Sodium borohydride in carboxylic acid media: a phenomenal reduction system

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CHEMICAL SOCIETY REVIEWS

The union of sodium borohydride and carboxylic acids has yielded an amazingly versatile and efficient set of reducing reagents. These acyloxyborohydride species reduce and *N*-alkylate indoles, quinolines, isoquinolines, related heterocycles, imines, enamines, oximes, enamides, and similar functional groups. They reduce amides and nitriles, aryl alcohols and ketones, aldehydes in the presence of ketones, and β-hydroxyketones to 1,3-diols stereoselectively. This reagent is also extraordinarily useful for the *N*-alkylation of primary and secondary amines with aldehydes and ketones in a novel reductive amination process.

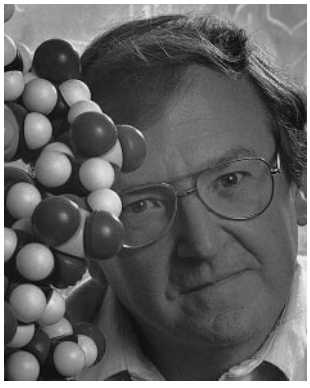
1 Introduction

Like an artist without paint, the synthetic chemist is impotent without the necessary chemical reagents to synthesize molecules of interest. As synthetic targets increase in complexity, so must the tools of the chemist increase in efficiency and selectivity. The present article summarizes the enormous range of chemical transformations available through the use of the relatively new reagent combination of sodium borohydride in carboxylic acids, leading to the generation of sodium acyloxyborohydrides [eqns. (1) and (2)]. The less reactive sodium triacyloxyborohydrides **1** form with 3 equivalents of a carboxylic acid (or excess), and the more reactive sodium acyloxyborohydrides **2** form with one equivalent of a carboxylic acid.[1,2]

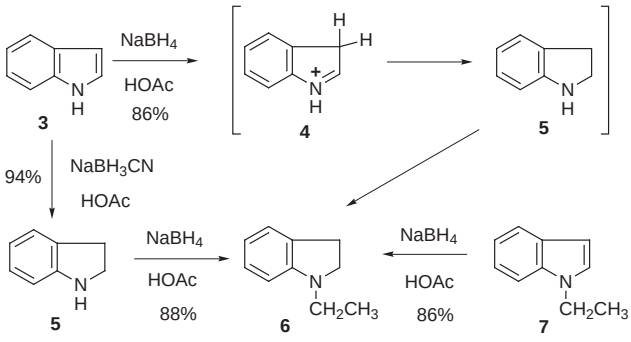
$$NaBH_4 + 3RCO_2H \longrightarrow NaBH(OCOR)_3 + 3H_2 \qquad (1)$$

$$NaBH_4 + RCO_2H \longrightarrow NaBH_3OCOR + H_2 \qquad (2)$$

Gordon W. Gribble was born in San Francisco, California, and received his undergraduate training at the University of California, Berkeley. He obtained his PhD at the University of Oregon with Lloyd J. Dolby in 1967, and did postdoctoral research at the University of California, Los Angeles, with Frank A. L. Anet. Professor Gribble has been at Dartmouth since 1968. In addition to his research program on heterocyclic chemistry and natural product synthesis, he has a fascination with naturally occurring organohalogen compounds, and he has published more than 160 papers in these areas. As an amateur winemaker, he also has a strong interest in the chemistry of wine and winemaking.



Following a report by Marshall and Johnson on the compatibility of $NaBH_4$ and acetic acid (HOAc) in the reduction of enamines,[3] we investigated this unlikely chemical combination as a possible new indole (**3**) reduction method. Surprisingly, not only is the indole double bond rapidly and efficiently reduced, presumably *via* indolenium ion **4**, but the nitrogen is alkylated by the acetic acid solvent to afford *N*-ethylindoline (**6**) (Scheme 1).[4] Further study of this novel transformation revealed that the *N*-alkylation can be circumvented using $NaBH_3CN$–HOAc to afford indoline (**5**) in essentially quantitative yield.[4,5]



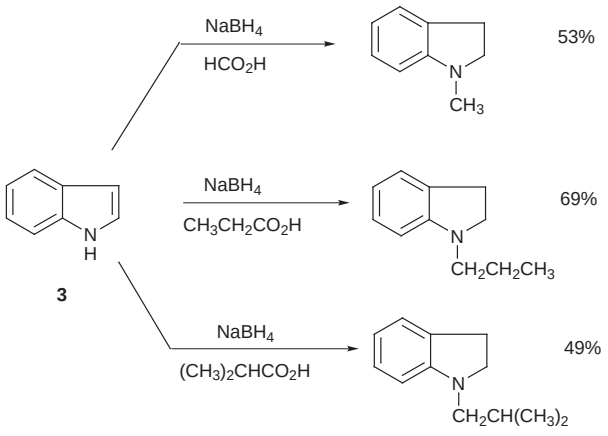
Scheme 1

These fascinating results sparked our further studies with the $NaBH_4$–RCO_2H reagent system, an odyssey that has continued for 25 years and has led to an extraordinarily versatile, unique, and efficient set of reducing agents.[1,2] Throughout this presentation uncited reactions can be found in the reviews.[1,2]

2 Chemistry of acyloxyborohydrides

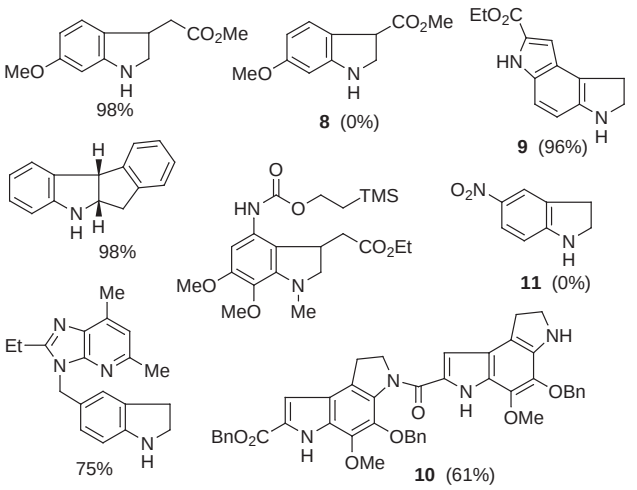
2.1 Reduction of indoles

The reduction and *N*-alkylation of indoles with $NaBH_4$–RCO_2H to give *N*-alkylindoles (Scheme 2)[4] and the reduction of indoles with $NaBH_3CN$–HOAc to give indolines are quite general

