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Iodine-Catalyzed Aminosulfonation of Hydrocarbons by Imidoiodinanes. a Synthetic and Mechanistic Investigation

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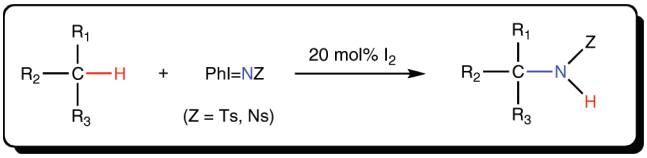

The amino-functionalization of a range of benzylic and some aliphatic saturated and unsaturated hydrocarbons by reaction with imido-iodinanes ($PhI{=}NSO_2Ar$) is catalyzed by I_2 under operationally simple and mild conditions. The first examples of 1,2-functionalization of unactivated C−H bonds using imido-iodinanes as aminating agents are reported. Mechanistic investigations, including Hammett analysis, kinetic isotope effects, a cyclopropane clock experiment, and stereoselectivity tests, are indicative of a stepwise pathway in C−N bond formation. Investigation into the nature of the active aminating species has led to the isolation of a novel aminating agent formulated as $(ArSO_2N)_xI_y$ ($x = 1, y = 2$; or $x = 3, y = 4$).

Introduction

The direct nitrogen-functionalization of saturated hydrocarbons remains a challenging yet important goal because of both the abundance of the hydrocarbon substrates and the value of the nitrogen-containing products as synthetic building blocks and/or end products.[1] Many of the recent developments involving reactions that effect direct C−H oxamination of hydrocarbons have focused on reactive benzylic substrates, employing imido-iodinanes (ArI=NTs), chloramine-T (TsNNaCl), or arylsulfonyl azides as aminating agents in conjunction with various metal catalysts, including those of rhodium,[2] ruthenium,[3] cobalt,[4] manganese,[3a,b,5] silver,[6] gold,[7] palladium,[8] iron,[9] copper,[10] and zinc.[11] Despite the large number of systems that have been discovered and developed synthetically for transition metal-catalyzed amidation of hydrocarbons, relatively few mechanistic

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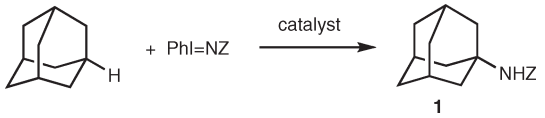
SCHEME 1



studies have been reported.[2a,f,k,3e,4a,10f] Generally, the experimental and computational mechanistic probes of these systems support the intervention of metal-imido (nitrene) complexes as the active aminating species with C−H insertion occurring by either a concerted or a stepwise pathway. Since most of the transition metal catalysts are not environmentally friendly, there is need for the development of "greener" chemical procedures for such transformations.

Recently, Fan and co-workers reported a metal-free aminating system utilizing aryl sulfonamides as *N*-reagents promoted by $PhI(OAc)_2/I_2$ that effects sp^3 C−H bond aminosulfonation intramolecularly[12a] and intermolecularly.[12b] The intermolecular version is effective on primary and secondary benzylic hydrocarbons, employing excess $PhI(OAc)_2$, $ArSO_2NH_2$ as aminating agents and the hydrocarbon as solvent. With little direct supporting evidence both variants were proposed to involve sulfonamidyl radicals and corresponding alkyl/benzylic radicals as intermediates. The development of more efficient, non-metal-catalyzed C−H amination reactions with broad substrate scope and the acquisition of a deeper understanding of the reactive intermediates involved in such reactions are important practical and fundamental goals.

During a contemporaneous follow-up study of the novel zinc halide-catalyzed benzylic aminations by PhI=NTs,[11] we have discovered a new iodine-catalyzed C−H amination of hydrocarbons by imidoiodinanes that is effective for a broad range of benzylic and some types of saturated hydrocarbons and also provides rare examples of 1,2-difunctionalization of saturated hydrocarbons. We report here on these discoveries and the probes of the reactive nitrogen intermediates generated therein.

Results and Discussion

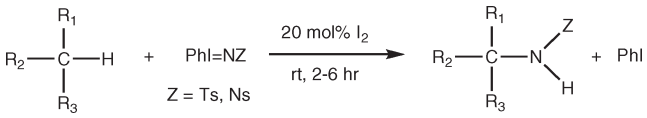
Catalyst Screening and Optimization. Following our recent discovery of hydrous zinc halide-catalyzed aminosulfonation of benzylic and allylic hydrocarbons employing imido-iodinanes,[11] we turned our attention toward expanding the substrate scope beyond benzylic hydrocarbons by utilizing Brønsted−Lowry acid catalysts. In our initial catalyst screening using the saturated adamantane, we observed modest yields of aminosulfonated product **1**, comparable to the hydrous zinc-catalyzed system, using a catalytic amount of aqueous hydriodic acid (Scheme 1, Table 1, entries 1−3). In addition, hydrous InI_3 was a more efficient catalyst than $ZnBr_2$, providing a 49% yield (Table 1, entry 5). Suspecting a possible role of trace amounts of free I_2 acting as the catalytic species in the HI and InI_3 systems, iodine itself (20 mol %) was tested as a catalyst (Table 1, entry 6). To our surprise and satisfaction, the reaction resulted in an improved yield (55%) of **1** with the inexpensive and conveniently handled iodine. After further optimization of reaction time, temperature, solvent, and stoichiometry, it was determined that the most effective conditions employed 5 equiv of hydrocarbon (good yields can also be obtained using hydrocarbon as limiting reagent, entry 8), 1 equiv of imidoiodinane, and 0.2 equiv of I_2, at room temperature under argon for 2 h. Using PhI=NNs as the aminating agent (Ns = *p*-nitrophenylsulfonyl), a nearly quantitative yield of **1** was isolated. The reaction is highly regioselective for the tertiary C−H of adamantane with no secondary C−H aminated product detected, in contrast to some transition-metal-catalyzed systems for which ratios of 3−15:1 of tertiary:secondary aminated products have been found.[2f,k,10c] It should also be noted that the reaction does not require anhydrous solvents or anaerobic conditions (Table 1, entry 11). This reaction thus provides an efficient one-step preparation of a precursor to the antiviral drug amantadine.[13]

