Why Does *o*-Fluorine Substitution Raise the Barrier to Ring Expansion of Phenylnitrene?

William L. Karney*,† and Weston Thatcher Borden*

Contribution from the Department of Chemistry, Box 351700, University of Washington, Seattle, Washington 98195-1700

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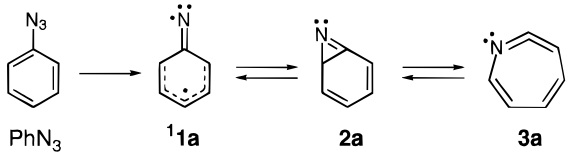
Abstract: In an attempt to understand the dramatic difference in reactivity between phenylnitrene (**1a**) and pentafluorophenylnitrene (**1b**), the ring expansion reactions of several fluorinated arylnitrenes have been studied computationally at the CASPT2N/cc-pVDZ//CASSCF(8,8)/6-31G* + ZPE level of theory. The nitrenes considered include 2,6-difluorophenylnitrene (**1c**), 3,5-difluorophenylnitrene (**1d**), 4-fluorophenylnitrene (**1e**), and 2-fluorophenylnitrene (**1f**). In all cases ring expansion of the open-shell singlet nitrenes (**1**) to the ketenimines (**3**) was calculated to occur via the same two-step mechanism as that predicted for the parent system (**1a**), with the first step—cyclization to the azirines (**2**)—being rate-determining. The calculated barrier of 13.4 kcal/mol for cyclization of **1c** is 3.5−4.5 kcal/mol higher than the corresponding barriers for nitrenes **1e** and **1f**, and for **1a**. For nitrene **1f**, the calculated barrier of 13.0 kcal/mol for cyclization toward fluorine is 3 kcal/mol higher than the barrier for cyclization away from fluorine. These calculated differences in barrier heights are consistent with known experimnental data for nitrenes **1a**−**f** and are attributed largely to steric repulsion in the transition state when the nitrogen atom cyclizes toward fluorine. This steric explanation is based on an analysis of the optimized geometries of the transition states and is supported by calculations on the cyclization reactions of 2-chlorophenylnitrene (**1h**) and 2-methylphenylnitrene (**1j**).

Aryl azides (ArN_3) have been used for photoaffinity labeling of enzymes, a technique to determine the amino acid residues present in the active sites.[1] This application is most efficient when intermolecular insertion reactions of the arylnitrenes (ArN), formed by photolysis or thermolysis of the azides,[2] are faster than their intramolecular rearrangements.[1] As exemplified by pentafluorophenylnitrene (**1b**), fluorine substituents have been found to slow the rate of intramolecular rearrangements,[3] thus making fluorinated aryl azides popular reagents for photoaffinity labeling studies.

Banks and co-workers first demonstrated that polyfluorinated arylnitrenes give increased yields of insertion products.[4] Subsequent experimental studies of these molecules have determined, *inter alia*, the rate constants for the competing processes of rearrangement and intersystem crossing of the singlet nitrenes to the triplet ground states.[5] Platz and co-workers have found that fluorine substitution at both *ortho* positions is necessary to effectively inhibit ring expansion.[6]

Platz and co-workers postulated that ring expansion occurs in one step from the closed-shell π^2 configuration, which is dominant in the 2^1A_1 state of the singlet nitrene, and that this configuration is less accessible if *o*-fluorines are present.[6b,7] Recent DFT calculations by Smith and Cramer have, in fact, found that *o*- and *p*-fluorine substituents destabilize the 2^1A_1 state of phenylnitrene, relative to the lower, closed-shell, singlet state (1^1A_1), in which the σ^2 configuration is dominant.[8] Smith and Cramer state that "to the extent that 2^1A_1 state character is reflected in the transition state ..., this rationalizes the increased barrier [to ring expansion in fluorinated arylnitrenes]."

However, the importance of the relative energy of the 2^1A_1 state to the rate of ring expansion of arylnitrenes is called into question by the results of our recent CASSCF and CASPT2N calculations on the ring expansion of singlet phenylnitrene (**^{1}1a**) to ketenimine **3a**. Our calculations find that this reaction occurs not in one, but in two steps, as shown in eq 1.[9,10] The first



(1)

step—cyclization of **^{1}1a** to bicyclic azirine **2a**—is computed to be rate-determining, and it is not clear why the relative energy of the 2^1A_1 excited state of **^{1}1a** should have a significant effect on the activation energy for the cyclization of **^{1}1a** to **2a**.

