Properties of Bis(trifluoroacetoxy)borane as a Reducing Agent of Organic Compounds[1]

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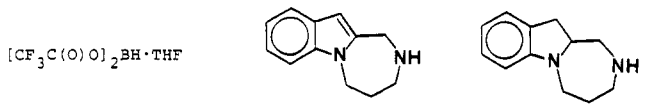
Reactions of bis(trifluoroacetoxy)borane–THF (1) with compounds containing representative organic functional groups were studied to determine the usefulness of 1 as a selective reducing agent. Reducible functionalities were indoles, ketones, aldehydes, imines, and compounds that readily generate carbocations in trifluoroacetic acid. Many functionalities were inert to 1. Epoxides and ortho esters suffered decomposition under the reaction conditions. Olefins and acetylenes were not hydroborated, and carboxylic acids were not reduced by 1.

Mono- and disubstituted boranes are useful reagents in organic synthesis for selective reduction and for hydroboration.[2] Thus, agents such as thexylborane,[3a] diisopinocamphenylborane, chloroborane,[3b] catecholborane,[3c,d] dihaloboranes,[3b,e] disiamylborane,[3f] and 9-borabicyclo[3.3.1]nonane[3g] have received considerable attention from synthetic organic chemists.[2] We recently communicated some selective reducing properties of bis(trifluoroacetoxy)borane–tetrahydrofuran (1) which is readily prepared from BH_3·THF and trifluoroacetic acid (TFA).[4] An important characteristic of 1 is its sufficient stability in TFA to allow its employment as a reducing agent of organic compounds in this strongly acidic medium; 1 can also be employed under nonacidic conditions.



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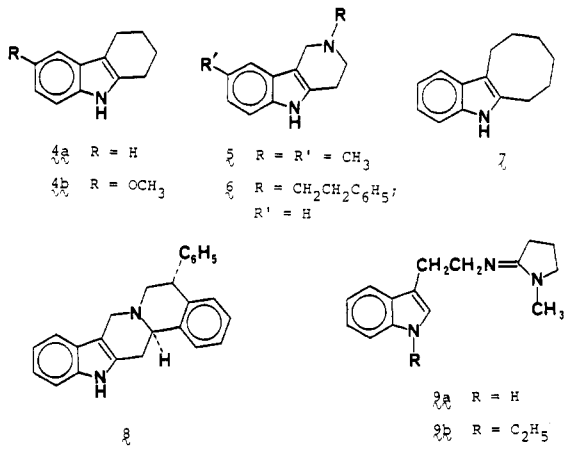
Acyloxyboron hydride species have been discussed in other papers.[5] For several years, mono- and bis(acyloxy)boranes were merely supposed intermediates in the reaction of carboxylic acids with borane complexes,[5a,b,e,g] but now their existence has been sufficiently established.[4,5f] Although bis derivatives have been identified by us[4] and others,[5c,f] the general properties of bis(acyloxy)boranes in organic reductions have not been explored. We have continued studies with bis(trifluoroacetoxy)borane and report our detailed results in this article.

Chart I



Results and Discussion

Indoles. A variety of methods for the reduction of indoles to indolines are known. These can be broadly classified as follows: (1) metal/acid, (2) catalytic hydrogenation, (3) metal/ammonia, (4) boron hydrides and hydridoborates.[6] A critical discussion of the relative merits of available procedures has recently appeared.[7]

Although borane complexes and hydridoborate reagents are unreactive to indoles alone, they can be effective reducing agents under acidic conditions. With acidic conditions, indole reduction often competes with destruction of the reducing agent, necessitating a large stoichiometric excess of "hydride". Indole reductions have been achieved with diborane or BH_3·THF,[8,9] borane–amine complexes,[10]

(1) Presented in part at the following: the 12th Middle Atlantic Regional Meeting of the American Chemical Society, Hunt Valley, MD, Apr 1978; the 2nd IUPAC Symposium on Organic Synthesis, Jerusalem/Haifa, Israel, Sept 1978; the 14th Middle Atlantic Regional Meeting of the American Chemical Society, King of Prussia, PA, Apr 1980.

(2) Pelter, A. *Chem. Ind. (London)* **1976**, 888. Brown, H. C. "Boranes in Organic Chemistry"; Cornell University Press: Ithaca, NY, 1972. Brown, H. C. "Organic Synthesis via Boranes"; Wiley: NY, 1975.

(3) (a) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Org. Chem.* **1972**, *37*, 2942. (b) Brown, H. C.; Ravindran, N. *Ibid.* **1977**, *42*, 2533; *J. Am. Chem. Soc.* **1976**, *98*, 1785. (c) Kabalka, G. W.; Baker, J. D., Jr.; Neal, G. W. *J. Org. Chem.* **1977**, *42*, 512. (d) Lane, C. F.; Kabalka, G. W. *Tetrahedron* **1976**, *32*, 981. (e) Brown, H. C.; Ravindran, N. *J. Am. Chem. Soc.* **1977**, *99*, 7097. Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1980**, *45*, 384. Brown, H. C.; Campbell, B., Jr. *Ibid.* **1980**, *45*, 389. (f) Brown, H. C.; Bigley, D. B.; Arora, S. K.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 7161. (g) Brown, H. C.; Krishnamurthy, S.; Yoon, N. M. *J. Org. Chem.* **1976**, *41*, 1778. Krishnamurthy, S.; Brown, H. C. *Ibid.* **1975**, *40*, 1864.

(4) Maryanoff, B. E.; McComsey, D. F. *J. Org. Chem.* **1978**, *43*, 2733. Also see: Maryanoff, B. E.; McComsey, D. F. U.S. Patent 4 210 590, 1980.

(5) (a) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637. (b) Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B. *J. Org. Chem.* **1974**, *39*, 3052. (c) Pelter, A.; Hutchings, M. G.; Levitt, T. E.; Smith, K. *J. Chem. Soc. D* **1970**, 347. (d) Lane, C. F. *Chem. Rev.* **1976**, *76*, 773. (e) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1960**, *82*, 1681. (f) Brown, H. C.; Stocky, T. P. *Ibid.* **1977**, *99*, 8218. (g) Collum, D. B.; Chen, S. C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393. By contrast, dialkyl(acyloxy)boranes were established entities for many years. See, e.g.: Köster, R.; Bellut, H.; Fenzl, W. *Justus Liebigs Ann. Chem.* **1974**, 54; Toporcer, L. H.; Dessy, R. E.; Green, S. I. E. *J. Am. Chem. Soc.* **1965**, *87*, 1236 and references therein.

