Chapter 11

Sodium Borohydride and Carboxylic Acids: A Novel Reagent Combination

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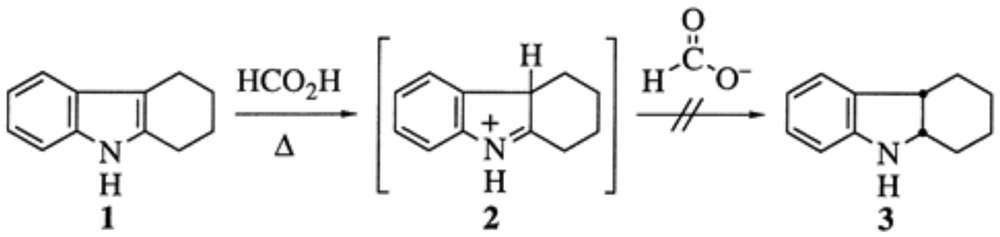
The combination of sodium borohydride ($NaBH_4$) and carboxylic acids – sodium acyloxyborohydrides – represents a remarkably versatile and powerfully efficient synthetic tool. This reagent manifold, the reactivity of which can be controlled depending on the nature and number of acyloxy groups, reduces and *N*-alkylates indoles, quinolines, isoquinolines, related heterocycles, imines, enamines, oximes, enamides, and similar functional groups. It reduces amides and nitriles to amines in the presence of esters, aryl alcohols and ketones to hydrocarbons, aldehydes to alcohols in the presence of ketones, and β-hydroxyketones to 1,3-diols stereoselectively. This reagent is also an extraordinarily useful methodology for the *N*-alkylation of primary and secondary amines, in a reaction sequence that is believed to involve sequential reduction of the carboxylic acid to the corresponding aldehyde followed by a standard reductive amination process. Frequently, the monoalkylation of primary amines can be achieved. The use of sodium cyanoborohydride ($NaBH_3CN$) militates against *N*-alkylation, and, for example, the union of $NaBH_3CN$/HOAc cleanly reduces indoles to indolines *sans* alkylation. Depending on the circumstances and conditions, alkenes can be hydroborated, esters and carboxylic acids can be reduced to alcohols, and arenes can be induced to undergo the Baeyer condensation. No other chemical system can boast of such amazing flexibility!

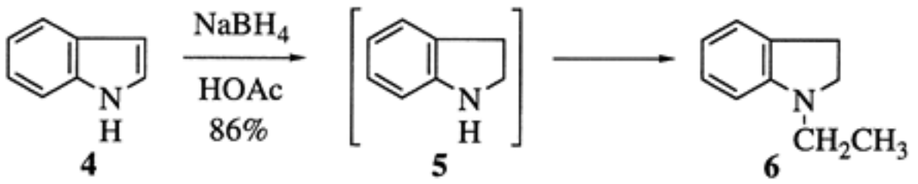
More than 20 years ago, as part of an undergraduate research project at Dartmouth, we decided to attempt the reduction of 1,2,3,4-tetrahydrocarbazole with neat formic acid. A general indole double-bond reduction method was lacking at that time (*1*) and we felt that a Leuckart-type reaction (*2*) on the protonated indole might occur (equation 1). However, the only product of this reaction was the *N*-formyl derivative of **1** (95%) (Gribble, G. W.; Strickman, D., Dartmouth College, unpublished result).

Nevertheless, since indoles are well known to undergo C-3 protonation in mineral acids (*1*, *3*), we felt that a better hydride source than formate might succeed in ambushing the presumed indolenium ion (*e.g.*, **2**), if indeed carboxylic acids are capable of protonating the indole double bond. We chose to study sodium borohydride



(1)

($NaBH_4$) and acetic acid (HOAc) since Marshall and Johnson had established the compatibility of these unlikely partners a few years earlier in the reduction of steroidal dienamines and enamines (*4*, *5*). Ironically, at about the same time, it was claimed that reductions involving $NaBH_4$ in glacial acetic acid could *not* be performed (*6*). In the event, treatment of indole (**4**) in glacial HOAc with $NaBH_4$ did not give indoline (**5**) (2,3-dihydroindole) but, rather, *N*-ethylindoline (**6**) in high yield (equation 2) (*7*). This very surprising result spawned the chemistry in this chapter.

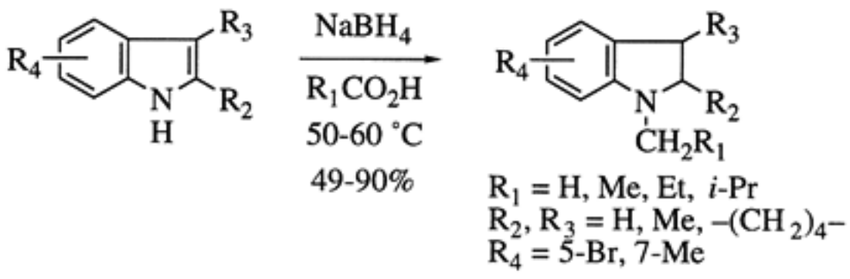


(2)

Since several reviews of this area have appeared (*8-10*), the present chapter focuses mainly on recent developments and the author's own work. The interesting history of the discovery of acyloxyborohydrides has been previously discussed (*8*, *9*).

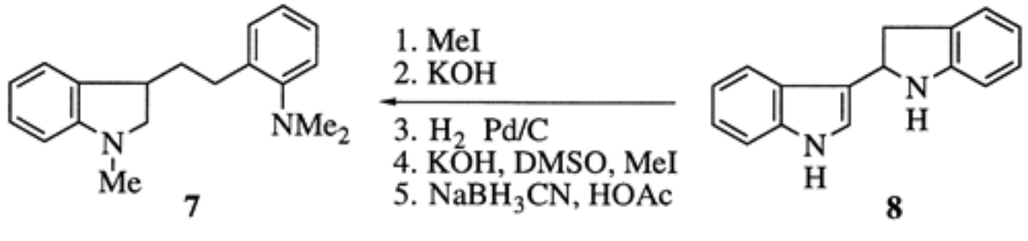
Reduction of Indoles.

The remarkable tandem reduction and *N*-alkylation of indole (equation 2) is reasonably general for indoles and carboxylic acids (equation 3) (*7*). Only pivalic acid gives the corresponding product (*N*-neopentylindoline) in low yield.



