

Hydrous zinc halide-catalyzed aminosulfonation of hydrocarbons†

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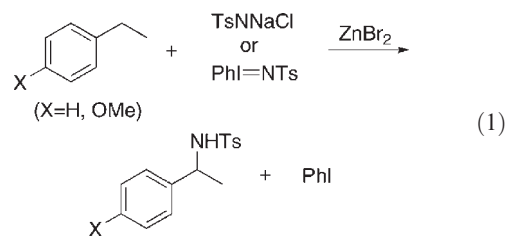
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Benzylic and allylic hydrocarbons are selectively converted to the corresponding sulfonamides by a $\text{ZnBr}_2\text{-H}_2\text{O}$ -catalyzed reaction with $\text{PhI}=\text{NTs}$; saturated adamantane is aminosulfonated at the tertiary C–H bond.

The direct N-functionalization of hydrocarbons by the activation of C–H and C=C bonds is a challenging and important goal because of the value of the derived amines and the abundance of the hydrocarbon substrates. The most well-developed of these reactions are the transition metal-catalyzed hydroamination,¹ aziridination² and allylic amination³ of alkenes. Reactions that effect direct benzylic C–H amination are receiving increasing attention, employing imido-iodinanes ($\text{TsN}=\text{IAr}$), chloramine-T (TsNNaCl) or tosyl azide as aminating agents in combination with various transition metal catalysts, including rhodium-carboxylates,⁴ ruthenium- and cobalt-porphyrins,^{5,6} manganese–Schiff base complexes,⁷ silver-phenanthrolines,⁸ gold(III) salts,⁹ and copper-pyrazolylborates¹⁰ and -salts.¹¹ The efficiency and scope of these reactions vary widely, hence there is a need for improved and general reactions of this type. Moreover, the reactive aminating species involved in these processes are unknown, but often are presumed to be “metal-nitrenoids” formed *via* redox transformations of the transition metal complexes with the N-reagent. Herein, we report what appear to be the first hydrocarbon C–H aminations catalyzed by non-transition metal (redox-inactive) salts.

Following our recent development of Cu^{I} -catalyzed aminosulfonation of benzylic hydrocarbons and ethers employing anhydrous chloramine-T,^{11b} we investigated the possibility of catalyzing such reactions with isoelectronic, but presumably redox-inactive, Zn^{II} salts. To our surprise and satisfaction, the reaction between chloramine-T and ethylbenzene (1.2 : 1) in the presence of 15 mol% ZnBr_2 ¹² (CH_3CN , 70 °C, 12 h) produced the benzylic sulfonamide (X = H, 25% yield) accompanied by TsNH_2 (eqn (1)).



Economic and toxicity considerations caused us to optimize and explore the scope of the Zn-catalyzed reactions. Using 4-ethyl anisole (eqn (1), X = OMe) as a test substrate, a survey of N-reagents, Zn^{II} salts, solvents, temperature and stoichiometry (see ESI†) found the best conversion and yield with 2–3 equivalents of $\text{PhI}=\text{NTs}$,¹³ 15 mol% ZnBr_2 with oven dried (110 °C) 4 Å molecular sieves in benzene at rt (24–30 h) or 50 °C (12 h), providing the amidation product in 71% isolated yield.† A survey of the reactions with other benzylic substrates under these conditions was conducted, with the results being summarized in Table 1 (entries 1–8). It can be seen that the reaction is moderately effective and highly regioselective with a variety of secondary benzylic reactants (entries 1–6). Substrates with *p*-electron-releasing substituents (*e.g.* entries 1, 3) react faster and give higher conversions and yields than those with electron-withdrawing groups (entries 4, 5); the amount of the TsNH_2 by-product increased in the latter cases. Small amounts (<10%) of $\text{ArCH}(\text{OH})\text{Me}$ or $\text{ArC}(\text{O})\text{Me}$ were detected as well. Substrates with tertiary benzylic C–H bonds are also aminated with moderate efficiency (entries 7, 8).

The scope of the Zn-catalyzed aminosulfonation goes beyond benzylic substrates. Thus, representative allylic substrates such as 1,3-diphenylpropene and cyclohexene undergo primarily allylic amination (entries 9, 10) rather than addition to the double bond (to form aziridines), often a major pathway with transition metal-catalyzed reactions. A minor addition product, *cis*-1-bromo-2-sulfonamidocyclohexane, was isolated from the reaction with cyclohexene. Finally, and perhaps most remarkably, the imido-iodinane– ZnBr_2 system is even capable of aminating the 3° C–H bonds of saturated hydrocarbons as illustrated by the reaction with adamantane, which produced 1-tosylaminoadamantane in modest yield (entry 11). However, under similar conditions, neither cyclohexane nor benzene, both with stronger C–H bonds, were amidated.

