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Preparation of Aza-Polycyclic Aromatic Compounds via Superelectrophilic Cyclizations

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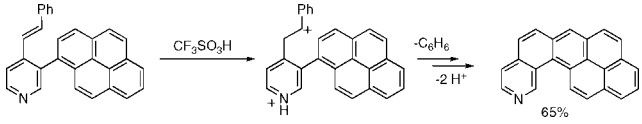


Alkenyl-substituted *N*-heterocycles react in superacidic CF_3SO_3H (triflic acid) to produce dicationic intermediates. These superelectrophiles undergo cyclizations to give varied aza-polycyclic aromatic compounds in generally good yields (27–99%, 16 examples). Theoretical calculations indicate a preference for charge-separated dicationic intermediates.

Superacidic media is well-known for its ability to generate reactive electrophilic species, many of which are useful in synthetic methodologies.[1] In some cases, it has been demonstrated that even di- and tricationic, superelectrophilic intermediates may be formed in superacids. Multiply charged superelectrophiles often exhibit novel chemistry, when compared to monocationic electrophiles.[2] The chemistry of superelectrophilic systems can include unusual rearrangements, reactions with very weak nucleophiles, functionalization at nonactivated bonds, remote functionalizations, and other reactions.[2] We recently described a group of reactions involving functionalized *N*-heterocycles which produce aza-polycyclic aromatic compounds (Scheme 1).[3] The chemistry involves the ionization of alcohols (i.e., **1**) in superacidic media to form dicationic superelectrophiles. Charge migration (**2** → **3**) leads to cyclization, and further loss of benzene provides the aza-polycyclic aromatic product (**4**). The chemistry provides access to a wide variety of condensed ring systems. In this paper, we report a significant improvement in this superelectrophilic chemistry and the preparation of functionalized aza-polycyclic aromatic compounds.

With the involvement of carbocation electrophiles in the cyclizations, we reasoned that olefinic systems would be superior to alcohols in generating the required superelectrophiles. In reactions with comparable alcohol substrates (**5a**−**9a**) and olefinic substrates (**5b**−**9b**), it was observed that the olefins consistently provided better yields of the condensation products

SCHEME 1. Ionization of Alcohol 1 in Superacid and Its Cyclization to Product

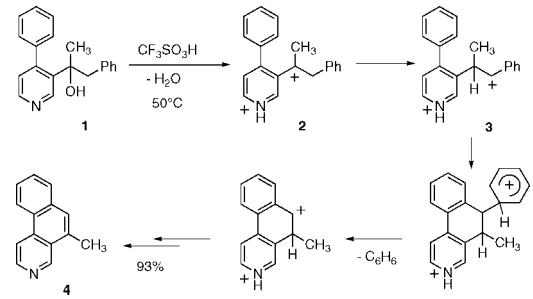
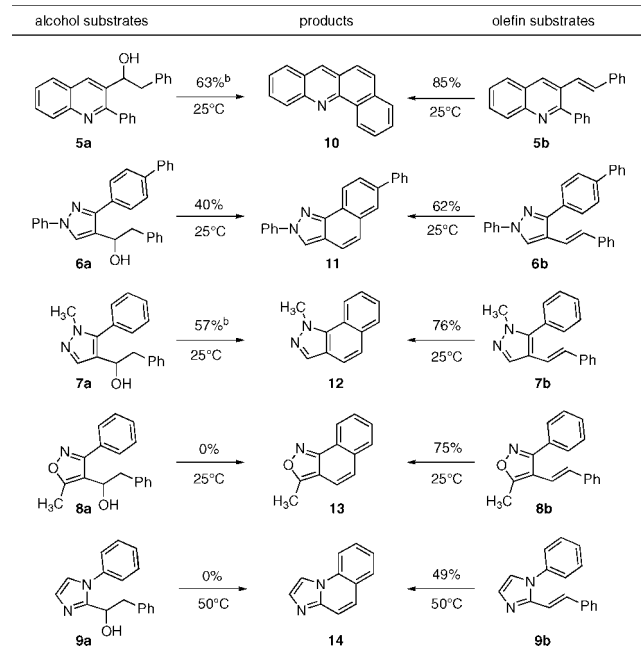


TABLE 1. Products and Yields from Reactions of Alcohol (5a−9a) and Olefin Substrates (5b−9b) with CF_3SO_3H (0.2 mmol of Substrate, 4 mL of Acid, 24 h)[a]



[a] Isolated yields. [b] From ref 3.