(6) (a) Robinson, B., *Chem. Rev.* **1969**, *69*, 785. Remers, W. A.; Gibs, G. J.; Pidacks, C.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 279. (b) Silicon hydride reduction of indoles can also be useful: Lanzilotti, A. E.; Littel, R.; Fanshawe, W. J.; Mackenzie, T. C.; Lovell, F. M. *J. Org. Chem.* **1979**, *44*, 4809 and ref 18 cited therein. Triethylsilane/TFA was effective in the reduction of 2 to 3, albeit rather slow.

(7) Gribble, G. W.; Hoffman, J. M. *Synthesis* **1977**, 859.

(8) (a) Monti, S. A.; Schmidt, R. R., III *Tetrahedron* **1971**, *27*, 3331. (b) Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1968**, *24*, 1145. (c) Plieninger, H.; Bauer, H.; Bühler, W.; Kurze, J.; Lerch, U. *Justus Liebigs Ann. Chem.* **1964**, *680*, 69. (d) Gannon, W. N.; Benigni, J. D.; Suzuki, J.; Daly, J. W. *Tetrahedron Lett.* **1967**, 1531. (e) Berger, J. G.; Teller, S. R. *Tetrahedron Lett.* **1975**, 1807. (f) Littell, R.; Allen, G. R., Jr. *J. Org. Chem.* **1973**, *38*, 1504. (g) Dolby, L. J.; Esfandiari, Z. *Ibid.* **1972**, *37*, 43. (h) De Witt Adams, C. U.S. Patent 3 983 123, 1976. (i) Berger, J. G.; Davidson, F.; Langford, G. *J. Med. Chem.* **1977**, *20*, 600.

(9) In the reduction of 2 to 3 using the methods described by Plieninger[8c] and Monti,[8a] most of the reduction occurred *during the acidic workup*. Workup with water showed considerably lower conversion of 2 to 3. Thus, the acid added to destroy excess hydride in the workup appears to be largely responsible for indoline production in these procedures.[8a,c]

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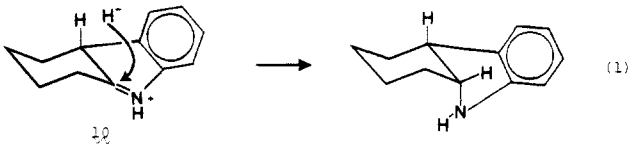
and hydridoborate species.[7,9,11]

In our preliminary report[4] we investigated the application of reduction procedures to the difficult conversion of azepindole[12] (2) to dihydro derivative 3.[13] The reagents of choice turned out to be 1/TFA or BH_3·THF/TFA, borane–pyridine/TFA (see ref 10c), and $NaBH_3CN$/TFA. BH_3·THF in TFA generally constitutes a convenient, mild, rapid, high-yield method for the conversion of indoles to indolines (Table I). Indoles were reduced to indolines in 60–90% isolated yields (Table I). 2-Phenylindole and ethyl indole-2-carboxylate were recovered unchanged.

Table I contains several reductions which illustrate the selectivity of 1. This topic will be dealt with later in the paper, but we can note here that ester, nitrile, nitro, ether, amide, carboxylic acid, and amidine functionalities are inert to reagent 1.

Indoles with 2,3-fused six-membered rings (4–6, 8; see Chart I) gave only cis indolines on reduction with 1. Protonation of a fused indole such as tetrahydrocarbazole (4a) should generate 3*H*-indolenium ion 10, which undergoes equatorial attack by 1 (eq 1). The reductions of 2,3-dimethylindole and 7 lack this steric control.



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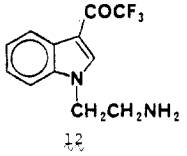
In reductions of primary or secondary amino compounds, trifluoroacetylation and trifluoroethylation have been observed with prolonged reaction times, but indole reduction with 1 is fast enough to minimize this problem. The reduction of 2 with $NaBH_4$/TFA[11a] was unsuccessful because of rapid, competitive trifluoroacetylation and trifluoroethylation. The desired indoline 3 (35%) was accompanied by CH_2CF_3-substituted indoline (10%), CH_2CF_3-substituted indole (15%), and $C(O)CF_3$-substituted indole (15%), assayed and identified by GLC/mass spectrometry. The position of substitution (indole 3-carbon or nitrogen) was not determined.

In studying the reduction of 1-(2-aminoethyl)indole (11) by normal addition, we found a byproduct that could be avoided by inverse addition. This byproduct also formed rapidly when 11 was simply dissolved in TFA. The new material was isolated and identified as 3-substituted derivative 12 by mass spectrometry and ^1H NMR.[14] Al-



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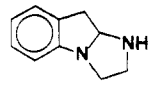

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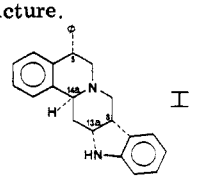
though no trifluoroacetylation of the amine nitrogen was observed, trifluoroacetamide possibly was formed and then

Table I. Reduction of Indoles to Indolines[a]

substrate	yield of indoline, %[b]	remarks
tetrahydrocarbazole (4a)	80 (90)[c]	only cis product[d-f]
4b[g]	90[h]	only cis product[d]
tryptamine	86[i]	*d*
2-methylindole	88	*d*
5-nitroindole	(70)	25% "dimeric" product[d]
indole	(84)	
2,3-dimethylindole	82	trans/cis ratio ~2[d,f]
1-cyanomethylindole[j]	73[k]	
1-(2-aminoethyl)indole[l]	~65[k]	
5[m]	80[n]	only cis product[d]
6[o]	70	only cis product[d,n]
7[p]	80[q]	isomer ratio = ~2.5[d]
N-benzoyltryptamine[r]	80[s]	
2[t]	86 (98)[u]	*d*
4-(3-indolyl)butanoic acid	85[v]	
8[w]	92[x]	*d*
9a[y]	81[z]	*d*
9b[aa]	79[bb]	*d*

