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The Synthetic Versatility of Acyloxyborohydrides

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Abstract:

Acyloxyborohydrides are unsurpassed in their versatility as reagents in organic synthesis. In addition to their superior ability in effecting reductive amination of aldehydes and ketones, acyloxyborohydrides can reduce nitrogen heterocycles (indoles, quinolines, isoquinolines), imines, enamines, oximes, amides, nitriles, benzylic alcohols, aryl ketones, aldehydes (but not ketones), acetals, β-hydroxy ketones, and other substrates. The ability to control chemoselectivity, regioselectivity, and stereoselectivity by adjusting the carboxylic acid, borohydride reagent, stoichiometry, and temperature has no parallel in the repertoire of the organic chemist.

1. Introduction

From a quiet and inauspicious beginning 50 years ago, acyloxyborohydrides as reducing agents in synthesis have matured into a powerful and versatile set of organic reagents.[1] Following the preparation of an acyloxyborohydride (**1**) by Wartik and Pearson from the reaction of $NaBH_4$ and CO_2 (eq 1),[2] Brown and Rao postulated the existence of acyloxyborohydrides from $NaBH_4$ and carboxylic acids.[3] Independently, Reetz isolated and characterized $NaBH_3OCOCH_3$ as a water-sensitive, white solid (eq 2).[4]

$$NaBH_4 + 3CO_2 \xrightarrow[\text{sealed tube}]{Me_2O,\ 25\ ^\circ C} NaBH(OCH)_3 \qquad (1)$$

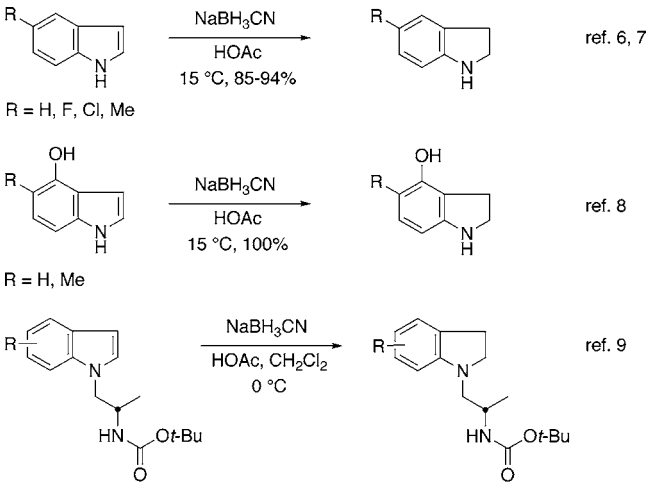
$$NaBH_4 + CH_3CO_2H \xrightarrow[-30\ ^\circ C \rightarrow 40\ ^\circ C]{THF} NaBH_3OCCH_3 \qquad (2)$$

Since the earlier reviews cover the chemistry of acyloxyborohydrides up until 1996,[1] the present article includes mainly work described over the past decade. The organization follows that utilized earlier.[1d]

2. Chemistry of Acyloxyborohydrides

2.1. Reduction of Indoles. Our discoveries some 30 years ago of the ability of $NaBH_4-RCO_2H$ to effect the reduction and *N*-alkylation of indoles to give *N*-alkylindolines[5] and of $NaBH_3CN-HOAc$ to reduce indoles to indolines,[6] sans alkylation, have been widely exploited and continue to be simple, efficient transformations (Scheme 1).

Scheme 1. **Reduction of simple indoles**



This mild indole reduction was used to prepare indolines **1**−**5**. Triethylsilane in trifluoroacetic acid, which is often comparable to $NaBH_3CN$ or $NaBH_4$ in RCO_2H, afforded **1** in lower yield (48%).[10] However, this is not always the case; for example, **4** is obtained in higher yield using Et_3SiH/CF_3CO_2H than using $NaBH_4/CF_3CO_2H$ (56%) or $NaBH_4$/HOAc (0%).[12]

2.2. Amine Alkylation (Reductive Amination of Aldehydes and Ketones). Our initial *N*-alkylation of amines with $NaBH_4/RCO_2H$ involved the generation of an aldehyde, RCHO (or an equivalent species), from the RCO_2H solvent as the source of the alkyl group.[5,14] Although this method continues to find some use for the introduction of simple

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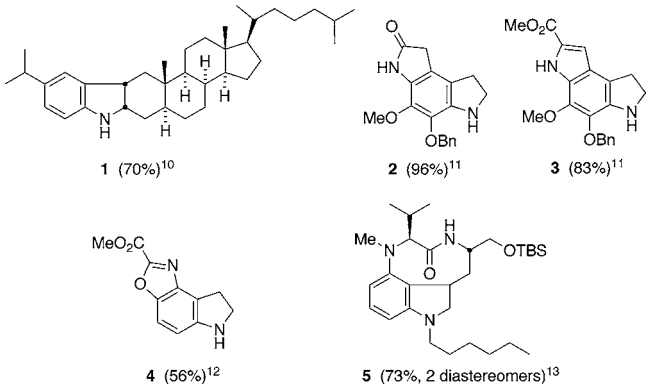


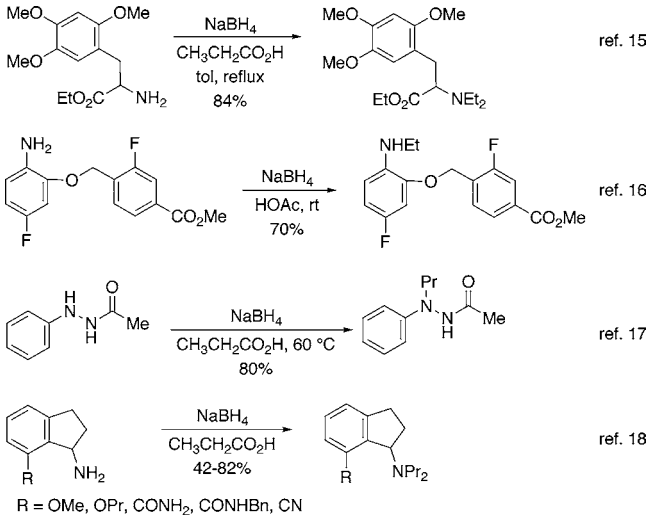
alkyl groups (Scheme 2),[15−18] a superior variation was developed later by Abdel-Magid (vide infra).

Abdel-Magid and co-workers made use of our previously isolated $NaBH(OAc)_3$[19] to effect reductive amination of aldehydes and ketones with amines,[20] thus avoiding the use of excess carboxylic acid as both the reaction solvent and the source of aldehyde. Moreover, ketones can be reductively aminated using this method. This variation has seen enormous utility in synthesis, and only a relatively few examples can be illustrated in this review. The commercial availability and its lack of toxicity compared with those of $NaBH_3CN$ make $NaBH(OAc)_3$ the reagent of choice for reductive amination of aldehydes and ketones. Alternatively, $NaBH(OAc)_3$ can be generated in situ from $NaBH_4$ and acetic acid.[19]

Sodium acetoxyborohydride efficiently unites primary and secondary amines with aldehydes, and myriad examples are known.[20] Some recent applications are shown in Scheme 3.

The $NaBH(OAc)_3$-promoted reductive amination of aldehydes with amines has been extended to the solid-phase,[25] is an undergraduate laboratory experiment,[26] has been used to introduce tritium into amines,[27] and can be applied to the industrial scale.[28] The method is an important step in syntheses of novel 1,3-diaminopropanes and 9-aminoacridines,[29] aminocyclodextrins,[30] azacrown ethers,[31] fulleropyrrolidines,[32] nicotine analogues (pyridotropanes),[33] and related diamino-7-azabicyclo[2.2.1]heptanes[34] and has played a role in the synthesis of the natural products buflavine,[35] (+)-papuamine,[36] motuporamines,[37] and madindoline A.[38] A

Scheme 2. **Amine alkylation using $NaBH_4/RCO_2H$**



selection of other amines synthesized via reductive amination of aldehydes is summarized in Scheme 4, in which the formed bond is indicated in bold. These examples illustrate the chemoselectivity of the method.