(**10**–**14**; Table 1). Thus, ionization of the alcohol derivative **5a** gives benzo[*c*]acridine (**10**) in fair yield (63%), while the olefin derivative **5b** provides compound **10** in 85%. Alcohol **8a** does not give the desired condensation product **13**; however, an intermediate cyclization product (without benzene elimination) can be isolated in 17% yield (see the Supporting Information). In the case of *H*-imidazo[1,2-*a*]quinoline (**14**), the alcohol substrate **9a** likewise does not provide the desired product. The corresponding olefin (**9b**), however, provides the aza-polycyclic aromatic compound (**14**) in fair yield.

In order to further explore the scope of this chemistry, a variety of functionalized aza-polycyclic aromatic compounds (**25**–**34**) were synthesized from the respective olefinic substrates (**15**–**24**; Table 2). These products include substituted benzoisoquinolines (**25** and **27**) and benzo[*c*]acridine derivatives (**28**–**30**). In the case of substrate **19**, demethylation occurs in the

(1) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley: New York, 1985.

(2) (a) Olah, G. A.; Klumpp, D. A. *Superelectrophiles and Their Chemistry*; Wiley: New York, 2008. (b) Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, *37*, 211. (c) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767.

(3) Li, A.; Kindelin, P. J.; Klumpp, D. A. *Org. Lett.* **2006**, *8*, 1233.

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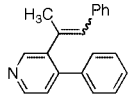
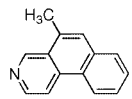
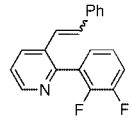
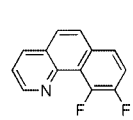
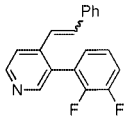
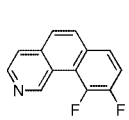
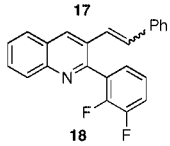
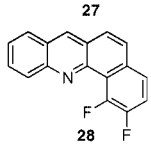
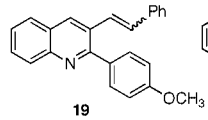
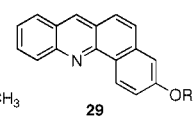
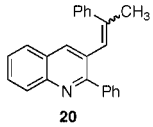
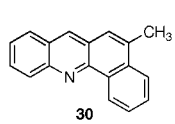
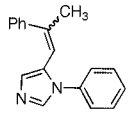
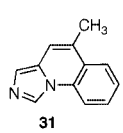
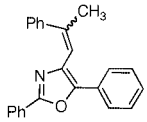
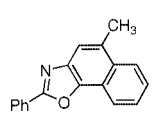
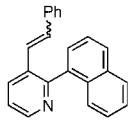
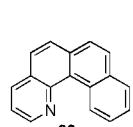
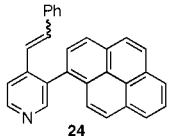
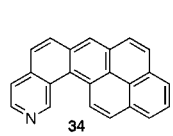
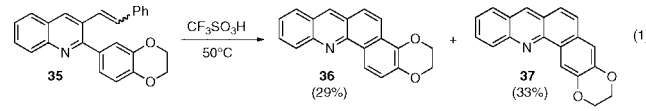
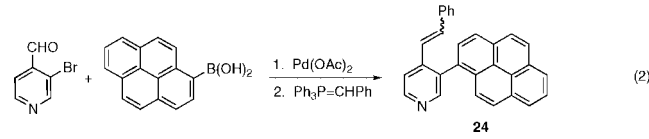
TABLE 2. Products and Yields from the Reactions of 15–24 with CF_3SO_3H (0.2 mmol of Substrate, 4 mL of acid, 24 h)

olefin substrate	product	yield[a]
 **15**	 **25**	99%[c]
 **16**	 **26**	81%[d]
 **17**	 **27**	99%[d]
 **18**	 **28**	75%[d]
 **19**	 **29**	99%[d] (**29a**, R=H) 31%[b] (**29b**,R=CH_3)
 **20**	 **30**	98%[c]
 **21**	 **31**	27%[c]
 **22**	 **32**	99%[c]
 **23**	 **33**	50%[c]
 **24**	 **34**	65%[c]

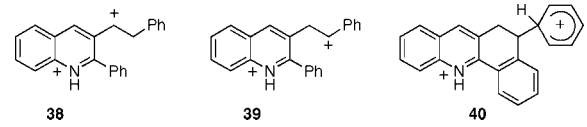
[a] Isolated yield of pure product. Reaction run at: [b] 0 °C. [c] 25 °C. [d] 50 °C.