TABLE 1. Catalyst Screening and Optimization of the Aminosulfonation of Adamantane with Imido-iodinanes

entry	Z	temp (°C)	equiv catalyst	anhydrous solvent	time (h)	yield (%) **1**
1	Ts	45	0.2 HI (aq)	benzene	10	20[a]
2	Ts	45	0.2 HI (aq)	CH_2Cl_2	12	34[a]
3	Ts	RT	0.2 HI (aq)	CH_2Cl_2	12	31[b]
4	Ts	50	0.15 $ZnBr_2$[c]	benzene	12	32[a]
5	Ts	45	0.15 InI_3[c]	CH_2Cl_2	12	49[b]
6	Ts	45	0.2 I_2	CH_2Cl_2	8	55[b]
7	Ts	45	0.05 I_2	CH_2Cl_2	8	34[b]
8[d]	Ts	25	0.2 I_2	CH_2Cl_2	2	82[b]
9	Ts	RT	0.2 I_2	CH_2Cl_2	2	63[a], 66[b]
10	Ns	RT	0.2 I_2	CH_2Cl_2	2	97[a]
31	Ns	RT	0.2 I_2	wet CH_2Cl_2	2	97[b], 86[b,e]

[a]Isolated yield. [b]Calculated by GC using naphthalene as internal standard. [c]Plus 1 equiv of H_2O. [d]1 equiv of adamantane, 2 equiv of PhI=NTs. [e]Open to air.

SCHEME 2



Substrate Scope and Reactivity Trends. With an optimized procedure in hand, the substrate scope of the iodine-catalyzed aminosulfonation reaction was investigated (Scheme 2), and the results are summarized in Table 2. Benzylic substrates generally gave moderate to excellent yields with formation of the sulfonamide $ArSO_2NH_2$ as the main byproduct (Table 2, entries 2−9). In most cases the I_2-catalyzed system is more efficient than the Zn-catalyzed one.[11] Substrates with electron-donating and -withdrawing groups are reactive with secondary benzylic substrates, though the reaction is more efficient for electron-rich ones (entries 2−6). Yields with PhI=NTs and secondary substrates are slightly better than with PhI=NNs (entries 2−4). However, PhI=NTs either produced complex mixtures or little reaction with primary and tertiary benzylic

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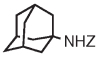
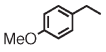
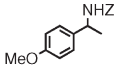
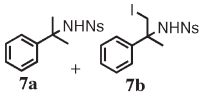
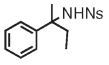
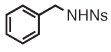
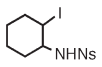
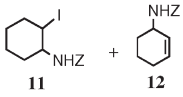
TABLE 2. I_2-Catalyzed Aminosulfonation of Representative Hydrocarbons[a]

entry	PhI=NZ	substrate	product		isolated yield (%)
1	Z = Ts Z = Ns			**1a** = Ts **1b** = Ns	63 97
2	Z = Ts Z = Ns			**2a** = Ts **2b** = Ns	78 73
3	Z = Ts Z = Ns			**3a** = Ts **3b** = Ns	91 80
4	Z = Ts Z = Ns			**4a** = Ts **4b** = Ns	72 60
5	Z = Ns			**5**	50
6	Z = Ns			**6**	57
7	Z = Ns				7a = 40 7b = 14
8	Z = Ns			**8**	24
9	Z = Ns			**9**	13
10	Z = Ns			**10**	20
11[b]	Z = Ns			**11b**	17 (83)[c]
12	Z = Ts (a) Z = Ns (b)				39 (1:1)[d] 24 (2:3)[e]
13[f]	Z = Ts Z = Ns				No Reaction

[a] 5 equiv of hydrocarbon, 1 equiv of PhI=NZ, 0.2 equiv of I_2, CH_2Cl_2, Ar, rt, 2−6 h. [b] DCE, 75 °C. [c] Relative to I_2. [d] Ratio of **11a**: **12a** determined by ^{1}H NMR. [e] Ratio of **11b**: **12b** determined by ^{1}H NMR. [f] In CH_2Cl_2 or neat, rt or reflux.