[a] All indoles and indolines are known compounds unless otherwise noted. Indoline products were characterized by ^1H NMR and, when appropriate, by IR, UV, and melting point data. [b] Isolated yield; the GLC yield, obtained by using an internal reference and a detector response factor is given in parentheses. [c] Smith A.; Utley, J. *J. Chem. Soc. C* **1970**, 1. [d] Substrate added prior to borane·tetrahydrofuran (see Experimental Section).[4] [e] Booth, H.; Masamune, T. *J. Chem. Soc., Perkin Trans. 2* **1972**, 354. [f] Anet, F. A. L.; Muskowski, J. M. *Chem. Ind. (London)* **1963**, 81. [g] Chalmers, J. R.; Openshaw, H. T.; Smith, G. F. *J. Chem. Soc.* **1957**, 1115. [h] Campaign, E.; Lake, R. D. *J. Org. Chem.* **1959**, *24*, 478. [i] Daly, J. W.; Manger, A. B.; Yonemitsu, O.; Antonov, V. K.; Takase, K.; Witkop, B. *Biochemistry* **1967**, *6*, 652. [j] Bell, M. R. U.S. Patent 3 354 174, 1967. [k] Mull, R. P. U.S. Patent 3 093 632, 1963. [l] Pfiel, E.; Harder, U. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 178. [m] Chattanach, C. J.; Cohen, A.; Heath-Brown, B. *J. Chem. Soc. C* **1968**, 1235. [n] Barkov, N. K.; Kucherov, N. F.; Kochetkov, N. K.; Zhukova, I. G.; Sharkova, N. M. U.S. Patent 3 657 254, 1972. [o] Reference 8i. [p] Witkop, B.; Patrick, J. B.; Rosenblum, M. *J. Am. Chem. Soc.* **1951**, *73*, 2641. [q] Lemke, T.; Johnson, R.; Murray, H.; Duchamp, D.; Chidester, C.; Hester, J., Jr.; Heinzelman, R. *J. Org. Chem.* **1971**, *36*, 2823. [r] Ho, B. T.; McIsaac. W. M.; Tansey, L. W.; Kralik, P. M. *J. Pharm. Sci.* **1968**, *57*, 1998. [s] Reference 10b. [t] Reference 12. [u] Reference 13. [v] Ethyl ester reported in ref 10b. The methyl ester, prepared herein by using CH_2N_2, was characterized by GLC/MS. [w] Prepared from (7α,11bα)-1,3,4,6,7,11b-hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizin-2-one and phenylhydrazine.[40a] [x] Fully characterized as a propanoyl derivative.[40a] It should be noted that the reduction of 8 produced only one of the two possible cis-fused indolines, the 5α,8α,13aα,14aα isomer shown below as structure I. [y] Poos, G. I. U.S. Patent 3 501 487, 1970. [z] Verified by IR, UV, ^1H NMR, and elemental analysis (C, H, N) and synthesized also from 2,3-dihydrotryptamine and 2-ethoxy-*N*-methylpyrrolidinium fluoborate. [aa] Prepared from the sodium salt of 9a and iodoethane and characterized by IR, UV, ^1H NMR, and elemental analysis (C, H, N). [bb] UV, IR, ^1H NMR, and elemental analysis (C, H, N) confirmed this structure.



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(10) (a) Berger, J. G. *Synthesis* **1974**, 508. (b) Kikugawa, Y. *J. Chem. Res.* **1977**, 272; (c) *Ibid.* **1978**, 184.

(11) (a) Gribble, G. W.; Lord, P.; Skotnicki, J.; Dietz, S.; Eaton, J.; Johnson, J. *J. Am. Chem. Soc.* **1974**, *96*, 7812. (b) Kikugawa, Y. *Chem. Pharm. Bull.* **1978**, *26*, 108. (c) Chavdarian, C. G.; Karashima, D.; Castagnoli, N., Jr.; Hundley, H. K. *J. Med. Chem.* **1978**, *21*, 550.

(12) (a) Reynolds, B. E.; Carson, J. R. U.S. Patent 3 867 374, 1975; U.S. Patent 3 689 503, 1972. (b) Jonas, R.; Müller-Calgan, H.; Schleip, H.-J. U.S. Patent 3 980 797, 1976.

(13) Amidines are susceptible to borohydride reduction in acidic media. See: Moad, G.; Benkovic, S. *J. Am. Chem. Soc.* **1978**, *100*, 5495.

(14) Coupling between fluorine and the indole 4-proton ($^6J_{CF}$ = 1.0 Hz) was confirmed by a ^{19}F-decoupling experiment. (We thank Ms. Mary Baum of Princeton University for this determination.)

Table II. Reducible Functional Groups

entry	functionality	substrate	product (% yield[a])
1	indole	see Table I	indoline (see Table I)
2	ketone	2-phenylcyclohexanone	2-phenylcyclohexanols (76)[b]
3	ketone	acetophenone	1-phenylethanol (77)
4	aldehyde	benzaldehyde	benzyl alcohol (90)
5	aldehyde	decanal	1-decanol (96)
6	imine	22[c]	amine[d] (83)
7	oxime	cyclohexanone oxime	c-$C_6H_{11}NHOH$ (70)
8	arylcarbinol	$(C_6H_5)_2CHOH$	$(C_6H_5)_2CH_2$ (61)
9	arylcarbinol	$(C_6H_5)_3COH$	$(C_6H_5)_3CH$ (66)
10	arylcarbinol	19	alkane (90[e])
11	diaryl ketone	$(C_6H_5)_2CO$	$(C_6H_5)_2CH_2$ (75)[f]
12	ether	$C_6H_5C(OCH_3)_3$	$C_6H_5CH_2OCH_3$[g] (10[h])
13	ether	21	*N*-phenylpyrrolidin-2-one (81)
14	epoxide	styrene oxide	2-phenylethanol[d] (10[h])
15	epoxide	cyclohexene oxide	*i*
16	azaheterocycle	14	15 (86)
17	azaheterocycle	16	17 (*j*)
18	tosylhydrazone	23	cyclohexylbenzene (65)
19	tosylhydrazone	24	tosylhydrazine[k] (86)

