clean formation of Bco_2BCl (δ 80 ppm in ether). The solvent ether was removed by a water aspirator (15–20 mm) and the resulting Bco_2BCl (>98% pure based on the ^{11}B NMR), a colorless liquid, was used as such, since it decomposes on attempted distillation at 0.1 mm.

Synthesis of Ketones. Ethyl *tert*-butyl ketone was prepared directly by the chromic acid two-phase (ether–water) oxidation[19] of the corresponding alcohol (commercially available). Distillation provided >99% GC pure ketone and ^1H NMR confirmed the structure.

Spectra. ^1H NMR spectra were recorded on T-60 and 300-MHz instruments. ^{11}B NMR spectra were recorded on FT-80A and 300-MHz instruments. The chemical shift values are in δ (ppm) relative to $BF_3{\cdot}OEt_2$.

General Procedure for the Enolboration of Ketones with R_2BCl/Et_3N. A simple and general procedure for the enolization of ketones is described as follows. To a stirred solution of R_2BCl (5.15 mmol) and Et_3N (0.72 mL, 5.16 mmol) in CCl_4 (17 mL), cooled at 0 °C (except for ethyl *tert*-butyl ketone which requires 25 °C) under a N_2 atmosphere, was added the ketone (5.0 mmol) dropwise. The enolborinate was generated instantaneously with concurrent formation and precipitation of $Et_3N{\cdot}HCl$. An internal standard, benzene (0.50 mmol), was added for quantification of the enolborinate by ^1H NMR analysis, except in the case of propiophenone, where the aromatic ring was used as the internal standard. The molarity was adjusted to 0.2–0.3 M. The reaction mixture was stirred for 1 h and transferred into a centrifuge vial using a double-ended needle (18 guage). Centrifugation results in the separation of the enolborinate solution from the precipitated $Et_3N{\cdot}HCl$. In representative cases, the solid $Et_3N{\cdot}HCl$ was collected, washed, dried, and weighed. Essentially quantitative yields were obtained. The enolborinate solution was then transferred into an NMR tube using a double-ended needle. The ^1H NMR analysis gives the extent of enolboration and ^{11}B NMR (borinate region, usually broad, around 50–56 ppm) also confirms the formation of enolborinates. The ^1H NMR data of the olefinic protons of the enolborinates are given in our earlier papers.[13]

General Procedure for the Aldolization with Benzaldehyde. To a solution of enolborinate in diethyl ether (or hexane), generated under a N_2 atmosphere from 5.0 mmol of the ketone using R_2BCl/Et_3N as described above, was added benzaldehyde (5.0 mmol) dropwise at −78 °C. The reaction mixture was stirred for 2–3 h and then allowed to warm up overnight slowly to attain room temperature. The absence of residual benzaldehyde confirms the essentially quantitative formation of enolborinate, as indicated by ^1H NMR analysis. Then 10 mL of methanol was added to dissolve the precipitate ($Et_3N{\cdot}HCl$) and 1.7 mL of H_2O_2 (30%) was added at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at 25 °C for 5–6 h. The solvent and methanol were then removed by a water aspirator (15–20 mm) and the reaction mixture was extracted with ether, washed with dilute HCl and water, and then dried over anhyd Na_2SO_4. The solvent was removed and the products were analyzed as such by ^1H NMR (in $CDCl_3$) to determine the syn/anti ratio.

Acknowledgment. We gratefully acknowledge financial support from the United States Office of Naval Research, which made this research possible.

Supplementary Material Available: ^1H NMR spectra of the benzaldehyde aldols of the various ethyl ketones, EtCOR, with R = Et (anti), Ph (anti), *i*-Pr (anti), Chx (anti), *t*-Bu (anti), *i*-Bu (mixture), and other ketones *n*-Pr_2CO (anti) and *n*-Bu_2CO (anti) (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(19) Brown, H. C.; Garg, C. P.; Liu, K.-T. *J. Org. Chem.* 1971, *36*, 387.

Convenient Halodeamination and Hydrodeamination of Primary Amines[1]

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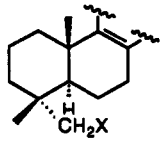
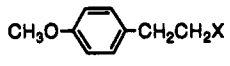
Treatment of *p*-toluenesulfonamides of primary amines with 2 equiv of chloroamine at room temperature in the presence of base leads to reductive deamination. If excess chloroamine is present, the corresponding alkyl or aryl halides are obtained instead in good yields. Both reactions presumably proceed via tosylhydrazine and diazene intermediates; the course of the reaction is often governed by steric hindrance. Treatment of the isolated tosylhydrazine intermediate with base and chloroamine, bromine, or iodine also leads to the corresponding halides in very good yields.