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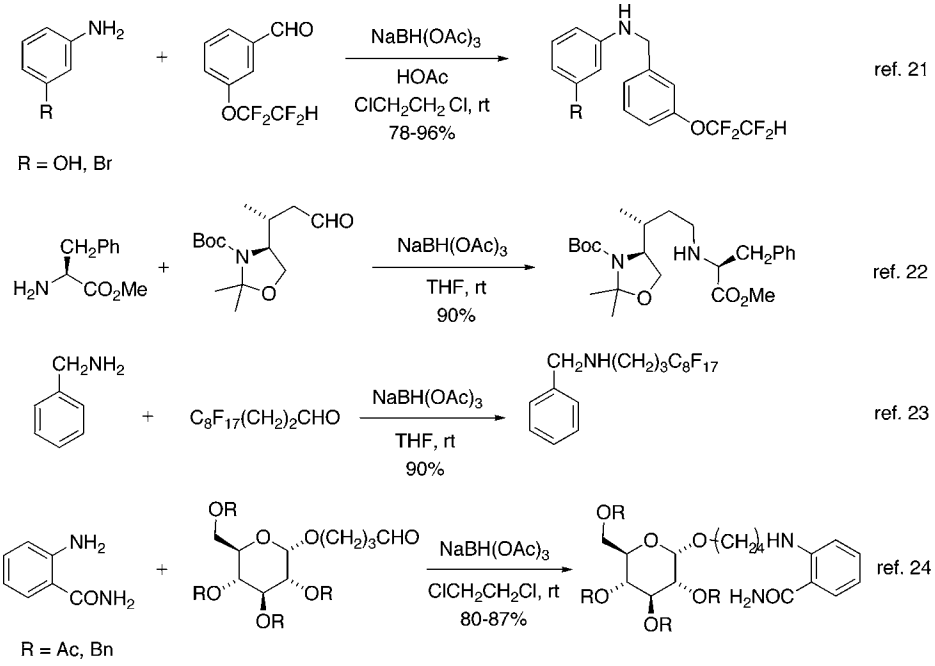
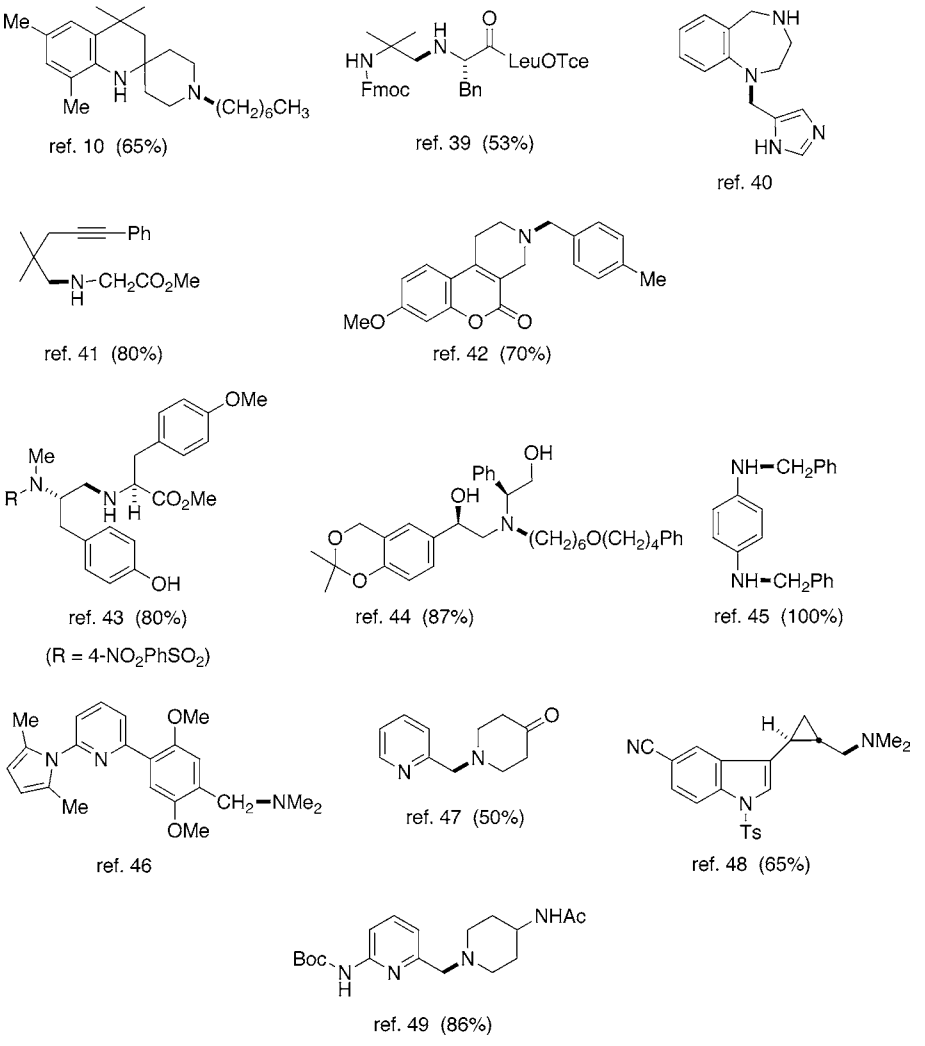
Scheme 3. **Reductive amination of aldehydes using $NaBH(OAc)_3$**

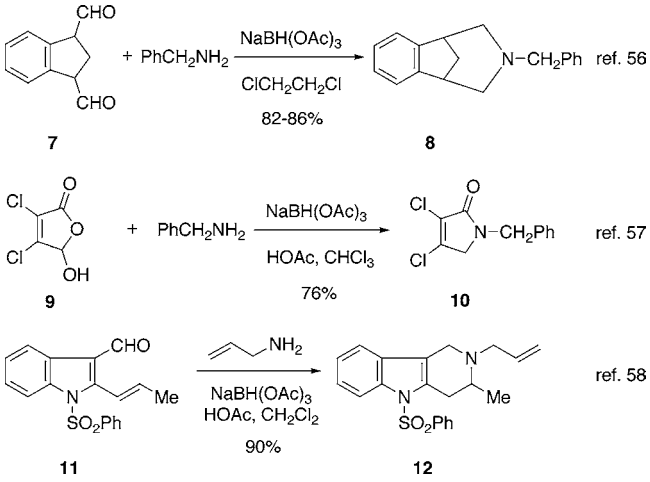


Scheme 4. **Products of reductive amination of aldehydes using $NaBH(OAc)_3$**



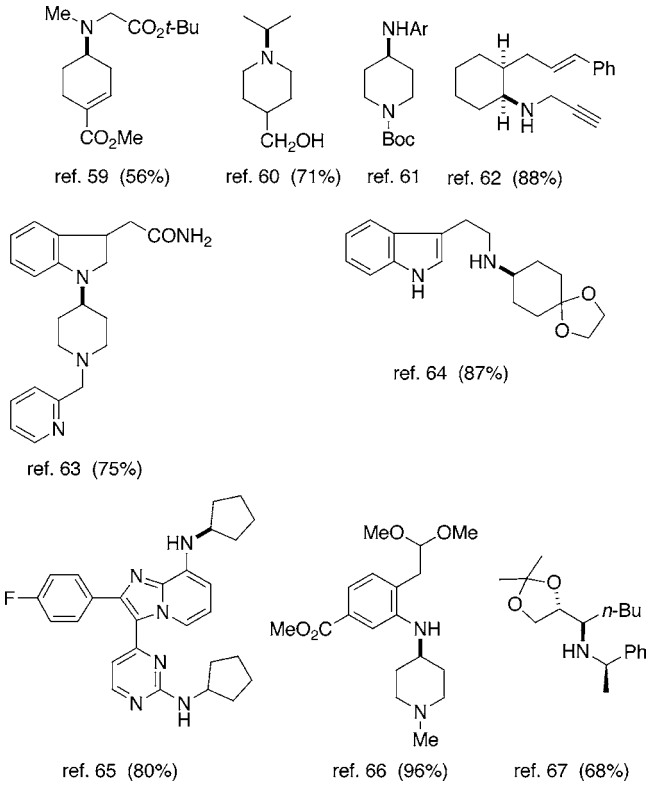
Two major applications of this aldehyde reductive amination methodology involve the modification of tryptamines, tryptophans, and related amino indoles,[50] and amino acid substrates.[51] Other notable examples of $NaBH(OAc)_3$ in

reductive amination reactions are the synthesis of aplysamine analogues,[52] novel alkylated piperazines[53] and piperidines,[54] and oxanorbornene-derived polyheterocycles.[55] Dialdehyde **7** is converted to amine **8** with $NaBH(OAc)_3$ and benzylamine,[56] and lactol **9** likewise affords lactam **10** under similar conditions.[57] Indole aldehyde **11** undergoes reductive amination with allylamine (and others) to give tetrahydro-γ-carboline **12**.[58]

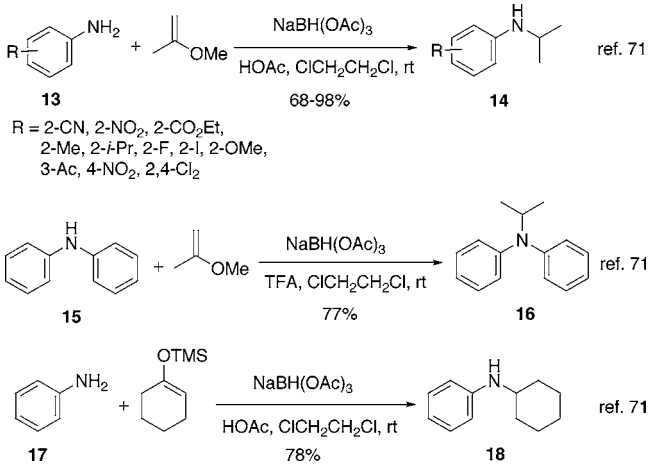


In contrast to aldehydes, the reductive amination of ketones with $NaBH(OAc)_3$ is rarer. Some of the known examples are summarized in Scheme 5 (reaction bond in bold). Ketone reductive amination was used to synthesize (−)-papuamine and (−)-haliclonadiamine,[68] squalamine-related 3-aminosteroids,[69] and C-glycosides of nojirimycin.[70]

Scheme 5. **Products of reductive amination of ketones using $NaBH(OAc)_3$**



Enol ethers can serve as ketone alternatives in the reductive alkylation of aromatic amines as shown for **13**−**16**.[71] Trimethylsilyl enol ethers also function in this reaction (**17** to **18**).[71]



2.3. Reduction of Other Heterocycles. Surprisingly, despite the early reported reductions of several other heterocyclic rings (quinolines, isoquinolines, acridines, some pyrroles, quinazolines, etc.),[1] recent years have seen very few reports of the use of $NaBH_4/RCO_2H$ to reduce heterocycles.