The low activation energy computed for this step is easily explained[9] on the basis of the wave function for the lowest-

† Present address: Department of Chemistry, Streitwieser Group, University of California, Berkeley, CA 94720-1460.

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(10) The idea that ring-expanded trapping products arise via initial cyclization of **1a** to **2a** was first proposed by Huisgen and co-workers: Huisgen, R.; Vossius, D.; Appl, M. *Chem. Ber.* **1958**, *91*, 1. Huisgen, R.; Appl, M. *Chem. Ber.* **1958**, *91*, 12.

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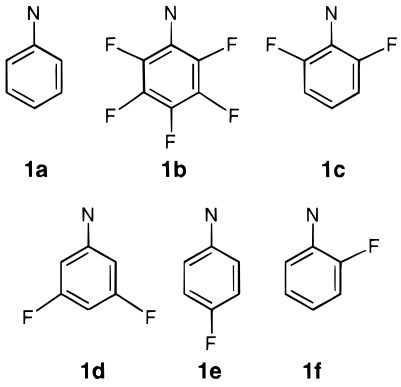
energy singlet state ($^1A_2$) of **^{1}1a**.[11] In this state an unpaired σ and an unpaired π electron of opposite spin are localized in different regions of space, as depicted schematically in the structure drawn for **^{1}1a**.[11a,b] Cyclization of **^{1}1a** to **2a** only requires bending of the nitrogen in **^{1}1a** out of the plane of the benzene ring, so that bonding can occur between the singly-occupied σ AO on nitrogen and the p-π AO on one of the *ortho* carbons.

In order to understand why *o*-fluorine substituents slow the rate of ring expansion of fluorinated arylnitrenes, we have performed *ab initio* CASSCF and CASPT2N calculations. These calculations find that **1c**−**f** all rearrange by the same



mechanism as the parent system (**1a**) and that the first step of the ring expansion is again rate-determining.[12] Our results for the fluorinated arylnitrenes, as well as additional computational results for chloro- and methyl-substituted arylnitrenes, suggest that steric effects are largely responsible for the increased barrier heights to ring expansion that are caused by *ortho* substituents.

Results and Discussion

Geometries of stationary points were optimized at the CASSCF(8,8)/6-31G* level of theory,[13] and single-point energies were calculated using the CASPT2N method[16] with both the 6-31G*[13b] and cc-pVDZ[17] basis sets. The calculated energies for the species of interest here are provided in Table 1. Results for the unsubstituted case[9] are also provided for comparison. The following discussion uses CASPT2N/cc-pVDZ+ZPE energies for **1a** and **1c**−**f** and CASPT2N/6-31G* energies for **1h** and **1j**.

Table 1. Calculated Relative Energies (kcal/mol) for Species Involved in the First Step of the Ring Expansion of Substituted Phenylnitrenes[a]

species[b]	CAS/6[c]	ZPE[d]	coeffs[e]	PT2/6[f]	PT2/cc[g]
^{1}1a[h]	−284.56720	59.5	83.7, 2.4	−285.39523	−285.42145
TS1a[h]	8.9	59.5	75.5, 9.3	8.6	9.3
2a[h]	4.7	60.9	84.7, 2.3	1.6	3.5
^{1}1c	−482.25755	49.2	84.0, 2.2	−483.42762	−483.51483
TS1c	13.9	49.2	75.5, 9.4	13.0	13.4
2c	2.1	50.7	85.3, 2.1	−0.5	1.0
^{1}1d	−482.26440	48.9	84.3, 2.2	−483.43277	−483.52034
TS1d	8.5	48.9	74.8, 10.6	7.9	8.6
2d	3.2	50.5	85.5, 1.8	−0.7	1.1
^{1}1e	−383.41578	54.4	83.7, 2.5	−384.41595	−384.48417
TS1e	7.9	54.3	75.6, 9.6	8.5	9.1
2e	3.3	55.6	84.9, 2.2	1.6	3.3
^{1}1f	−383.41308	54.5	83.9, 2.2	−384.41203	−384.48036
TS1f	9.5	54.5	77.1, 8.0	9.5	9.9
2f	6.1	55.7	84.7, 2.0	3.6	4.8
TS1g	13.6	54.3	74.3, 10.3	12.3	13.0
2g	0.7	55.9	85.3, 2.5	−2.4	−0.3
^{1}1h	−743.46315[i]	*i*	83.7, 2.4	−744.43493[i]	
TS1h	8.0		76.1, 8.7	8.0	
2h	3.2		84.6, 2.2	0.8	
TS1i	12.1		72.3, 12.2	11.7	
2i	0.3		85.2, 2.4	−2.9	
^{1}1j	−323.60350[i]	*i*	83.7, 2.5	−324.57075[i]	
TS1j	6.3		76.1, 9.0	6.4	
2j	0.9		84.9, 2.3	−1.3	
TS1k	8.6		74.7, 10.3	8.4	
2k	1.5		84.8, 2.4	−1.3	