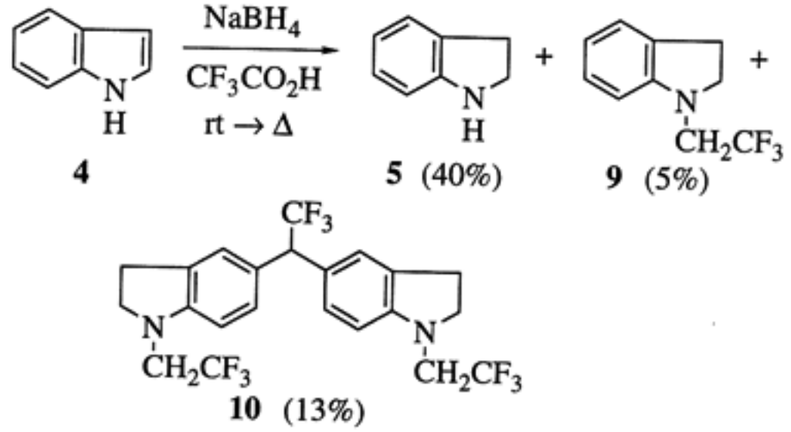
(3)

The reaction of indole with $NaBH_4$/formic acid, which is exceptionally vigorous, leads to by-product **7**, the structure of which was confirmed by independent synthesis from the well-known indole dimer **8** (*11*).



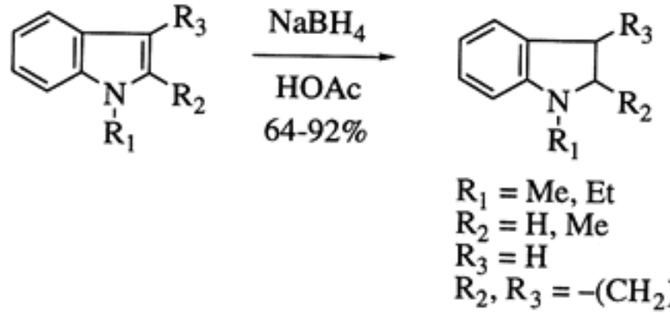
In an effort to suppress the *N*-alkylation reaction, we attempted the reduction of indole with $NaBH_4$ and the stronger trifluoroacetic acid (TFA). Indeed, this reaction affords indoline (**5**) and a small amount of *N*-trifluoroethylindoline (**9**), in addition to the interesting Baeyer condensation product (**10**) (equation 4) (*12*). The structures of

9 and **10** were confirmed by independent syntheses and conversion to known compounds. For example, reaction of **9** under these conditions gives **10** in 57% yield.



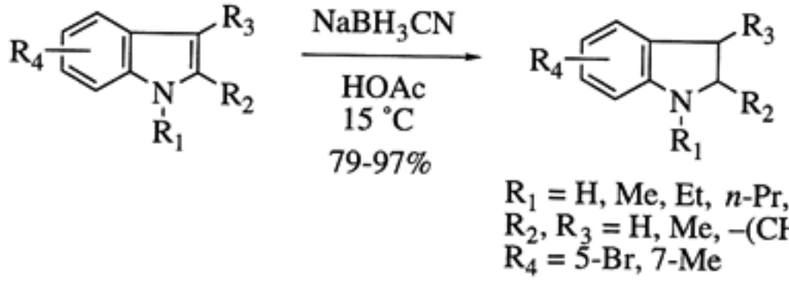
(4)

The formation of **10** and the *N*-alkylation of indoles with $NaBH_4/RCO_2H$ suggested to us that aldehydes, or their synthetic equivalent, were the source of the alkyl group. This pathway is discussed in the next section. As expected, treatment of the *N*-alkylindoles with $NaBH_4$/HOAc affords the corresponding *N*-alkylindolines (equation 5) (*7*).



(5)

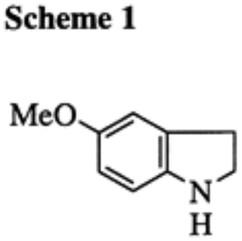
Since the original goal of this research program was to discover a new indole to indoline reduction method, *sans N*-alkylation, we examined the reaction of indole with sodium cyanoborohydride ($NaBH_3CN$) in HOAc. Much to our delight, this reaction afforded indoline (**5**) in 91% distilled yield, with no trace of *N*-ethylindoline (*7*, *13*). At higher temperatures, *N*-ethylation is observed (*13*, *14*). The reaction is rapid, general, and efficient (equation 6), failing only with electron-withdrawing substituents on the indole ring (e.g., 5-nitro- and 2,3-diphenylindole.



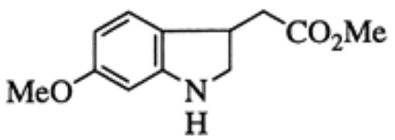
(6)

This very useful indole reduction method has been employed by many groups and some of the indolines thusly prepared are shown in Scheme 1.

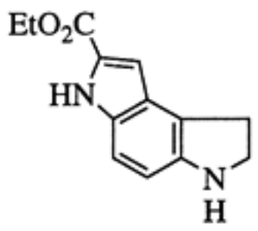
Scheme 1



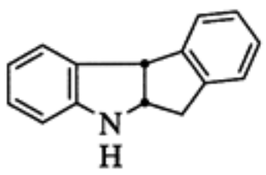
74% (*15*)



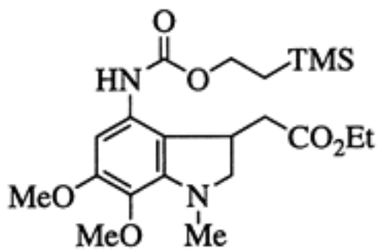
98% (*16*)



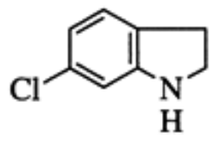
11 96% (*17*)



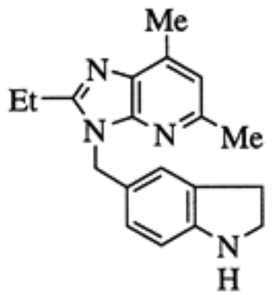
98% (*18*)



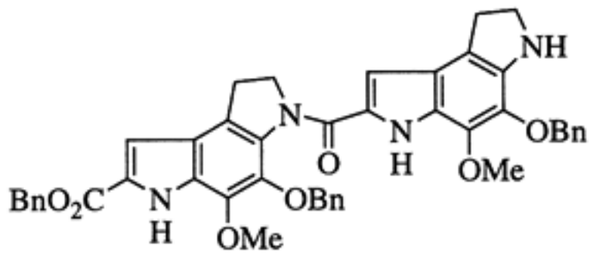
(*19*)



