ 358.1681; Found 358.1668. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1761, 1612, 1542, 1469, 1423, 1371, 1328, 1213, 1153, 1024, 953, 738, 680.

*(E)-3-((1-Methyl-1H-indol-3-yl)methylene)dihydrofuran-2(3H)-one (**16b**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (t, 1H, J = 2.7 Hz), 7.81 (app dt, 1H, J = 1.1, 7.7 Hz), 7.36−7.19 (m, 4H), 4.40 (app t, 2H, J = 7.4 Hz), 3.83 (s, 3H), 2.97 (app td, 2H, J = 2.8, 7.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2 (C), 136.9 (C), 130.4 (CH), 128.1 (C), 127.8 (CH), 123.4 (CH), 121.3 (CH), 119.0 (C), 116.9 (CH), 112.1 (C), 109.9 (CH), 65.2 (CH_2), 33.6 (CH_3), 28.4 (CH_2). HRMS (EI) m/z: [M] Calcd for $C_{14}H_{13}O_2N$ 227.0946; Found 227.0950.

*3-(Bis(1-methyl-1H-indol-3-yl)methyl)tetrahydro-2H-pyran-2-one (**17a**).* To a CH_2Cl_2 solution (10 mL) of **3i-BF$_4$** (270 mg, 0.750 mmol, 1.00 equiv) was added **8b** (157 mg, 0.911 mmol, 1.21 equiv), and the solution was stirred for 10 min at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, gradient eluent: *n*-pentane/EtOAc = 80/20 to 50/50) to give **17b** as a yellow oil (30 mg, 0.12 mmol, 16%), R_f (*n*-pentane/EtOAc = 70/30) = 0.2 and **17a** as a colorless solid (131 mg, 0.352 mmol, 47%), mp 64−76 °C, R_f (*n*-pentane/EtOAc = 70/30) = 0.09. ^{1}H NMR ($CDCl_3$, 300 MHz) of **17a** δ 7.55−7.46 (m, 2H), 7.29−7.11 (m, 4H), 7.06−6.93 (m, 4H), 5.35 (d, 1H, J = 4.4 Hz), 4.42−4.19 (m, 1H), 4.17−4.01 (m, 1H), 3.72 (s, 6H), 3.50−3.40 (m, 1H), 2.14−1.70 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3 (C), 137.2 (2 × C), 128.2 (CH), 128.1 (C), 127.9 (C), 127.5 (CH), 121.7 (CH), 121.5 (CH), 120.4 (CH), 119.6 (CH), 119.0 (2 × CH), 116.0 (C), 115.1 (C), 109.3 (CH), 109.2 (CH), 69.0 (CH_2), 45.8 (CH), 35.3 (CH), 33.0 (2 × CH_3), 23.6 (CH_2), 23.0 (CH_2). HRMS (EI) m/z: [M] Calcd for $C_{24}H_{24}O_2N_2$ 372.1838; Found 372.1828. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 1720, 1612, 1423, 1371, 1327, 1260, 1152, 1084, 1012, 960, 910, 770, 737, 646.

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656

*(E)-3-((1-Methyl-1H-indol-3-yl)methylene)tetrahydro-2H-pyran-2-one (**17b**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (t, 1H, J = 2.2 Hz), 7.87 (app d, 1H, J = 7.8 Hz), 7.38−7.20 (m, 4H), 4.35 (app t, 2H, J = 5.2 Hz), 3.85 (s, 3H), 2.72 (app td, 2H, J = 2.2, 6.7 Hz), 2.09−1.99 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1 (C), 136.6 (C), 133.1 (CH), 130.9 (CH), 128.7 (C), 123.3 (CH), 121.2 (CH), 119.3 (CH), 119.0 (C), 112.0 (C), 109.7 (CH), 68.3 (CH_2), 33.6 (CH_3), 27.1 (CH_2), 22.9 (CH_2). HRMS (EI) m/z: [M] Calcd for $C_{15}H_{15}O_2N$ 241.1103; Found 241.1081.