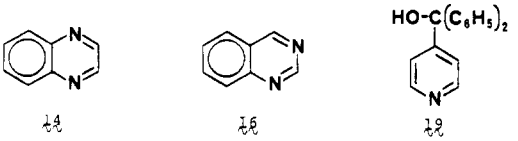
[a] Isolated and purified yield, unless otherwise noted. [b] Cis/trans ratio of 1/1. [c] Reference 40. [d] Reference 41. [e] GLC yield. [f] $(C_6H_5)_2CHOH$ was observed as an intermediate. [g] Polymerization of solvent. [h] THF polymer makes isolation of the product difficult. [i] Substrate was destroyed. [j] Starting material was completely consumed; three new compounds were produced (see text). [k] Reference 39.

hydrolyzed during the mild alkaline workup. In the course of this reaction, an intermediate was detected by TLC, which may have been 13 (or a trifluoroacetamide derivative of 13), a cyclic tautomer related to the tryptamine tautomers described by Hino and Taniguchi.[15] Hexahydropyrrolo[2,1-*b*]indole 13 would exist in equilibrium with starting indole 11, which is eventually trapped as 12. Trifluoroacetylation of indole with $(CF_3CO)_2O$ has been reported to occur at the 1- and/or 3-positions,[16] so 3-position substitution of 11 is not unprecedented; however, rapid trifluoroacetylation with TFA is unusual.[17] This reaction was not observed with any other indoles examined. Some indoles (e.g., indole, 2-methylindole, 5-nitroindole) suffered dimerization in TFA, and 1-(cyanomethyl)indole reacted with TFA in an unidentified manner. In all instances where acid-induced side reactions were observed, addition of the indole last to the reagent, as opposed to addition of the BH_3·THF last to the indole in TFA, alleviated the difficulties.

In our early work,[4] we found that pyridine–borane in TFA gave similar results to BH_3·THF in TFA for the reduction of 2 to 3. This suggested that pyridine–borane is an adequate substitute for BH_3·THF in indole reductions, but we have not pursued this further. Indeed, concurrent with our communication, Kikugawa reported that pyridine–borane in TFA is an excellent, selective reducing agent for indoles,[10c] giving superior results compared to those of their earlier procedure involving pyridine–borane in ethanolic HCl.[10b] Since Kikugawa applied the pyridine–borane/TFA method to various tryptophan derivatives with much success, we have refrained from extending the BH_3·THF/TFA method to such substrates. However, we point out that these reduction methods, because of their high chemoselectivity for indole reduction, may offer a means for conversion of tryptophan residues in polypeptides (proteins) to 2,3-dihydrotryptophan residues.

Other Heterocycles. Isoquinoline and quinoline were not reduced by BH_3·THF in TFA under our standard conditions, even with prolonged reaction times. Starting materials were quantitatively recovered (GLC). Pyridine–borane in acetic acid was reported to reduce quinoline and isoquinoline at room temperature, whereas trimethylamine–borane in acetic acid does not.[18a] Quinoline and isoquinoline can also be reduced by treatment with BH_3·THF, followed by 20% HCl.[18b] Sodium tetrahydridoborate and cyanotrihydridoborate in carboxylic acid media are both capable of reducing quinoline and isoquinoline, the former reagent also resulting in N-alkylation (as with indoles and other amines[20]).[19] Trimethylamine–borane in refluxing dioxane/hydrochloric acid was reported to reduce quinoline.[10a,19] Gribble and co-workers[19] found that passage of diborane into a solution of quinoline in acetic acid gives a 1-acetyl-1,2-dihydro product.

Diazaheterocycles 14 (quinoxaline) and 16 (quinazoline) were reduced by 1 in TFA/THF (Table II; entries 16 and 17). In the case of 14, 1,2,3,4-tetrahydroquinoxaline was



14 16 19

obtained in 86% isolated yield. The reaction of 16 occurred in more than one way. Depending on the conditions, 1 caused reduction of 16 to 1,2-dihydroquinazoline (17) and ring cleavage to give *o*-(methylamino)benzylamine (18) or reduction to 1,2,3,4-tetrahydroquinazoline.[21] Sodium tetrahydridoborate in TFA has been reported to reduce 14 to tetrahydro derivative 15 and to reduce 16 to 1,2-dihydro derivative 17 in good yields;[22] pyridine–borane in acetic acid and BH_3·THF have been reported to reduce 14 to 15 in good yield.[18]

(15) Hino, T.; Taniguchi, M. *J. Am. Chem. Soc.* **1978**, *100*, 5564.
(16) Cipiciani, A.; Clementi, S.; Linda, P.; Savelli, G.; Sebastiani, G. V. *Tetrahedron* **1976**, *32*, 2595.
(17) Mild trifluoroacetylation with trifluoroacetate derivatives of weak acids, such as H_2O, is not unreasonable. For example, peroxytrifluoroacetic acid (weak acid is H_2O_2) has been reported to trifluoroacetylate alcohols at room temperature: Holbert, G. W.; Ganem, B. *J. Chem. Soc., Chem. Commun.* **1978**, 248.
(18) (a) Kikugawa, Y.; Saito, K.; Yamada, S. *Synthesis* **1978**, 447. (b) Nose, A., Kudo, T., *Yakugaku Zasshi* **1979**, *99*, 1240.
(19) Gribble, G. W.; Heald, P. W. *Synthesis* **1975**, 650.
(20) Gribble, G. W. *Eastman Org. Chem. Bull.* **1979**, *51*, 1.
(21) The occurrence of ring cleavage during reduction of quinazoline compounds has been reported: Smith, R. F.; Briggs, P. C.; Kent, R. A.; Albright, J. A.; Walsh, E. J. *J. Heterocycl. Chem.* **1965**, *2*, 157.
(22) Bugle, R. C.; Osteryoung, R. A. *J. Org. Chem.* **1979**, *44*, 1719.