C−H bonds, as with toluene and cumene. Utilization of PhI=NNs with the aforementioned benzylic hydrocarbons more effectively produced amidated products (entries 7 and 9). From tertiary benzylic substrates (entries 7 and 8), modest yields were obtained of the amidated products **7a** and **8** along with the unexpected 1,2-difunctionalized product **7b** (14%). This is a rare example of 1,2-difunctionalization of a saturated hydrocarbon[14] and the first example of this reactivity seen with imidoiodinanes. The chemo- and regioselectivity for the present I_2-catalyzed reactions are similar to their Zn-catalyzed counterparts, with secondary benzylic C−H bonds selectively amidated over primary, as in the reaction with 4-ethyltoluene (entry 5). Also, tertiary C−H bonds are selectively amidated in the presence of secondary and primary ones (entries 7 and 8). Similar to the primary and tertiary benzylics, the saturated hydrocarbons cyclohexane and norbornane showed little reactivity toward PhI=NTs, but amidated products were obtained in modest yields with PhI=NNs. A single isomer, identified by comparison to reported ^{1}H NMR data as the 2-*exo* derivative **10**,[2f] was isolated from the amidation of norbornane (entry 10). The reaction with cyclohexane provided another example of novel 1,2-difunctionalization producing iodo-amidated derivative **11b**, probably the result of initial dehydrogenation to an intermediate alkene either via radical disproportion[15] or carbocation deprotonation. The variable and curious specificity of these reactions toward different saturated hydrocarbons (e.g., entries 1, 10, 11) is further highlighted by the absence of appreciable monoamidation product from the reaction with *cis*-decalin or *endo*-tetrahydrodicyclopentadiene. Two representative unsaturated hydrocarbons were also tested in the aminosulfonation reaction (entries 12 and 13). With cyclohexene the reaction gave an inseparable ~1:1 mixture of allylic amination product **12** and the 1,2-iodoamidated compound **11** as determined by ^{1}H NMR, but no detectable aziridine (entry 12). Finally, benzene, either in CH_2Cl_2 or neat, did not generate any insertion or addition products at room temperature or at reflux with either of the imido-iodinane reagents (entry 13).

Mechanistic Investigations

Trapping Test for Free Nitrene. Because free nitrenes are known to insert into C−H bonds,[16] it was of interest to determine if such a species, e.g. N-Ts, could be the reactive intermediate responsible for amination. Accordingly, a trapping test for free NTs(Ns) was conducted on the basis of its established reaction with benzene to produce anilines via C−H insertion and azepines via C−C addition/ring-expansion (Scheme 3).[17] In the event, the reaction of PhI=NTs/I_2 with benzene at 20−75 °C produced the sulfonamide ZNH_2 (Z = Ts, Ns) but neither of the established nitrene-trapping products PhNHNs (**13**) or azepine **14**, excluding the intervention of free NTs(Ns).

Kinetic Isotope Effect. To probe the nature of the C−H bond-breaking process, particularly whether C−H cleavage is rate-limiting, we conducted a kinetic isotope effect study. Given the highly efficient reaction of PhI=NZ/I_2 system with adamantane, an intramolecular isotope effect experiment employing 1,3-d_2-adamantane **15**[18] was carried out. A 2:1

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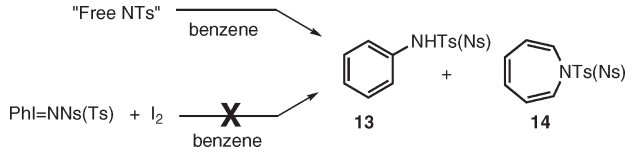
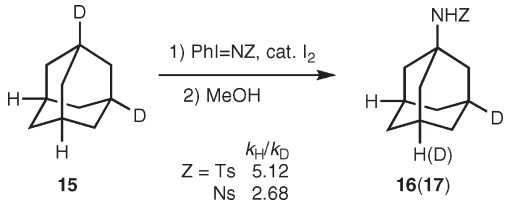
SCHEME 3



SCHEME 4



mixture of 1,3-d_2-adamantane (98.4% D_2) and PhI=NNs in CH_2Cl_2 was allowed to react to completion, providing a 55% yield of sulfonamidated product **16**/**17**. After redissolving the product in MeOH multiple times to effect N-D/N-H replacement, ESI-MS indicated a D_2-D_1 ratio of 2.51, which after calculational correction for the ratio of [D_2-D_1]-adamantane gave a value for k_H/k_D of 2.68 (Scheme 4). The reaction with PhI=NTs provided a 52% yield of sulfonamidated products **16** and **17** and a corrected k_H/k_D value of 5.12. Both results are indicative of a primary isotope effect, with C−H(D) bond-breaking substantially involved in the rate-limiting step. The values are similar to the KIE value of 3.5 that was obtained in the PhI=NNs/$Rh_2(OAc)_4$ promoted reaction.[2f] The larger value obtained for PhI=NTs suggests that the bond-breaking step has a more symmetrical and probably later transition state than that for PhI=NNs.