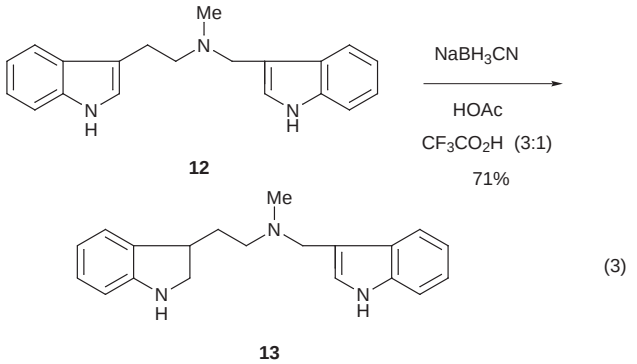


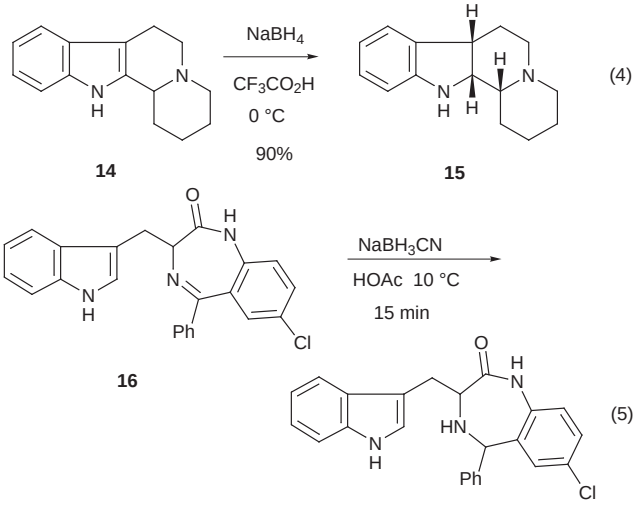
Scheme 2

processes. The latter reaction is the preeminent method for reducing the indole double bond, provided that electron-withdrawing groups are not present to retard the initial indole protonation (*i.e.*, **3**→**4**). Thus, an indole double bond containing an ester group at C-2 or C-3 (**8**–**10**) is inert to the action of $NaBH_3CN$–HOAc. Likewise, 5-nitroindole is not reduced to **11** under these conditions. Such selectivity has been of great utility in the synthesis of the antitumor agent CC-1065 and analogues. However, at higher temperatures one may encounter *N*-ethylation with $NaBH_3CN$–HOAc.



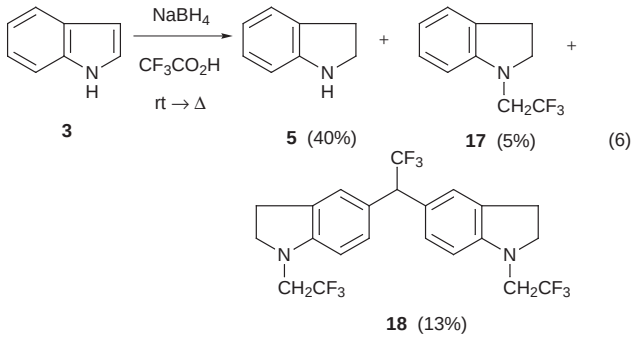
A remarkable illustration of the selectivity of this indole reduction method is seen in **12** → **13** [eqn. (3)],[6] in which the protonated basic nitrogen presumably prevents a second protonation of the proximal indole double bond.





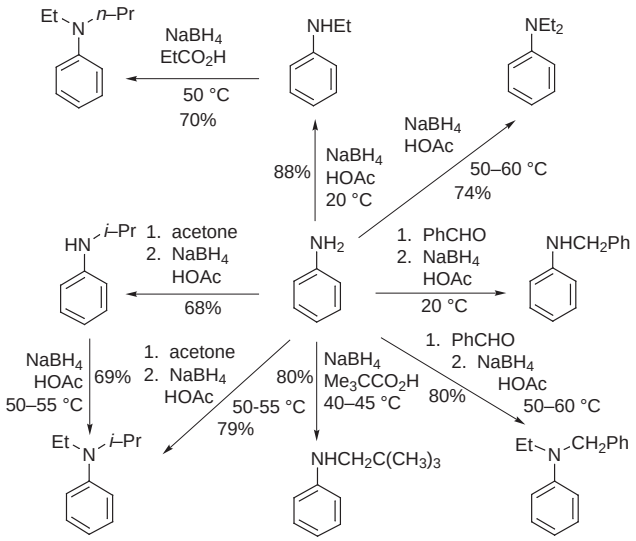
Generally, compounds containing a basic nitrogen atom, such as the ubiquitous indolo[2,3-*a*]quinolizidine alkaloids (*e.g.*, **14**), can only be reduced using $NaBH_4$ in trifluoroacetic acid (TFA) [eqn. (4)].[4,7] Thus, only the imine and not the indole bond in **16** is reduced with $NaBH_3CN$–HOAc [eqn. (5)].

Under the influence of $NaBH_4$–TFA, indole (**3**) is converted to a mixture of indoline (**5**), *N*-trifluoroethylindoline (**17**), and the Baeyer condensation product **18** [eqn. (6)].[8]



2.2 *N*-Alkylation of amines

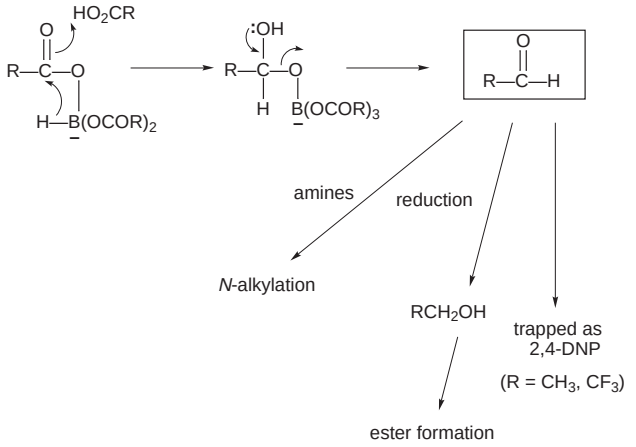
Our observation that $NaBH_4$–HOAc gives *N*-ethylation of indoline (**5**) (Scheme 1) led us to explore the scope of this unprecedented amine *N*-alkylation reaction. Reactions of aniline with $NaBH_4$–RCO_2H are shown in Scheme 3.[4] One can



Scheme 3

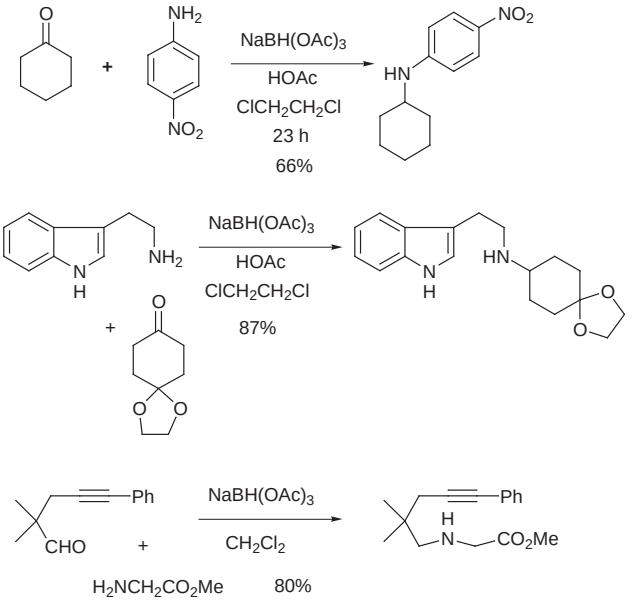
effect mono- or dialkylation, depending on the temperature, and, thus, achieve the conversion of a primary amine to an unsymmetrical tertiary amine in one pot. The reductive amination of added aldehydes or ketones increases the versatility of the method. Pivalic acid affords *N*-neopentylaniline in 80% yield. Similar chemistry is observed with benzylamine and other aliphatic amines.[9]

Control experiments revealed that the mechanism of this *N*-alkylation does not involve reduction of a precursor amide,[4] and gas evolution measurements and isolation studies[10] indicated that the borohydride species formed under these conditions of excess acetic acid is $NaBH(OAc)_3$ (**1**, R = Me) [eqn. (1)]. Furthermore, we were able to isolate the 2,4-DNP derivative of acetaldehyde from the evolved gases of the reaction of $NaBH_4$ with glacial HOAc. Therefore, we believe that the $NaBH(OCOR)_3$ species undergoes self-reduction to free aldehyde (or a synthetic equivalent) which then reacts with the amine in a typical reductive amination sequence (Scheme 4).