*3-(Bis(1,2-dimethyl-1H-indol-3-yl)methyl)dihydrofuran-2(3H)-one (**18a**).* To a CH_2Cl_2 solution (10 mL) of **3k-BF$_4$** (327 mg, 0.842 mmol, 1.00 equiv) was added **8a** (230 mg, 1.45 mmol, 1.73 equiv), and the solution was stirred for 1 h at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, gradient eluent: *n*-pentane/EtOAc = 80/20 to 50/50) to give **18b** as a colorless solid (20 mg, 0.08 mmol, 10%): mp 157−164 °C, R_f (*n*-pentane/EtOAc = 80/20) = 0.08 and **18a** as a yellow solid (86 mg, 0.22 mmol, 27%): mp 206−213 °C, R_f (*n*-pentane/EtOAc = 80/20) = 0.37. ^{1}H NMR ($CDCl_3$, 200 MHz) of **18a** δ 7.65 (app d, 1H, J = 7.3 Hz), 7.39−6.96 (m, 6H), 6.95−6.78 (m, 1H), 5.11 (d, 1H, J = 5.3 Hz), 4.24−4.03 (m, 1H), 3.93−3.74 (m, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 2.76−2.51 (m, 1H), 2.50−2.30 (m, 1H), 2.41 (s, 3H), 2.19 (s, 3H). The product is not sufficiently stable in $CDCl_3$ to measure the carbon NMR; it decomposed within 1 h into compound **18b** and the indole **1c**. HRMS (EI) m/z: [M] Calcd for $C_{25}H_{26}O_2N_2$ 386.1994; Found 386.1987. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3048, 2911, 1750, 1608, 1541, 1468, 1411, 1365, 1332, 1247, 1214, 1165, 1134, 1070, 1020, 965, 945, 925, 902, 821, 738, 695, 663, 608.

*(E)-3-((1,2-Dimethyl-1H-indol-3-yl)methylene)dihydrofuran-2(3H)-one (**18b**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (app t, 1H, J = 2.5 Hz), 7.63−7.57 (m, 1H), 7.34−7.11 (m, 3H), 4.36 (app t, 2H, J = 7.3 Hz), 3.70 (s, 3H), 3.13 (app td, 2H, J = 2.5, 7.3 Hz), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6 (C), 140.3 (C), 137.5 (C), 131.2 (CH), 126.0 (C), 122.1 (C), 120.7 (CH), 120.1 (CH), 119.0 (CH), 109.6 (CH), 109.0 (C), 65.7 (CH_2), 30.1 (CH_3), 29.2 (CH_2), 11.5 (CH_3). HRMS (EI) m/z: [M] Calcd for $C_{15}H_{15}O_2N$ 241.1103; Found 241.1106.

*3-(Bis(1,2-dimethyl-1H-indol-3-yl)methyl)tetrahydro-2H-pyran-2-one (**19a**).* To a CH_2Cl_2 solution (5 mL) of **3k-BF$_4$** (310 mg, 1.03 mmol, 1.00 equiv) was added **8b** (354 mg, 2.06 mmol, 2.00 equiv), and the solution was stirred for 30 min at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, gradient eluent: *n*-pentane/EtOAc = 90/10 to 60/40) and recrystallized from (*n*-pentane/EtOAc) to give **19b** as colorless solid (129 mg, 0.506 mmol, 49%): mp 144−153 °C and **19a** as a colorless solid (48 mg, 0.12 mmol, 12%): mp 188−197 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) of **19a** δ 7.69 (app d, 1H, J = 7.2 Hz), 7.58 (app d, 1H, J = 8.0 Hz), 7.29 (app d, 2H, J = 5.1 Hz), 7.19−6.90 (m, 4H), 5.04 (d, 1H, J = 9.4 Hz), 4.55−4.30 (m, 2H), 4.26−4.05 (m, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 2.46 (s, 3H), 2.34 (s, 3H), 2.01−1.81 (m, 2H), 1.76−1.50 (m, 2H). The product is not sufficiently stable in $CDCl_3$ to measure the carbon NMR; it decomposed within 1 h into compound **19b** and the indole **1c**. HRMS (EI) m/z: [M] Calcd for $C_{26}H_{28}O_2N_2$ 400.2151; Found 400.2144.