superacidic media at 50 °C to give benzo[*c*]acridine-3-ol (**29a**). At 0 °C, the methoxy-substituted product (**29b**) is formed, albeit in low yield. When the 2-phenyl-1-propenyl (**20**–**22**) or the 1-phenyl-2-propenyl groups (**15**) are used, methyl-substituted arenes (**25**, **30**–**32**) are formed. Other aza-polycyclic aromatic compounds (**33** and **34**) were prepared in reasonably good yields by cyclization toward naphthyl and pyrenyl ring systems. Reaction of derivative **35** in CF_3SO_3H gives a mixture of isomers **36** and **37** in 62% overall yield (eq 1). The olefinic substrates (**15**–**24** and **35**) were generally prepared using Wittig and Suzuki coupling reactions, for example in the preparation of substrate **24** from 3-bromo-4-pyridinecarboxaldehyde (eq 2).





The superacid-promoted cyclizations of the olefinic substrates likely occur by a mechanism similar to that proposed for the alcohol substrates (cf. Scheme 1). The key steps involve formation of two types of dicationic intermediates: the dication leading to a cyclization and *ipso*-protonated dication (i.e., **39** and **40**). The increased product yields from the olefinic substrates (compared to similar alcohol substrates) may be the result of at least two factors. First, ionization of the alcohol leads to an elimination of water. The water elimination leads to an overall decrease in the acidity of the reaction media. Second, cyclization of an alcohol substrate requires a charge migration step (**38** → **39**). This may slow the conversion and lead to lower yields. With the olefinic substrates, the required superelectrophilic intermediate (**39**) is produced directly from the olefin. Due to charge–charge repulsive effects, the requisite dication is formed regioselectively, and this leads to rapid and efficient cyclization.



In order to further study this aspect of the chemistry, the two possible superelectrophilic regioisomers arising from diprotonation of **5b** (**38** and **39**) were compared by theoretical calculations using the Gaussian program suite.[4] Structures **38** and **39** were optimized without symmetry constraints at the HF/6-31G(d) level and the stationary points shown to be minima at this level by frequency analysis. The structures were then reoptimized at the levels listed in Table 3. Energies of the gas-phase structures were corrected using the appropriately scaled zero-point energy determined by the frequency analysis.[5] At all levels of theory, the charge-separated dication **39** is found to be considerably more stable than the isomeric dication **38**. Using the solution-phase model IPCM (single point)//MPW1/6-311G(d) (dielectric constant $\epsilon = 100$), **39** remains 7.4 kcal mol^{-1} more stable than **38**. Interestingly, the decreased energy

(4) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Rega, N.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A.11.4*; Gaussian, Inc.: Pittsburgh, PA, 2002.

(5) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

TABLE 3. Calculated Relative Energies of Dications 38 and 39

level of theory	relative energy (kcal·mol^{-1}) 39	38
HF/6-311G (d)	0.0	18.0
B3LYP/6-311G (d)	0.0	14.9
PBE1/6-311G (d)	0.0	10.0
MP2/6-311G (d)	0.0	10.3
IPCMsp//MPW1/6-11G (d)	0.0	7.4

difference (between **38** and **39**) with the solvation model probably reflects the impact of the solvation cavity on the dicationic species. The less stable ion (with more closely oriented charges) **38** is expected to benefit more form solvolytic stabilization than does the charge-separated ion **39**. Though calculations have only been done on this one system (**5b** to **38** and **39**), it seems reasonable to expect that other systems will exhibit similar energy trends. Indeed, the energy difference may even be greater for other pairs of isomeric dications. This may further explain the increased yields of aza-polycyclic aromatic products for olefinic versus alcohol substrates (Table 1). Ionization of the alcohol substrates requires formation of the higher energy dications with more closely oriented charges.

In summary, we have found that the superacid-promoted reactions of alkenyl-substituted *N*-heterocycles can provide a wide variety of aza-polycyclic aromatic compounds. It is proposed that the reactions involve the cyclizations of super-electrophilic intermediates, formed regioselectively due to charge–charge repulsive effects. Formation of the condensed aromatic system is achieved in subsequent steps by *ipso*-protonation of a phenyl group and elimination of benzene. From the examples studied above, this is clearly a useful and general synthetic route to an important class of compounds, the aza-polycyclic aromatic compounds.

Experimental Section

General Methods. Triflic acid was purchased from a commercial supplier and distilled from a dry Ar atmosphere immediately prior to use. Benzene was dried over 4 Å sieves prior to use, and all other reagents (except those noted below) were obtained from commercial suppliers and used as received. High-resolution mass spectra were obtained from the Mass Spectroscopy Laboratory at the University of Illinois at Champaign−Urbana.