In the course of our studies into the applications of readily available chiral compounds as starting materials for complex natural products synthesis we were interested in converting dehydroabietylamine (**1a**) to dehydroabietane (**1b**). A number of published methods are available for this hydrodeamination transformation.[2] Of these methods, Nickon's reaction of primary amine *p*-toluenesulfonamide derivatives with hydroxylamine-*O*-sulfonic acid in the presence of aqueous base appeared to be the most convenient procedure.[2c] Unfortunately, reaction of the *N*-abietyl-*p*-toluenesulfonamide under these conditions afforded the reduced product in only 4% yield, presumably because of the insolubility of this substrate



1 a X=NH_2
b X=H
c X=NHTs
d X=Cl
e X=$N(NH_2)$Ts



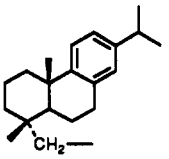
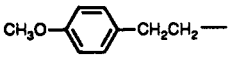
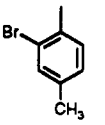
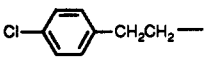
2 a X=$N(NH_2)$Ts
b X=Cl

(1) Presented at the 4th Chemical Congress of North America, 202nd American Chemical Society National Meeting, New York, Aug 1991, ORG 108.

(2) (a) Doldouras, G. A.; Kollonitsch, J. *J. Am. Chem. Soc.* 1978, *100*, 341. (b) Bumgardner, C. L.; Martin, K. J., Freeman, J. P. *J. Am. Chem. Soc.* 1963, *85*, 97. (c) Nickon, A.; Hill, A. S. *J. Am. Chem. Soc.* 1964, *86*, 1152. (d) Hutchins, R. O.; Cistone, F.; Goldsmith, B.; Heuman, P. *J. Org. Chem.* 1975, *40*, 2018. (e) Katritzky, A. R.; Horvath, K.; Plau, B. *J. Chem. Soc., Perkin Trans. 1*, 1980, 2254. (f) Barton, D. H. R.; Bringmann, G.; Lamotte, G. *Tetrahedron Lett.* 1979, *24*, 2291. (g) Baumgarten, R. J.; Curtis, V. A. *The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; John Wiley and Sons: New York, 1982; Part 2, p 929. (h) A related reductive transformation of 1,2-disubstituted tosylhydrazines has also been reported: D. S. Cram, J. S. Bradshaw, *J. Am. Chem. Soc.* 1963, *85*, 3525.

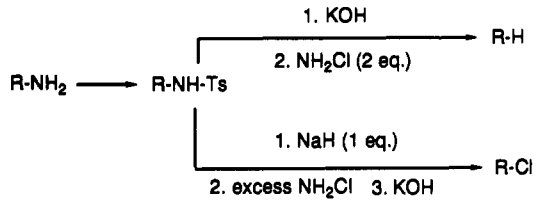
0022-3263/92/1957-3772$03.00/0

Table I. Yields of Isolated Hydrodeamination Products[a]

R–NH–Ts R =	products RH, %	R–NH–Ts R =	products RH, %
	64 (89)[b]		1[c] (10% RCl)
			2[c] (5% RCl)
	56		16[c]
	57		
$CH_3(CH_2)_{13}$–	93		

[a] Yields have not been optimized. [b] Yield based on recovered starting materials. [c] Yield based on GC.

Scheme I



in the aqueous medium of the reaction. Nickon reported a similar unsuccessful attempted reduction of 3β-amino-5α-cholestane.[2c] Our attempts at adding organic cosolvents also failed to improve the yield of the reduced product.

In an attempt to carry out the analogous transformation under nonaqueous conditions, we treated the *p*-toluenesulfonamide **1c** with ethereal chloroamine[3] in the presence of KOH–methanol. This reaction afforded the desired alkane **1b** in 64% yield (89% yield based on recovered starting material). In attempts at optimizing this reduction, we found that the course of the reaction could be changed completely by changing the order of addition of reagents and the amount of chloroamine. Treatment of the *N*-abietyl-*p*-toluenesulfonamide in dry THF with 1 equiv of sodium hydride was followed by addition of excess ethereal chloramine and then addition of excess KOH methanol. Under these reaction conditions, unexpectedly 18-chlorodehydroabietane (**1d**) could be isolated in 61% yield (88% based on recovered starting material) (Scheme I).

Both the hydrodeamination and chlorodeamination presumably involved a tosylhydrazine intermediate formed via amination of the toluenesulfonamide. Under basic conditions the diazene intermediate formed could lose nitrogen affording a carbanion which could be protonated leading to the reduced product or react with excess chloroamine via a displacement affording the chlorinated derivative. Alternatively the halogenated product could form via deprotonation and chlorination of the diazene intermediate followed by nitrogen extrusion (Scheme II).[5] When the presumed intermediate 1,1-disubstituted hydrazines **1e** and **2a** were independently prepared and subjected to conditions of the hydro- and chlorodeamination reactions, the expected reduced and halogenated products **1b** and **2b** were each obtained in 95% yield.