[a] Energies pertain to CASSCF(8,8)/6-31G* optimized geometries, and are in units of kcal/mol relative to the corresponding nitrenes, for which the energies are in hartrees (1 millihartree = 0.6275 kcal/mol). [b] All nitrenes are open-shell singlet states. [c] CASSCF(8,8)/6-31G* energy. [d] CASSCF(8,8)/6-31G* zero-point vibrational energies, in kcal/mol. [e] Weights (%) of the two most important electronic configurations in the CASSCF wave function. [f] CASPT2N/6-31G* energy. [g] CASPT2N/cc-pVDZ energy. [h] Data for **^{1}1a**, **TS1a**, and **2a** are taken from ref 9. [i] Vibrational analyses were not performed on C_6H_4ClN or C_7H_7N stationary points. Therefore the energies for these systems are not corrected for ZPE differences.

As shown by the computational results in Table 1 for **1a** and **1c**−**e**, the ca. 3 kcal/mol higher barrier found experimentally for ring expansion of **1b**,[5c] compared to **1a**,[18] can be attributed to the presence of the two *o*-fluorines in **1b**. The CASPT2N/cc-pVDZ barrier of 13.4 kcal/mol for rearrangement of 2,6-difluorophenylnitrene (**1c**) to **2c** is 4.1 kcal/mol higher than the corresponding barrier for **1a** → **2a**. In contrast, the calculated barriers to rearrangement of 3,5-difluorophenylnitrene (**1d**) and 4-fluorophenylnitrene (**1e**) are very similar to that computed for unsubstituted phenylnitrene (**1a**).

These computational results are consistent with the observed reluctance of pentafluorophenylnitrene (**1b**)[5] and 2,6-difluorophenylnitrene (**1c**) to rearrange[6,19] and with the relative ease of ring expansion in 4-fluorophenylnitrene (**1e**).[6,20] Moreover, our results are in good quantitative agreement with the laser flash photolysis studies of Marcinek and Platz, who found the

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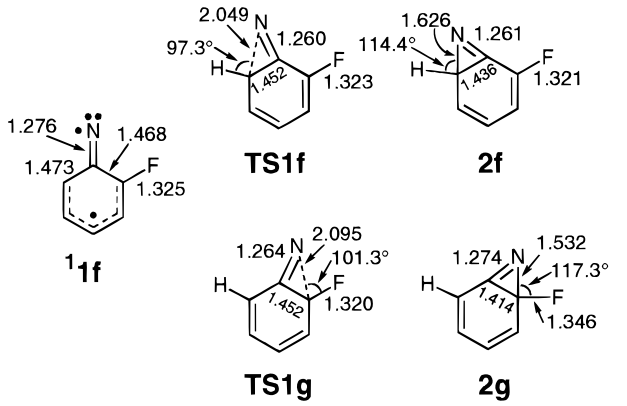
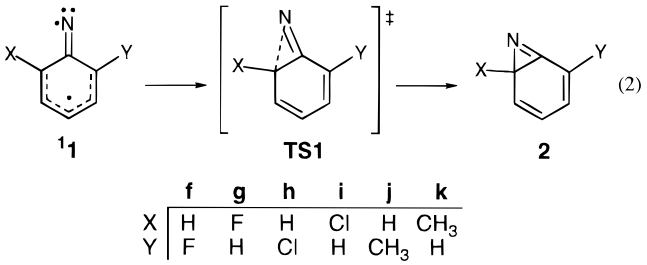