*(E)-3-((1,2-Dimethyl-1H-indol-3-yl)methylene)tetrahydro-2H-pyran-2-one (**19b**).* ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.12 (app t, 1H, J = 1.7 Hz), 7.44 (app d, 1H, J = 7.6 Hz), 7.29 (app d, 1H, J = 7.5 Hz), 7.24−7.11 (m, 2H), 4.41 (app t, 2H, J = 5.5 Hz), 3.70 (s, 3H), 2.69−2.58 (m, 2H), 2.39 (s, 3H), 1.93−1.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 167.4 (C), 138.6 (C), 137.1 (C), 136.3 (CH), 126.3 (C), 122.8 (C), 121.7 (CH), 120.3 (CH), 120.1 (CH), 109.3 (CH), 108.8 (C), 69.5 (CH_2), 30.0 (CH_3), 27.1 (CH_2), 23.7 (CH_2), 11.8 (CH_3). HRMS (EI) m/z: [M] Calcd for $C_{16}H_{17}O_2N$ 255.1259; Found 255.1249.

*4-(Bis(1,2-dimethyl-1H-indol-3-yl)methyl)morpholine (**20**).* To a CH_3CN solution (10 mL) of **3k-BF$_4$** (220 mg, 0.567 mmol, 1.00 equiv) was added **8m** (172 mg, 1.98 mmol, 3.49 equiv) and stirred for 5 min at 20 °C. Solvent and volatile compounds were evaporated under reduced pressure. The crude product was recrystallized from Et_2O, EtOAc, and acetonitrile to give **20** as a colorless solid (83 mg, 0.21 mmol, 38%). ^{1}H NMR (CD_3CN, 400 MHz) δ 7.98 (br d, 2H, J = 8.0 Hz, H-4), 7.22 (app dt, 2H, J = 0.9, 8.2 Hz, H-7), 7.03 (distorted ddd, 1H, J = 1.2, 7.1, 8.2 Hz, H-6), 6.93 (distorted ddd, 1H, J = 1.1, 7.0, 8.1 Hz, H-5), 4.97 (s, 1H, H-10), 3.66 (app t, 4H, J = 4.7 Hz, H-13), 3.58 (s, 6H, H-1), 2.49 (s, 6H, H-2), 2.43 (br s, 4H, H-12). ^{13}C NMR (CD_3CN, 101 MHz) δ 138.0 (C8), 135.4 (C2), 128.2 (C9), 121.5 (C4), 121.4 (C6), 119.8 (C5), 113.0 (C3), 110.0 (C7), 68.4 (C12), 63.1 (C10), 54.6 (C11), 30.3 (C1), 11.9 (C13). HRMS (EI) m/z: [M] Calcd for $C_{25}H_{29}ON_3$ 387.2311; Found 387.2312.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01298.

Details of the kinetic experiments, quantum chemical calculations for compounds **3a−e**, copies of the NMR (for compounds: **3a−k**, **5−6**, **9−20**) and IR spectra (for compounds: **3a−k**, **6**, **11**, **12**, **15**, **16a**, **17a**, **18a**) (PDF)

X-ray crystallographic data files (CIF) for compounds **3b−c,e,l,k** (CIF)

X-ray crystallographic data files (CIF) for compound **19b** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: herbert.mayr@cup.uni-muenchen.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Alexander von Humboldt Foundation (grant for G.B.) and the Deutsche Forschungsgemeinschaft (SFB 749, project B1). We thank Dr. A. R. Ofial for help in the preparation of the manuscript (Munich, Germany), Dr. D. Stephenson (Munich, Germany), Dr. S. Lakhdar (Caen, France), Dr. P. Byrne (Munich, Germany), Prof. D. Lupton (Victoria, Australia), and Prof. F. Terrier (Versailles, France) for helpful discussions. Dedicated to Professor Stefan Spange on the occasion of his 65th birthday.

■ REFERENCES

(1) Xiao, Y.-C.; Zhou, Q.-Q.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Org. Lett.* **2012**, *14*, 5940−5943.

(2) (a) Zhuo, M.-H.; Jiang, Y.-J.; Fan, Y.-S.; Gao, Y.; Liu, S.; Zhang, S. *Org. Lett.* **2014**, *16*, 1096−1099. (b) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661−5665. (c) Iwao, T.; Shimizu, M. *Heterocycles* **2009**, *77*, 767−772.

(3) (a) Marsili, L.; Palmieri, A.; Petrini, M. *Org. Biomol. Chem.* **2010**, *8*, 706−712. (b) Fu, T.-h.; Bonaparte, A.; Martin, S. F. *Tetrahedron Lett.* **2009**, *50*, 3253−3257. (c) Harisson, C.-A.; Leineweber, R.; Moody, C. J.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 8527−8530. (d) Comins, D. L.; Stroud, E. D. *Tetrahedron Lett.* **1986**, *27*, 1869−1872.