Although the chemo- and regioselectivity for the Zn-catalyzed amination reactions are similar to the Cu^{I} -catalyzed counterparts,¹¹ some significant differences are evident. For

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Table 1 Zn-catalyzed aminosulfonation of representative hydrocarbons

Entry	Substrate	Product	Temperature/°C	Yield ^a (conversion) ^b
1			RT	71 (81)
2			RT 50	40 48 (75)
3			50	52 (75)
4			50	42 (50)
5			50	10
6			50	41
7			50	38
8			50	38
9			50	28
10			50	50 (40, 10)
11			50	22

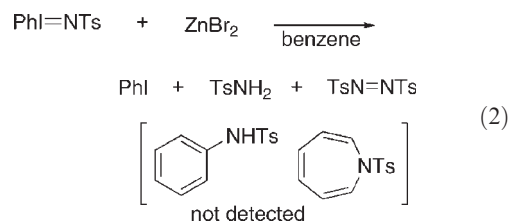
^a % Isolated yield. ^b % Conversion of hydrocarbon substrate.

example, the Zn^{II}-promoted reaction with *p*-ethyltoluene (entry 3) is completely selective for the 2° C–H bond, whereas the [Cu(CH₃CN)₄]PF₆-catalyzed reaction gives a 3 : 1 ratio of 2° : 1° amination products.¹⁴ Cumene (entry 7) is aminated completely selectively by the Zn catalyst, whereas the Cu^I-promoted reaction also produces some of the corresponding allyl amine from dehydrogenation.^{11b} Additionally, although the saturated adamantane is aminated by the Zn-catalyst (entry 11), it is unreactive towards chloramine-T-[Cu(CH₃CN)₄]-PF₆.¹⁴

With an eye to determining the origin of the TsNH₂ by-product, enhancing the reaction's efficiency, and gaining mechanistic insights, we briefly examined the role of the metal ion, water,

and the counter anion. An initial survey of other group 12 salts revealed that ZnCl₂, ZnI₂, CdCl₂, and HgCl₂ also promote the amidation of ethylbenzene under similar conditions; the yield increased in the order ZnCl₂ < ZnBr₂ < ZnI₂. In contrast, Zn(OTf)₂ and neutral bromide ion sources, *e.g.* Bu₄N⁺Br⁻, NaBr, are ineffective. When rigorously dry conditions were employed for the reaction of PhINTs with ethylbenzene promoted by ZnBr₂,¹⁵ the yields of the amination product (*ca.* 3%) and TsNH₂ were greatly reduced, while inclusion of a controlled amount of water (0.1–1.0 equiv.), together with ZnBr₂, provided the product in 20–40% yield. The more economical use of PhINTs (1 : 10 iodine-hydrocarbon) was enabled by employing 0.15 equivalents of ZnBr₂ and 1.0 equivalents of H₂O (50 °C, 12 h, benzene) to afford moderate yields of the amination products derived from ethylbenzene (45%), ethylanisole (54%) and adamantane (32%). Since Zn^{II}-H₂O-containing systems can be acidic,¹⁶ we tested and confirmed that HBr-H₂O and HBr-HOAc also promote the amidation of ethylbenzene (10–20% yield), apparently the first example of a protic acid-catalyzed C–H amination. Finally, *p*-methoxyphenol was found to strongly inhibit the hydrous ZnBr₂-PhINTs amidation of ethylbenzene, suggestive of a radical process,¹⁷ consistent with the observed anion effects. The viability of a Zn-amido intermediate, *e.g.* XZn-NBrTs, and its potential for C–H insertion is supported by: (1) the isolable (ArSO₂NCl)₂Zn;¹⁸ (2) the formation of TsNHC₆H₁₁ from TsNCl₂ + Zn in cyclohexane;¹⁹ and (3) the ZnI₂-promoted conversion of dienyl azides to pyrroles.²⁰

Although the nature of the active aminating species in these reactions is as yet uncertain, our initial experiments suggest that a free nitrene is not involved. Since TsN: itself is known to undergo C–H insertion and addition reactions with benzene,²¹ we examined the reaction of ZnBr₂ with PhI=NTs in benzene at 20–50 °C in the absence of a benzylic substrate (eqn (2)). The only organic products detected were PhI, TsNH₂ and TsN=NTs. Neither of the established nitrene-trapping products, PhNHTs or the azepine, was found, providing evidence against the intervention of the free nitrene.



In conclusion, we have found that benzylic, allylic and tertiary aliphatic C–H bonds can be amino-functionalized by PhI=NTs and zinc halide salts. That such transformations are not the exclusive domain of transition metal catalysts may presage the development of more efficient and uniquely selective reactions for the preparation of diverse organonitrogen compounds from abundant, yet typically unreactive hydrocarbons.

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Notes and references

‡ **Caution:** the dry solids TsN=IPh and ZnBr₂ should not be mixed together as a strongly exothermic process has been observed upon

combining the two compounds in mmol quantities. Representative procedure: to an oven-dried Schlenk tube (or a test tube) under N₂ was transferred anhydrous ZnBr₂ (15 mol% of the substrate) and 2 mL of dry benzene. To this was added TsN=IPh (1.0 mmol), oven dried (110 °C) 4 Å molecular sieves or 1.0 mmol H₂O, 4-ethyl anisole (0.50 mmol), and another 3 mL of dry benzene by syringe. The suspension was stirred at room temperature (or at 50 °C, Table 1) under N₂. Another 0.5 mmol of TsN=IPh was added to the reaction mixture after 5–6 h and stirring was continued for the specified time. When TLC analysis indicated no further conversion, the reaction mixture was filtered, the solid collected, washed with CHCl₃ (~15–20 mL), and the filtrate concentrated by rotary evaporation. The residue was purified by flash chromatography or preparative TLC on silica gel eluting with 1 : 10 ethyl acetate–petroleum ether. Characterization data for isolated products are provided in the ESI.†

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