However, the combination of $NaBH_3CN$ in acetic acid does reduce 2-*n*-heptylquinoline (**19**) to the corresponding 1,2,3,4-tetrahydroquinoline **20**.[72] The same conditions reduce quinoline **21** to dihydroquinoline **22**, and isoquinoline **23** to 2-ethyl-1,2,3,4-tetrahydroisoquinoline **24**.[73]

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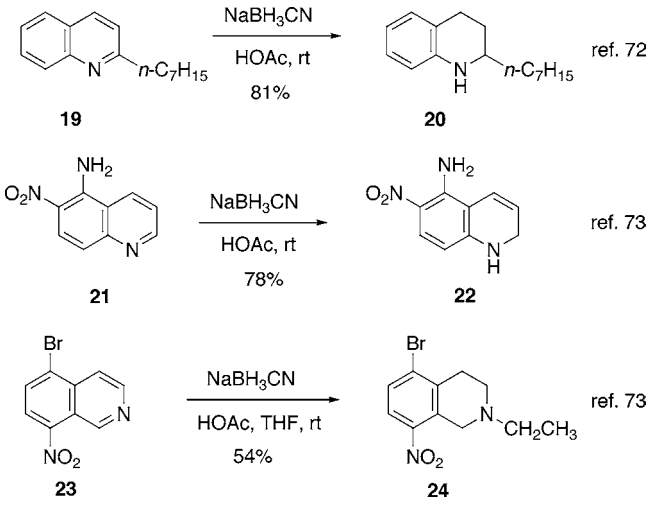
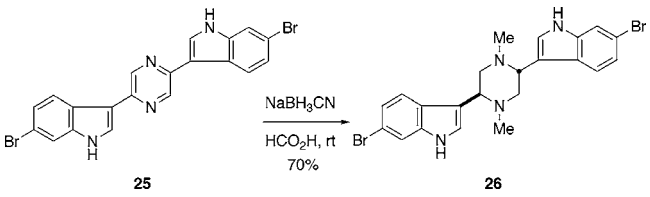


A synthesis of the marine alkaloid dragmacidin B (**26**) features the selective reductive methylation of the pyrazine ring in **25** using $NaBH_3CN/HCO_2H$.[74] With $NaBH_3CN$/HOAc only reduction of the pyrazine ring is observed.

2.4. Reduction of Imines, Enamines, and Related Compounds. The initial applications of $NaBH_4$ in carboxylic acid media in synthesis were described by Marshall and Johnson and involved the reduction of steroidal dienamines to unsaturated amines and the hydroboration of olefins.[75] The latter reaction was quickly adopted by others,[76] and Djerassi described the reduction of the vinylogous urethan double bond in the indole alkaloid vallesiachotamine.[77] The intervening 40 years have seen the extensive utility of $NaBH_4$-($NaBH_3CN$)/RCO_2H for the selective reduction of imines, enamines, vinylogous amines and carbamates, and related compounds, in each case involving acid-promoted formation of an iminium or immonium ion followed by borohydride reduction.[1]



Some recent examples of the reduction of vinylogous amides and carbamates are illustrated in Scheme 6. As can be seen, this reaction provides a simple route to β-amino acids. Palmieri has exploited this approach extensively, including the reduction of homochiral β-enamino esters with good diastereoselectivity and enantioselectivity.[78] The combination of $NaBH_3CN/CF_3CO_2H$ also accomplishes this reduction,[79] and *C*-glycosyl enamino esters are reduced with $NaBH(OAc)_3$.[80]

The method has been applied to the reduction of other vinylogous carbamates,[81] including the industrial scale,[28a] vinylogous ureas[82] (e.g., **27** to **28**),[82b] and indole alkaloids that possess this linkage.[83] The combination $NaBH_3CN$/TFA reduces β-sulfonylenamines en route to indolizidine alka-

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(79) (a) Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T. *J. Org. Chem.* **1996**, *61*, 4882−4883. (b) Toyooka, N.; Yoshida, Y.; Yotsui, Y.; Momose, T. *J. Org. Chem.* **1999**, *64*, 4914−4919.

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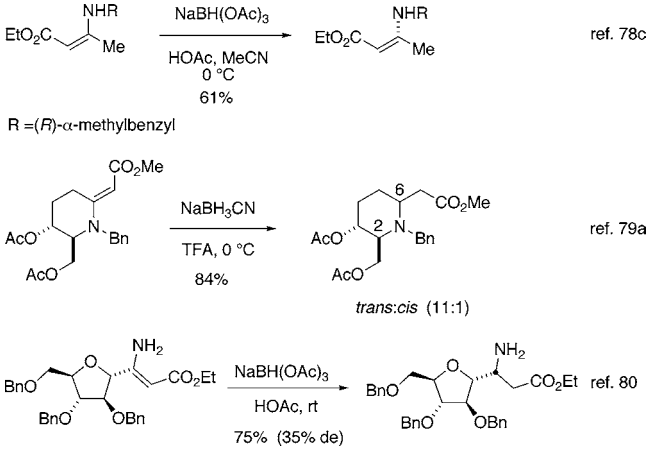
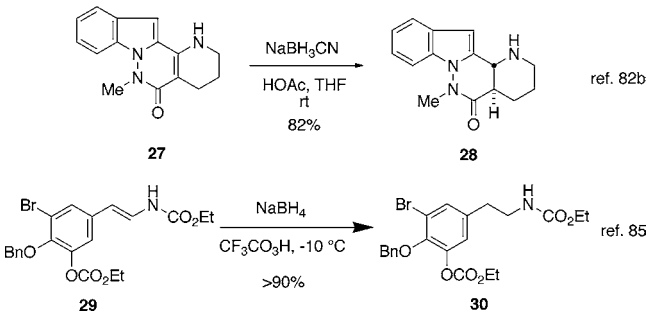
(83) (a) Kuehne, M. E.; Brook, C. S.; Frasier, D. A.; Xu, F. *J. Org. Chem.* **1994**, *59*, 5977−5982. (b) Putkonen, T.; Tolvanen, A.; Tokela, R. *Tetrahedron Lett.*, **2001**, *42*, 6593−6594.

Scheme 6. **Reduction of vinylogous carbamates using $NaBH(OAc)_3$ ($NaBH_3CN$/TFA)**



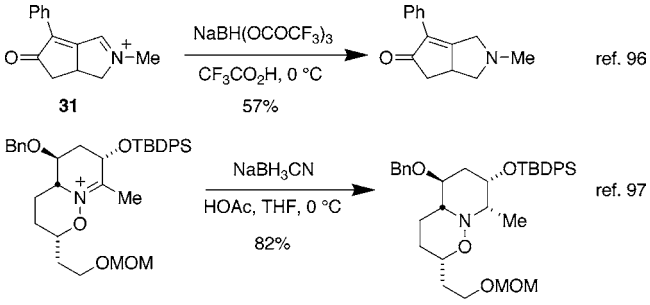
loids.[84] Likewise, enamides (*N*-vinyl carbamates) are smoothly reduced, **29** to **30**,[85] as are dienamides in a formal synthesis of strychnine.[86]



It is not surprising that imines are easily reduced with acyloxyborohydrides under the acidic conditions of this reaction, and many examples are known.[1] Some recent examples are depicted in Scheme 7.

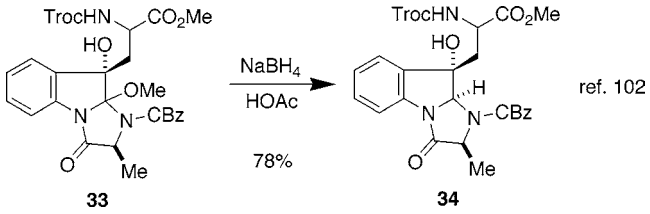
The reduction of imines with $NaBH(OAc)_3$ (or $NaBH_3CN$) in acetic acid was used in syntheses of 1,4-dibenzodiazepines,[90] tetrahydroisoquinolines,[91] octahydroindole alkaloids,[92] vinblastine derivatives,[93] and swainsonine synthetic approaches.[94] Several hydroxyl-directed reductions of imines and derived iminium ions with $NaBH_4$ have also-been reported.[95] This tactic is discussed further in section 2.13.

Preformed iminium and immonium ions undergo facile reduction with $NaBH(OAc)_3$ and $NaBH_3CN$ in HOAc to afford amines. These methods are illustrated by the two examples shown below,[96,97] which again reveal the remarkable chemoselectivity of acyloxyborohydride reductions. Immonium ion **31** is generated by the trifluoroacetic acid decomposition of a Fischer chromium carbonyl carbene complex.[96]



Likewise, aminocarbinols and similar compounds that form iminium/immonium ions under acidic conditions are readily reduced to amines with acyloxyborohydrides or cyanoborohydride (Scheme 8). Amine **32** is an example of reductive amination using $TiCl(O\textit{i}\text{-}Pr)_3$ to form the iminium ion.[99] Again, with the last example we see that $NaBH_3CN$, or an acyloxy derivative thereof, serves a similar role as $NaBH_4$ in carboxylic acid media.

This reduction method was employed in syntheses of fumiquinazoline fungal metabolites (e.g., **33** to **34**)[102] and vinblastine analogues,[103] and in the total synthesis of ecteinascidin743.[104]



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(95) (a) Palmieri, G. *Eur. J. Org. Chem.* **1999**, *805*, 5−811. (b) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4336−4338. (c) Sugiyama, S.; Arai, S.; Ishii, K. *Heterocycles* **2005**, *65*, 149−159.
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(98) (a) Xu, Y.-M.; Zhou, W.-S. *Tetrahedron Lett.* **1996**, *37*, 1461−1462. (b) Zhang, H.-X.; Xia, P.; Zhou, W.-S. *Tetrahedron* **2003**, *59*, 2015−2020.
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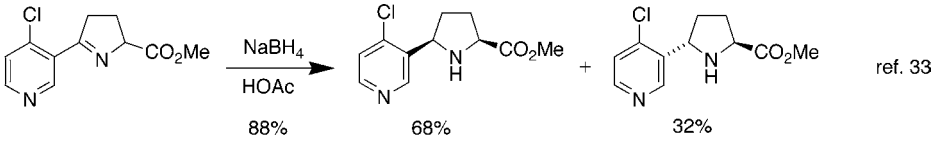
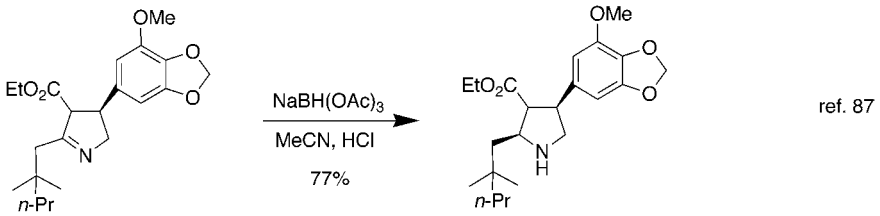
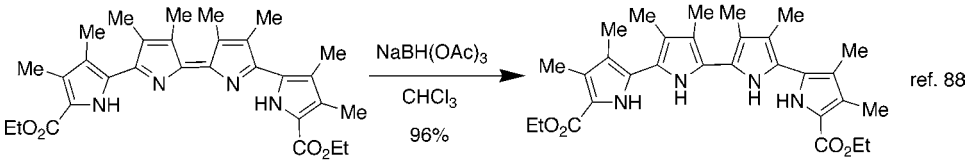
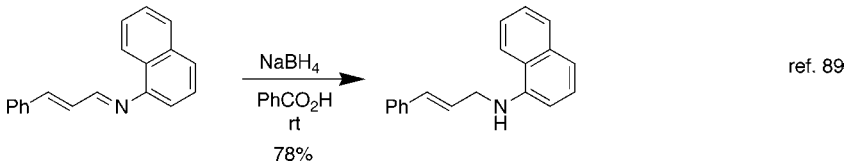
(103) Kuehne, M. E.; Qin, Y.; Huot, A. E.; Bane, S. L. *J. Org. Chem.* **2001**, *66*, 5317−5328.
(104) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552−6554.