Preparation of Olefin Substrates: Method A [Compounds 6b, 7b, 8b, 15, and 22 ($Ph_3PC(CH_3)Ph$ Used)]. Benzyltriphenylphosphonium (4.8 mmol) bromide is suspended in anhydrous THF (20 mL) and cooled to –78 °C. To this solution was added butyllithium (2.4 mL, 4.8 mmol, 2.0 M solution in cyclohexane) and the mixture stirred for 2 h. The aldehyde or ketone (4 mmol) was dissolved in anhydrous THF (5 mL) and then slowly added into the reaction. The solution was then warmed to 25 °C and stirred for 4 h. The product mixture was quenched with H_2O and extracted with ether (3 × 40 mL). The organic extracts were washed with brine and then dried with anhydrous Na_2SO_4. The crude olefins were then purified by column chromatography (hexane/ether).

Preparation of Olefin Substrates: Method B [Compounds 9b and 21 ($Ph_3PC(CH_3)Ph$ Used)]. Phenylimidazole (12 mmol) was dissolved in anhydrous THF (40 mL) and cooled to 0 °C. Butyllithium (2.4 mL, 4.8 mmol, 2.0 M solution in cyclohexane) was added. The solution was then warmed to 25 °C and stirred for 2 h. Anhydrous DMF (5 mL) was slowly added to the reaction mixture and stirred overnight. The product mixture was quenched with H_2O. Extraction with ether was followed by aqueous washes of brine and drying with anhydrous Na_2SO_4. The product was then purified by silica gel chromatography (hexane/ether). The resulting aldehyde, 1-phenylimidazole-2-carbaldehyde, was converted to olefin substrates **9b** and **21** by method A.

Preparation of Olefin Substrates: Method C [5a, 16–19, 20 ($Ph_3PC(CH_3)Ph$ used), 23, 24, and 35]. The aldehyde (6 mmol) and boronic acid (9 mmol) were dissolved in 1,4-dioxane (50 mL). Potassium phosphate (9 mmol) was added to the solution, followed by palladium(II) acetate (5 mol %). The mixture was refluxed overnight, and then H_2O (2 mL) was added. The product was extracted into ether (3 × 40 mL), washed with brine, and dried on Na_2SO_4. The crude mixture was subjected to silica gel column chromatography. The product was further reacted with a Wittig reagent as described in method A.

Reactions of Olefin Substrates. The olefin substrate (1 mmol) was added slowly to CF_3SO_3H (4 mL, 45 mmol) with stirring. If necessary, $CHCl_3$ (2 mL) could be used as a cosolvent to dissolve the olefin substrate. After at least 4 h of reaction, the product mixture was carefully poured over ca. 15 g of ice. The solution was made basic by slow addition of 10 M NaOH, and then it was extracted with two 30 mL portions of $CHCl_3$. The organic phase was then washed with water followed by brine. After drying over anhydrous Na_2SO_4, the product was then purified by silica gel chromatography or recrystallization.

2,7-Diphenyl-2*H*-benzo[*g*]indazole (11): yellow solid; mp 99–101 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.49 (m, 4H), 7.53–7.62 (m, 4H), 7.81 (d, J = 7.4 Hz, 1H)), 7.91 (dd, J = 8.3, 1.6 Hz, 1H), 7.99 (d, J = 7.7 Hz, 1H), 8.07 (d, J = 1.5 Hz, 1H), 8.39 (s, 1H), 8.81 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 118.8, 120.2, 120.5, 121.2, 123.2, 124.7, 124.8, 126.0, 126.8, 127.4, 128.9, 129.6, 133.2, 139.8, 140.6, 141.2, 147.5; HRMS calcd for $C_{23}H_{16}N_2$ 320.1313, found 320.1309.

9,10-Difluorobenzo[h/quinoline (26): yellow solid; mp 72–74 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48–7.56 (m, 3H), 7.57–7.64 (m, 1H), 7.69–7.71 (m, 1H), 8.15 (dd, J = 8.0,1.8 Hz, 1H), 9.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 117.5 (d,, J = 19.1 Hz), 121.7, 122.1, 123.9, 125.8, 127.1, 127.3, 131.6, 135.7, 145.9, 148.6 (dd, J = 263, 14.8 Hz), 149.7 (dd, J = 250, 15 Hz); EI MS (low res) 215 (M+), 188, 94; HRMS calcd for $C_{13}H_7F_2N$ 215.0547, found 215.0545.