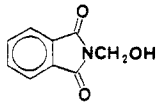
Table III. Nonreducible Functional Groups

functionality	substrate	% recovery
azaheterocycle	quinoline	99
azaheterocycle	isoquinoline	99
nitro	5-nitroindole[a-c]	
ether	5-methoxycarbazole[a]	
ether	$C_6H_5CH_2OCH_3$	95
nitrile	1-(cyanomethyl)indole[a]	
ester	2-(carboethoxy)indole	81
ester	$C_6H_5CH_2CO_2CH_3$	65[d]
amide	*N*-benzoyltryptamine[a]	
amide	*N*-phenylpyrrolidin-2-one[e]	
acid	4-(3-indolyl)butanoic acid[a]	
acid	*p*-toluic acid	63
acid	phenylacetic acid	79
acid chloride	4-phenylbenzoyl chloride	60[d]
amidine	**9a**[a]	
amidine	**9b**[a]	
imide	*N*-benzylsuccinimide	74
imide	*N*-hydroxymethylphthalimide	90
olefin	styrene	99[c]
olefin	1,1-diphenylethylene	95[c]
olefin	1-decene	84[c]
acetylene	phenylacetylene	81[c]
acetylene	1-heptyne	78[c]
sulfoxide	$(C_6H_5)_2SO$	86
sulfoxide	$(C_6H_5CH_2)_2SO$	87
disulfide	$(C_6H_5S-)_2$	87
alkyl chloride	*N*-(3-chloropropyl)piperidine	84
heterocycle	*N*-methylpyrrole	95[c]
heterocycle	benzofuran	99[c]

[a] See Table I. [b] 95% total nitro group not reacted (includes dimeric product). [c] GLC quantitation using an internal reference and detector response factors. [d] Recovered as the acid. [e] See Table II.

Benzofuran and *N*-methylpyrrole were not reduced by 1 in TFA (Table III).

Carbinols and Other Carbocation Precursors. Diaryl and triarylmethanols were reduced by 1/TFA in good yields (Table II; entries 8–11). In the case of **19**, the pyridyl moiety caused no adverse effects. Arylcarbinols, which are capable of forming carbocations in TFA, have also been deoxygenated with $NaBH_4$ in TFA.[23] Benzyl alcohols (see Table II; entries 3 and 4) were not reduced. Imide methyl alcohol **20** (Table III) was not reduced by 1 in TFA to *N*-methylphthalimide, probably because of failure to form an acyliminium ion.[24]



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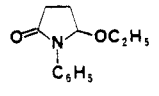

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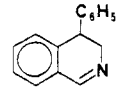

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Ethers capable of forming carbocations in TFA were reduced with 1/TFA (Table II; entries 12 and 13). Thus, trimethyl orthobenzoate was converted within 5 min to methyl benzyl ether (poor yield),[25] which underwent no further reduction by 1 in TFA (Table III). This example demonstrates both reduction of an ortho ester and of an acetal [i.e., $C_6H_5CH(OCH_3)_2$]. Reduction of acetals to ethers with $NaBH_3CN$ and methanolic HCl was reported to take place rapidly,[26] but reduction with BH_3·THF requires a reaction time of several hours.[27] Ether **21**, obtained by reduction of *N*-phenylsuccinimide with $NaBH_4$ in acidic ethanol,[28] was readily reduced with 1/TFA to *N*-phenylpyrrolidin-2-one.

1,1-Diphenylethylene, which was reduced by Gribble with $NaBH_4$/TFA to 1,1-diphenylethane,[23] was not reduced with 1 in TFA (Table III).

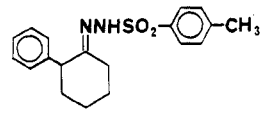
Treatment of styrene oxide with 1 in THF (no excess TFA) produced 2-phenylethanol in poor isolated yield (Table II; entry 14).[25] Because of the polymerization of THF, an attempt was made to reduce styrene oxide with $HB(O_2CCF_3)_2$·$(CH_3)_2S$, prepared from BH_3·$(CH_3)_2S$ and TFA (2 equiv)[4] in CH_2Cl_2, but no reaction occurred. Cyclohexene oxide underwent total decomposition by 1 in THF (no excess TFA).[25] With both oxides, extensive polymerization occurred. Reduction of epoxides with $NaBH_3CN$ in the presence of BF_3 has been reported.[30] The reaction proceeds by hydride attack at the site best able to accommodate a carbocation (e.g., styrene oxide produced 2-phenylethanol).[30]

Ketones, Aldehydes, and Their Derivatives. Ketone and aldehyde functionalities were readily reduced with 1 in TFA/THF to the carbinol group (Table II; entries 2–5, 11). When the carbinol was a suitable precursor to a carbocation (vide supra), it was reduced further to a C–H group (Table II; entry 11). Thus, acetophenone and benzaldehyde afforded alcohols in good yield without overreduction to hydrocarbons (1 mol of excess reducing agent was present), whereas benzophenone was easily converted to diphenylmethane.[31] Sodium tetrahydridoborate in TFA also reduced diaryl ketones to alcohols and hydrocarbons.[32] In the reduction of aldehydes we did not observe "dimeric" ethers, in contrast to the findings with pyridine–borane in TFA.[33] 2-Phenylcyclohexanone, which was readily reduced to a 1:1 mixture of cis and trans alcohols in good yield under standard conditions, was also rapidly reduced when the reaction was conducted in the absence of excess TFA. Thus, the acid (TFA) was not overtly facilitating carbonyl reduction.

The imine group in **22** was readily reduced to the amine (Table II; entry 6), and the oxime group was reduced to the hydroxylamine (Table II; entry 7). Reduction of oximes to hydroxylamines has been effected with $NaBH_4$ and $NaBH_3CN$ in a carboxylic acid medium,[34] and with pyridine–borane in aqueous hydrochloric acid.[35] Reduction of oximes to amines can, of course, be accomplished with stronger reducing agents (e.g., $LiAlH_4$).