Scheme 4

Using the isolated reducing reagent $NaBH(OAc)_3$, Abdel-Magid has extended this amine *N*-alkylation method into a powerful, general reductive amination protocol for aldehydes and ketones.[11] Some recent examples are shown in Scheme 5.[11–13]

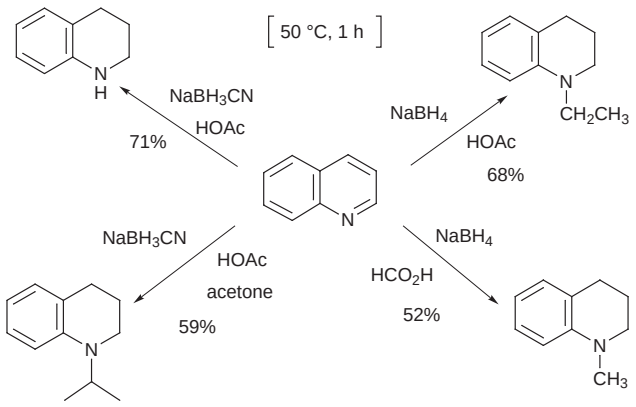


Scheme 5

Obviously, these amine *N*-alkylations (reductive aminations) succeed because $NaBH(OAc)_3$ only slowly reduces aldehydes and ketones relative to the rapid reduction of iminium and immonium ions.

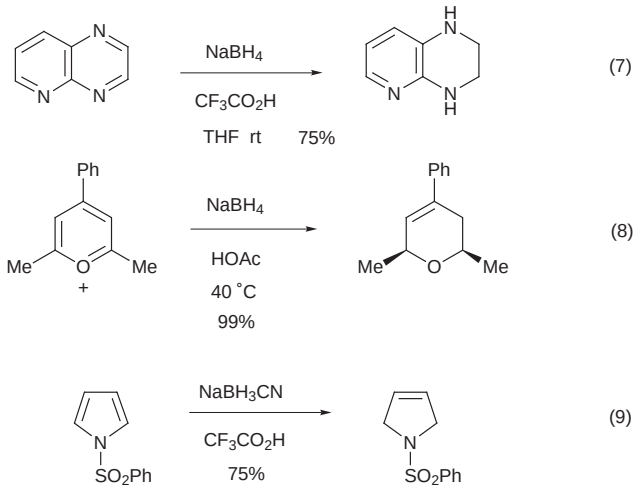
2.3 Reduction of other heterocycles

The facile reduction of indole (**3**) (Scheme 1) with $NaBH_4$–RCO_2H portended that other nitrogen-containing heterocycles that are susceptible to protonation would undergo a similar reduction/alkylation sequence. Indeed, quinolines, isoquinolines, acridines, quinazolines, quinoxalines, phthalazines, pteridines, benzoxazines, adenines, some pyrroles, and pyrylium salts are reduced by $NaBH_4$–RCO_2H.[1,2] More aromatic pyridines are normally unaffected by $NaBH_4$–RCO_2H. Illustrative of the versatility of this methodology is the chemistry shown in Scheme 6 involving quinoline.[14]



Scheme 6

Some additional examples are shown below [eqns. (7)–(9)].



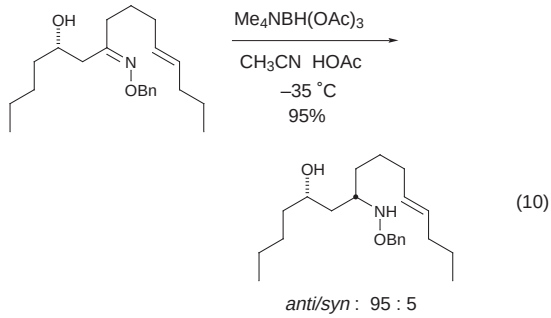
2.4 Reduction of imines, enamines and related compounds

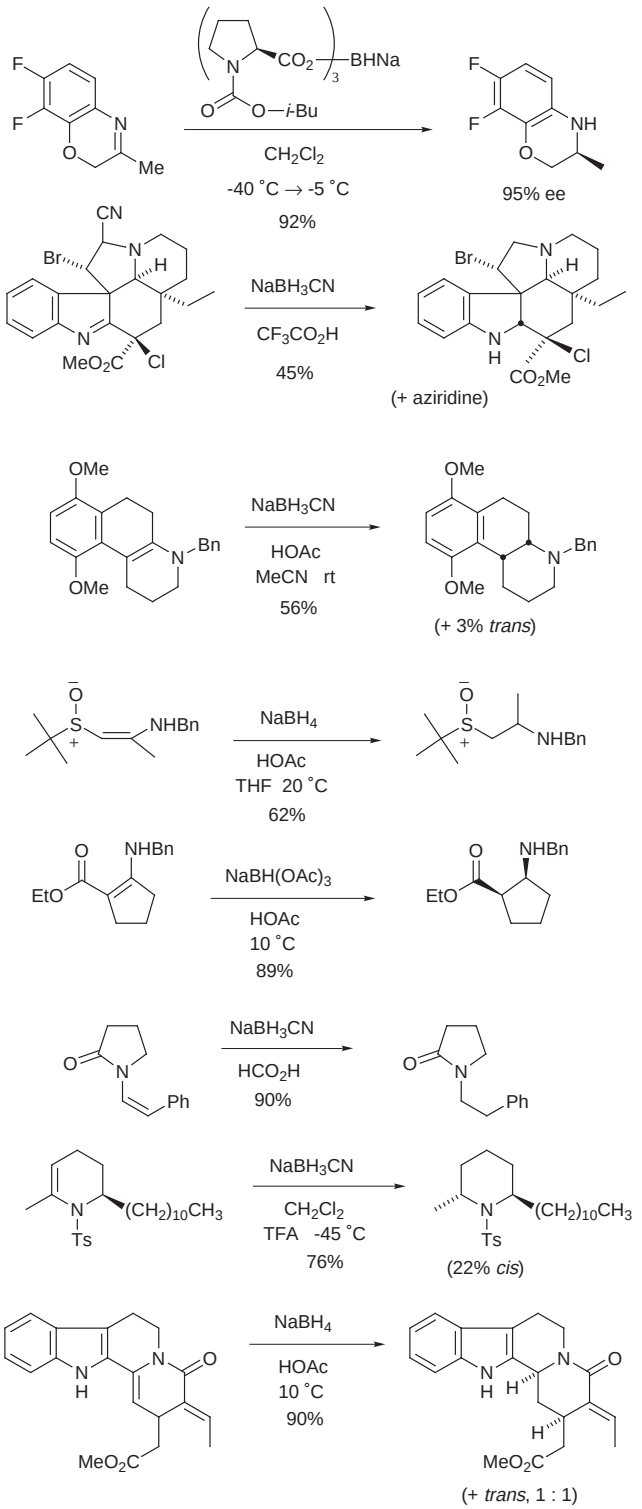
A wide range of imines, enamines, enamides, vinylogous amides, and carbamates can be reduced using $NaBH_4$–RCO_2H (Scheme 7).

2.5 Reduction of oximes

Oximes are reduced and reductively alkylated with $NaBH_3CN$–HOAc and $NaBH_4$–RCO_2H, respectively (Scheme 8).[15] Whereas at room temperature cyclohexanone oxime is reduced to cyclohexylhydroxylamine with $NaBH_4$–HOAc, at higher temperatures the reaction proceeds to afford *N*,*N*-diethylcyclohexylamine.

Similarly, oxime ethers are reduced to *O*-alkylated hydroxylamines under these conditions. Such an example involving a hydroxy-directed reduction is illustrated in eqn. (10).