Scheme 7. **Reduction of imines using $NaBH(OAc)_3$**

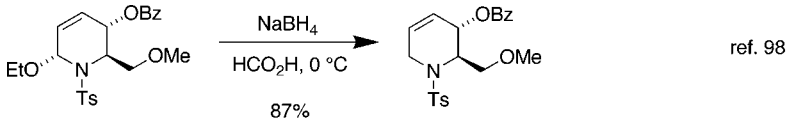


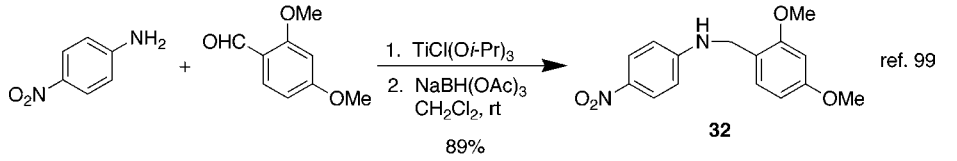


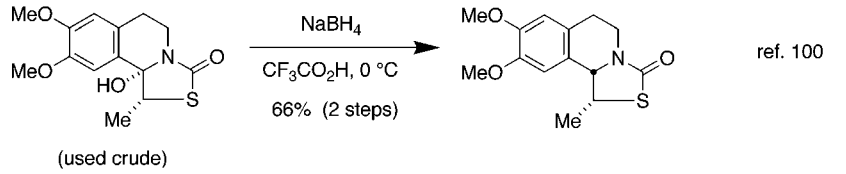


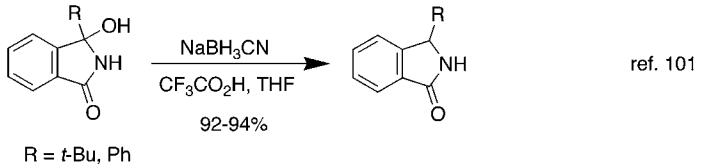


Scheme 8. **Reduction of aminocarbinols and related compounds using $NaBH(OAc)_3$**









Not surprisingly, enamines are smoothy reduced to amines with $NaBH_4$/HOAc as shown for **35**−**37**.[105−107] This method has been applied to dienamines.[108]

The reduction of imines using acyloxyborohydrides has been utilized in syntheses of macrocyclic spermine alkaloids[109] and (*S*)-coniine.[110]

2.5. Reduction of Oximes. Depending on the conditions, oximes are reduced to hydroxylamines or reductively alkylated to tertiary amines with $NaBH_3CN$/HOAc or $NaBH_4$/RCO_2H, respectively.[1,111] For example, oxime **38** is reduced

(105) Cossy, J.; Belotti, D.; Bellosta, V.; Boggio, C. *Tetrahedron Lett.* **1997**, *38*, 2677−2680.
(106) Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003**, *7*, 275−300.
(107) Willis, M. C.; Brace, G. N. *Tetrahedron Lett.* **2002**, *43*, 9085−9088.
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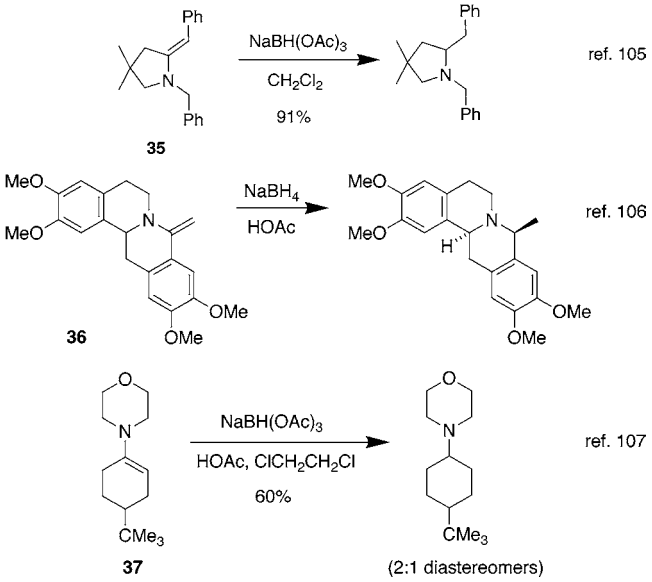
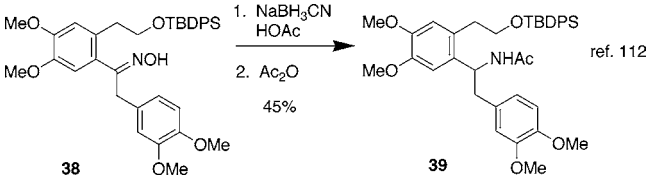
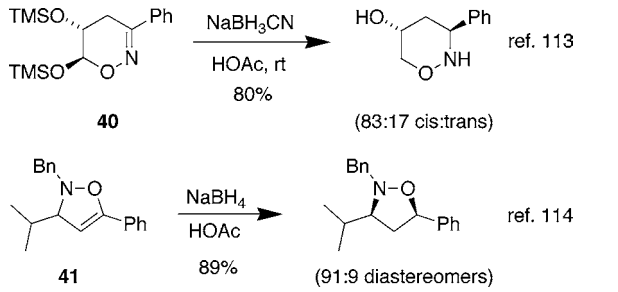
(110) Hayes, J. F.; Shipman, M.; Twin, H. *Chem. Commun.* **2001**, 1784−1785.
(111) Gribble, G. W.; Leiby, R. W.; Sheehan, M. N. *Synthesis* **1977**, 856−859.



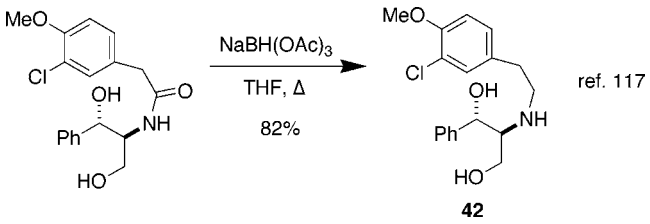
and acetylated to afford amide **39**.[112]



In addition, several examples of oxime ether reduction are known, as shown for **40** and **41**.[113,114]



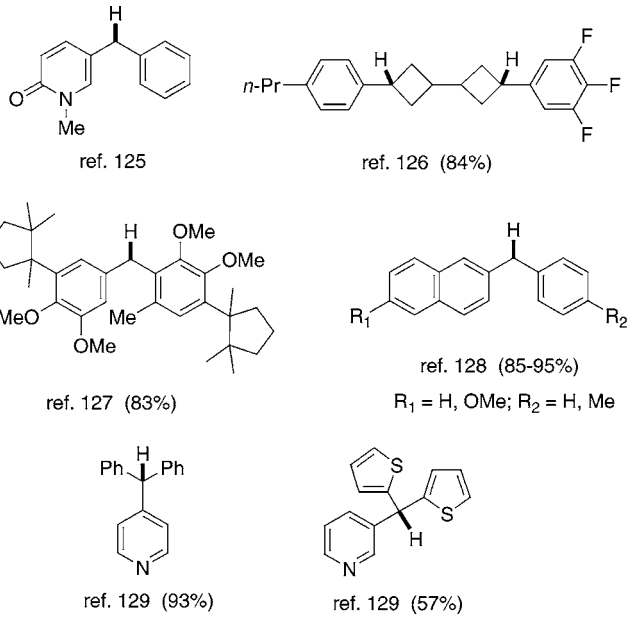
2.6. Reduction of Amides. Considering the narrow chemoselectivity presented in the previous sections, including many amide functionalities, it is surprising that amides can be reduced to amines with acyloxyborohydrides. In fact, this reduction, which requires the more reactive $NaBH_3OAc$, was announced by Umino et al. in 1976,[115] and many applications were subsequently described,[1] although this amide reduction does not always succeed.[116] However, it has been employed in the industrial scale synthesis of **42**, an intermediate in the synthesis of a D1 antagonist.[117]



2.7. Reduction of Nitriles. Umino also discovered that the more reactive $NaBH_3OCOR$ reagents can reduce nitriles to amines,[118] and this variation has found synthetic utility.[1] Although no recent examples are available, an attempt to reduce the cyano group in 4-cyano-2-iodofluorobenzene resulted in deiodination.[119]

2.8. Reduction of Alcohols to Hydrocarbons. One of the early discoveries of the synthetic power of $NaBH_4/CF_3CO_2H$ was the reduction of benzylic alcohols to hydrocarbons via the initial formation of relatively stable carbocations.[1,120] Given its inherent limitations, this particular reaction has proven to be very useful in synthesis (Scheme 9).

Some additional diarylmethane products that are obtained from the corresponding alcohols are shown below (site of reduction in bold).