(4) (a) Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313−1316. (b) Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8707−8710. (c) Armenise, N.; Dughera, S.; Gualandi, A.; Mengozzi, L.; Barbero, M.; Cozzi, P. G. *Asian J. Org. Chem.* **2015**, *4*, 337−345. (d) Guo, C.; Song, J.; Luo, S.-W.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5558−5562. (e) Xu, B.; Shi, L.-L.; Zhang, Y.-Z.; Wu, Z.-J.; Fu, L.-N.; Luo, C.-Q.; Zhang, L.-X.; Peng, Y.-G.; Guo, Q.-X. *Chem. Sci.* **2014**, *5*, 1988−1991. (f) Guo, Z.-L.; Xue, J.-H.; Fu, L.-N.; Zhang, S.-E.; Guo, Q.-X. *Org. Lett.* **2014**, *16*, 6472−6475.

(5) Wang, D.-S.; Tang, J.; Zhou, Y.-G.; Chen, M.-W.; Yu, C.-B.; Duan, Y.; Jiang, G.-F. *Chem. Sci.* **2011**, *2*, 803−806.

(6) For reviews, see: (a) Wang, L.; Chen, Y.; Xiao, J. *Asian J. Org. Chem.* **2014**, *3*, 1036−1052. (b) Bartoli, G.; Bencivenni, G.; Dalpozzo, R.

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656

Chem. Soc. Rev. **2010**, *39*, 4449−4465. (c) Palmieri, A.; Petrini, M.; Shaikh, R. R. *Org. Biomol. Chem.* **2010**, *8*, 1259−1270. (d) Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250−2293. (e) Loh, C. C. J.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 46−48.

(7) (a) Barbero, M.; Cadamuro, S.; Cauda, F.; Dughera, S.; Gervasio, G.; Venturello, P. *J. Org. Chem.* **2012**, *77*, 4278−4287. (b) Barbero, M.; Buscaino, R.; Cadamuro, S.; Dughera, S.; Gualandi, A.; Marabello, D.; Cozzi, P. G. *J. Org. Chem.* **2015**, *80*, 4791−4796. (c) Lv, X.; Liu, J.; Liu, Y.; Zhao, Y.; Sun, Y.-Q.; Wang, P.; Guo, W. *Chem. Commun.* **2011**, *47*, 12843−12845. (d) Erdelmeier, I.; Gérard-Monnier, D.; Yadan, J.-C.; Chaudière, J. *Chem. Res. Toxicol.* **1998**, *11*, 1184−1194. (e) Johannes, H.-H.; Grahn, W.; Dix, I.; Jones, P. G. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1997**, *53*, 1432−1434. (f) Brooker, L. G. S.; Sprague, R. H. *J. Am. Chem. Soc.* **1941**, *63*, 3203−3213. (g) Brooker, L. G. S.; Sprague, R. H.; Smyth, C. P.; Lewis, G. L. *J. Am. Chem. Soc.* **1940**, *62*, 1116−1125.

(8) (a) Kikuchi, S.; Iki, M.; Ikeda, C.; Imafuku, K. *Heterocycles* **2005**, *66*, 275−283. (b) Kogan, N. A. *Chem. Heterocycl. Compd.* **1980**, *16*, 373−376. (c) Battiste, M. A.; Hill, J. H. M. *Tetrahedron Lett.* **1968**, *9*, 5541−5544. (d) Huffman, R. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 6243−6251.

(9) (a) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500−9512. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77. (c) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807−1821. (d) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957. (e) Mayr, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3612−3618. (f) Database for *N*, s_N, and *E* parameters and references to original literature: www.cup.lmu.de/oc/mayr/DBintro.html. (g) Richter, D.; Mayr, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1958−1961. (h) Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 6579−6587.