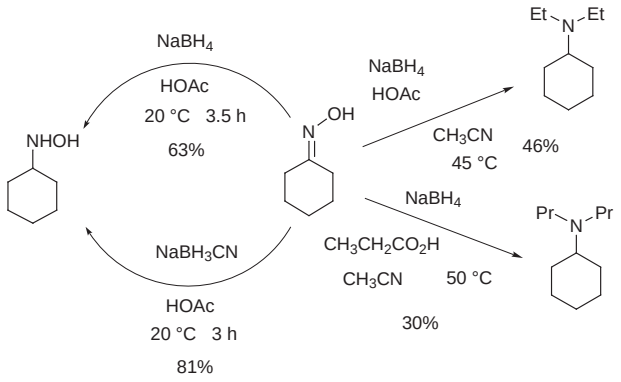
Scheme 7

2.6 Reduction of amides to amines

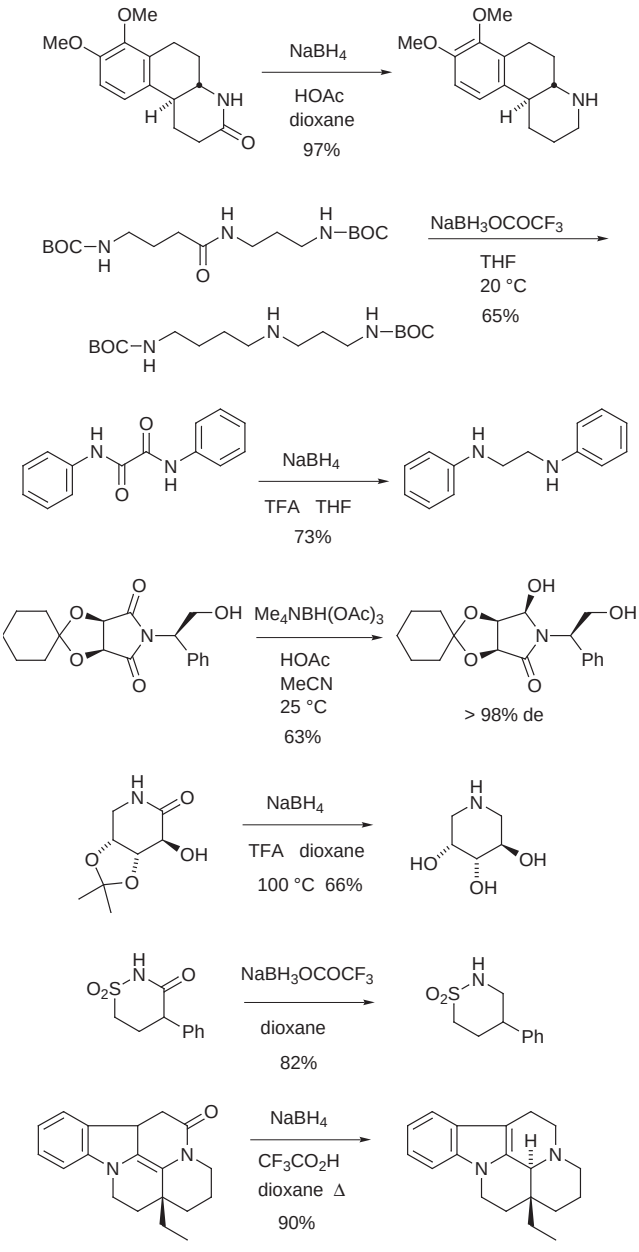
Although $NaBH(OCOR)_3$ (**1**) does not reduce amides, Umino discovered that $NaBH_3OCOR$ does reduce amides and lactams to the corresponding amines.[16] Some examples of this useful reaction are listed in Scheme 9. Note that carbamates and sultams are unaffected by these conditions. Interestingly, the indole double bond in the last example is not reduced.[17]

2.7 Reduction of nitriles to primary amines

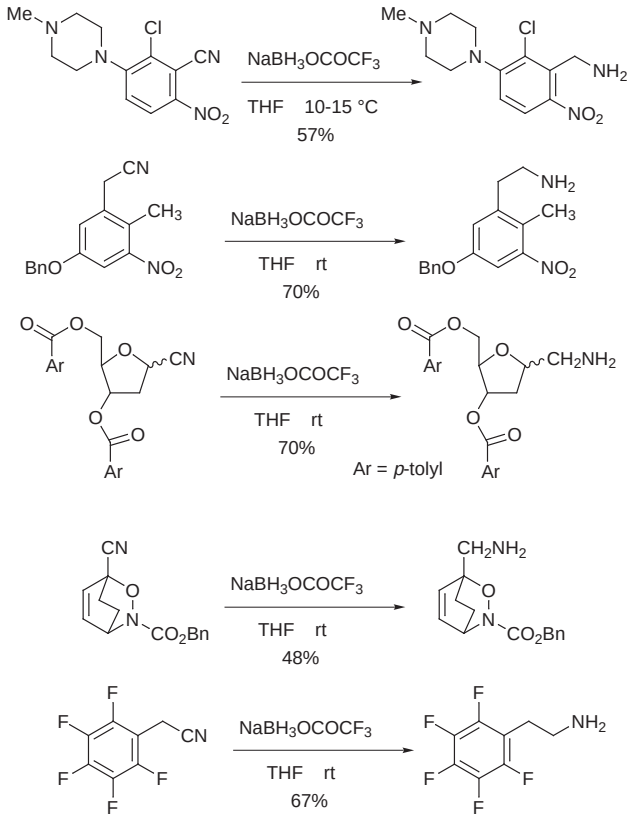
Umino also discovered that $NaBH_3OCOR$, particularly $NaBH_3OCOCF_3$, reduces nitriles to primary amines.[18] A selection of examples is shown in Scheme 10. Noteworthy is that this reduction reaction occurs in the presence of nitro and 1,2-oxazine functionalities.



Scheme 8



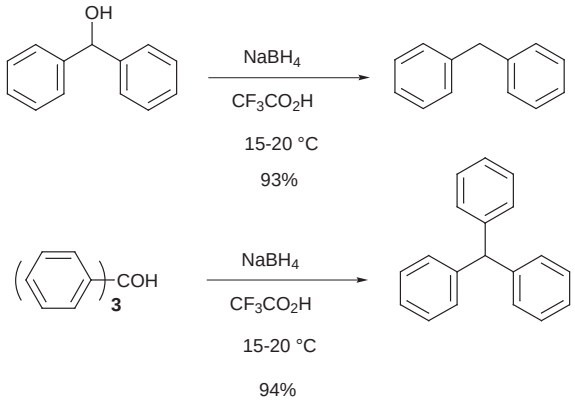
Scheme 9



Scheme 10

2.8 Reduction of alcohols to hydrocarbons

Early in our studies we thought that $NaBH_4$–CF_3CO_2H (TFA) might serve to reduce certain alcohols to hydrocarbons, in view of the propensity of TFA to stabilize carbocations. Indeed, this reagent combination provides an efficient and general method for reducing di- and triarylcarbinols to di- and triarylmethanes (Scheme 11).[19] Other alcohols, unless the derived carbocation is highly stabilized, are not reduced cleanly under these conditions.[19]