Figure 1. Selected CASSCF(8,8)/6-31G* optimized bond lengths (Å) and angles (deg) for open-shell singlet 2-fluorophenylnitrene (**^{1}1f**), the transition states for cyclization away from fluorine (**TS1f**) and toward fluorine (**TS1g**), and the corresponding azirine products (**2f** and **2g**).

barriers for ring expansion of **1b** and **1c** both to be ca. 3 kcal/mol higher than that for ring expansion of **1a**.[5,21]

Table 1 also reveals that **1c** is calculated to be 3.8 kcal/mol *less stable* than **1d**. Therefore, the higher barrier for **1c** → **2c**, compared to that for **1d** → **2d**, cannot be explained on the basis of stabilization of the nitrene by *ortho* fluorines.[7]

Our calculations on 2-fluorophenylnitrene (**1f**) find that the transition state for cyclization at the fluorinated *ortho* carbon (**TS1g**) is ca. 3 kcal/mol higher than that for cyclization at the unfluorinated *ortho* carbon (**TS1f**, eq 2). These results are in



agreement with experimental observations that nitrene **1f** rearranges rapidly to a ketenimine in solution[6a] and that 2,4-difluorophenylnitrene undergoes ring expansion some 15 times faster than 2,6-difluorophenylnitrene (**1c**).[6b] Both **1f** and 2,4-difluorophenylnitrene can cyclize at an unfluorinated *ortho* carbon; but this is not possible in 2,6-difluorophenylnitrene (**1c**), since both *ortho* carbons are fluorinated in **1c**.

Our calculations also find that 2-fluorophenylnitrene (**1f**) is 2.5 kcal/mol less stable than 4-fluorophenylnitrene (**1e**), indicating again that an *o*-fluorine substituent actually *destabilizes* the open-shell singlet nitrene. In addition, the calculations predict that, of the two possible cyclization modes of 2-fluorophenylnitrene (**1f**), the higher energy transition state (**TS1g**) actually leads to the more stable azirine product (**2g**). Therefore, the relative energies of azirine products **2f** and **2g** cannot be responsible for the relative energies of the transition states leading to them.

The optimized geometries of **2f** and **2g** (Figure 1) suggest a simple explanation for the lower energy of the latter. In **2g** the C−N single bond length (1.532 Å) is significantly shorter than that in either **2f** (1.626 Å) or in unfluorinated azirine **2a** (1.622 Å). The bridging C−C bond is also significantly shorter in **2g** (1.414 Å) than in **2f** (1.436 Å) and in **2a** (1.438 Å), but the C═N bond is slightly longer in **2g** (1.274 Å) than in **2f** (1.261 Å) and **2a** (1.259 Å). In addition, the C−F bond is longer in **2g** (1.346 Å) than in **2f** (1.321 Å).

These differences in bond lengths can be explained on the basis of mixing between the C═N π MO and the C−F σ^* MO in **2g**. This interaction, which is absent in both **2a** and **2f**, results in the delocalization of electron density from the C═N π bond into the C−F σ^* orbital in **2g**. This in turn causes the lengthening of the C═N and C−F bonds and the shortening of the C−N single bond and the bridging C−C bond that are calculated for **2g**. The same effect has been observed in 3-fluorocyclopropenes,[22] and we believe that this interaction between the filled C═N π MO and the unfilled C−F σ^* MO in **2g** is at least partly responsible for the lower energy computed for **2g** relative to **2f**.

Unlike the geometries of azirines **2f** and **2g**, the geometries of the two transition states, **TS1f** and **TS1g** (Figure 1), that connect **1f** to the azirines offer fewer clues as to why **TS1f** is lower in energy than **TS1g**. However, the N−C−F angle of 101.3° in **TS1g** is 4.0° larger than the corresponding N−C−H angle in **TS1f**, suggesting the possible existence of some steric repulsion between the incoming nitrogen and the fluorine attached to the carbon at which the nitrogen is forming a bond. The N−C−F angle of 101.7° in **TS1c** is even larger than that in **TS1g**, and the N−C−H angles in **TS1a** (95.9°), **TS1d** (97.0°), and **TS1e** (95.7°) are all smaller than that in **TS1f**. As expected, the N−C−F bond angles in **2c** and **2g** are also bigger than the N−C−H bond angles in **2a**, **2d**, **2e**, and **2f**.[23]