92% (*20*)

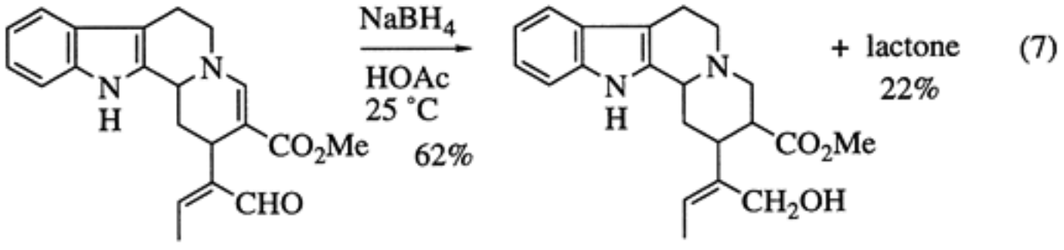


75% (*21*)



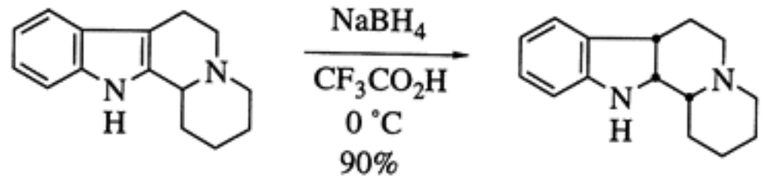
12 61% (*22*)

In particular, this reagent combination has been very successful in the selective reduction of the more basic indole double bond in CC-1065 and PDE precursors (*17*, *22-27*), such as **11** and **12** in Scheme 1. Not surprisingly, treatment of indole with $NaBH_3CN$/HOAc in the presence of added acetaldehyde affords *N*-ethylindoline in 87% yield (Gribble, G.W. Dartmouth College, unpublished result). Thus, it would appear that $NaBH_3CN$ is less effective than $NaBH_4$ in generating aldehydes (or their equivalents) from carboxylic acids. Ironically, the first report of the treatment of an indole with $NaBH_4$/HOAc did *not* result in the reduction of the indole double bond (equation 7) (*28*). We believe that this lack of reduction in this and related systems that contain a basic nitrogen (*29-31*) is due to protonation of the basic nitrogen which prevents a second protonation of the indole double bond.



(7)

Indeed, we found that TFA in combination with $NaBH_4$ smoothly reduces basic indoles such as indolo[2,3-*a*]quinolizidines (equation 8) (*32*).



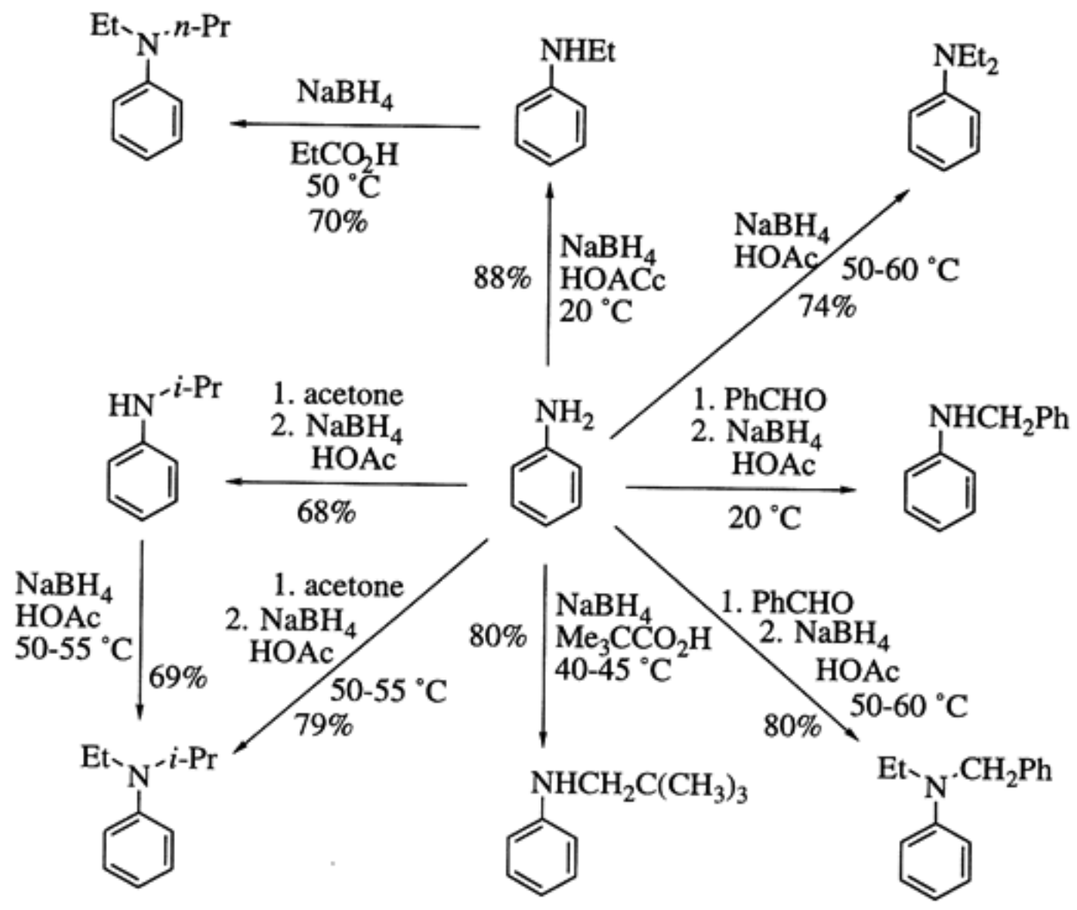
(8)

Several other workers have used the combination of $NaBH_4$/TFA to reduce the indole double bond of yohimbine (*33*), carbolines (*34*), and other amino indoles (*35*, *36*). In some cases, $NaBH_3CN$/TFA is superior in this regard (*37*, *38*). Indeed, this latter combination efficiently reduces *N*-(phenylsulfonyl)indoles to the corresponding indolines and 2- and 3-acyl-*N*-(phenylsulfonyl)indoles to the corresponding 2- and 3-alkyl-*N*-(phenylsulfonyl)indolines (*39*). This ketone to hydrocarbon reduction is discussed later.

N-Alkylation of Amines.