Scheme II

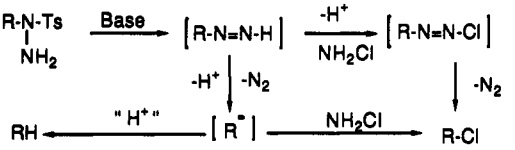
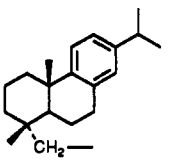
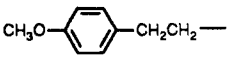
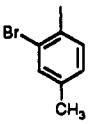
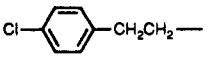
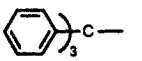


Table II. Yields of Isolated Chlorodeamination Products[a]

R–NH–Ts R =	products RCl, %	R–NH–Ts R =	products RCl, %
	61 (88)[b]		41
			32
	52		17 (79)[c]
	59		
$CH_3(CH_2)_{13}$–	43		5 (41)[c]

[a] Yields have not been optimized. [b] Yield based on recovered starting material. [c] Yield of hydrodeamination product.

Hydrodeamination. The hydrodeamination reaction works well for primary amines attached to primary carbons (Table I). The required *p*-toluenesulfonamides are readily prepared in high yield, and the ethereal chloroamine reagent can also be easily prepared from ammonia and sodium hypochlorite.[3] As will be noted from the table, primary amines attached to more hindered secondary, aryl, or tertiary carbons are hydrodeaminated in only poor yield, the main products being recovered starting material and the chlorodeaminated byproducts. Presumably, formation of the tosylhydrazine intermediate is inhibited in these cases, and the tosylhydrazine, as formed, reacts further even with limited chloroamine. Increasing the amount of chloroamine increases hydrazine formation and lowers the amount of recovered sulfonamide but also increases chlorodeaminated products. Still, even in the case of a hindered primary amine attached to a neopentyl carbon, this procedure provides an inexpensive and convenient route to hydrodeamination.

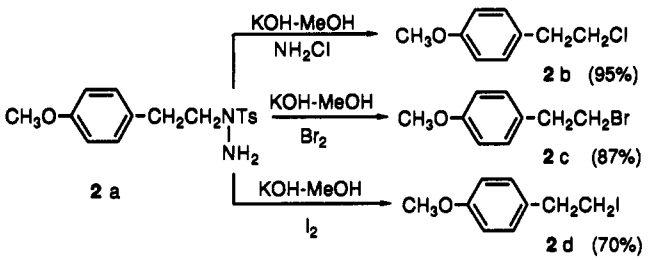
Halodeamination. As seen from Table II, the chlorodeamination reaction appears to be a general reaction for primary amines including those attached to primary, secondary, tertiary, and aromatic carbons. Reaction con-

(3) (a) Coleman, G. H.; Johnson, H. L. *Inorganic Syntheses*; Booth, H. S., Ed.; McGraw Hill: New York, 1939; Vol. 1, p 59. (b) Theilacker, W.; Wegner, E. *Angew. Chem.* **1960**, *4*, 127.

(4) With the exception of the transformation of **1a** to **1b** and **1d**, reaction conditions have not been optimized.

(5) While a radical process can not be discounted in the halodeamination reactions, addition of benzoquinone does not change the course of the reaction, eliminating a radical chain process.

Scheme III



ditions are mild, and the reagents are again inexpensive and easily prepared.

In our initial hydrodeamination study, the ethereal chloroamine used was not dried. The chlorodeamination reaction is, however, in some cases affected by the amount of water present in the chloroamine reagent. For example, when the attempted chlorodeamination was carried out on *N*-adamantanyl-*p*-toluenesulfonamide, the yield was greatly improved from 9 to 52% when the ethereal chloroamine was dried over calcium chloride at 5 °C for 1 h. When the chloroamine solution was not dried, large quantities of unreacted sulfonamide were recovered. We noted, however, that yields in chlorodeaminations of sulfonamides attached to primary carbons were little affected by drying the ethereal chloroamine. It is possible that reprotonation of sulfonamide anions competes with amination in hindered cases, particularly if moderate quantities of water are present in the reaction mixture.

Steric hindrance also appears to affect yields in the chlorodeamination reaction in other ways. When *N*-triphenylmethyl-*p*-toluenesulfonamide and *N*-(2-bromo-4-methylphenyl)-*p*-toluenesulfonamide were subjected to the chlorodeamination reaction conditions, the corresponding chloro compounds were obtained in yields of only 5% and 17% yield, respectively. The major products formed instead were the reduced products triphenylmethane and 3-bromotoluene, isolated in 41% and 70% yields. Presumably, approach of chloroamine to the tritylcarbanion intermediate formed from *N*-(triphenylmethyl)-*p*-toluenesulfonamide under chlorodeamination conditions is sterically unfavorable relative to protonation. Similarly, the bulky *o*-bromine substituent may inhibit formation of 3-bromo-4-chlorotoluene.