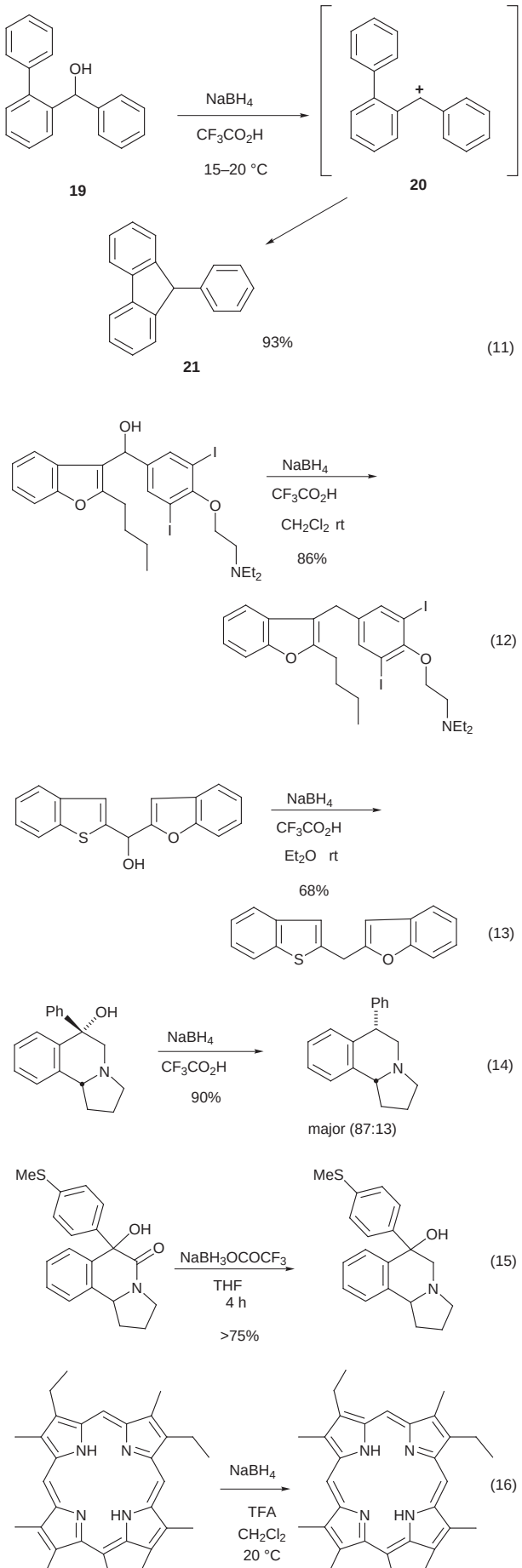
Scheme 11

In the case of carbinol **19**, the intermediate carbocation **20** is ambushed by the *o*-phenyl group prior to reduction, affording only 9-phenylfluorene (**21**) [eqn. (11)].[19]

The generality and selectivity of this reduction method is illustrated by the examples in eqns. (12)–(16). The chemoselectivity exhibited by $NaBH(OCOCF_3)_3$ *vis-à-vis* $NaBH_3OCOCF_3$ in eqns. (14)–(15) is remarkable.

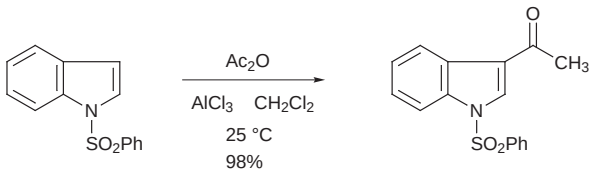
2.9 Reduction of ketones to hydrocarbons

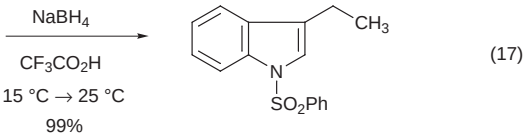
Diarylketones are smoothly reduced to diarylmethanes with $NaBH_4$–TFA.[20] As we have seen, a wide range of functional



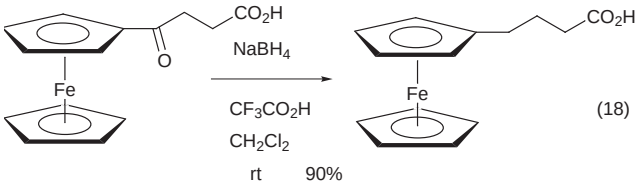
groups will tolerate these reaction conditions (Scheme 12). The mechanism presumably involves reduction to the diarylmethanol, solvolysis to the carbocation, and reduction to the hydrocarbon. Only in the case of strong electron-withdrawing groups (*e.g.*, *p*-NO_2) is the reaction incomplete. The last reaction appears to be the first reduction of a formyl group to a methyl group using this methodology.

This method provides for a very useful synthesis of 3-alkylindoles [eqn. (17)] and alkyl-substituted ferrocenes [eqn. (18)].[21]



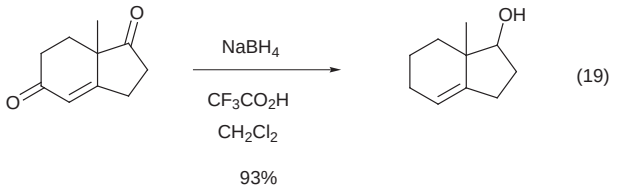


(17)



(18)

The combination of $NaBH_4$–TFA converts enones to alkenes [eqns. (19) and (20)],[22,23] and isopropylidene acylmalonates, 5-acylbarbituric acids, and 3-acyl-4-hydroxycoumarins are all reduced to the corresponding methylene derivatives with $NaBH_3CN$–HOAc [*e.g.*, eqn. (21)].



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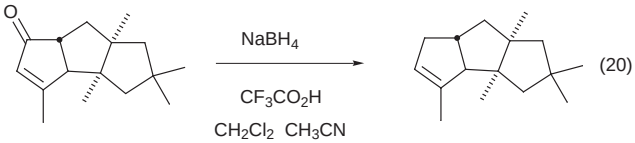

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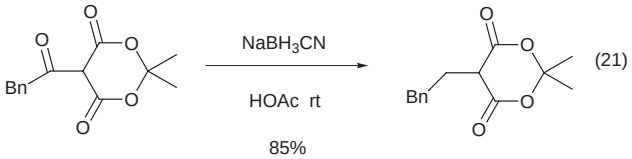
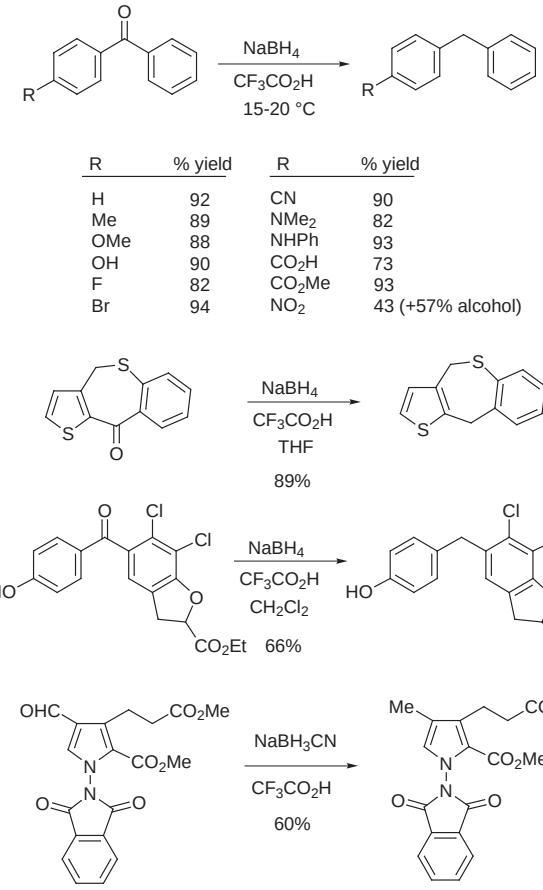


(21)

2.10 Reductive cleavage of acetals, ketals, ethers, and related compounds

The action of $NaBH_4$–TFA serves to reductively cleave a variety of acetals, ketals, ethers and ozonides as summarized in Scheme 13.[24–26] The deoxygenation of 1,4-epoxy-1,4-dihydroarenes is particularly useful for the synthesis of polycyclic aromatic hydrocarbons.