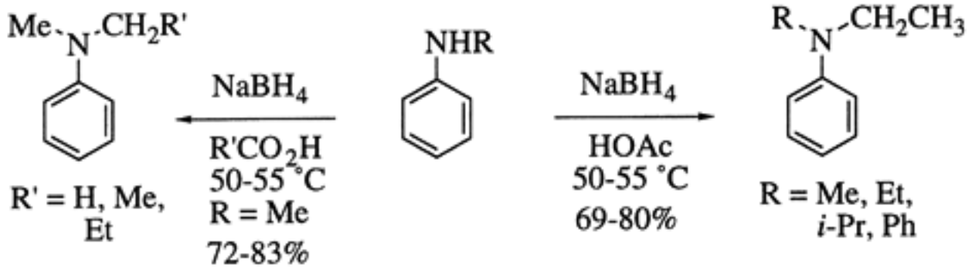
The unexpected propensity of $NaBH_4$ in carboxylic acids to effect the *N*-alkylation of primary and secondary amines led us to explore the scope of this novel and potentially useful method. Depending on the temperature, aniline can be mono- or dialkylated (Scheme 2) (*7*, Gribble, G.W. Dartmouth College, unpublished results). Moreover, the incorporation of an aldehyde or ketone in this protocol allows for the formation of unsymmetrical tertiary amines in one pot, including the introduction of the bulky neopentyl group (from pivalic acid).

Scheme 2



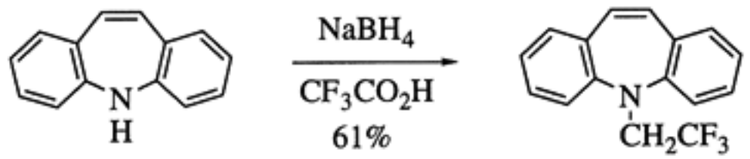
This *N*-alkylation is general for a range of secondary to tertiary anilines as well as for different carboxylic acids (equation 9) (*7*, Gribble, G.W. Dartmouth College,

unpublished results), including solid carboxylic acids in a cosolvent (*40*). Even the weakly basic carbazole can be *N*-ethylated with $NaBH_4$/HOAc (92% yield) (*7*).

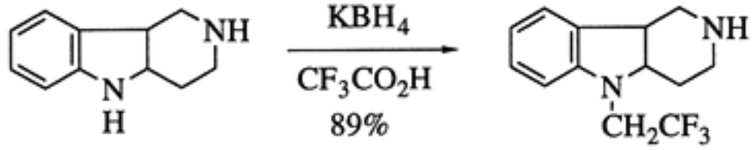


(9)

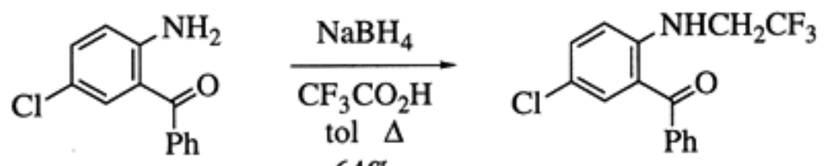
Although it is generally sluggish, in some cases, the combination of $NaBH_4$/TFA leads to *N*-trifluoroethylation of aromatic amines (e.g., equations 10-12) (*12*, *34*, *41*).



(10)



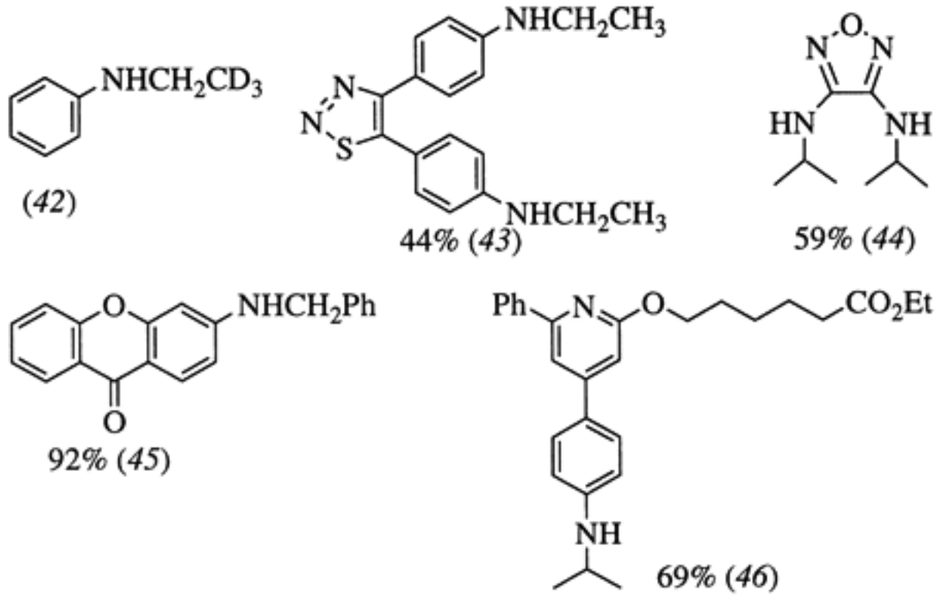
(11)



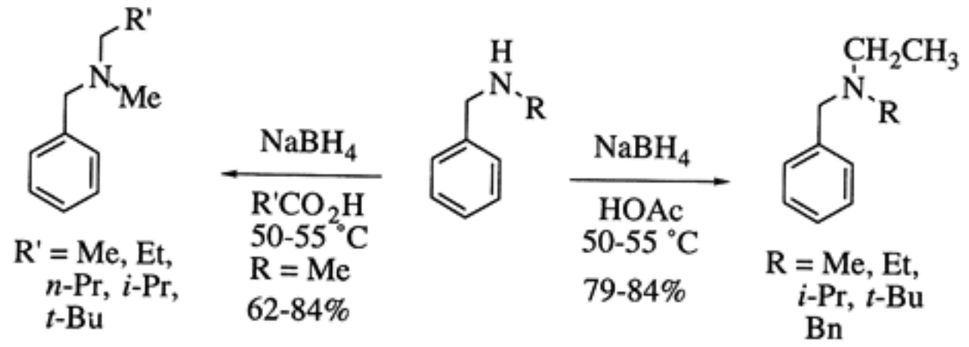
(12)

This very useful aromatic amine alkylation has been employed many times in recent years and a few of the resulting compounds are shown in Scheme 3. In some cases, the alkyl group is derived from added aldehyde or ketone.