Hammett Substituent Effects Study. The electronic nature of the transition state for the amination reaction was further probed in a series of competitive reactivity experiments between ethyl benzene and various *p*-substituted-ethyl benzenes. In each run 5 equiv each of ethyl benzene and a *p*-substituted derivative together with 1 equiv of PhI=NNs and 20 mol % I_2 were allowed to react to completion at room temperature. The ratio of aminosulfonated products was determined by GC integration. A moderate preference for electron-rich substrates is exhibited in the reaction (Figure 1). Using σ^+ Hammett parameters gave a ρ-value with poor linearity, as did radical parameters.[3e] The best linear fit (R^2 = 0.976) was achieved using the standard σ_P parameters,[19] providing a ρ-value of −2.8 that is indicative of substantial positive charge development in the transition state (Figure 1). This suggests that C−H abstraction is effected by a highly electrophilic species such as an electron-deficient radical or cation.[20]

Amination of a Radical Clock Substrate. In order to differentiate a concerted (one-step) insertion from a two-step radical- or cation-producing process the amination of a radical clock substrate was investigated. [(2-Phenylcyclopropyl)methyl]-benzene **18** was selected because of its reactive

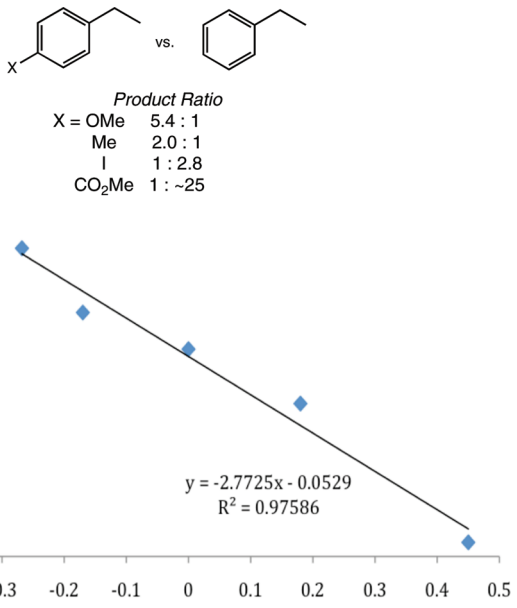
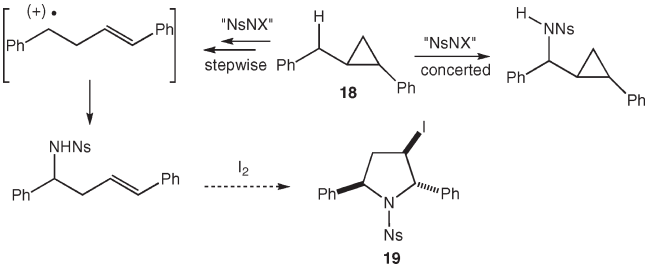


FIGURE 1. Hammett substituent effect plot for amination of substituted ethyl benzenes.

SCHEME 5



secondary benzylic C−H bond.[21] In the reaction of **18** with PhI=NNs and I_2, pyrrolidine derivative **19** was isolated in 14% yield (69% relative to I_2) as the sole aminosulfonated product (Scheme 5); it was identified by spectroscopic comparison to the known pyrrolidine-NTs derivative.[22] Analysis of its NOESY ^{1}H NMR spectrum enabled determination of the relative stereochemistry shown (data in Supporting Information). Production of the ring-expanded amination product **19** can best be accounted for by a reaction sequence involving hydrogen or hydride abstraction from **18**, cyclopropyl carbinyl radical (or cation) ring opening, trapping of the radical (cation) by the aminating species, and finally I^+-promoted cyclization of the intervening alkenyl sulfonamide (Scheme 5).[23] An alternative process involving concerted C−H insertion followed by I^+-promoted cyclopropane ring opening with *N*-nucleophilic participation to form **19** directly appears to be without literature precedent but cannot be excluded.

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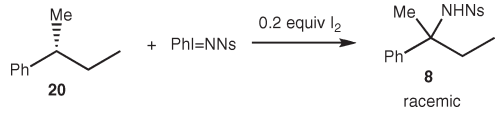
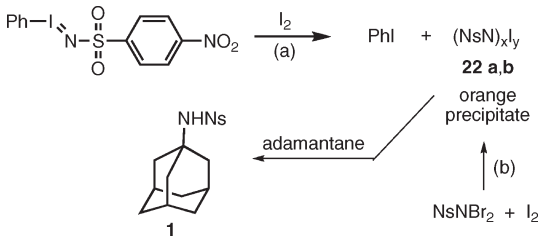
SCHEME 6



SCHEME 7



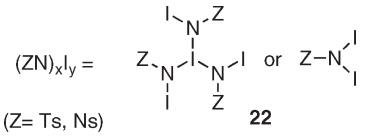
Stereochemical Probe of C−H Insertion. In order to more definitively establish whether the amination reaction proceeds through a concerted or a stepwise C−H insertion process, the chiral 2-phenylbutane **20** was selected to probe the stereochemical change occurring during insertion, since a stepwise process (through intermediate radical or cation) would likely result in at least partial configurational erosion. The viability of *rac*-**20** as an amination substrate with $PhINTs/I_2$ was first established, giving a 24% yield of tertiary-aminosulfonated **8** without an appreciable amount of the 1,2-difunctionalized product. Enantio-enriched (*R*)-2-phenylbutane **20** was then allowed to react with $PhI{=}NNs/I_2$ at room temperature (Scheme 6).[2f] The product sulfonamide **8** was analyzed by HPLC (Chiralcel-OJ) and found to be completely racemic (ca. 50:50 *R*:*S*). The formation of both enantiomers gives strong evidence for a stepwise process during C−H insertion via an intermediate that loses its stereochemical integrity.