Tosylhydrazones were reduced in good yield (Table II; entries 18 and 19). Aliphatic tosylhydrazone **23** was reductively deoxygenated without isolation of the tosylhydrazine (alkaline workup), whereas aromatic-conjugated tosylhydrazone **24** provided the relatively stable, inter-

(23) Gribble, G. W.; Leese, R. M.; Evans, B. E. *Synthesis* **1977**, 172.
(24) (a) Auerbach, J.; Zamore, M.; Weinreb, S. M. *J. Org. Chem.* **1976**, *41*, 725. (b) $NaBH_3CN$ in TFA is effective for reduction of amide methylols. See: Basha, A.; Orlando, J.; Weinreb, S. M. *Synth. Commun.* **1977**, *7*, 549.
(25) This reaction is accompanied by rapid, extensive polymerization of the THF solvent, which makes isolation of the product (or unreacted starting material) more difficult.
(26) Horne, D. A.; Jordan, A. *Tetrahedron Lett.* **1978**, 1357.
(27) Flemming, B.; Bolker, H. I. *Can. J. Chem.* **1974**, *52*, 888.
(28) (a) Hubert, J. C.; Wijnberg, B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *32*, 1437. (b) Imides are generally reduced with $NaBH_4$ to ring-opened *n*-hydroxy amides (n = imide ring size − 1), while $NaBH_4/H^+$ to (n + 1)-oxygenated azacyclan-2-ones,[28a] and with BH_3·THF to azacyclan-2-ones and/or azacyclanes.[29] Note that $NaBH_4/H^+$ does not afford azacyclan-2-ones.
(29) Süess, R. *Helv. Chim. Acta* **1979**, *60*, 1650.
(30) Hutchins, R. O.; Natale, N. R. *Org. Prep. Proced. Int.* **1979**, *11*, 201.
(31) It is difficult to stop the reduction at the carbinol stage with benzophenone since the benzhydrol is competitively reduced to diphenylmethane.
(32) Gribble, G. W.; Kelly, W. J.; Emery, S. E *Synthesis* **1978**, 763.
(33) Kikugawa, Y. *Chem. Lett*, **1979**, 415.
(34) Gribble, G. W.; Leiby, R. W.; Sheehan, M. N. *Synthesis* **1977**, 856.
(35) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1977**, 1279. Kawase, M.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 643.



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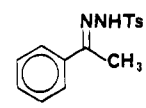

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mediate tosylhydrazine, which could be converted to ethylbenzene on being heated with base.[36] Tosylhydrazones have been reductively deoxygenated with $NaBH_4$ and $NaBH_3CN$ in the presence of acid[30,37] and with catecholborane followed by $NaOAc{\cdot}3H_2O$.[38] With pyridine–borane in acidic ethanol, tosylhydrazines are produced in high yield.[39]

Alkenes and Alkynes. Since hydroboration of olefins and acetylenes is such an important reaction process in organic chemistry, we explored the potential of 1 in this area. Styrene, 1-decene, phenylacetylene, and 1-heptyne were inert to 1, generated in THF at ambient temperature (Table III). Since prolonged (>2 h) monitoring of these reactions was prohibited because of THF polymerization, we also tested 1-decene and phenylacetylene with $HB(O_2CCF_3)_2{\cdot}(CH_3)_2S$, prepared from borane–methyl sulfide and TFA,[4] in 1,2-dichloroethane. After 4 and 1.5 h, respectively, at reflux, no reaction of the unsaturated substrates was detected. 1,1-Diphenylethylene was also inert to 1 in THF with excess TFA present. Catecholborane is very sluggish in hydroboration reactions,[3c] but it appears that $HB(O_2CCF_3)_2{\cdot}X$ (X = nucleophile such as THF) is even less reactive.

Nonreducible Functional Groups. Reagent Selectivity. Bis(trifluoroacetoxy)borane in TFA appears to be capable of reducing a small class of organic functional groups: (1) indoles (also probably other enamines), (2) diazaheterocycles, (3) carbocation precursors, and (4) ketones, aldehydes, and their derivatives. A wide range of functional groups did not react with 1 in TFA (Table III). During the indole reduction studies, the following groups were found to be unharmed while indole reduction was complete: nitro, aromatic ether, nitrile, ester, amidine, carboxylic acid, amide. We have also examined the reactivity of various functional groups to the reagent in the absence of the indole functionality; the following groups did not react: benzyl ether, ester, carboxylic acid, acid chloride, alkyl chloride, imide, alkene, alkyne, sulfoxide, disulfide, aliphatic epoxide, and certain heterocycles (Table III). An additional demonstration of selectivity is given by the reduction of *trans*-cinnamaldehyde to *trans*-cinnamyl alcohol in 99% yield.

Reagent 1 is related to catecholborane in that it has two oxygen ligands connected to boron. This parallelism is represented in their properties as reducing agents (Table IV). Catecholborane may be less selective in certain cases than 1, but a comparison is hampered by differences in reaction conditions. For example, since THF solutions of 1 polymerize, it is impossible to monitor the reactions for more than about 3 h at room temperature. This can be circumvented by generation of bis(trifluoroacetoxy)borane, using borane–methyl sulfide, but the reagent shows some differences in chemical behavior from that of 1, viz., the reduction of styrene oxide and the reduction of **2**.[4]

A comparison of 1/TFA with some related reducing agents is presented in Table IV. Since this reagent is readily generated from $BH_3{\cdot}THF$ and TFA and since it exhibits clear-cut reduction selectivity among organic functional groups, it should be a useful addition to the organic chemists' armamentarium.

Table IV. Functional Group Selectivity of 1 and Comparison with Related Reducing Agents[a]

functionality	1/ TFA	$BH_3{\cdot}$ THF[b]	catechol-borane[c]	AlH_3[d]	$NaBH_4$/ H^+[e]
aldehyde	+	+	+	+	+
ketone	+	+	+	+	+
imine, oxime	+	+	*f*	+	+
tosyl-hydrazone	+	+	+		+
acid chloride	–	–	±	+	*f*
ester	–	±	–	+	–
carboxylic acid	–	+	±	+	
anhydride		+	±	+	
amide	–	+	±	+	+
imide	–	+		*f*	+
lactone		+	–	+	
carbinol	+	–		–	+
acetal, etc.	+	+	+	+ (?)	
epoxide	±	+	+	+	*f*
olefin	– (+[g])	+[h]	±[h] (+[g])	–	+[i]
nitrile	–	+	±	+	+
nitro	–	–	–	–	–
sulfoxide	–		+	+	
acetylene	–	+[h]	+[h]		

[a] A ± sign means very slow reaction; + means reduction readily occurs; – means no reduction. [b] Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1960**, *82*, 681. Lane, C. F. *Aldrichimica Acta* **1973**, *6*, 21. Reference 5d. [c] Reference 3c. [d] Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464. [e] $NaBH_4$ plus HOAc or TFA at various stoichiometries; see ref 20. [f] Expected +. [g] Indole to indoline; no hydroboration of normal olefins. [h] Hydroboration. [i] In enamines and terminal olefins, quinoline/isoquinolines, and indolines.