On the basis of the previously mentioned high yield chlorination of the isolated tosylhydrazine **2a**, we also investigated the possibility of extending the reaction for the introduction of other halogens during the deamination. If the proposed mechanism for the chlorodeamination were in fact correct, the intermediate carbanion or diazene anion could conceivably be captured by other electrophiles. When an ether solution of tosylhydrazine **2a** was treated with KOH–methanol in the presence of bromine or iodine, the corresponding bromo- and iododeamination products **2c** and **2d** were obtained in yields of 87% and 70%, respectively (Scheme III).

Halodeamination has been previously carried out as described in a number of published procedures.[6] These reactions involve converting the primary amines into derivatives with significantly increased leaving-group ability, for example, the *N*,*N*-bis-toluenesulfonamides of Baumgarten[6a,b] and the 2,6-disubstituted pyridinium salts of Katritzky.[6c,d] Unfortunately, these procedures have some severe limitations. Synthesis of the required disulfonamides and pyridinium salt intermediates occurs in poor yield with hindered amines located on primary carbons and is impossible for more severely hindered amines, such as 1-aminoadamantane.[2g,7] The mechanisms of these halodeaminations also involve nucleophilic displacements, seriously limiting potential substrates.[2g,8] Moreover, these reactions often involve more vigorous conditions or expensive reagents. Halodeamination of toluenesulfonamides via in situ generated tosylhydrazines provides a milder and more convenient route for this transformation. In addition, the proposed anion mechanisms should afford halodeaminated products with stereochemical retention of configuration, complementing the inversion predicted in the published procedures. Investigations into the scope and limitations of these reactions and applications to complex synthesis are continuing.

Experimental Section

Melting points were obtained on a Fisher Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1600 series FTIR. 200-MHz ^{1}H-NMR were recorded with a Varian XL 200 spectrometer; 400-MHz ^{13}C-NMR were recorded with a Varian Unity 400 spectrometer. GC was carried out with a Hewlett-Packard Model 5880A. GC–MS were obtained with a Varian Saturn-3400 and a Hewlett-Packard 5995A. Mass spectra were also obtained on a Hitachi RMU-6U mass spectrometer. Microanalyses were performed by Desert Analytics, Tucson, AZ. Tetrahydrofuran was distilled from benzophenone–sodium. Pyridine was dried over KOH. All other commercial reagents were used without further purification.

Chloroamine. A modification of the published procedure was used for the preparation of chloroamine.[3a] In the receiver of a vacuum-adapted distillation apparatus was placed dry ice cooled ether (90 mL). In a 500-mL round-bottom distilling flask was placed concentrated NH_4OH (5.5 mL), water (90 mL), and ice (50 g) to cool the mixture to 0 °C. A solution of sodium hypochlorite (110 mL, 5.5%) was added to the mixture, and the apparatus was immediately attached to a vacuum pump. A pressure of about 15 Torr was desirable. The distilling flask was heated in a water bath to 40–45 °C and the distillation carried out for 60 min. At the end of this period, the distillation was stopped and the ether in the receiver was at once decanted from the ice into a flask cooled with acetone and dry ice. More ether (70 mL) was added to the receiver which still contained ice. The ice was melted by immersing the flask in warm water (not above 40 °C). The ether phases were combined and contained about 30 mmol of monochloroamine. Dried chloroamine could be obtained by treating the ethereal chloroamine with anhydrous $CaCl_2$ for 1 h at 5 °C.[3b]

Dehydroabietane (1b). The typical hydrodeamination reaction was carried as follows: A solution of *N*-dehydroabietyl-*p*-toluenesulfonamide (**1c**) (100 mg, 0.23 mmol) in methanol (10 mL) containing KOH (500 mg) was added dropwise at 0 °C to a solution of freshly prepared dry chloroamine (~0.5 mmol) in ether (200 mL). The mixture was heated to reflux overnight, and the ether solution was washed with water and brine. Evaporation of the solvent gave an oil which was purified using preparative thin-layer chromatography to afford dehydroabietane (**1b**) as a pale yellow oil, 40 mg, 64% yield (89% yield based on recovered starting material): NMR ($CDCl_3$) δ 7.19 (1 H, d, J = 8.0 Hz), 6.93 (1 H, d, J = 2.0 Hz), 6.91 (1 H, s), 2.9–2.7 (3 H, complex), 2.4–0.8 (9 H, complex), 1.22 (6 H, d, J = 7.0 Hz), 1.18 (3 H s), 0.94 (3 H, s), 0.92 (3 H, s); IR (neat) 3015, 2926, 1696, 1497, 1458, 1328, 1161, 1100, 821, 758, 665 cm^{-1}. This material was identical to dehydroabietane prepared using a published procedure.[9]