Isolation of a Novel Active Aminating Agent from the Reaction of PhI=NNs + I_2. After indirectly establishing some of the electronic and reactivity properties of the intermediate species generated from the $PhI{=}NZ/I_2$ aminating system, we sought to determine its composition and, if possible, its structure.

First a series of experiments were conducted in which the reactants were combined sequentially while monitoring by ^{1}H NMR (Scheme 7). Upon addition of I_2 (1 equiv) to a slurry of sparingly soluble PhI=NNs (1 equiv) in CD_2Cl_2 at room temperature, the mixture gradually changed to a dark red solution containing a pinkish orange precipitate. After 15 min ^{1}H NMR analysis of the solution clearly showed the presence of iodobenzene but very little else, i.e., no nitrophenyl unit was detected. After addition of 1 equiv of adamantane and stirring for 2 h, the mixture became homogeneous and its ^{1}H NMR spectrum showed a 2:1 mixture of aminosulfonated adamantane **1** to $NsNH_2$. This observation indicates that a relatively stable intermediate species is produced in the $PhI{=}NNs/I_2$ reaction that is responsible for amination.

The precipitate **22a** that forms in the I_2 + PhI=NNs reaction is isolable and moderately stable when stored at <0 °C, thermally decomposes at 132 °C, and is soluble in DMSO, acetone, or acetonitrile. The ^{1}H NMR spectrum of **22a** in DMSO displays only two doublets in the aromatic region from the Ns group and no peaks derived from -NH or -IPh units, consistent with complete loss of PhI in its formation from I_2 + PhI=NNs. MS-ESI$^-$ data on **22a** in either acetone or acetonitrile revealed ions with *m*/*e* of 781 $([N\text{-}Ns]_2I_3)^-$ and 327 $([N\text{-}Ns]I)^-$, suggestive of a higher nuclearity species. Elemental analysis of **22a** showed a N to I ratio of 1.5:1 which, given the MS data, is most consistent with a $[NsN]_3I_4$ composition. To assess the aminating ability of **22a**, the isolated solid was added to a solution of adamantane in CD_2Cl_2; ^{1}H NMR analysis of the mixture after several minutes indicated the formation of a 2.5:1 ratio of aminosulfonated adamantane **1** to $NsNH_2$ (Scheme 7). The cogeneration of iodine during the reaction was confirmed by visible spectroscopic monitoring, during which the absorbance of iodine at 504 nm increased to a maximum in 40 min.

Among the various possible formulations for the isolable intermediate above we considered the unknown compound *N*,*N*-diiodo-4-nitro-sulfonamide. Using a procedure reported for the related *N*,*N*-diiodo-benzenesulfonamide,[24] an orange precipitate formed in the reaction of *N*,*N*-dibromo-4-nitrosulfonamide **23** with 1 equiv of I_2 with obvious liberation of Br_2. This solid, **22b**, like that produced from the iodinane and I_2, **22a**, was insoluble in CH_2Cl_2 and displayed ^{1}H NMR and IR spectra virtually identical to those of **22a**. When the putative *N*,*N*-diiodo-4-nitro-sulfonamide **22b** was added to adamantane in CH_2Cl_2 at room temperature, a roughly 2:1 mixture of aminosulfonated adamantane **1** and $NsNH_2$ was detected by GC, demonstrating the viability of **22b** as an aminating agent. This result suggests that the species formed in both preparative methods is likely the same, **22**, and is probably either *N*,*N*-diiodo-4-nitro-sulfonamide or an oligomeric species, e.g., $[NsN]_3I_4$ (which would better satisfy the elemental analysis and ESI-MS). Unfortunately, attempts to crystallize **22** for X-ray analysis have been thwarted by its gradual solution decomposition; hence its exact structure remains unknown.



Mechanistic Proposal. Taken together, the results of our mechanistic and intermediate isolation studies indicate that the I_2-catalyzed reaction of imido-iodinanes with hydrocarbons proceeds by a multistep process involving: (i) I_2-promoted conversion of the imido-iodinane to an intermediate reagent **22a/b**; (ii) transformation of **22a/b** to a reactive intermediate that (iii) inserts "NTs(Ns)" into the hydrocarbon C−H bond with I_2 regeneration (Scheme 8). The kinetic isotope effect, Hammett study, stereochemical outcome, and radical clock test together indicate that the C−H/NTs(Ns) insertion is rate-limiting and stepwise, proceeding via an electron-deficient carbon radical or carbocation. It is uncertain which of these species is involved, but we favor the radical pathway in light of the homolytic weakness of N−I bonds,[25] the determined magnitude of ρ, and the weakly