Scheme 3

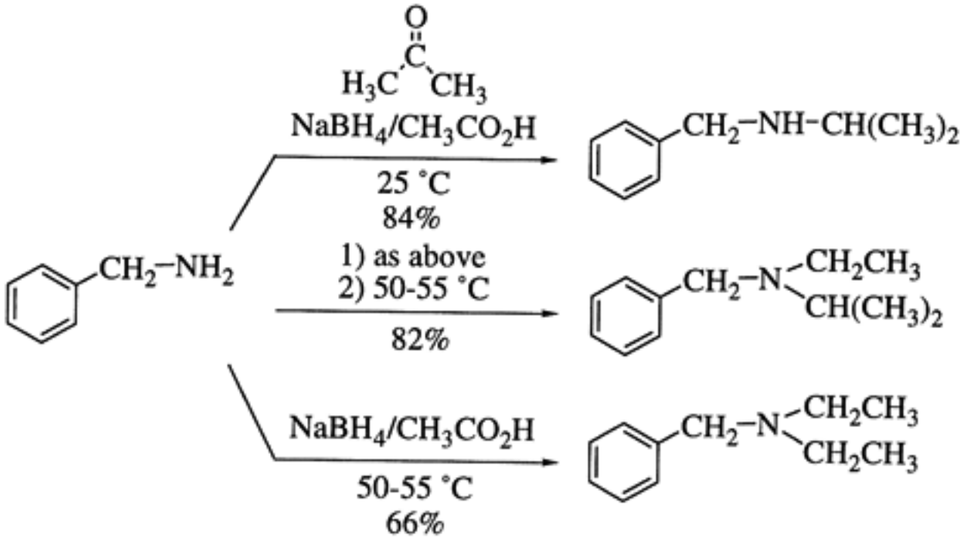


We also discovered that the *N*-alkylation of more basic aliphatic amines could be accomplished with $NaBH_4/RCO_2H$ (*47*). Thus, *N*-alkylbenzylamines can be *N*-ethylated with $NaBH_4$/HOAc and *N*-methylbenzylamine can be *N*-alkylated with $NaBH_4/RCO_2H$ (equation 13).



(13)

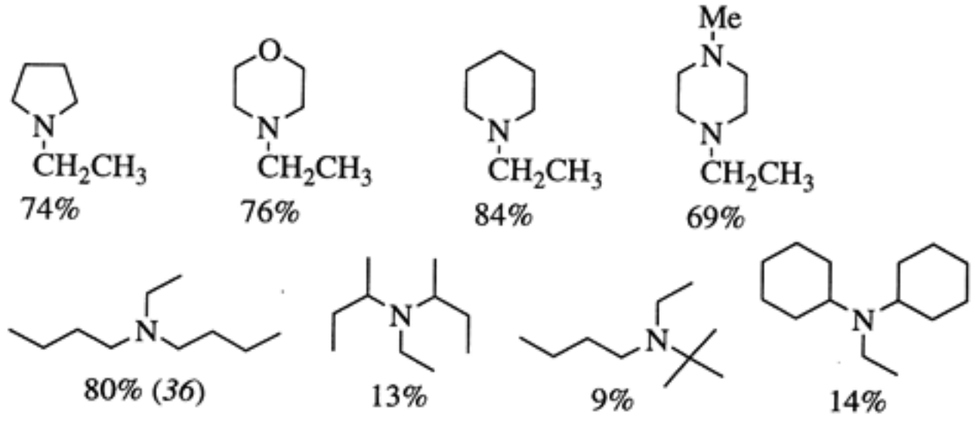
Furthermore, *N*-benzylamine can be manipulated in the same way that aniline can be (Scheme 2), as summarized in equation 14 (*47*). The preparation of the unsymmetrical tertiary amine, *N*-ethyl-*N*-*i*-propylbenzylamine in one pot is noteworthy.



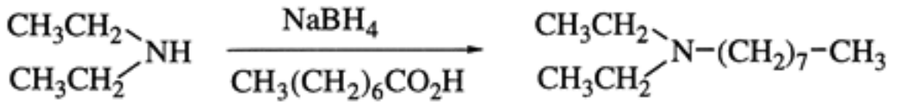
(14)

Some additional aliphatic amines that we have *N*-ethylated using $NaBH_4$/HOAc are shown in Scheme 4 (*47*), Gribble, G.W. Dartmouth College, unpublished results). Only in the case of highly hindered secondary amines or with hindered carboxylic acids does this alkylation proceed poorly.

Scheme 4



Longer chain carboxylic acids can be used to alkylate diethylamine and dimethylamine (equations 15, 16) (*47*).



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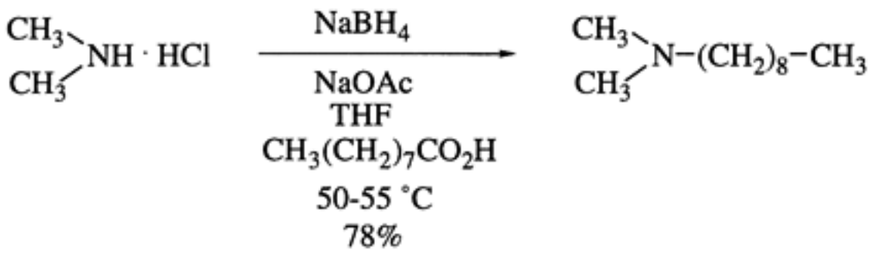
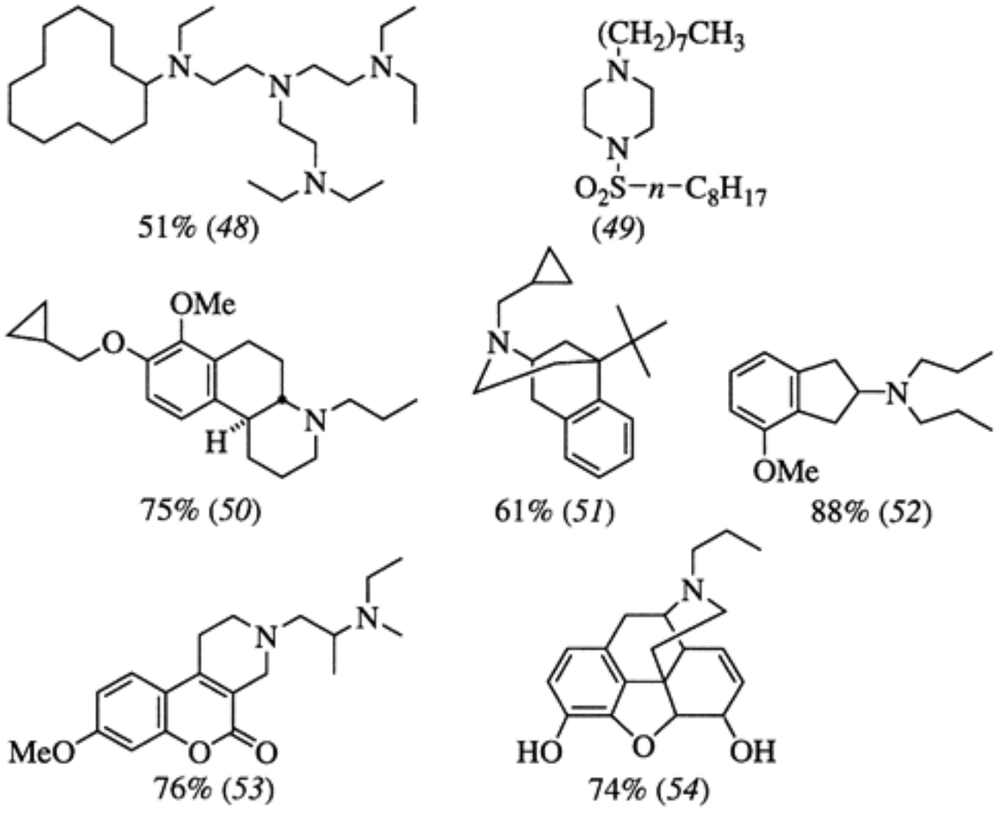