(6) (a) DeChristopher, P. J.; Adamek, J. P.; Lyon, G. D.; Galante, J. J.; Haffner, H. E.; Boggio, R. J.; Baumgarten, R. J. *J. Am. Chem. Soc.* **1969**, *96*, 2384. (b) DeChristopher, P. J.; Adamek, J. P.; Lyon, G. D.; Klein, S. A.; Baumgarten, R. J. *J. Org. Chem.* **1974**, *39*, 3525. (c) Katritzky, A. R.; Gruntz, U.; Ikizler, A. A.; Kenny, D. H.; Leddy, B. P.; *J. Chem. Soc., Perkin Trans. 1* **1979**, 436. (d) Katritzky, A. R.; Horvath, K.; Plau, B. *Synthesis*, **1979**, 437.

(7) Hutchins, R.; Kandasamy, D.; Dux, F., III; Marynoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2559.

(8) (a) Katritzky, A. R.; Musumarra, G. *Chem. Soc. Rev.* **1984**, *13*, 47. (b) Muller, P.; Thi, M. P. N. *Helv. Chim. Acta* **1980**, *63*, 2168.

Tetradecane. Prepared as described for **1b**: 93% yield; NMR ($CDCl_3$) δ 1.26 (24 H, m), 0.88 (6 H, t, J = 8.0 Hz); IR (neat) 2956, 2922, 2852, 1467, 1328, 1092, 814 cm^{-1}.[10,11]

4-Chloroethylbenzene. Prepared as described for **1b**: 57% yield; NMR ($CDCl_3$) δ 7.22 (2 H, d, J = 8.0 Hz), 7.01 (2 H, d, J = 8.3 Hz), 2.61 (2 H, q, J = 7.7 Hz), 1.21 (3 H, t, J = 8.4 Hz); IR (neat) 3014, 2960, 2930, 2870, 1610, 1513, 1248, 1160, 1035, 826, 644 cm^{-1}.[10,12]

4-Ethylanisole. Prepared as described for **1b**: 56% yield; NMR ($CDCl_3$) δ 7.12 (2 H, d, J = 8.6 Hz), 6.83 (2 H, d, J = 8.5 Hz), 3.97 (3 H, s), 2.59 (2 H, q, J = 7.6 Hz), 1.12 (3 H, t, J = 7.5 Hz); IR (neat) 3029, 2961, 1610, 1513, 1464, 1252, 1177, 1037, 828 cm^{-1}.[10,13]

***N*-Dehydroabietyl-*p*-toluenesulfonamide (1c).** Dehydroabietylamine (**1a**) (4.5 g, 15.8 mmol) was dissolved in dry pyridine (26 mL), and tosyl chloride (3.61 g, 18.96 mmol) was added with stirring at 0 °C. The mixture was stirred overnight at room temperature, 2% aqueous lactic acid (1 mL) was added, and the mixture was stirred for another 30 min, poured into water, and extracted with ether. The extract was washed with 1 N HCl solution, saturated $NaHCO_3$ solution, and brine. Drying and removal of the solvent afforded a solid which was recrystallized from absolute alcohol to afford *N*-dehydroabietyl-*p*-toluenesulfonamide (**1c**) as colorless crystals: 6.20 g; 90% yield, mp 152–155 °C; IR ($CHCl_3$) 3378, 3281, 2961, 2871, 1600, 1459, 1332, 1160, 1094 cm^{-1}; NMR ($CDCl_3$) δ 7.73 (2 H, d, J = 8.1 Hz), 7.30 (2 H, d, J = 8.6 Hz), 7.15 (1 H, d, J = 8.2 Hz), 6.98 (1 H, d, J = 8.0 Hz), 6.87 (1 H, s), 4.57 (3 H, complex), 2.9–2.6 (4 H, complex), 2.4–1.8 (9 H, complex), 2.43 (3 H, s), 1.22 (6 H, d, J = 6.90 Hz), 1.18 (3 H, s), 0.89 (3 H, s). 0.89 (3 H, s). Anal. Calcd for $C_{27}H_{37}NO_2S$: C, 73.76; H, 8.48, N, 3.19. Found: C, 73.86; H, 8.68; N, 2.96.