(10) For earlier attempts to organize electrophilic and nucleophilic reactivities, see: (a) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141−147. (b) Edwards, J. O. *J. Am. Chem. Soc.* **1954**, *76*, 1540−1547. (c) Edwards, J. O. *J. Am. Chem. Soc.* **1956**, *78*, 1819−1820. (d) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1−32. (e) Bunnett, J. F. *Annu. Rev. Phys. Chem.* **1963**, *14*, 271−290. (f) *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; Advances in Chemistry Series: American Chemical Society: Washington, DC, 1987; Vol. *215*. (g) Pearson, R. G.; Sobel, H. R.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319−326. (h) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348−354. (i) Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239−2250. (j) Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev.* **1984**, *84*, 525−543.

(11) The CCDC numbers are as follows: for **3b**, 996884; for **3c**, 996885; for **3e**, 1011256; for **3i**, 996886; for **3k**, 996887; for **19b**, 996888. For related X-ray structures of indolylmethylium ions, see refs 7a and 7e. For X-ray structures of Michael acceptors similar to **19b**, see: (a) Grošelj, U.; Bevk, D.; Jakše, R.; Meden, A.; Rečnik, S.; Stanovnik, B.; Svete, J. *Synthesis* **2005**, 1087−1094. (b) Lóránd, T.; Forgó, P.; Földesi, A.; Ôsz, E.; Prókai, L. *Eur. J. Org. Chem.* **2002**, 2996−3003.

(12) (a) Pindur, U.; Müller, J. *J. Heterocycl. Chem.* **1987**, *24*, 159−163. (b) Pindur, U.; Flo, C.; Akgün, E.; Tunali, M. *Liebigs Ann. Chem.* **1986**, 1621−1627. (c) Müller, J.; Pfeuffer, L.; Pindur, U. *Monatsh. Chem.* **1985**, *116*, 365−370. (d) Müller, J.; Pindur, U. *Arch. Pharm. (Weinheim, Ger.)* **1984**, *317*, 555−561. (e) Akgün, E.; Pindur, U.; Müller, J. *J. Heterocycl. Chem.* **1983**, *20*, 1303−1305. (f) Berti, C.; Greci, L.; Marchetti, L. *J. Heterocycl. Chem.* **1978**, *15*, 433−437.

(13) Santoso, M.; Kumar, N.; Black, D. S. C. *Collect. Czech. Chem. Commun.* **2009**, *74*, 1137−1150.

(14) In contrast, the additions of π-nucleophiles to aryl(ferrocenyl)-methylium ions, which are structural analogues of aryl(indol-3-yl) methylium ions **3**, were reported to occur with good diastereoselectivities; see: Richards, C. J.; Hibbs, D.; Hursthouse, M. B. *Tetrahedron Lett.* **1994**, *35*, 4215−4218.

(15) Fridkin, G.; Boutard, N.; Lubell, W. D. *J. Org. Chem.* **2009**, *74*, 5603−5606.

(16) In the case of indolylmethylium ions, which are not substituted at nitrogen, Barbero et al. (ref 7a) reported, however, that some counteranions can form hydrogen bonds with the NH of indole and can change the reactivities of the indolylmethylium ions.

(17) (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195. (b) Zenz, I.; Mayr, H. *J. Org. Chem.* **2011**, *76*, 9370−9378.

(18) (a) Christensen, J. J.; Izatt, R. M.; Wrathall, D. P.; Hansen, L. D. *J. Chem. Soc. A* **1969**, 1212−1223. (b) Hinman, R. L.; Lang, J. *J. Am. Chem. Soc.* **1964**, *86*, 3796−3806. (c) Marshall, H. P.; Grunwald, E. *J. Am. Chem. Soc.* **1954**, *76*, 2000−2004.

(19) Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. *J. Org. Chem.* **2006**, *71*, 9088−9095.

(20) (a) Exner, O. *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988. (b) Hill, E. A.; Gross, M. L.; Stasiewicz, M.; Manion, M. *J. Am. Chem. Soc.* **1969**, *91*, 7381−7392.

(21) Praveen, P. J.; Parameswaran, P. S.; Majik, M. S. *Synthesis* **2015**, *47*, 1827−1837.

(22) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644−5645.

(23) Boeckman, R. K.; Pero, J. E., Jr.; Boehmler, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 11032−11033.

(24) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490−11495.

(25) Weng, Z.-T.; Li, Y.; Tian, S.-K. *J. Org. Chem.* **2011**, *76*, 8095−8099.

DOI: 10.1021/acs.joc.5b01298
J. Org. Chem. 2015, 80, 8643−8656