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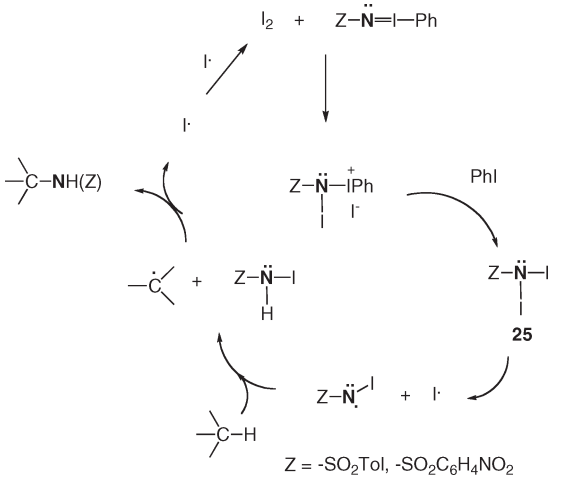
SCHEME 8



ionizing medium of the reactions. Alkyl radicals could be generated via H-atom abstraction by Z(I)N$^{\bullet}$; the radical could then be converted to the *N*-alkyl sulfonamide by homolytic substitution on ZNHI.[26] The 1,2-iodoamination products may be derived from an alkene intermediate (undetected), produced via alkyl radical disproportionation (or by carbocation deprotonation), which undergoes additive iodoamination.

Conclusions

Non-transition-metal catalysis of hydrocarbon amidation represents a mild and direct route to amine derivatives from abundant, nonfunctionalized feedstocks. In this study, we have found that primary, secondary, and tertiary benzylic substrates along with some saturated and unsaturated hydrocarbons can be amino-functionalized by reaction of PhI=NZ catalyzed by inexpensive and easily handled iodine. This system represents the first non-metal-catalyzed system utilizing imido-iodinane reagents to efficiently aminosulfonate benzylic and nonbenzylic saturated hydrocarbons. In addition, the first examples of 1,2-functionalization of unactivated C–H bonds in a single reaction using imido-iodinanes have been observed.

Through a combination of data obtained from competition experiments and substrate probes, we have found that the reaction pathway proceeds through a stepwise process involving *in situ* production of a reactive aminating species. The aminating agent, formulated as $[NsN]_xI_y$, has been produced by two different preparative methods, including one using inexpensive and relatively benign reagents.

Experimental Section

General Methods. Hydrocarbon substrates were obtained commercially and used without any purification. Toluene and benzene were distilled prior to use over Na/benzophenone; dichloromethane, acetonitrile, and dichloroethane were all distilled prior to use over CaH_2. Visualization of the developed chromatogram was performed under UV light or I_2 stain. ^{1}H NMR spectra were obtained at 300 MHz and ^{13}C NMR spectra at 75 MHz. Mass spectra were acquired by ESI. Naphthalene was used as an internal standard for GC yield determinations. [{(*p*-Toluene)sulfonyl}imino]phenyliodinane (PhI=NTs)[27] and [{(4-nitrophenyl)sulfonyl}imino]phenyliodinane (PhI=NNs)[28] were prepared as reported previously. Compounds **15**,[18] **18**,[21] and **20**[2f] were prepared according to the cited literature procedures and were deemed pure by comparison to known data. Products **1a**,[11] **1b**,[2f] **2a**,[11] **2b**,[2f] **3a**,[11] **3b**,[2f] **4a**,[11] **4b**,[2f] **5**,[2f] **7a**,[2f] **8**,[2f] **9**,[2f] **10**,[2f] and **12**[11,2f] are all known compounds, and all were judged pure (>95%) by comparison to reported data.

General Procedure for the I_2-Catalyzed Aminosulfonation of Hydrocarbons. To a mixture of 1.25 mmol of hydrocarbon, 0.05 mmol I_2, and 1−2 mL of CH_2Cl_2 was added 0.25 mmol of PhI=NZ all at once. The reaction vessel was then flushed with argon and stirred at room temperature 2−6 h. Upon completion of the reaction, solvent was removed under vacuum, and the crude mixture was isolated via flash chromatography over silica gel with CH_2Cl_2 as eluant (R_f of product typically 0.3−0.5), affording the amidated products, typically as solids. All compounds were spectroscopically pure (>95%) and exhibited appropriate ^{1}H NMR and MS data (provided in Supporting Information). Naphthalene was used as an internal standard for GC yield determinations. Characterizational data for the new products are provided below; characterizational data for previously reported compounds are provided in the Supporting Information.

4-Nitro-*N*-[1-(4-iodo-phenyl)-ethyl]-benzenesulfonamide (6). The title compound was prepared in 57% yield by the general procedure from 4-iodo-ethylbenzene, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. White solid, mp 192−194 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (dd, 2H, J = 8.1 and 1.8 Hz), 7.73 (dd, 2H, J = 8.1 and 1.8 Hz), 7.43 (dd, 2H, J = 6.6 and 1.8 Hz), 6.76 (dd, 2H, J = 6.6 and 1.8 Hz), 4.85 (d, 1H, J = 6.3 Hz), 4.51−4.46 (m, 1H), 1.38 (d, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$ 75 MHz) δ 146.4, 140.6, 137.7, 128.2, 124.1, 110.0, 93.4, 53.7, 23.4. HRMS (ESI) calcd for $C_{14}IN_2SO_4H_{13}$ ($M + Na^+$) requires m/z 454.9538, found m/z 454.9560.