18-Chlorodehydroabietane (1d). *N*-Dehydroabietyl-*p*-toluenesulfonamide (**1c**) (100 mg, 0.23 mmol) in dry THF (5 mL) was added to a suspension of NaH (6.4 mg, 0.25 mmol) in dry THF (8 mL). The mixture was stirred for 20 min and then added dropwise to a freshly prepared monochloroamine solution in ether (200 mL). KOH (500 mg) in methanol (8 mL) was then added, and the mixture was heated to reflux overnight. The organic solution was decanted and washed with water and brine. Removal of solvent afforded an oil, which was purified by preparative thin-layer chromatography affording 18-chlorodehydroabietane (**1d**): 57 mg; mp 60–62 °C; 65% yield; IR (neat) 2958, 2868, 1718, 1611, 1497, 1460, 1382, 1217, 909, 822, 758, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (1 H, d, J = 8.0 Hz), 6.98 (1 H, d, J = 7.9 Hz), 6.89 (1 H, s), 3.37 (2 H, dd, J = 10.7 Hz), 2.9–2.7 (3 H, complex), 2.4–0.8 (9 H, complex), 1.23 (6 H, d, J = 5.2 Hz), 1.21 (3 H, s), 1.00 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 147.1 (s), 145.7 (s), 134.7 (s), 126.8 (d), 124.4 (d), 123.9 (d), 56.8 (t), 44.4 (d), 38.3 (t), 37.9 (s), 37.4 (s), 35.5 (q), 33.5 (d), 30.1 (t), 25.2 (t), 24.4 (q, superimposed), 18.8 (t), 18.8 (t), 18.7 (q); MS M^+ = 304 (30 %), 291 (34), 289 (100), 254 (15), 195 (26), 181 (10), 159 (60), 139 (32), 91 (22). Anal. Calcd for $C_{20}H_{29}Cl$: C, 78.78; H, 9.59. Found: C, 78.59; H, 9.78.

1-Tosyl-1-dehydroabietylhydrazine (1e). *N*-Dehydroabietyl-*p*-toluenesulfonamide (**1c**) (3.0 g, 6.8 mmol) in dry THF (30 mL) was added to a suspension of NaH (164 mg, 6.8 mmol) in dry THF (150 mL). Chloroamine (~10 mmol) in ether (200 mL) was then added at 0 °C under nitrogen. The mixture was stirred overnight at room temperature. The ether layer was decanted and concentrated to 15 mL. A white solid was collected and washed with $CHCl_3$. Concentration of the filtrate afforded crystals **1e**: 278 mg; 10% isolated yield; mp 55–70 °C; IR ($CHCl_3$) 3368, 3022, 2932, 1598, 1496, 1458, 1344, 1162, 1091 cm^{-1}; NMR ($CDCl_3$) δ 7.73 (2 H, d, J = 7.6 Hz), 7.37 (2 H, d, J = 8.1 Hz), 7.18 (1 H, d, J = 7.2 Hz), 6.98 (1 H, d, J = 8.5 Hz), 6.88 (1 H, s), 3.60 (2 H, s), 2.85–2.7 (3 H, complex), 2.46 (3 H, s), 1.9–0.8 (3 H, complex), 1.22 (6 H, d, J = 6.9 Hz), 1.22 (3 H s), 0.94 (3 H, s). 1,1-Disubstituted tosylhydrazines often proved to be extremely unstable and difficult to purify. This compound decomposed on preparative TLC, upon attempted recrystallization from warm solvents, and even upon sitting at room temperature. Starting *p*-toluenesulfonamide (2.5 g) could also be recovered from reaction mixture.

Dehydroabietane (1b) via Tosylhydrazine 1e. 1-Tosyl-1-dehydroabietylhydrazine (**1e**) (63 mg, 0.138 mmol) in dry THF (10 mL) was added to a solution of potassium *tert*-butoxide (34.1 mg, 0.30 mmol) in dry THF (15 mL) at room temperature. The mixture was heated to reflux overnight under nitrogen. The mixture was poured into water and was acidified with 1 N HCl to pH ~ 3 and extracted with hexanes. The extracts were washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Concentration of solvent afforded 36 mg of the dehydroabietane (**1b**) as an oil, 95% yield, identical to **1b** described above.

1-Tosyl-1-[2-(4-methoxyphenyl)ethyl]hydrazine (2a). [(4-Methoxyphenyl)ethyl]-*p*-toluenesulfonamide (6.0 g, 19.7 mmol) in dry THF (30 mL) was added to a suspension of NaH (480 mg, 20 mmol) in dry THF (200 mL). Chloroamine (~20 mmol) in ether (300 mL) was added to the above mixture at 0 °C under nitrogen. The mixture was stirred overnight at room temperature. The ether layer was decanted and concentrated. The resulting solid was collected and washed with water to afforded colorless crystals (**2a**): 4.37 g; 70% yield; mp 111–113 °C dec; IR ($CHCl_3$) 3530, 3380, 3030, 2959, 2838, 2010, 1918, 1882, 1713, 1612, 1513, 1464, 1348, 1249, 1163, 1091, 1036, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (2 H, d, J = 8.2 Hz), 7.33 (2 H, d, J = 8.2 Hz), 7.12 (2 H, d, J = 8.4 Hz), 6.83 (2 H, d, J = 8.6 Hz), 3.79 (3 H, s), 3.38 (2 H, s), 3.25 (2 H, t, J = 7.0 Hz), 2.92 (2 H, t, J = 8.3 Hz), 2.44 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 158.0 (s), 144.2 (s), 131.2 (s), 130.9 (s), 129.1 (d), 127.7 (d), 113.2 (d), 54.8 (q), 53.4 (t), 33.0 (t), 21.9 (q); MS M^+ = 320 (15), 305 (20), 184 (20), 155 (66), 121 (100), 91 (51). Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 60.22; H, 6.43; N, 8.96.