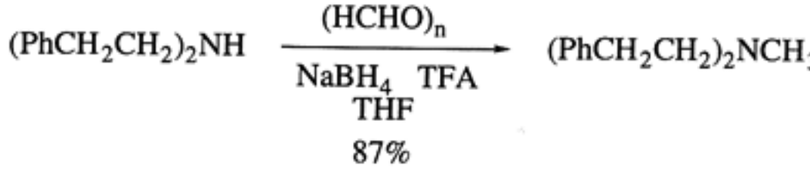
(16)

Several other examples of the *N*-alkylation of aliphatic amines have been described in recent years and a few of these are summarized in Scheme 5. In most examples, either an ethyl or *n*-propyl group has been introduced, and, in some cases, multiple *N*-alkylation is the objective.

Scheme 5



Because the reaction of $NaBH_4$ with formic acid (HCO_2H) is exceptionally vigorous, we have developed an alternative *N*-methylation protocol that utilizes paraformaldehyde in conjunction with $NaBH_4$/TFA or $NaBH_3CN$/HOAc (*55*) (equations 17, 18).



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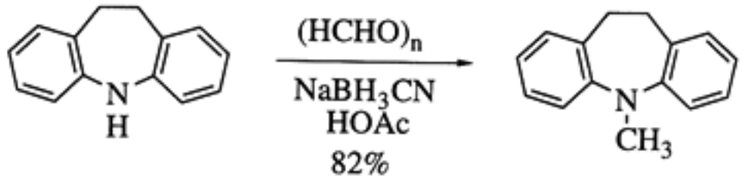
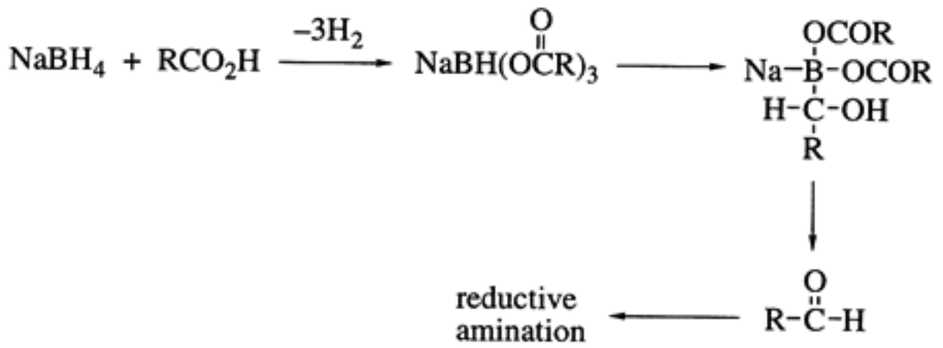


(18)

An important variation on this reductive amination methodology has been developed by Abdel-Magid and is presented in a separate Chapter in this volume.

We believe that the mechanism of the *N*-alkylation of amines with $NaBH_4/RCO_2H$ involves the *in situ* generation of a triacyloxyborohydride species, which forms in the presence of excess carboxylic acid and which has been isolated and characterized (*7*, *9*, *40*, *41*, *56*, *57*). This material then suffers self-reduction to generate either the free aldehyde or a boron species at the aldehyde oxidation level. Reductive amination of this aldehyde species completes the *N*-alkylation sequence (Scheme 6). Control experiments reveal that *N*-acylation is not involved since, for example, neither *N*-acetylindoline nor *N*-acetylindole are reduced to *N*-ethylindoline under the reaction conditions (*7*). However, as will be seen, amides are reduced to amines with the more reactive monotriacyloxyborohydride (*vide infra*). Support for the intermediacy of aldehydes is the fact that added aldehydes readily undergo reductive amination under the reaction conditions (Gribble, G.W. Dartmouth College, unpublished results), and that acetaldehyde can be trapped as its 2,4-DNP derivative from the evolved gases when $NaBH_4$ reacts with excess HOAc (*7*).