Experimental Section

General Procedures. GLC analyses were performed on a Perkin-Elmer 3920B instrument (flame-ionization detector) equipped with a Hewlett-Packard Model 3352 data system and a Hewlett-Packard 18652A A/D converter and employing an SE-30 glass column ($^1/_8$ in. × 6 ft, 3% SE-30 on Chromasorb Q). Triphenylmethane was used as an internal GLC reference. ^1H NMR spectra were measured on a Varian EM-360 instrument (60 MHz). TLC separations were conducted by using Analtech, Inc., silica gel GF 250-μm plates. Melting points were determined by using a Thomas-Hoover melting point apparatus and are corrected. IR spectra were obtained by using a Perkin-Elmer 727B spectrophotometer.

Materials. Commercially available reagents and substrates were used without further purification. Borane–tetrahydrofuran solution and trifluoroacetic acid were purchased from Aldrich Chemical Co. Anhydrous tetrahydrofuran was stored over 4A molecular sieves. In many cases products were compared with commercially available or independently synthesized samples. References to materials not available commerically are given in the tables.

General Reduction Procedure with Excess Trifluoroacetic Acid. Trifluoroacetic acid (10 mL, 130 mmol) was added to dry THF (10 mL) with ice-bath cooling (0–5 °C) under nitrogen. $BH_3{\cdot}THF$ (20 mL, 1 M solution, 20 mmol) was added dropwise with continued cooling, and the solution was stirred for 5 min. The substrate (10 mmol) was added at 0–5 °C, and the reaction was maintained at this temperature. The reaction was commonly monitored by GLC or TLC by quenching an aliquot with water. After 45 min or less, the remaining hydride was destroyed by slow addition of water (15 mL), and the solution was stirred at room temperature for 10 min. Four different workup methods (A–D), which are described separately below, have been employed.

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(37) Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299.
(38) Kabalka, G. W.; Baker, J. D., Jr. *J. Org. Chem.* **1975**, *40*, 1834. Kabalka, G. W.; Yang, D. T. C.; Chandler, J. H.; Baker, J. D., Jr. *Synthesis* **1977**, 124.
(39) Kikugawa, Y.; Kawase, M. *Synth. Commun.* **1979**, *9*, 49.

Variants on the General Reduction Procedure. When a substrate possessed acidic protons or could undergo more than one reduction, an additional equivalent of borane–tetrahydrofuran was added for each acidic proton or each additional, intended reduction. The reduction of cyclohexanone oxime is representative of this procedure. In some instances, the substrate was added prior to addition of BH_3·THF, as was the case with many indole reductions previously reported.[4] If substrate stability in acid was questionable, then 2 equiv of TFA for each equivalent of BH_3·THF was employed, instead of excess TFA.

Workup Method A. The aqueous solution was made alkaline (pH >10) with 10% NaOH, stirred for 15 min, and then extracted with ether or CH_2Cl_2. The organic layer was washed with H_2O and saturated NaCl solution and dried over K_2CO_3 or $MgSO_4$. The organic solution was evaporated to give the desired product or recovered starting material.

Workup Method B. This was the same as method A except, after the extraction, the aqueous phase was made acidic (pH ~1) with concentrated HCl and extracted with ether or CH_2Cl_2. The organic phase was washed and dried as in method A and evaporated to give material.

Workup Method C. The solution was evaporated to a solid, which was partitioned between aqueous NaOH and CH_2Cl_2. The organic layer was washed and dried as in method A and evaporated to give material.

Workup Method D. This was the same as method A except saturated $NaHCO_3$ solution was used in place of 10% NaOH.

Reduction of 3,4-Dihydro-4-phenylisoquinoline.[40] The general procedure was used to prepare the bis(trifluoroacetoxy)borane 1 in TFA. 3,4-Dihydro-4-phenylisoquinoline (2.07 g, 10 mmol) was added as a slurry in THF. TLC (ethyl acetate/hexane, 1:1) showed that the reaction was complete after 1 min. Workup (method A) yielded 1.72 g (83%) of oily 4-phenyl-1,2,3,4-tetrahydroisoquinoline, mp (HBr salt) 218.5–221 °C (lit.[41] mp 223–225 °C).

Benzaldehyde Reduction. The general procedure was followed by employing 30 mL of BH_3·THF. Benzaldehyde (1.06 g, 10 mmol) was added and, after 1 min, GLC indicated complete reaction and no noticeable toluene. Workup (method A) gave 0.95 g (ca. 90%) of benzyl alcohol which upon distillation gave a colorless liquid, bp 78–79 °C (2.5 torr).

Attempted Reduction of 2-Phenylacetic Acid. The general procedure was followed; however, in this instance 40 mL of the 1 M BH_3·THF complex was used to generate 40 mmol of 1. 2-Phenylacetic acid (1.36 g, 10 mmol) was added slowly. After 2 h, TLC indicated no reduction. Workup (method B) gave a 79% recovery of starting material, mp 77–78 °C.

Cyclohexanone Oxime Reduction. The general procedure was followed by using 30 mL of 1 M BH_3·THF. Cyclohexanone oxime (1.13 g, 10 mmol) was added, and the reaction was monitored by GLC. After 45 min, water was added, and the solution was evaporated to half the volume. HCl (3 N, 25 mL) was added, and the mixture was extracted with ether. The aqueous solution was made alkaline with 10% NaOH, and the white cyclohexylhydroxylamine was filtered; mp 138–142 °C.