1-(2-Chloroethyl)-4-methoxybenzene (2b). A general chlorodeamination procedure for the preparation 1-(2-chloroethyl)-4-methoxybenzene is as follows: *N*-(4-Methoxyphenethyl)-*p*-toluenesulfonamide (1.00 g, 3.28 mmol) in dry THF (15 mL) was added to a suspension of NaH (78.9 mg, 3.28 mmol) in dry THF (80 mL). The mixture was stirred for 20 min, and then a freshly prepared chloroamine solution (~50 mmol) in ether (200 mL) was added dropwise. KOH (3.6 g) in MeOH (20 mL) was then added, and the mixture was heated to reflux overnight. The organic solution was decanted and washed with water and brine. Removal of solvent yielded an oil which was purified by flash chromatography on silica gel (hexanes:ether = 1:1), R_f = 0.85, affording a colorless oil: 291 mg, 52% yield; NMR ($CDCl_3$) δ 7.15 (2 H, d, J = 8.7 Hz), 6.86 (2 H, d, J = 8.6 Hz), 3.80 (3 H, s), 3.68 (2 H, t, J = 7.5 Hz), 3.01 (2 H, t, J = 7.6 Hz); IR (neat) 3031, 2956, 2835, 2058, 1883, 1734, 1612, 1513, 1464, 1302, 1247, 1178, 1036, 822, 769 cm^{-1}; MS M^+ = 170 (76), 135 (9), 121 (100), 91 (12), 77 (8).[11,14]

2-Chloroadamantane: 43% yield; MS M^+ = 170 (3.3), 134 (100), 119 (23), 105 (14,5), 93 (32.5), 92 (83.3), 83 (63.1), 67 (6.1); NMR ($CDCl_3$) δ 4.40 (1 H, s), 1.76 (15 H, m).[15,16]

1-Chloroadamantane: 52% yield; MS M^+ = 170 (1.5), 135 (100), 93 (12.3), 79 (19.5), 67 (6.1).[15,17]

3-Bromo-4-chlorotoluene: 17% yield, MS 208 (13.4), 206 (63.3), 204 (46.6), 171 (28.2), 169 (30.1), 127 (29.9), 126 (8.8), 125 (100), 90 (19.1), 89 (69.7), 85 (35.1), 83 (46.7), 63 (45.3); NMR ($CDCl_3$) δ 7.38 (1 H, s), 7.11 (2 H, m), 2.33 (3 H, s).[15,18]

1-(2-Chloroethyl)-4-chlorobenzene: 59% yield; NMR ($CDCl_3$) δ 7.30 (2 H, d, J = 8.5 Hz), 7.16 (2 H, d, J = 8.3 Hz), 3.70 (2 H, t, J = 7.1 Hz), 3.04 (2 H, t, J = 7.3 Hz); IR (neat) 2927, 1594, 1492, 1376, 1092, 1015, 812, 655 cm^{-1}.[10,19]

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1-Chlorotetradecane: 43% yield; NMR ($CDCl_3$) δ 3.54 (2 H, t, J = 6.9 Hz), 1.81 (2 H, q, J = 6.9 Hz), 1.26 (22 H, m), 0.88 (3 H, t, J = 6.3 Hz); IR (neat) 2924, 2853, 1628, 1466, 1377, 1287, 1090, 722 cm^{-1}.[12,15]

1-(2-Chloroethyl)-4-methoxybenzene (2b) via Tosylhydrazine 2a. 1-Tosyl-1-[2-(4-methoxyphenyl)ethyl]hydrazine (**2a**) (100 mg, 0.314 mmol) was added to a solution of dry chloroamine in ether (100 mL) in one portion at 0 °C. A solution of KOH (100 mg) in MeOH (10 mL) was added immediately to the above mixture at 0 °C. The mixture was heated to reflux overnight under nitrogen. After the mixture was cooled to room temperature, water (80 mL) was added and the mixture was stirred for another 20 min. The organic layer was separated and concentrated. The residue was dissolved in hexanes (190 mL) and washed with saturated $NaHCO_3$ and brine. Drying and removal of hexanes afforded **2b** as a crude oil, 114 mg (51% purity by GC), 95% calculated yield. Spectra were identical to **2b** described above.