Scheme 6

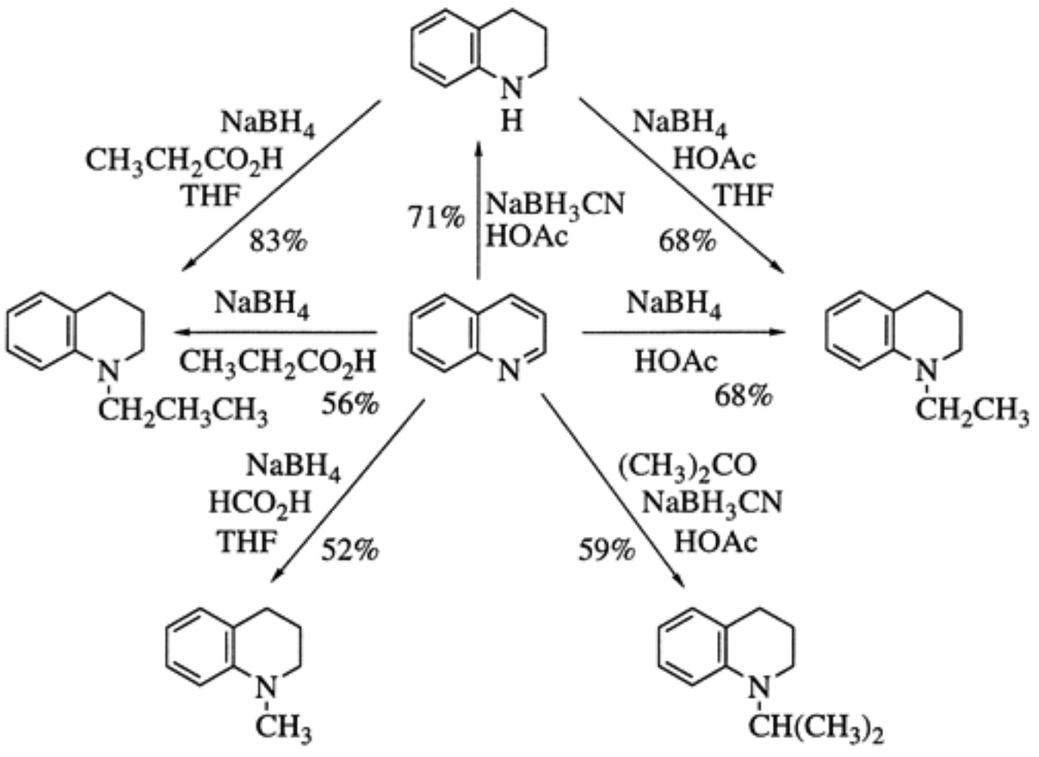


Reduction of Other Heterocycles.

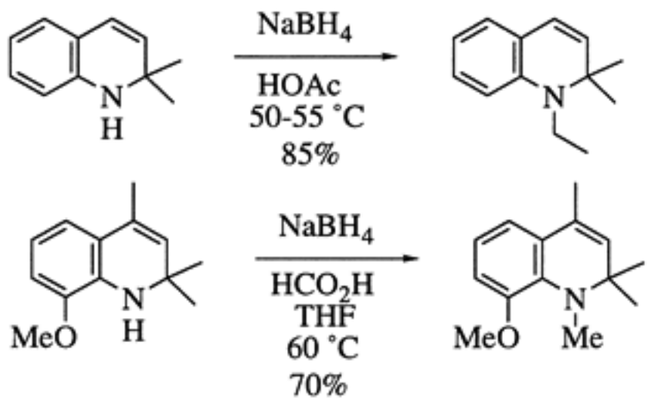
Not surprisingly, a variety of other nitrogen and oxygen heterocycles are reduced and *N*-alkylated by the action of $NaBH_4$ and RCO_2H.

Following an earlier report on the partial reduction of nitroquinolines with $NaBH_4$/HOAc (*58*), we examined this reaction with quinoline and isoquinoline in some detail (*59*). These two heterocycles exhibit a similar reaction manifold as summarized for quinoline in Scheme 7. Once again the reaction conditions may be varied to allow or to avoid *N*-alkylation, and to introduce secondary alkyl groups using a ketone additive.

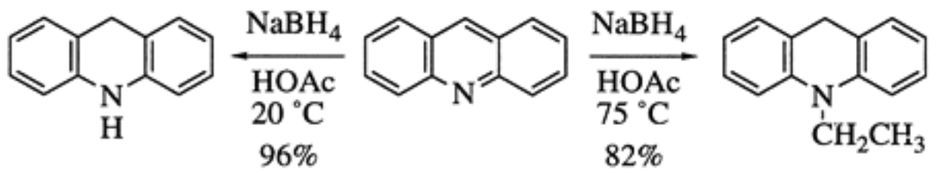
Scheme 7



Interestingly, the isolated double bond in dihydroquinolines is not reduced under the typical reaction conditions (equations 19, 20) (Gribble, G.W. Dartmouth College, unpublished results; *60*).

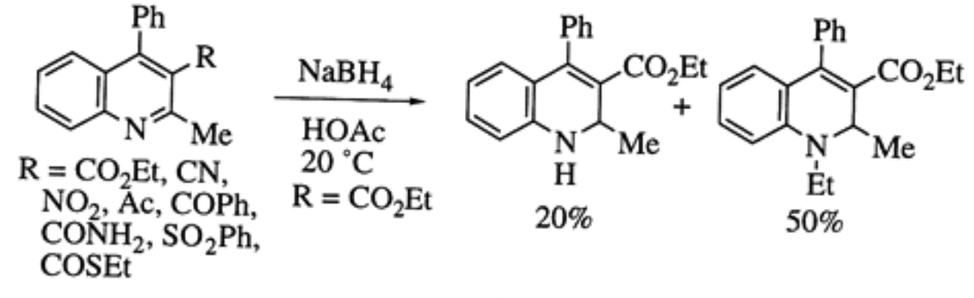


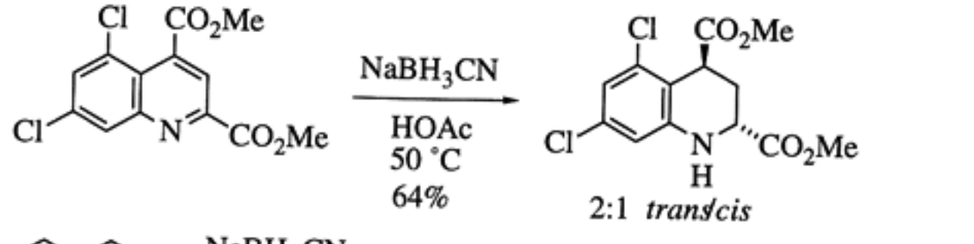
Acridine is reduced to acridan at 20 °C and converted to *N*-ethylacridan at higher temperature (equation 21) (Gribble, G.W. Dartmouth College, unpublished results).