In order to test this steric explanation, we performed similar calculations on the analogous cyclization reactions of 2-chlorophenylnitrene (**1h**) and 2-methylphenylnitrene (**1j**). Once again we investigated both possible cyclization modes for each nitrene (eq 2). If the higher barrier for cyclization to a fluorinated carbon in **1a**−**f** were purely electronic, one might not expect to see energetic preferences of a similar magnitude for cyclization away from chlorine in **1h** and away from the methyl group in **1j**. Similarly, if the differences in both the transition state and product geometries for cyclization to fluorinated and unfluorinated carbons were purely electronic in **1a**−**f**, they might not appear in the transition states for and products from cyclization of **1h** and **1j**.

As shown in Table 1, the CASPT2N/6-31G* barrier for cyclization of **1h** toward Cl (via **TS1i**) is 3.7 kcal/mol higher than the barrier for cyclization away from Cl (via **TS1h**). Comparison of the optimized geometries of azirines **2h** and **2i** (Figure 2) reveals differences in bond lengths similar to but larger than those found for **2f** and **2g** (Figure 1). The N−C−Cl angles in the transition state for and product from cyclization toward Cl are respectively 6.9° and 3.5° larger than the N−C−H angles in the transition state for and product from cyclization toward H (Figure 2). Moreover, the N−C−Cl angle of 103.8° in **TS1i** is 2.5° larger than the N−C−F angle in **TS1g** (Figure 1). We attribute the slightly larger differences in both energies and bond angles for cyclization toward and away from chlorine in **1h** than for cyclization toward and away from fluorine in **1f**

(21) Although our CASPT2N/cc-pVDZ results agree fairly well with the experimentally determined *differences* in barrier heights, the agreement with experimentally determined *barriers* is less good. However, MRCI calculations indicate that CASPT2N overestimates the barrier to ring expansion of **1a**,[9] and a downward correction of the CASPT2N values by 2−3 kcal/mol brings them into excellent agreement with the most recent experimental value of $E_a = 6.2 \pm 0.4$ kcal/mol.[18b]

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(23) The ca. 3° differences between the N−C−F and N−C−H bond angles in the cyclization products are slightly smaller than the differences in the transition states leading to these products. The fully formed C−N bonds in the products presumably allow less flexibility in the geminal N−C−F bond angles than do the partially formed C−N bonds in the transition states, so the smaller differences between the N−C−F and N−C−H bond angles in the products than in the transition states are understandable.

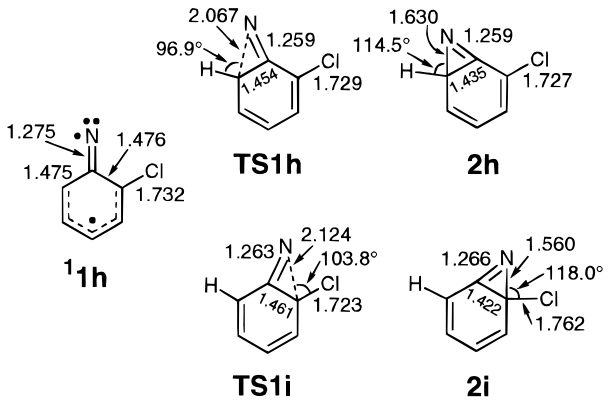

Figure 2. Selected CASSCF(8,8)/6-31G* optimized bond lengths (Å) and angles (deg) for open-shell singlet 2-chlorophenylnitrene (**^{1}1h**), the transition states for cyclization away from chlorine (**TS1h**) and toward chlorine (**TS1i**), and the corresponding azirine products (**2h** and **2i**).

to the larger size of chlorine.[24] An explanation of the differences between the transition states for cyclization toward hydrogen, chlorine, and fluorine that is based purely on the electronic differences between these substituents at the *ortho* carbons seems untenable.