1-(2-Bromoethyl)-4-methoxybenzene (2c). Bromine (55.2 mg, 0.345 mmol) was added to a solution of 1-tosyl-1-[2-(4-methoxyphenyl)ethyl]hydrazine (100 mg, 0.314 mmol) in dry ether (100 mL) at 0 °C. A solution of KOH (100 mg) in MeOH (10 mL) was added dropwise immediately to the above mixture at 0 °C. The mixture was heated to reflux overnight under nitrogen, and water (50 mL) was added after it cooled to room temperature. The ether layer was collected and washed with water, $NaHSO_3$, saturated $NaHCO_3$, and brine. Drying and removal of solvent afforded **2c** as a crude oil: 101 mg (58% purity by GC-MS); 85% calculated yield; GC-MS M^+ = 214 (1.2), 135 (7), 121 (100), 91 (6.7); NMR ($CDCl_3$) δ 7.14 (2 H, d, J = 8.3 Hz), 6.68 (2 H, d, J = 7.8 Hz), 3.80 (3 H, s), 3.53 (2 H, t, J = 7.9 Hz), 3.10 (2 H, t, J = 7.7 Hz); IR (neat) 3000, 2950, 2830, 1620, 1518, 1360, 1175, 1030, 990, 878, 765 cm^{-1}.[20]

1-(2-Iodoethyl)-4-methoxybenzene (2d). Iodine (159 mg, 0.628 mmol) was added to a solution of 1-tosyl-1-[2-(4-methoxyphenyl)ethyl]hydrazine (100 mg, 0.314 mmol) in dry ether (100 mL) at 0 °C. A solution of KOH (100 mg) in MeOH (10 mL) was added dropwise immediately to the above mixture at 0 °C. The mixture was heated to reflux overnight under nitrogen, and water (50 mL) was added after it cooled to room temperature. The ether layer was collected and washed with water, $NaHSO_3$, saturated $NaHCO_3$, and brine. Drying and removal of solvent afforded **2d** as a crude oil: 76 mg (76% purity by GC-MS): 70% calculated yield; GC-MS M^+ = 262 (0.4), 135 (13), 121 (100), 91 (16), 77 (13); NMR ($CDCl_3$) δ 7.12 (2 H, d, J = 8.3 Hz), 6.85 (2 H, d, J = 8.7 Hz), 3.80 (3 H, s), 3.32 (2 H, t, J = 6.7 Hz), 3.11 (2 H, t, J = 7.4 Hz); IR (neat) 3000, 2958, 2834, 1611, 1512, 1463, 1247, 1177, 1036, 818, 755 cm^{-1}.[20]

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Multifunctionalization of Imidazole via Sequential Halogen-Metal Exchange: A New Route to Purine-Ring Analogs†

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A new method for the synthesis of purine-ring analogs based upon the sequential halogen-metal exchange functionalization of 1-[(benzyloxy)methyl]-2,4,5-triiodoimidazole (1) has been developed and is illustrated by the synthesis of (1*H*)-imidazo[4,5-*d*]pyridazin-4(5*H*)-one (2-aza-3-deazahypoxanthine, 8). Treatment of 1 with BuLi followed by quench with PhSSPh afforded the 2-(phenylthio) derivative, which upon treatment with BuLi followed by quench with DMF gave the 5-carboxaldehyde. This aldehyde was converted into its ethylene acetal, which was treated with BuLi followed by quench with $ClCO_2CH_3$ to afford a 4-(methoxycarbonyl)imidazole. Removal of the phenylthio group with Al(Hg) and the (benzyloxy)methyl and ethylene acetal protecting groups concomitantly with 3 M HCl afforded methyl 5(4)-formylimidazole-4(5)-carboxylate, which underwent cyclocondensation with ethanolic NH_2NH_2 to give target 8. This synthetic approach was found amenable to modification by efficient "one-pot" multistep transformations. Thus, treatment of 1 with (a) BuLi, (b) $(CH_3)_3SiCl$, (c) BuLi, (d) $(CH_3)_2NN(CH_3)CHO$, (e) BuLi, and (f) $(CH_3OCO)_2O$ afforded the N-protected 4-(methoxycarbonyl)-imidazole-5-carboxaldehyde (13) in 25% yield *directly from* 1. Imidazole 13 was then elaborated to 8 in two steps. 1-Formyl-1,2,2-trimethylhydrazine is a recommended replacement for DMF as a tandem formylating/ortho-metalation directing agent.

The development and/or refinement of synthetic methods for functionalizing the carbon atom positions of imidazole[1-7] continues to be a central concern in the pursuit of bioactive synthetic analogs of naturally-occurring imidazole-based compounds. A major obstacle in carbanion-based versions of these efforts arises from the fact that the most readily-generated sp^2 carbanion, namely that at the C2 position,[2] is seldom the one desired. In the synthesis of analogs of the amino acid histidine, for example, one needs to achieve an efficient regioselective preparation of an imidazol-4(5)-yl carbanionic species. Both the latest imidazol-4-yl monoanion-based methodology developed by Turner et al.[1a] and the imidazole-1,4-diyl dianion-based one developed in Katritsky's laboratory[1b] address this need. In the pursuit of requisite imidazole precursors to

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