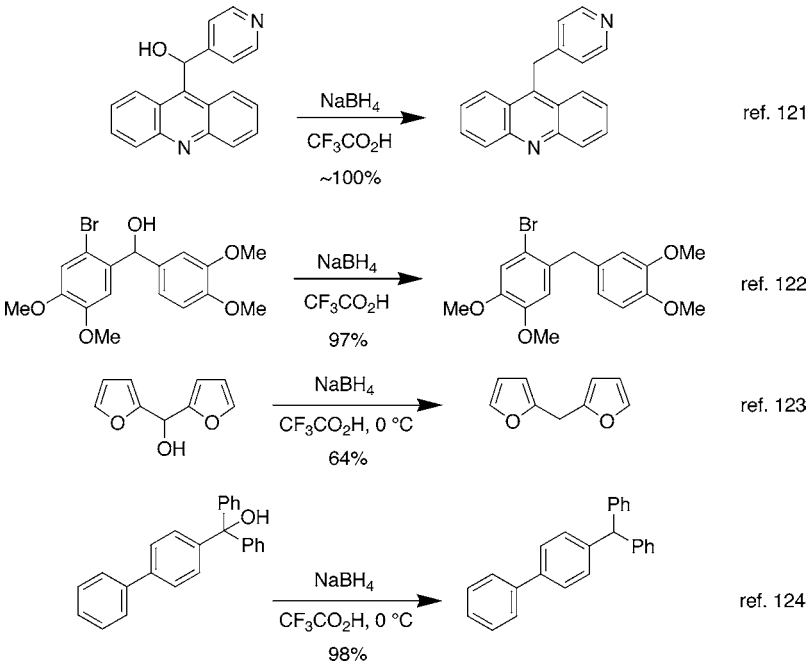


This reduction method succeeds with other doubly benzylic alcohols, such as calix[4]arenes in which four diphenylmethanol units are reduced to the corresponding diphenylmethanes,[130] and glycosylated diarylmethanols.[131]

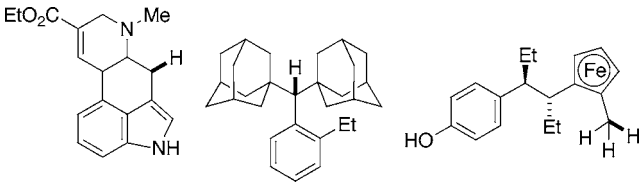
Although we found early on that benzyl alcohol itself is not reduced to toluene with $NaBH_4/CF_3CO_2H$, some "active"

(112) Sotomayor, N.; Domínguez, E.; Lete, E. *J. Org. Chem.* **1996**, *61*, 4062−4072.
(113) Zimmer, R.; Arnold, T.; Homann, K.; Reissig, H.-U. *Synthesis* **1994**, 1050−1056.
(114) Aschwanden, P.; Kvaerno, L.; Geisser, R. W.; Kleinbeck, F.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 5741−5742.
(115) Umino, N.; Iwakuma, T.; Itoh, M. *Tetrahedron Lett.* **1976**, *17*, 763−766.
(116) (a) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594−5598. (b) Dorn, I. T.; Neumaier, K. R.; Tampé, R. *J. Am. Chem. Soc.* **1998**, *120*, 2753−2763.
(117) Wu, G.; Wong, Y.; Steinman, M.; Tormos, W.; Schumacher, D. P.; Love, G. M.; Shutts, B. *Org. Process Res. Dev.* **1997**, *1*, 359−364.
(118) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, *17*, 2875−2876.
(119) Vaidyanathan, G.; Affleck, D. J.; Zalutsky, M. R. *J. Med. Chem.* **1994**, *37*, 3655−3662.
(120) Gribble, G. W.; Leese, R. M.; Evans, B. E. *Synthesis* **1977**, 172−176.
(121) MacQueen, D. B.; Eyler, J. R.; Schanze, K. S. *J. Am. Chem. Soc.* **1992**, *114*, 1897−1898.
(122) Maddaford, S. P.; Charlton, J. L. *J. Org. Chem.* **1993**, *58*, 4132−4138.
(123) Musau, R. M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2881−2888.
(124) Saito, S.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1996**, *61*, 8089−8093.
(125) Hartmann, R. W.; Reichert, M. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 145−153.

Scheme 9. **Reduction of benzylic alcohols using $NaBH_4/CF_3CO_2H$**

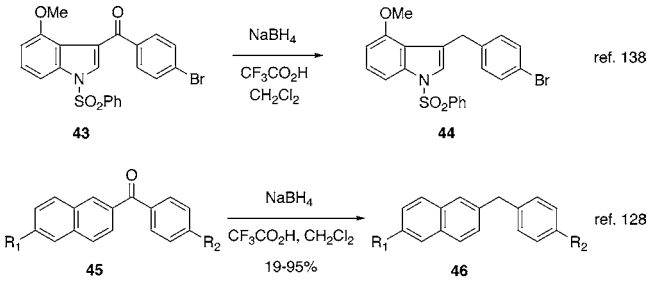


monobenzylic alcohols can be hydrogenated under these conditions to the corresponding hydrocarbons, as illustrated here.



Two other examples of the reduction of monobenzylic alcohols are seen in syntheses of bacteriopetroporphyrins[135] and vindoline derivatives.[136]

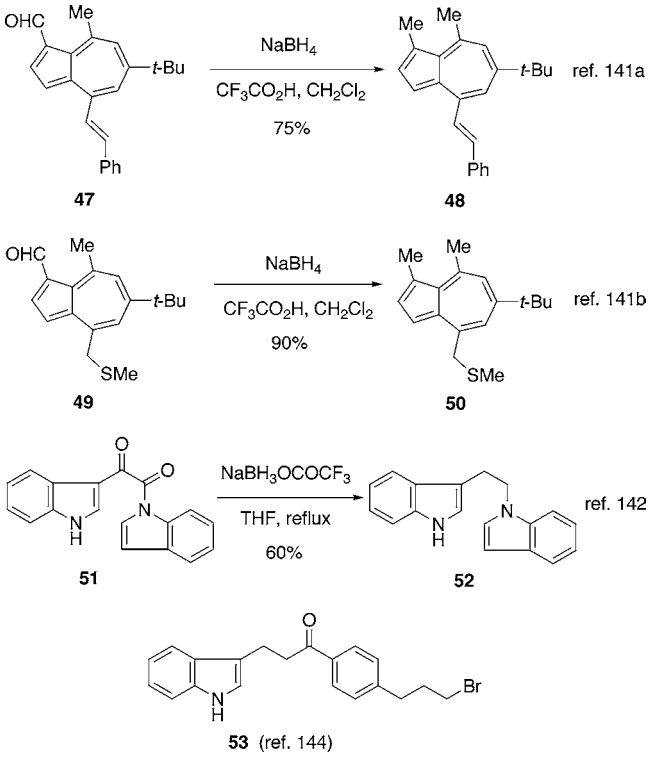
2.9. Reduction of Ketones. Given the facile reduction of diarylmethanols to diarylmethanes (vide supra), it is not surprising that diaryl ketones (benzophenones) are similarly converted to diarylmethanes with $NaBH_4/CF_3CO_2H$.[1] Thus, benzophenone is converted to diphenylmethane in 92% purified yield under these conditions.[137] A recent example of a diaryl ketone reduction to a diarylmethane is **43** to **44**.[138] Other examples involve glycosylated analogues of benzophenones[131] and a series of naphthyl phenyl ketones (**45** to **46**).[128] Occasionally the method fails due to product instability in trifluoroacetic acid and the formation of byproducts.[139] Thus, reduction of 2-(4′-bromobenzoyl)-1,4-dimethoxybenzene gives the expected diarylmethanes in only modest yields (31−63%), accompanied by dimeric byproducts.[139] However, this is the rare exception. For example, the combination of $NaBH_4/CF_3CO_2H$ reduces the three carbonyl groups to methylene groups in a tricalix[5]arene in 95% yield.[140] This level of efficiency is generally the rule.



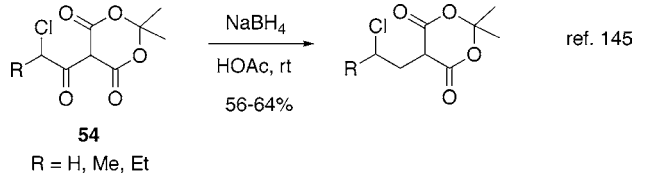
Aryl ketones that can form relatively stable carbocations—like their monobenzylic alcohol counterparts (vide supra)—can be reduced to the corresponding methylene compounds. For example, azulene aldehydes (**47** and **49**) are converted to **48** and **50**, respectively.[141] Both carbonyl groups in **51**

(126) (a) Dehmlow, E. V.; Kinnius, J.; Buchholz, M.; Hannemann, D. *J. Prakt. Chem.* **2000**, *342*, 409−413. (b) Kinnius, J.; Dehmlow, E. V. *J. Prakt. Chem.* **2000**, *342*, 421−423.
(127) Bringmann, G.; Pabst, T.; Henschel, P.; Michel, M. *Tetrahedron* **2001**, *57*, 1269−1275.
(128) Utley, J. H. P.; Rozenberg, G. G. *Tetrahedron* **2002**, *58*, 5251−5265.
(129) Nutaitis, C. F.; Greshock, T. J.; Houghton, S. R.; Moran, L. N.; Walter, M. A. *Org. Prep. Proc. Int.* **2002**, *34*, 332−335.
(130) Arduini, A.; Giorgi, G.; Pochini, A.; Secchi, A.; Ugozzoli, F. *J. Org. Chem.* **2001**, *66*, 8302−8308.
(131) Bellamy, F.; Horton, D.; Millet, J.; Picart, F.; Samreth, S.; Chazan, J. B. *J. Med. Chem.* **1993**, *36*, 898−903.
(132) Hendrickson, J. B.; Wang, J. *Org. Lett.* **2004**, *6*, 3−5.
(133) Lomas, J. S.; Vaissermann, J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2589−2595.
(134) Gruselle, M.; Malezieux, B.; Sokolov, V. I.; Troitskaya, L. L. *Inorg. Chem. Acta* **1994**, *222*, 51−61.
(135) Smith, N. W.; Smith, K. M. *Energy Fuels* **1990**, *4*, 675−688.
(136) Fahy, J.; duBoullay, V. T.; Bigg, D. C. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 505−507.
(137) Gribble, G. W.; Kelly, W. J.; Emery, S. E. *Synthesis* **1978**, 763−765.
(138) Zhang, X.; Urbanski, M.; Patel, M.; Cox, G. G.; Zeck, R. E.; Bian, H.; Conway, B. R.; Beavers, M. P.; Rybczynski, P. J.; Demarest, K. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1696−1701.
(139) Waterlot, C.; Hasiak, B.; Couturier, D.; Rigo, B. *Tetrahedron* **2001**, *57*, 4889−4901.
(140) Wang, J.; Gutsche, C. D. *J. Org. Chem.* **2002**, *67*, 4423−4429.
(141) (a) Song, J.; Hansen, H.-J. *Helv. Chim. Acta* **1999**, *82*, 309−314. (b) Song, J.; Hansen, H.-J. *Helv. Chim. Acta* **1999**, *82*, 1690−1706. (c) Singh, G.; Linden, A.; Abou-Hadeed, K.; Hansen, H.-J. *Helv. Chim. Acta* **2002**, *85*, 27−59.