Scheme 12

2.11 Alkylation of arenes (Baeyer condensation)

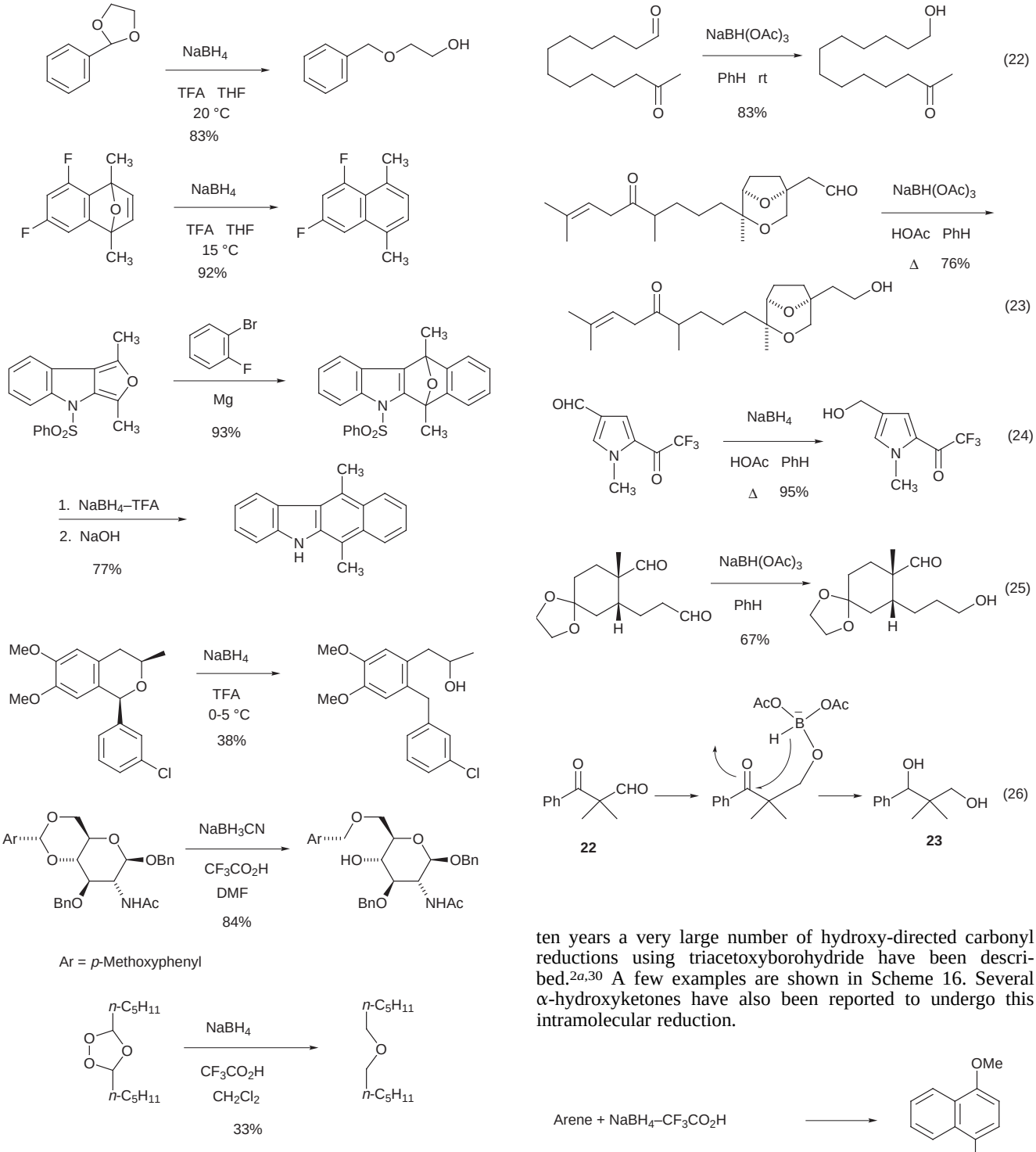
As noted earlier, indole (**3**) with $NaBH_4$–TFA gives some of the Baeyer condensation product **18** [eqn. (6)]. Indeed, this alkylation reaction of arenes, involving the generation of trifluoroacetaldehyde, is reminiscent of the synthesis of DDT from chlorobenzene, trichloroacetaldehyde (chloral), and sulfuric acid. We have found that several arenes give analogous products under these conditions (Scheme 14).[27] Congested arenes like durene and mesitylene stop at the carbinol stage.

2.12 Selective reduction of aldehydes

The reduction of aldehydes and ketones to alcohols is one of the most important reactions in organic chemistry. Although many reagents are available for this reaction, few are chemoselective for aldehydes and such methods are in great demand.

From the beginning of our work in this area, it was clear that aldehydes and, especially, ketones were reduced relatively slowly by these acyloxyborohydrides. Indeed, this is precisely why the *N*-alkylation of amines works! Thus, although benzaldehyde is completely reduced to benzyl alcohol after 1 hour at 15 °C with a large excess of $NaBH_4$ in glacial acetic acid, acetophenone is only reduced to the extent of 60% at 25 °C after 40 hours! By comparison, in alcoholic solution both reductions are complete in seconds. These and related observations paved the way for the chemoselective reduction of aldehydes in the presence of ketones.[10,28] The isolated reagents $NaBH(OAc)_3$[10] and *n*-$Bu_4NBH(OAc)_3$[28] work extremely well and some examples with the latter reagent are depicted in Scheme 15.[28]

Some additional examples with $NaBH(OAc)_3$ are listed in eqns. (22)–(25). Notable is the selective reduction of the aldehyde in the presence of a trifluoromethyl ketone [eqn. (24)]



Scheme 13

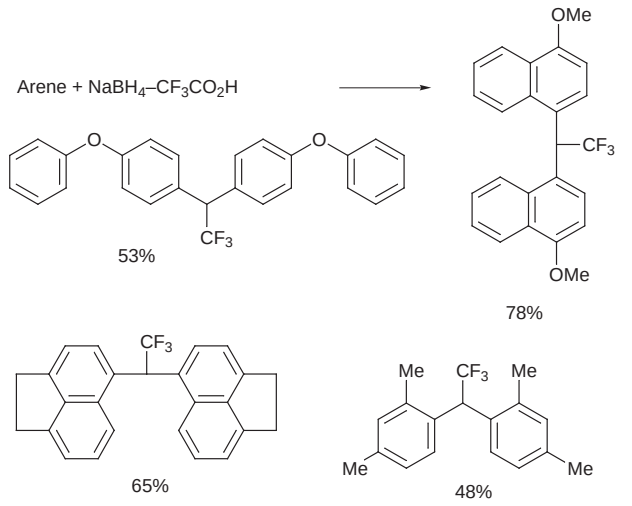
and the selective reduction of the less sterically encumbered aldehyde in a dialdehyde [eqn. (25)].[29]

2.13 Hydroxy-directed reduction of ketones

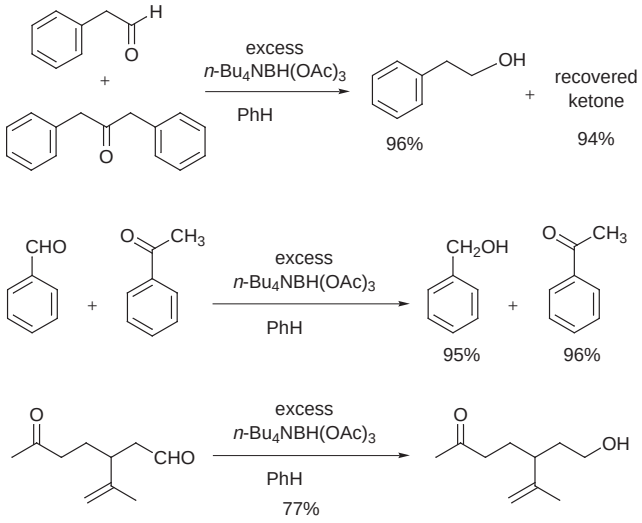
During our study of the chemoselective reduction of aldehydes in the presence of ketones, we observed the reduction of ketoaldehyde **22** to diol **23**, presumably involving internal hydride delivery as shown in eqn. (26).[28]