4-Nitro-*N*-(1-methyl-1-phenyl-2-iodoethyl)-benzenesulfonamide (7b). The title compound was prepared in 14% yield by the general procedure from cumene, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. Tan solid, mp 133−135 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, 2H, J = 9.0 Hz), 7.69 (d, 2H, J = 9.0 Hz), 7.19−7.13 (m, 5H), 5.29 (s, 1H), 3.78 (d, 1H, J = 10.8 Hz), 3.52 (d, 1H, J = 10.8 Hz), 1.76 (s, 3H). ^{13}C NMR ($CDCl_3$ 75 MHz) δ 152.3, 150.2, 142.0, 131.2, 131.0, 129.0, 127.1, 126.6, 62.9, 29.9, 23.1. HRMS (ESI) calcd for $C_{15}IN_2SO_4H_{15}$ ($M + Na^+$) requires m/z 468.9695, found m/z 468.9667.

***N*-(2-Iodo-cyclohexyl)-4-nitro-benzenesulfonamide (11b).** The title compound was prepared in 17% yield by the general procedure from cyclohexane, PhI=NNs, and I_2 in DCE at 75 °C. White solid, mp 177−180 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (d, 2H, J = 9.0 Hz), 8.02 (d, 2H, J = 9.0 Hz), 4.73 (d, 1H, J = 7.2 Hz), 3.84−3.75 (ddd, 1H, J = 10.8, 10.8, and 3.9 Hz), 3.25−3.16 (m, 1H), 2.42−2.20 (m, 2H), 2.00−1.83 (m, 1H), 1.79−1.70 (m, 1H), 1.48 (m, 1H), 1.40−1.10 (m, 3H). ^{13}C NMR (CD_2Cl_2 75 MHz) δ 148.7, 131.4, 127.0, 126.9, 63.1, 42.0, 37.6, 37.2, 30.0, 26.9. HRMS (ESI) calcd for $C_{12}IN_2SO_4H_{15}$ ($M + Na^+$) requires m/z 432.9695, found m/z 432.9696. The stereochemistry of **11b** is tentatively assigned as *trans* on the basis of comparison of coupling constants for the CHI resonance with the CHBr of *N*-*trans*-2-bromocyclohexyl)propanamide (J = 10.8, 10.8, 4.0 Hz).[29]

Kinetic Isotope Effect Determination. To a mixture of 1,3-d_2-adamantane **15** (40 mg, 0.290 mmol), iodine (7.4 mg, 0.029 mmol),

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and 1−1.5 mL of anhydrous CH_2Cl_2 was added PhI=NZ (Z = Ns, 59 mg; Z = Ts, 54 mg; 0.14 mmol) under argon at room temperature, and the mixture was stirred overnight. Upon completion of the reaction, solvent was removed under vacuum, and the crude mixture was isolated via flash chromatography over silica gel with CH_2Cl_2 as eluant. The isolated white solid was then dissolved in MeOH, and the solvent was removed via rotary evaporator a series of five times. The solid was then analyzed by MS-ESI and the theoretical natural abundance isotopic contribution of pure D_1-Ad-NHZ **16** was subtracted from the overall abundance of D_2-Ad-NHZ **17** (see Supporting Information).

Radical Clock Test. To a mixture of [(2-phenylcyclopropyl)-methyl]-benzene (131 mg, 0.625 mmol), iodine (6.8 mg, 0.025 mmol), and 1−2 mL of CH_2Cl_2 was added PhI=NNs (51.0 mg, 0.125 mmol) all at once. The reaction vessel was then flushed with argon, and the mixture was stirred at room temperature overnight. Upon completion of the reaction, solvent was removed under vacuum, and the crude mixture was isolated via preparative TLC with CH_2Cl_2 for development, affording 3-iodo-2,5-diphenyl-1-nosylpyrrolidine (**19**) as a white solid in 14% yield (69% relative to I_2); no amidated products were isolated. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 (dd, J = 11.1 Hz, J = 2.4 Hz, 2H), 7.30 (m, 9H), 7.16 (m, 3H), 5.41 (d, J = 2.4 Hz, 1H), 5.22 (dd, J = 9.3 Hz, J = 5.4 Hz, 1H), 4.36 (dt, J = 7.5 Hz, J = 2.4 Hz, 1H), 3.19 (m, 1H), 2.50 (dt, J = 13.5 Hz, J = 4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$ 75 MHz) δ 164.7, 149.1, 146.7, 138.8, 138.6, 129.3, 128.9, 128.6, 128.3, 128.1, 126.8, 123.3, 77.8, 65.5, 45.5, 24.5. HRMS (ESI) calcd for $C_{22}IN_2SO_4H_{19}$ (M + Na^+) requires m/z 557.0008, found m/z 556.9981. In the NOESY spectrum of **19**, cross-peaks were observed between H-**A**/H-**E**, H-**D**/H-**B**, and H-**E**/H-**C** (see Supporting Information).

Hammett Analysis of Competitive Reactions between Ethylbenzene Derivatives. To a mixture of 1.25 mmol of the *p*-substituted ethylbenzene, 1.25 mmol of ethylbenzene, 0.050 mmol of I_2, and 2 mL of CH_2Cl_2 was added 0.250 mmol of PhI=NNs. The reaction vessel was then flushed with argon and stirred overnight. Upon completion of the reaction samples were taken for GC analysis. The ratio of aminosulfonated products was determined using previously determined response factors for each product relative to naphthalene as internal standard.