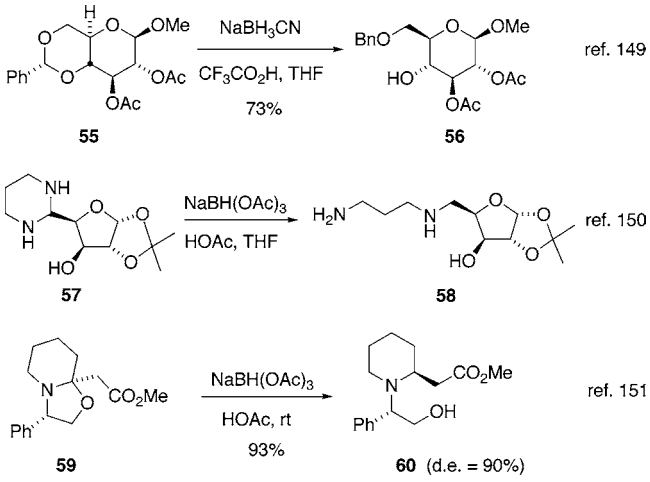
are reduced to biindole **52**,[142] and the monoactivated ketone in methyl pyropheophorbide-a is reduced to methylene in 75% yield.[143] As expected, unactivated acetophenones such as **53** fail to give the methylene product (reaction details not provided).[144]



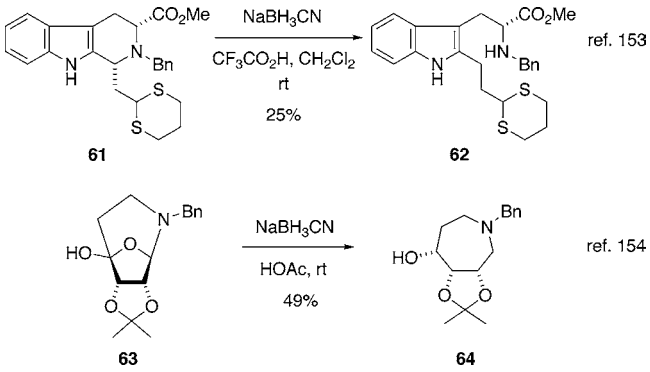
A different kind of carbonyl to methylene transformation is seen in the reduction of 5-haloacyl Meldrum's acids (**54**),[145] which was initially accomplished with $NaBH_3CN$/HOAc.[146] A related application of Meldrum's acids leads to an excellent synthesis of α-substituted acrylate esters.[145b]



2.10. Reductive Cleavage of Acetals, Ketals, Ethers, and Related Compounds. The strong trifluoroacetic acid in the presence of $NaBH_4$ can reductively cleave several susceptible functional groups, presumably via oxonium ion species, and several examples have been known for sometime.[1] The early discovery that $NaBH_3CN/CF_3CO_2H$ reductively cleaves acetals[147] has been employed in the synthesis of disaccharides[148,149] (**55** → **56**).[149] Interestingly, aminal **57** is cleaved to **58**, maintaining the acetal unit,[150] but in the azulene work cited earlier[141] some of the dimethylthioacetal azulene is reduced with $NaBH_4/CF_3CO_2H$.[141b] Oxazolidines are easily cleaved (**59** → **60**),[151] and this tactic was featured in the first enantiospecific synthesis of salinosporamide A.[152] The synthesis of swainosonine alkaloids features a similar reductive cleavage of tetrahydro-1,3-oxazines.[94]



The benzylic amine moiety in *cis*-tetrahydro-β-carboline **61** is cleaved to **62** with $NaBH_4/CF_3CO_2H$, but the reaction fails with the trans isomer.[153] Lactol **63**, which is presumably in equilibrium with the keto carbinol amine, undergoes ketone and immonium ion reduction to give **64**.[154] The acetal functionality remains unaffected, and only acetic acid is required.



2.11. Hydroxy-Directed Reduction of Ketones. Along with reductive amination, the acyloxyborohydride reduction of β-hydroxy ketones has proven extraordinarily useful in

(142) Gribble, G. W.; Pelcman, B. *J. Org. Chem.* **1992**, *57*, 3636−3642.
(143) Mettath, S.; Shibata, M.; Alderfer, J. L.; Senge, M. O.; Smith, K. M.; Rein, R.; Dougherty, T. J.; Pandey, R. K. *J. Org. Chem.* **1998**, *63*, 1646−1656.
(144) Bodwell, G. J.; Li, J.; Miller, D. O. *Tetrahedron* **1999**, *55*, 12939−12956.
(145) (a) Tóth, G.; Tamás, T.; Borbély, I. *Synth. Commun.* **2002**, *32*, 3659−3665. (b) See also: Hin, B.; Majer, P.; Tsukamoto, T. *J. Org. Chem.* **2002**, *67*, 7365−7368.
(146) Nutaitis, C. F.; Schultz, R. A.; Obaza, J.; Smith, F.-X. *J. Org. Chem.* **1980**, *45*, 4606−4608.
(147) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371−2374.
(148) Wang, Y.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468−481.
(149) Roën, A. Padrón, J. I.; Vázquez, J. T. *J. Org. Chem.* **2003**, *68*, 4615−4630.
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(151) Calvet, S.; David, O.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C. *Tetrahedron* **2003**, *59*, 6333−6339.
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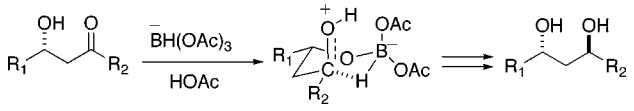
(153) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1997**, *62*, 44−61.
(154) Gallos, J. K.; Demeroudi, S. C.; Stathopoulou, C. C.; Dellios, C. C. *Tetrahedron Lett.* **2001**, *42*, 7497−7499.

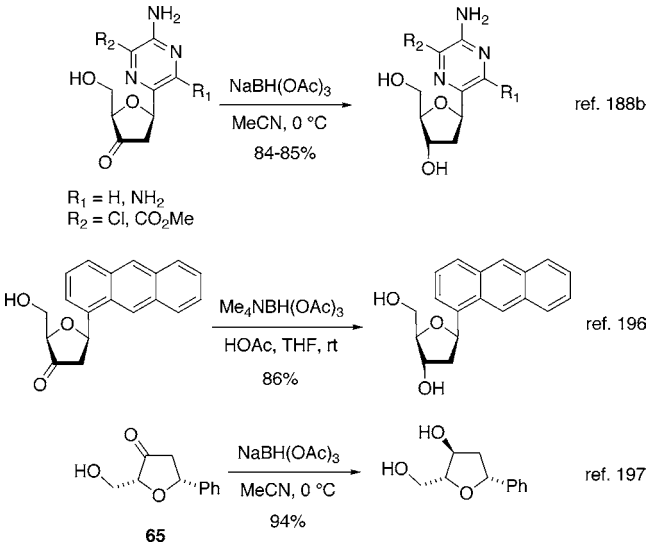
***Scheme 10.* β-Hydroxy directed ketone reduction using $BH(OAc)_3$**



organic synthesis.[1] Although discovered independently by us[155] and Saksena,[156] Evans parlayed this method into a powerful weapon, "anti-aldol reduction", in stereoselective synthesis (Scheme 10).[157]

Examples of this reduction far too numerous to show have been described in the past 10 years; therefore, our coverage is mostly limited to the past few years. The enormous power of the method is revealed in the list of natural product syntheses (or approaches thereto) that have employed β-hydroxy-directed reduction of ketones using $NaBH(OAc)_3$ (or $Me_4NBH(OAc)_3$ (in no special order): cyclophellitol,[158] sanglifehrin A,[159] aurisides A and B aglycon,[160] calyculin A,[161] nodulisporic acid A,[162] milbemycin,[163] rutamycin B,[164] parasitic wasp lactones,[165] rhizoxins,[166] omuralide and lactacystin,[167] pyripyropene A,[168] thiazinotrienomycin E,[169] scytophycin C,[170] hemibrevetoxin B,[171] FR-900482 analogues,[172] phorboxazole A,[173] bryostatins,[174] phorbol,[175] polycavernoside A,[176] serofendic acids,[177] spongistatin 1,[178] oleandolide,[179] callipeltoside A,[180] rottnestol and raspailols A and B,[181] mycosamine,[182] macrolactins and macrolactinic acid,[183] kendomycin,[184] spirastrellolide A,[185] dolabelide D,[186] and pericosine A[187]—in what certainly is an incomplete list. Selected examples are shown in Scheme 11.