Saksena independently discovered this same reaction and observed excellent stereoselectivities in the reduction of steroidal β-hydroxy ketones. Evans thoroughly explored the scope of this powerful methodology and he fully characterized several $BH(OAc)_3$ species for the first time.[30] In the intervening

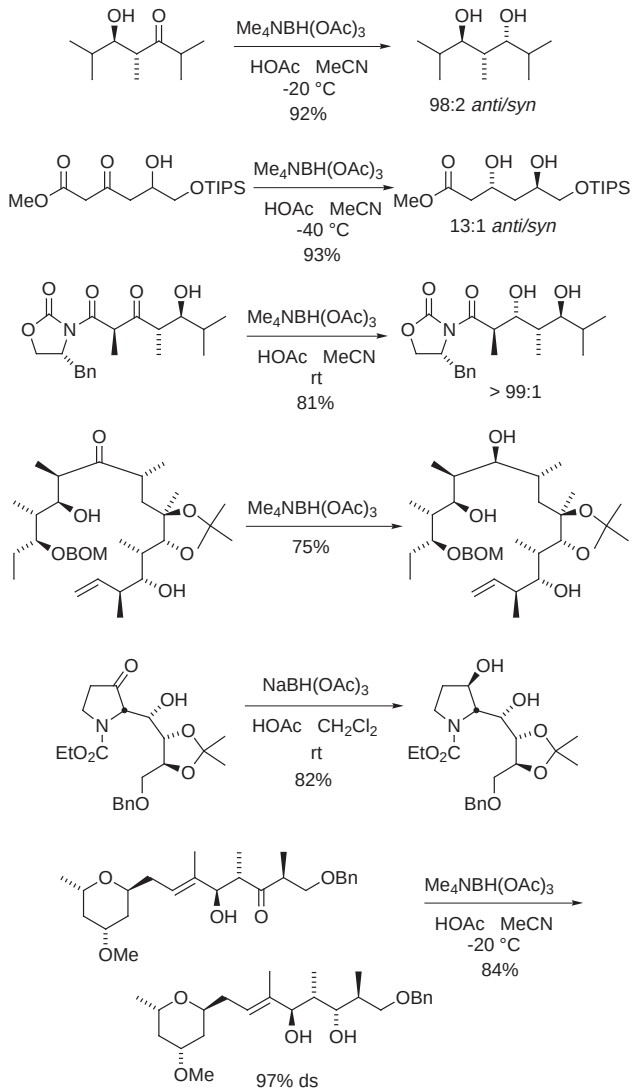
ten years a very large number of hydroxy-directed carbonyl reductions using triacetoxyborohydride have been described.[2a,30] A few examples are shown in Scheme 16. Several α-hydroxyketones have also been reported to undergo this intramolecular reduction.



Scheme 14



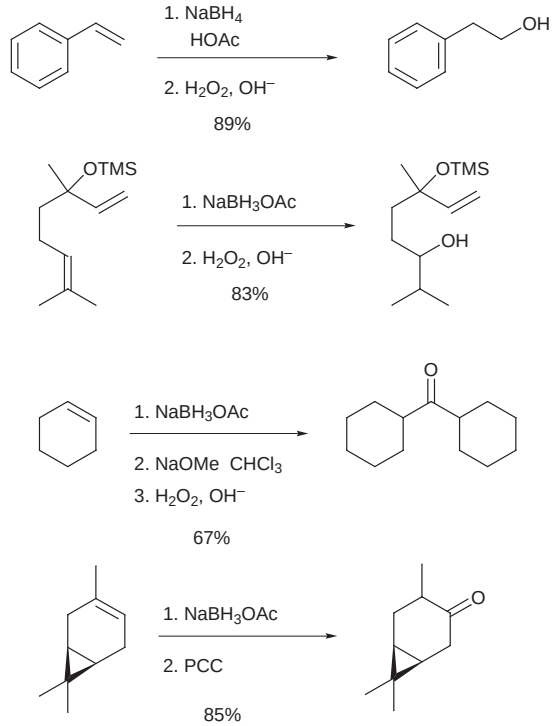
Scheme 15



Scheme 16

2.14 Hydroboration of alkenes

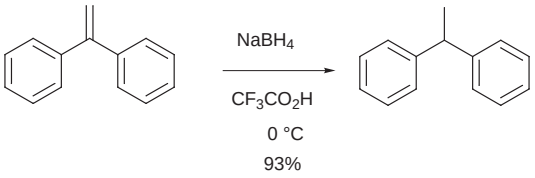
One of the first applications of the $NaBH_4$–HOAc reagent system was the hydroboration of alkenes as described by Marshall and Johnson.[3] The actual reagent is the more reactive $NaBH_3OAc$, which can also be generated from $NaBH_4$ and $Hg(OAc)_2$. Some examples of alkene hydroboration are listed in Scheme 17.



Scheme 17

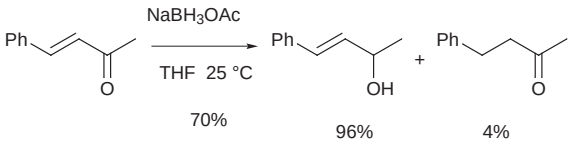
2.15 Miscellaneous reductions

Alkenes that yield stable carbocations upon protonation can be reduced to alkanes with $NaBH_4$–TFA [eqn. (27)],[19] but such examples are exceedingly rare. It seems likely that $NaBH_4$–CF_3SO_3H may work in this regard with other alkenes.

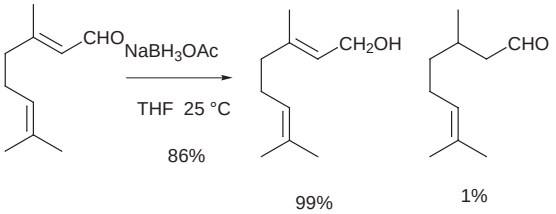


(27)

Enones and enals give primarily 1,2-reduction with $NaBH_3OAc$ [eqns. (28) and (29)]. Small amounts of the 1,4-reduction products were also found.

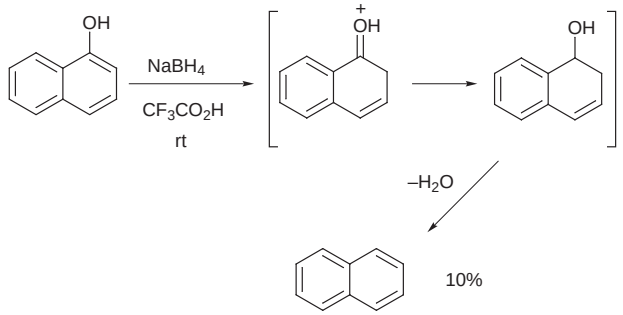


(28)



(29)

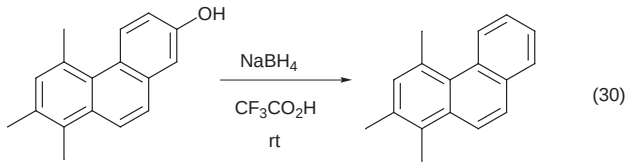
Twenty years ago we observed that both 1- and 2-naphthol yielded 10–20% naphthalene upon treatment with $NaBH_4$–TFA (Scheme 18). In fact, when the crude reaction products were



Scheme 18

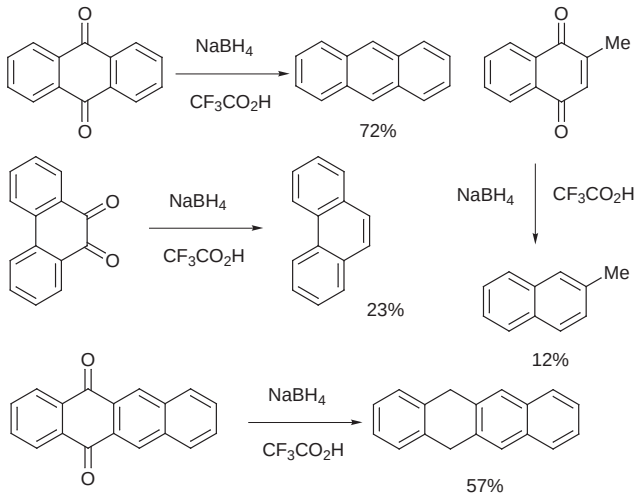
allowed to stand undisturbed for six months, pure naphthalene had sublimed onto the upper part of the flask. Presumably this transformation involves ring protonation, carbonyl reduction, and dehydration.