For 2-methylphenylnitrene (**1j**), cyclization toward CH_3 (via **TS1k**) is calculated at the CASPT2N/6-31G* level to have a barrier that is 2.0 kcal/mol higher than that for cyclization away from CH_3 (via **TS1j**). Dunkin and co-workers have, in fact, found that 2,6-dimethylphenylnitrene undergoes inefficient ring expansion in a N_2 matrix, and they suggested that the slow rate was due to steric blocking of the two *ortho* carbons by the methyl group attached to each of them.[25] In addition, Sundberg and co-workers found that photolysis of several 2-alkyl-substituted aryl azides (including the precursor to **1j**) in diethylamine afforded trapping products that are consistent with initial cyclization to only the unsubstituted *ortho* carbon.[26]

The energy of the transition state for cyclization toward methyl in **1j** (**TS1k**) increased by 1.5 kcal/mol when we increased the steric bulk of the methyl group, as felt by the nitrogen, by rigid rotation of the methyl group, so that a methyl C−H bond eclipsed the forming C−N bond. Relocating the transition state geometry with this constraint gave a transition state energy 1.1 kcal/mol higher (CASSCF/6-31G*) than the unconstrained transition state. In the constrained transition state the N−C−C(H_3) angle was 2.6° greater than in the unconstrained transition state, as would be expected if the size of this angle were related to the effective steric size of the methyl group.

In the cyclization of **1j**, unlike those of **1f** and **1h**, there is no low-lying C−X σ^* orbital to interact with the C═N π bond in the product formed from cyclization toward the substituted *ortho* carbon (**2k**). Due to the absence of this stabilizing interaction in **2k**, the two possible cyclization products, **2j** and **2k**, have about the same energy.

While our results support the existence of substantial steric effects on the cyclization of *ortho*-substituted arylnitrenes, they also suggest that steric effects alone may not provide a complete explanation of the computed barrier heights in these systems. For example, increasing steric destabilization of the reactant can explain why both the barrier heights for cyclization toward hydrogen and the relative energies of the resulting products decrease in the order **1f** > **1h** > **1j**. However, it is much less obvious how steric effects can explain why the barrier to cyclization toward hydrogen and the relative energy of the cyclization product are also higher in **1f** than in **1a**, **1d**, and **1e**.

Conclusions

In summary, our calculations indicate that an *ortho* substituent, even one as small as fluorine, interacts in a sterically repulsive manner with the attacking nitrogen in the transition states for cyclization at the *ortho* carbon to which the substituent is attached. In *o*,*o*′-disubstituted systems, such as pentafluorophenylnitrene (**1b**) and 2,6-difluorophenylnitrene (**1c**), this repulsion is unavoidable, and it leads to a considerably higher barrier to ring expansion than in phenylnitrene (**1a**). In contrast, in 2-fluorophenylnitrene (**1f**) cyclization away from fluorine is predicted to have a barrier comparable to that for phenylnitrene (**1a**), whereas cyclization toward fluorine is calculated to have a barrier some 3−4 kcal/mol higher. Our calculations also predict that in both 2-chloro- (**1h**) and 2-methylphenylnitrene (**1j**) only the product resulting from attack at the unsubstituted *ortho* carbon should be formed at low temperatures.

It has, in fact, been found that 2-methylphenylnitrene (**1j**) and other 2-alkylphenylnitrenes give rise to trapping products that are consistent with initial cyclization only at the unsubstituted *ortho* carbon.[26] It is also known that both 2-fluorophenylnitrene (**1f**) and 2,4-difluorophenylnitrene rapidly rearrange in solution to trappable cyclic ketenimines (**3**).[6] Based on our computational results, we predict that each of these fluorinated nitrenes gives rise, preferentially, to the ketenimine formed by initial attack of the nitrene nitrogen at the unsubstituted *ortho* carbon.

Finally, we note that, while our computational results point to substantial steric effects of *ortho* substituents on the relative rates of ring expansion of phenylnitrenes, electronic effects undoubtedly play a role as well. Further work is needed to elucidate completely all the factors affecting the barriers to ring expansion in substituted phenylnitrenes.

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Supporting Information Available: CASSCF(8,8)/6-31G* optimized Cartesian coordinates for all species considered here, and a table of calculated absolute electronic energies (9 pages). See any current masthead page for ordering and Internet access instructions.

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(24) These differences are rather small, but it should be noted that nitrogen attacks the substitued *ortho* carbon at an obtuse angle to the halogen and that the forming C−N bond is quite long (ca. 2.1 Å) in both transition states.

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