Reaction of (*R*)-20 with PhI=NNs. To a mixture of (*R*)-2-phenylbutane (13.5 mg, 0.100 mmol), iodine (6.8 mg, 0.025 mmol), and 1−2 mL of CH_2Cl_2 was added PhI=NNs (101 mg, 0.250 mmol) all at once. The reaction vessel was then flushed with argon and stirred at room temperature overnight. Solvent was removed under vacuum, and the crude mixture was isolated via preparative TLC with CH_2Cl_2 as eluant, affording the aminosulfonated product **8** as a white solid. Compound **8** was analyzed by chiral HPLC (Chiralcel-OJ, 1:19 isopropanol/hexane) and found to be racemic (50:50 *R*:*S*).

^{1}H NMR Monitoring of 22a Generation and Reaction with Adamantane. To a vial containing 1.5 mL of CD_2Cl_2 was added PhI=NNs (20 mg, 0.05 mmol), and the slurry was stirred for 15 min at room temperature in air; analysis of the solution phase by ^{1}H NMR showed little dissolved material. Iodine (12.6 mg, 0.050 mmol) was added, and the mixture was stirred an additional 15 min before ^{1}H NMR analysis of the solution phase showed largely the presence of PhI; an orange precipitate was present. Adamantane (6.3 mg, 0.050 mmol) was then added to the reaction mixture, and stirring was continued. ^{1}H NMR spectra of the solution were obtained after 15 min, 105 min, and 24 h, during which time increasing amounts of adamantyl-Ns and $NsNH_2$ were detected.

Isolation of 22. Method A. To a heterogeneous mixture of PhI=NNs (100 mg, 0.25 mmol) in 3−4 mL of CH_2Cl_2 was added iodine (63 mg, 0.25 mmol), and the mixture was stirred at room temperature in air 15 min. The dark orange precipitate **22a** was then filtered in air and rinsed three times with CH_2Cl_2. The solid (∼65 mg) was then dried *in vacuo* and flushed with argon before storage <0 °C. Samples stored at rt evolve I_2. Mp 128−130 °C (decomp); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.47 (dd, J = 7.8 Hz, J = 2.1 Hz, 2H), 8.15 (dd, J = 7.8 Hz, J = 2.1 Hz, 2H); ESI-MS (neg ion, CH_3CN) m/e 781 (85%, $[NsN]_2I_3)^-$ and 327 (100%, $[N\text{-}Ns]I)^-$; IR (KBr, cm^{-1}) 3100, 1620, 1520, 1350, 1320, 1200, 1150, 850, 800, 750, 650, 600. Elemental analysis: found (%) 16.0 C, 0.99 H, 5.93 N, 36.10 I; calcd for $C_{18}H_{12}N_6I_4O_{12}S_3$: C 19.5, H 1.1, I 45.7, N 7.5, O 17.3, S 8.6; calcd for $C_6H_4N_2I_2O_4S$: C 15.8, H 0.9, I 55.9, N 6.2, O 14.1, S 7.0.

Method B. To a solution of *N*,*N*-dibromo-4-nitrosulfonamide (472 mg, 1.31 mmol) in 10 mL of CH_2Cl_2 was added I_2 (333 mg, 1.31 mmol) in air, and the mixture was stirred for 30 min. The dark orange precipitate **22b** was filtered and rinsed three times with CH_2Cl_2. The solid was dried *in vacuo* and flushed with argon before storage at <0 °C. Mp 112 °C (decomp). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.47 (dd, J = 7.8 Hz, J = 2.1 Hz, 2H), 8.15 (dd, J = 7.8 Hz, J = 2.1 Hz, 2H); IR (KBr, cm^{-1}) 3100, 1620, 1520, 1350, 1320, 1200, 1150, 850, 800, 750, 650, 600.

Reaction of 22a with Adamantane. (Prepared by Method A) To 8 mg of adamantane in 1.5 mL of CD_2Cl_2 was added 8 mg of solid **22a**, and the initially heterogeneous mixture was stirred at room temperature in air for 2 h. The mixture became dark red and homogeneous; ^{1}H NMR analysis was performed directly on the solution (ICA-82-1, Supporting Information). (Prepared by Method B) To adamantane (175 mg, 1.3 mmol) in 2−3 mL of CH_2Cl_2 was added 50 mg of solid **22b**, and the heterogeneous mixture was stirred at room temperature under argon 2 h. The mixture became a dark red homogeneous solution, and GC analysis was performed with naphthalene added as internal standard.

Detection of Iodine from Reaction of Adamantane with 22a. To a quartz UV−vis cuvette was added 5.4 mg of adamantane, 3−4 mL of CH_2Cl_2, and 5.0 mg of orange solid **22a**. The absorbance of the mixture at 504 nm was measured immediately and then every 5 min as the mixture was stirred for 40 min.

Acknowledgment. We are grateful for financial support provided by the National Science Foundation. We also thank Dr. Susan Nimmo for assistance with the NMR-NOESY experiments.

Supporting Information Available: Characterizational data for all amination products; kinetic isotope effect MS analysis, NOESY NMR for **19**; HPLC analysis for **21**; IR, NMR spectra for **22a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.