Several groups have reported the β-hydroxyl-directed reduction of various ketonucleosides.[188−196] Simple systems also undergo this stereoselective reduction (e.g., **65**),[197] and the method has been applied to the synthesis of polypropionates.[198]



Although a chairlike transition state (Scheme 10) does not operate in the acylborohydride reduction of α-hydroxy ketones, these substrates nevertheless can be reduced via intramolecular hydride delivery leading to syntheses of allopumiliotoxin A,[199] the bruceantin quassinoids,[200] and the rocaglamides[201] (Scheme 12).

(155) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287−4290.
(156) Saksena, A.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273−276.
(157) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.
(158) McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 3250−3252.
(159) Duan, M.; Paquette, L. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3632−3636.
(160) Sone, H.; Suenaga, K.; Bessho, Y.; Kondo, T.; Kigoshi, H.; Yamada, K. *Chem. Lett.* **1998**, 85−86.
(161) Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958−1961.
(162) Smith, A. B., III; Cho, Y. S.; Ishiyama, H. *Org. Lett.* **2001**, *3*, 3971−3974.
(163) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449−5452.
(164) White, J. D.; Hanselmann, R.; Jackson, R. W.; Porter, W. J.; Ohba, Y.; Tiller, T.; Wang, S. *J. Org. Chem.* **2001**, *66*, 5217−5231.
(165) Paddon-Jones, G. C.; McErlean, C. S. P.; Hayes, P.; Moore, C. J.; Konig, W. A.; Kitching, W. *J. Org.* Chem. **2001**, *66*, 7487−7495.
(166) (a) Nakada, M.; Kobayashi, S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1035−1038. (b) White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Kolz, C. S. N.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750−7760.
(167) Corey, E. J.; Li, W.-D. Z. *Chem. Pharm. Bull.* **1999**, *47*, 1−10.
(168) Nagamitsu, T.; Sunazuka, T.; Obata, R.; Tomoda, H.; Tanaka, H.; Harigaya, Y.; Omura, S.; Smith, A. B., III. *J. Org. Chem.* **1995**, *60*, 8126−8127.
(169) Smith, A. B., III; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738−3753.
(170) Patterson, I.; Yeung, K.-S. *Tetrahedron Lett.* **1993**, *34*, 5347−5350.
(171) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200−6209.
(172) Kambe, M.; Arai, E.; Suzuki, M.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2001**, *3*, 2575−2578.
(173) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem. Int. Ed.* **2003**, *42*, 1258−1262.
(174) O'Brien, M.; Taylor, N. H.; Thomas, E. J. *Tetrahedron Lett.* **2002**, *43*, 5491−5494.
(175) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897−7898.
(176) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593−8595.
(177) Terauchi, T.; Asai, N.; Yonaga, M.; Kume, T.; Akaike, A.; Sugimoto, H. *Tetrahedron Lett.* **2002**, *43*, 3625−3628.
(178) Holson, E. G.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3719−3722.
(179) Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 9229−9230.
(180) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169−171.
(181) Czuba, I. R.; Zammit, S.; Rizzacasa, M. A. *Org. Biomol. Chem.* **2003**, *1*, 2044−2056.
(182) Franck-Neumann, M.; Miesch-Gross, L.; Gateau, C. *Tetrahedron Lett.* **1999**, *40*, 2829−2832.
(183) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935−3948.
(184) Williams, D. R.; Shamim, K. *Org. Lett.* **2005**, *7*, 4161−4164.
(185) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4125−4128.
(186) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796−2797.
(187) Usami, Y.; Ueda, Y. *Chem. Lett.* **2005**, *34*, 1062−1063.
(188) (a) Chen, J. J.; Walker, J. A., II; Liu, W.; Wise, D. S.; Townsend, L. B. *Tetrahedron Lett.* **1995**, *36*, 8363−8366. (b) Walker, J. A., II; Chen, J. J.; Hinkley, J. M.; Wise, D. S.; Townsend, L. B. *Nucleosides Nucleotides* **1997**, *16*, 1999−2012.
(189) Robins, M. J.; Sarker, S.; Samano, V.; Wnuk, S. F. *Tetrahedron* **1997**, *53*, 447−456.
(190) Wang, Z.-X.; Wiebe, L. I.; Balzarini, J.; De Clercq, E.; Knaus, E. E. *J. Org. Chem.* **2000**, *65*, 9214−9219.
(191) Kodama, T.; Shuto, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2002**, *67*, 7706−7715.
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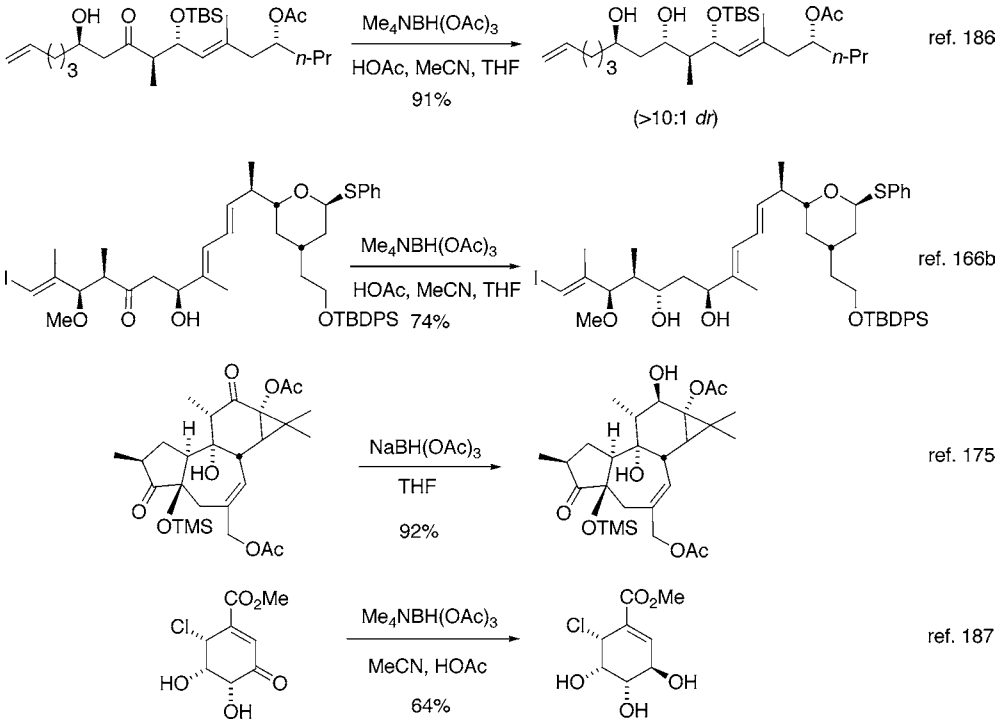
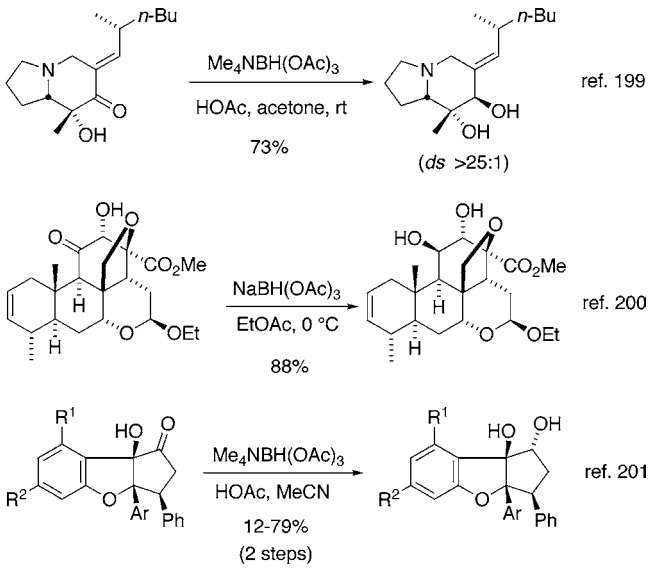
(193) Chirakul, P.; Sigurdsson, S. Th. *Org. Lett.* **2003**, *5*, 917−919.
(194) Nguyen-Trung, N. Q.; Botta, O.; Terenzi, S.; Strazewski, P. *J. Org. Chem.* **2003**, *68*, 2038−2041.
(195) Hutter, D.; Benner, S. A. *J. Org. Chem.* **2003**, *68*, 9839−9842.
(196) Coleman, R. S.; Mortensen, M. A. *Tetrahedron Lett.* **2003**, *44*, 1215−1219.
(197) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415−1419.
(198) (a) Marchionni, C.; Vogel, P. *Helv. Chim. Acta* **2001**, *84*, 431−472. (b) Schwenter, M.-E.; Vogel, P. *J. Org. Chem.* **2001**, *66*, 7869−7872.
(199) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179−1190.
(200) Chiu, C. K.-F.; Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 311−323.

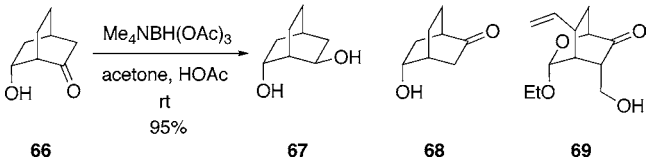
Scheme 11. **β-Hydroxy-directed reduction of ketones using $BH(OAc)_3$**



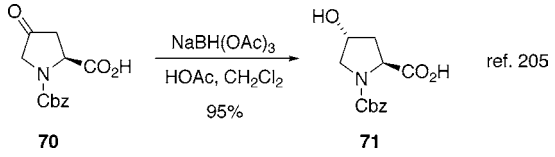
Scheme 12. **α-Hydroxy-directed ketone reduction**



Whereas bicyclic hydroxy ketone **66** is reduced smoothly to **67** via intramolecular hydride delivery, isomeric hydroxy ketone **68** fails to be reduced at all.[202] This lack of reactivity is ascribed to an overly long distance between the carbonyl group and the hydride to be transferred. Ketone **69** also undergoes β-hydroxy-directed ketone reduction with $NaBH(OAc)_3$ to afford the expected diol in 88% yield.[203] However, there are cases where the β-hydroxy-directed ketone reduction fails in seemingly plausible cases,[204] but these are rare!