9,10-Difluorobenzo[*h*]isoquinoline (27): yellow solid; mp 113–115 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (dd, J = 16.9, 8.8 Hz, 1H), 7.53–7.76 (m, 3H), 7.74 (d,, J = 7.3 Hz, 1H), 8.71 (s, 1H), 10.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 116.7 (d,, J = 19.3 Hz), 119.5 (d, J = 8), 121.1, 123.5, 124.8, 125.3, 129.9, 130.5, 136.4, 145.6, 147.9 (dd, J = 166, 14.1 Hz), 150.0 (dd, J = 139, 13.9 Hz); EI MS (low res) 215 (M^+), 188, 94; HRMS calcd for $C_{13}H_7F_2N$ 215.0547, found 215.0549.

1,2-Difluorobenzo[*c*]acridine (28): yellow solid; mp 194–196 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55–7.75 (m, 5H), 7.86–7.90 (m, 1H), 8.05–8.06 (d, J = 8.3, 1H), 8.43–8.45 (d, J = 8.6, 1H), 8.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ not sufficiently soluble for ^{13}C NMR spectrum; EI MS (low res) 265 (M^+), 246, 132; HRMS calcd for $C_{17}H_9F_2N$ 265.0703, found 265.0705.

5-Methyl-2-phenyl-1-oxa-3-azacyclopenta[*a*]naphthalene (32): white solid; mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.77 (s, 3H), 7.54–7.58 (m, 4H), 7.63–7.68 (m, 2H), 8.06 (d, J = 8.4 Hz, 1H), 8.28–8.34 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.0, 118.8, 120.4, 120.6, 125.3, 125.5, 126.5, 127.3, 127.5, 128.9, 130.8, 131.0, 131.8, 138.1, 145.4, 162.2; EI MS (low res) 259 (M^+), 128, 102; HRMS calcd for $C_{18}H_{13}NO$ 259.0997, found 259.0995.

Pyreno[2,1-*h*]isoquinoline (34): yellow solid; mp 136–138 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84–7.88 (m, 2H), 8.07–8.12 (m, 3H), 8.21–8.24 (m, 2H), 8.31 (d, J = 7.7 Hz, 1H), 8.36 (d, J = 9.3 Hz, 1H), 8.52 (s, 1H), 8.80 (d, J = 5.2 Hz, 1H), 9.34 (d, J = 9.3 Hz, 1H), 10.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 120.8, 123.7, 124.6, 124.9, 125.1, 125.2, 125.4, 125.5, 125.6, 126.5, 126.5, 126.9, 127.4, 127.9, 128.5, 130.3, 130.5, 130.9, 131.6, 132.0, 136.8, 144.5, 150.9; EI MS (low res) 303 (M^+), 151, 135; HRMS calcd for $C_{23}H_{13}N$ 303.1048, found 303.1053.

2,3-Dihydro-1,4-dioxa-12-azabenzo[*b*]chrysene (36): yellow solid; mp 144–146 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.45 (s, 2H), 4.51(s, 2H), 7.30 (d, J = 8.9 Hz, 1H), 7.57–7.60 (t, J = 7.5 Hz, 1H), 7.75 (d, J = 9.3 Hz, 1H), 7.80–7.84 (m, 1H), 8.02–8.06 (m, 2H), 8.35 (d, J = 8.9 Hz, 1H), 8.64 (s, 1H), 9.04 (d, J = 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 64.5, 64.6, 117.7, 118.5, 120.3, 124.5, 125.0, 125.5, 125.5, 126.2, 126.8, 127.8, 128.3, 129.6, 129.6, 135.0, 138.1, 143.2, 147.7, 148.0; EI MS (low res) 287 (M^+), 231, 203; HRMS calcd for $C_{19}H_{13}NO_2$ 287.0946, found 287.0949.

2,3-Dihydro-1,4-dioxa-13-azapentaphene (37): yellow solid; mp 161–163 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.44 (s, 4H), 7.34 (s, 1H), 7.56–7.67 (m, 3H), 7.80 (m, 1H), 8.02 (d, J = 7.8 1H), 8.35 (m, 1H), 8.60 (s, 1H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 64.4, 64.7, 112.9, 114.4, 124.1, 124.6, 125.6, 126.7, 126.8, 127.7, 129.3, 129.4, 129.5, 134.8, 134.8, 144.3, 145.7, 147.5, 147.5; EI MS (low res) 287 (M^+), 231, 203; HRMS calcd for $C_{19}H_{13}NO_2$ 287.0946, found 287.0948.

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Supporting Information Available: NMR spectra and computational methods and results. This material is available free of charge via the Internet at http://pubs.acs.org.

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