More recently this novel deoxygenation of phenols has been reported for a hydroxyphenanthrene [eqn. (30)].[31]



(30)

These results are consistent with our earlier observations that 9,10-phenanthrenequinone and 2-methyl-1,4-naphthoquinone undergo reduction to the corresponding aromatic hydrocarbons albeit in low yield (Scheme 19).[1]



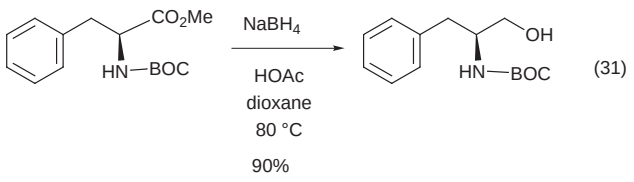
Scheme 19

Esters are not normally reduced to primary alcohols by $NaBH_4$–CO_2H, but such a reduction is observed at higher temperatures in the case of amino acid and peptide esters [eqns. (31) and (32)].[32] Importantly, racemization is not seen.

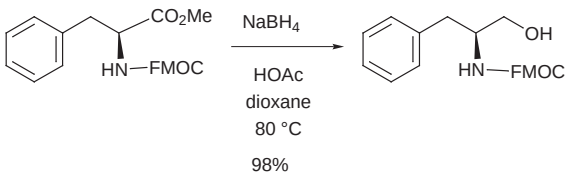
In view of the facile reduction of carboxylic acids to aldehydes with $NaBH_4$ in the course of the reductive amination sequence (*vide supra*), it is not surprising that complete reduction to primary alcohols has been found (Scheme 20).

Turnbull has recently described the reduction and subsequent *N*-trifluoroethylation of aroyl azides with $NaBH_4$–TFA [eqn. (33)].[33] The parent compound yielded the Baeyer condensation product **24** in 87% yield.

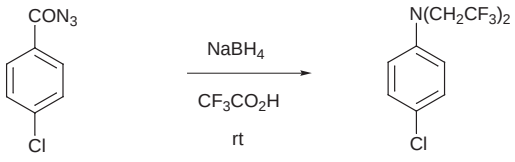
Organomercurials can be reduced to alkanes with $NaBH(OAc)_3$ [eqn. (34)],[34] and the $NaBH(OCOR)_3$ reagents can also acylate alcohols, phenols, and thiophenols [eqns. (35)–(38)], presumably by direct acylation of an acyloxyborohydride intermediate.



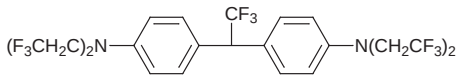
(31)



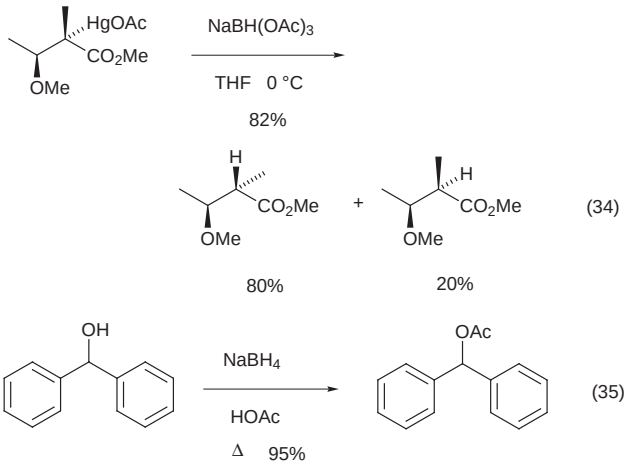
(32)



(33)

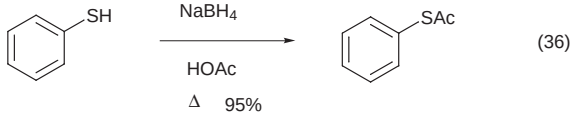


24

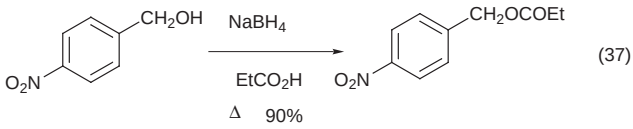


(34)

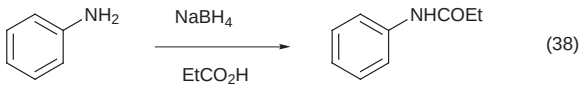
(35)



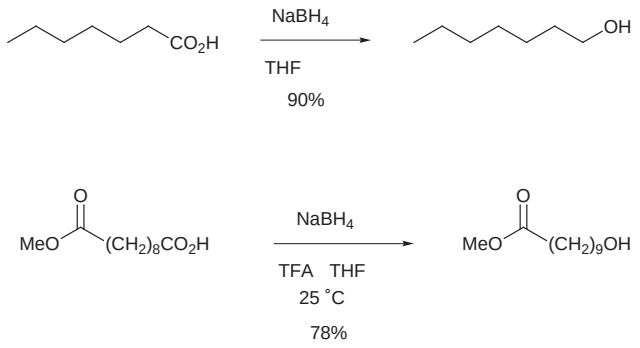
(36)



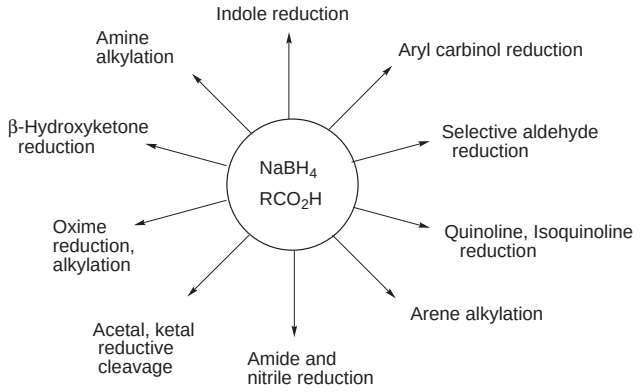
(37)



(38)



Scheme 20



Scheme 21

3 Concluding remarks

As summarized in Scheme 21 the combination of $NaBH_4$–RCO_2H, leading to acyloxyborohydrides, is a remarkably versatile and unique chemical system. These chemical species have emerged as the preeminent reagents of choice for a wide spectrum of chemical transformations. 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. Nevertheless, much work remains to be done with acyloxyborohydrides, particularly with regard to understanding the mechanisms of some of the reactions, in applying these reagents to asymmetric synthesis, and in uncovering new applications.

4 Acknowledgements

I am especially grateful to my many co-workers on this project over the past 25 years. In particular, graduate students Jerry Skotnicki at the beginning and Charlie Nutaitis in later years. But, my deepest appreciation goes out to the many Dartmouth undergraduates who explored and developed much of the chemistry presented here. These include Steve Dietz, Duncan Ferguson, Peter Heald, Bud Leese, Myles Sheehan, Joe Hoffman, Sandy Emery, Joe Jasinski, John Pellicone, and Steve Wright. Thank you all.

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