Related to hydroxy-directed ketone reduction is an example of apparent carboxy-directed ketone reduction, **70** → **71**.[205] The methyl ester of **70** fails to react with $NaBH(OAc)_3$.



It has been reported that *o*-amino- and *o*-hydroxyacetophenones and the corresponding *o*-substituted benzophenones undergo intramolecular hydride reduction.[206] Thus, whereas *o*-hydroxyacetophenone is reduced completely to the corresponding alcohol by $NaBH_4$/HOAc within 10 min at room temperature, acetophenone itself is reduced only to the extent of 23% under the same conditions, and *p*-hydroxyacetophenone is reduced only to the extent of 12%. Similar results obtain for *o*-amino- and *o*-dimethylaminoac-

(201) Diedrichs, N.; Ragot, J. P.; Thede, K. *Eur. J. Org. Chem.* **2005**, 1731−1735.
(202) Almqvist, F.; Ekman, N.; Frejd, T. *J. Org. Chem.* **1996**, *61*, 3794−3798.
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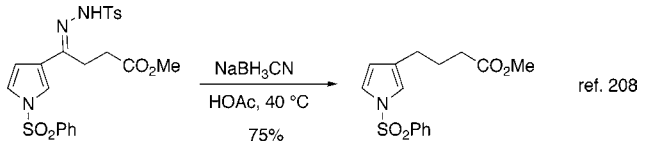
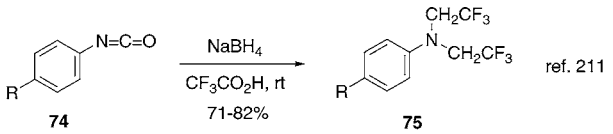
etophenone, but not for *o*-bromo- or *o*-methoxyacetophenones. Likewise, whereas benzophenone is completely reduced to diphenylmethanol in 60 h ($NaBH_4$/HOAc), *o*-hydroxybenzophenone is reduced completely to *o*-hydroxydiphenylmethanol in just 5 min.[206] Similarly, *o*-aminobenzophenone requires only 1 h for complete reduction to the corresponding alcohol, and *o*-methoxybenzophenone is fully reduced after 30 h. These studies involve the more reactive $NaBH_2(OAc)_2$, presumably formed from $NaBH_4$/HOAc (1:2).

2.12. Miscellaneous Applications of Acyloxyborohydrides. The Hutchins reductive cleavage of tosylhydrazones[207] has been used to prepare pyrrole **73**.[208] A Hutchins reduction of longer-chain ester derivatives of **72** leads to 11−21% of the corresponding 2,5-dihydropyrroles along with the expected pyrroles (68−73%).[209]



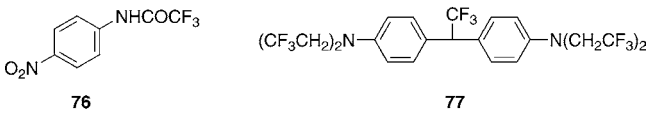
72 **73**

Turnbull, who described the reduction of aroyl azides with $NaBH_4/CF_3CO_2H$,[1,210] has discovered the related conversion of aryl isocyanates to the corresponding *N*,*N*-bis(2,2,2-trifluoroethyl)anilines, **74** → **75**.[211] Reduction of **74**, R = NO_2, leads to **76** (78%), and reduction of **74**, R = H, affords the "DDT-type" compound **77** (73%), both reaction types of which have precedents from our earlier work.[212]



74 **75**

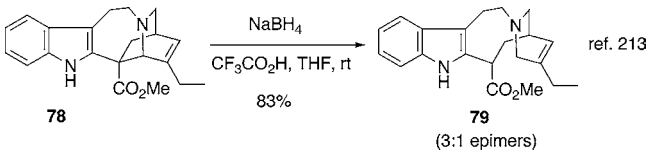
R = Cl, Br, Me, OMe



76 **77**

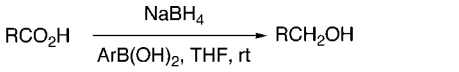
Although not a benzylic amine, catharanthine (**78**) behaves like tetrahydro-β-carboline **61** in undergoing facile cleavage with $NaBH_4/CF_3CO_2H$ to afford 18-carbomethoxycleavamine (**79**).[213]

The reduction of carboxylic acids to alcohols using $NaBH_4$ has never attracted much interest.[1] However, a recent method involving $NaBH_4$ with catalytic 3,4,5-trifluorophenylboronic acid ($ArB(OH)_2$) seems to be efficient and versatile as summarized here.[214]

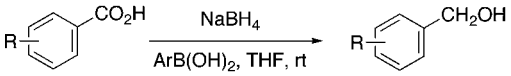


78 **79**

(3:1 epimers)

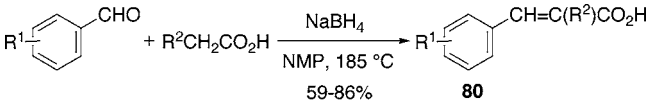


R = *n*-Octyl, $Br(CH_2)_3$, Bn, $N_3(CH_2)_4$



R = H, 4-Cl, 4-CN, 4-OH, 4-NO_2, 3,4,5-$(MeO)_3$, 2,4-$(MeO)_2$

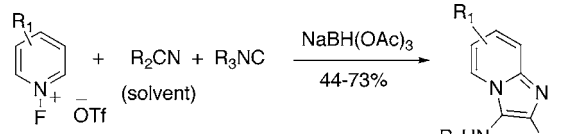
An interesting variation of the Perkin reaction features the union of aliphatic carboxylic acids (instead of carboxylic acid anhydrides), aromatic aldehydes, and $NaBH_4$ to afford cinnamic acids (**80**).[215]



80

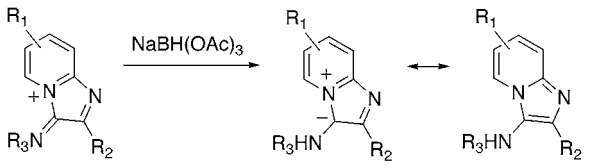
R^1 = H, 3-Cl, 4-Cl, 3-NO_2, 4-NO_2, 4-MeO
R^2 = H, Me

A fascinating transformation is the $NaBH(OAc)_3$-promoted conversion of *N*-fluoropyridinium triflates, isonitriles, and a nitrile solvent to imidazo[1,2-*a*]pyridines (**81**).[216] The $NaBH(OAc)_3$ is proposed both to act as a base to remove the acidic C-2 proton from the *N*-fluoropyridinium triflate, to initiate a three-component process, and ultimately to reduce putative intermediate **82** giving **81** directly. [Note: the paper incorrectly shows **81** as **not** being a resonance structure of the final product.]



81

R_1 = H, 2-Me, 4-Me, 4-*i*-Pr, 2-Ph, 3-Cl, 3-Me, 2-MeO
R_2 = Me, Et
R_3 = *i*-Pr, *t*-Bu, Ph, CH_2CO_2Et, Bn, cyclohexyl, Ar



82 **81**

3. New Acyloxyborohydrides

Two important advances in acyloxyborohydride reagents are the preparation, characterization, and reactions of tritiated

(207) Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299−2301.
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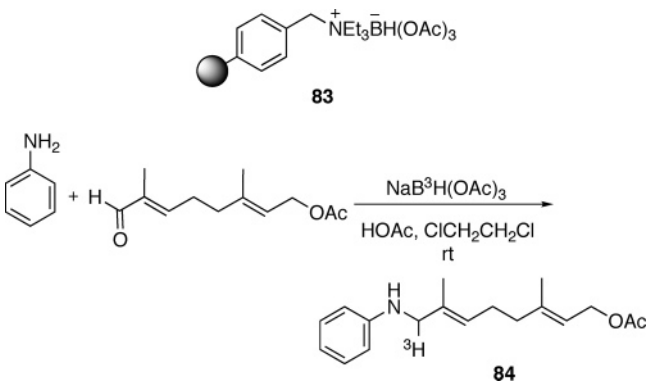
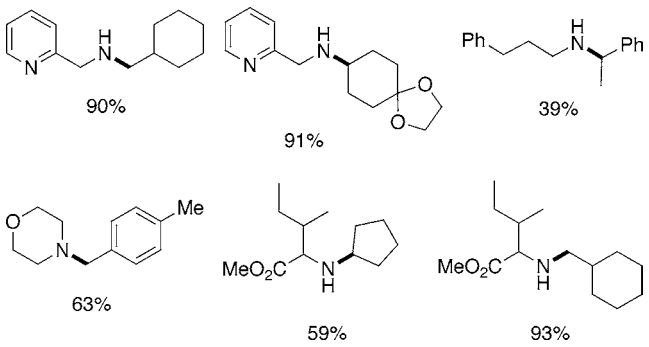
triacetoxyborohydride,[27] and the synthesis of a polymer-supported acetoxyborohydride **83**.[217] The former reagent allows for the introduction of tritium into compounds of interest to radiochemists. An example is the preparation of anilinogeranyl pyrophosphate (**84**).[27]



Reductive aminations of ketones and aldehydes using **83** proceed very well as summarized for the products shown here.[217]

(217) Bhattacharyya, S.; Rana, S.; Gooding, O. W.; Labadie, J. *Tetrahedron Lett.* **2003**, *44*, 4957−4960.



4. Concluding Remarks

The commercial availability and remarkable stability of sodium and tetramethylammonium triacetoxyborohydrides, the ease of in situ generation of other acyloxyborohydrides, and the special reduction properties of sodium borohydride and sodium cyanoborohydride in trifluoroacetic acid combine to make these reagents extraordinarily useful and widely applicable in organic synthesis.

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