Benzophenone Reduction. The general procedure was followed by using 22 mL (22 mmol) of BH_3·THF, 5.5 mL of TFA, and 5.5 mL of THF. Benzophenone (1.0 g, 5.5 mmol) was added, and the reaction mixture was stirred for 3 h. Workup (method A) gave a gelatinous substance from which 0.69 g (75%) of diphenylmethane was distilled; bp 110–120 °C (2 torr) [lit. bp 264 °C (760 torr)].

Quinoxaline Reduction. The general procedure was followed by using 63 mL (63 mmol) of BH_3·THF, 17 mL of TFA, and 17 mL of THF. Quinoxaline (1.0 g, 7.7 mmol) was added, and the reaction mixture was stirred at 0 °C for 30 min. Workup (method A) gave a solid which was recrystallized from ethyl acetate/hexane to give 0.89 g (86%) of 1,2,3,4-tetrahydroquinoxaline, mp 94–95 °C (lit.[22] mp 95–96 °C).

2-Phenylcyclohexanone Tosylhydrazone Reduction. The general procedure was followed by using 11.6 mL (11.6 mmol) of BH_3·THF, 5.5 mL of TFA, and 5.5 mL of THF. The tosylhydrazone (1.0 g, 2.9 mmol) was added, and the reaction mixture was stirred for 30 min at 0 °C. Workup by distillation gave 0.29 g (64%) of cyclohexylbenzene, bp 75 °C (0.05 torr; identical with an authentic sample).

Acetophenone Tosylhydrazone Reduction. The general procedure was followed by using 14.0 mL (14 mmol) of BH_3·THF, 7.2 mL of TFA, and 7.2 mL of THF. The tosylhydrazone (1.0 g, 3.5 mmol) was added, and the reaction mixture was stirred at 0 °C for 35 min. Workup (method A) gave 0.89 g (86%) of a crystalline solid, 1-phenethyltosylhydrazine, mp 107–108 °C (lit.[39] mp 108–110 °C).

Acknowledgment. We thank Mr. Martin Mutter, Ms. Joan Rogers, and Ms. Roberta Acchione for spectroscopic data.

Registry No. 1, 75626-03-8; 2, 26304-61-0; 3, 67177-54-2; 4a, 942-01-8; *cis*-4a dihydro, 4828-96-0; 4b, 13070-45-6; *cis*-4b dihydro, 75457-24-8; 5, 19686-05-6; *cis*-5-dihydro, 75494-88-1; 6, 6208-44-2; *cis*-6-dihydro, 62018-28-4; 7, 22793-63-1; *cis*-7 dihydro, 75457-25-9; *trans*-7 dihydro, 75626-04-9; 8, 75626-05-0; 5α,8α,13aα,14aα-8 dihydro, 75626-06-1; 9a, 26727-30-0; 9a sodium salt, 75626-07-2; 9a dihydro, 75626-08-3; 9b, 75626-09-4; 9b dihydro, 75626-10-7; 11, 13708-58-2; 11 dihydro, 46006-95-5; 12, 75626-11-8; 14, 91-19-0; 15, 3476-89-9; 16, 253-82-7; 17, 53378-34-0; 18, 20877-88-7; 19, 1620-30-0; 20, 118-29-6; 21, 55609-31-9; 22, 6187-58-2; 22 dihydro, 75626-12-9; 23, 41780-67-0; 24, 4545-21-5; 1,2,3,4-tetrahydroquinazoline, 1904-65-0; trifluoroacetic acid, 76-05-1; borane·THF, 14044-65-6; tryptamine, 61-54-1; 2,3-dihydrotryptamine, 13078-91-6; 2-methylindole, 95-20-5; 2-methylindoline, 6872-06-6; 5-nitroindole, 6146-52-7; 5-nitroindoline, 32692-19-6; indole, 120-72-9; indoline, 496-15-1; 2,3-dimethylindole, 91-55-4; *cis*-2,3-dimethylindoline, 10276-90-1; *trans*-2,3-dimethylindoline, 7356-42-5; 1-cyanomethylindole, 4414-73-7; 1-cyanomethylindoline, 50781-87-8; *N*-benzoyltryptamine, 75626-13-0; *N*-benzoyl-2,3-dihydrotryptamine, 69181-69-7; 4-(3-indolyl)butanoic acid, 133-32-4; methyl 4-(3-indolinyl)butanoate, 75626-14-1; iodoethane, 75-03-6; 2-phenylcyclohexanone, 1444-65-1; *cis*-2-phenylcyclohexanol, 16201-63-1; *trans*-2-phenylcyclohexanol, 2362-61-0; acetophenone, 98-86-2; 1-phenylethanol, 98-85-1; benzaldehyde, 100-52-7; benzyl alcohol, 100-51-6; decanol, 112-31-2; 1-decanol, 112-30-1; cyclohexanone oxime, 100-64-1; *N*-hydroxycyclohexylamine, 2211-64-5; benzhydrol, 91-01-0; diphenylmethane, 101-81-5; triphenylcarbinol, 76-84-6; triphenylmethane, 519-73-3; 4-(diphenylmethyl)pyridine, 3678-72-6; benzophenone, 119-61-9; trimethyl orthobenzoate, 707-07-3; benzyl methyl ether, 538-86-3; *N*-phenylpyrrolidin-2-one, 4641-57-0; styrene oxide, 96-09-3; 2-phenylethanol, 60-12-8; cyclohexylbenzene, 827-52-1; 1-(phenylethyl)tosylhydrazine, 60565-67-5; quinoline, 91-22-5; isoquinoline, 119-65-3; 2-(carboethoxy)indole, 3770-50-1; methyl phenylacetate, 101-41-7; *p*-toluic acid, 99-94-5; phenylacetic acid, 103-82-2; 4-phenylbenzoyl chloride, 14002-51-8; *N*-benzylsuccinimide, 2142-06-5; styrene, 100-42-5; 1,1-diphenylethylene, 530-48-3; 1-decene, 872-05-9; phenylacetylene, 536-74-3; 1-heptyne, 628-71-7; phenyl sulfoxide, 945-51-7; benzyl sulfoxide, 621-08-9; phenyl disulfide, 882-33-7; *N*-(3-chloropropyl)piperidine, 1458-63-5; *N*-methylpyrrole, 96-54-8; benzofuran, 271-89-6.

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