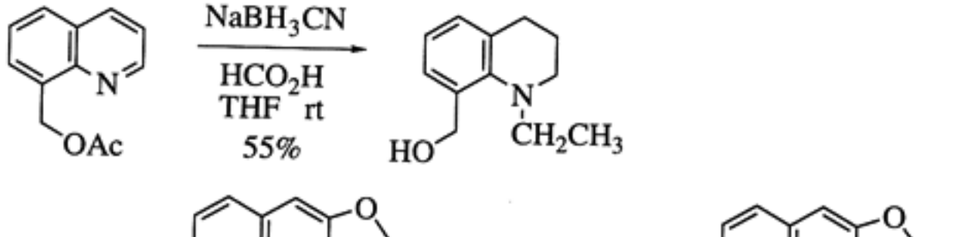


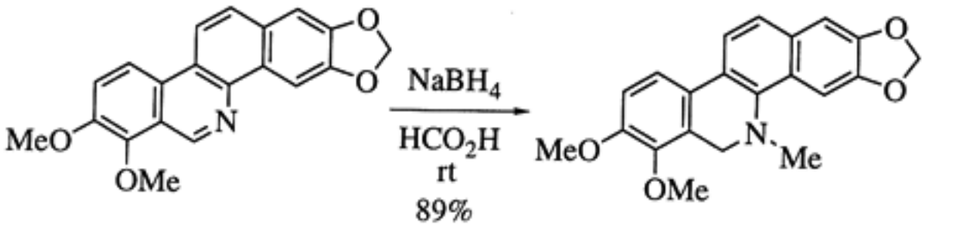
Several other examples of the reduction of quinolines and related heterocycles are summarized in equations 22-27 (*61-66*). The reaction shown in equation 24 involves an interesting migration of the acetyl group (*63*), and the reduction of the ketone in tryptanthrin (equation 26) (*65*) may involve amine-directed hydride transfer

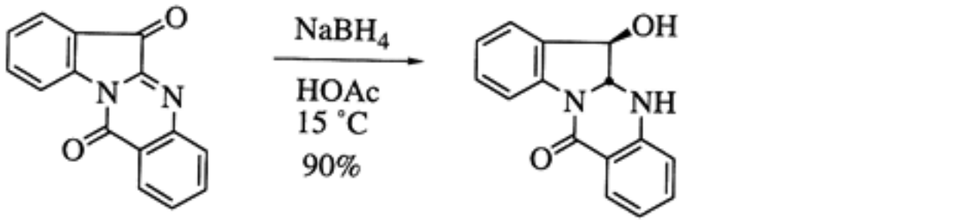
since ketones are normally not reduced under these conditions. The selective *N*-ethylation in equation 27 is noteworthy (*66*).

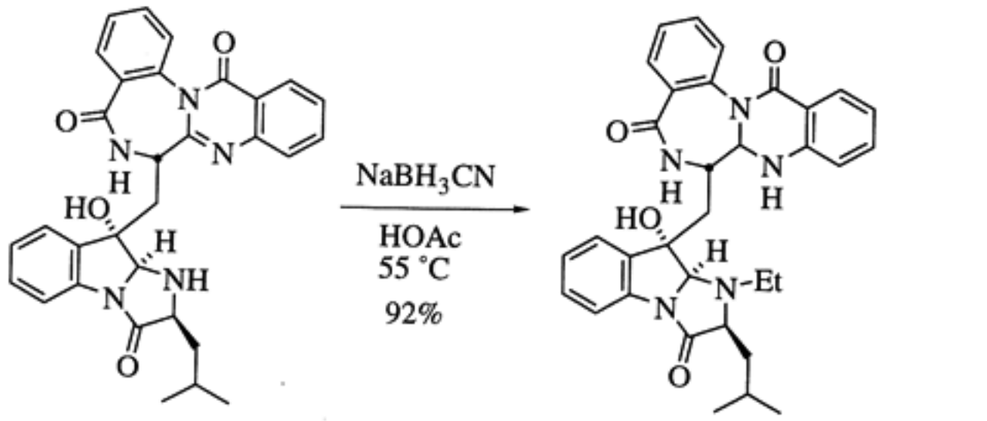






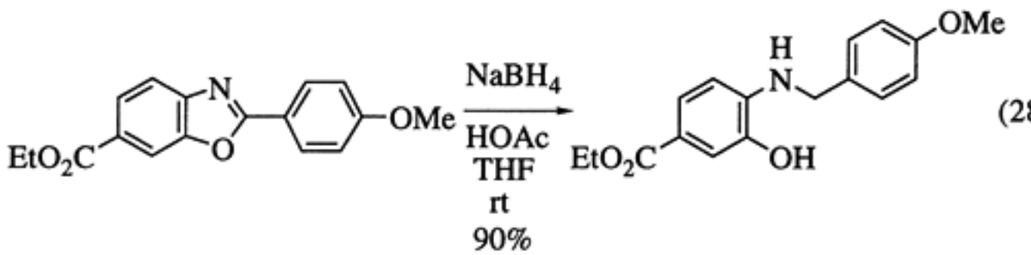




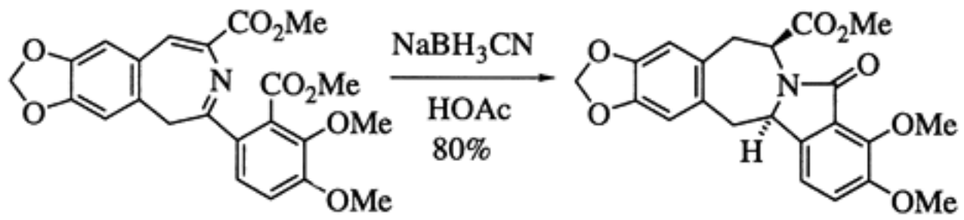


Other examples of imine reduction in nitrogen heterocycles have been uncovered. For example, benzoxazoles undergo reductive cleavage (equation 28) (*67*) and the synthesis of lennoxamine involves imine reduction and subsequent

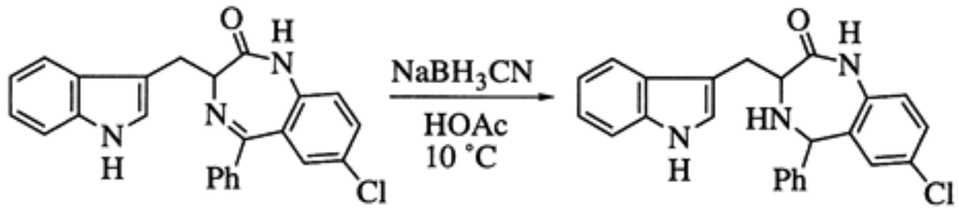
lactamization of a benzazepine (equation 29) (*68*). The imine group in a benzodiazepine is selectively reduced in the presence of an indole double bond (equation 30) (*69*). Presumably, the (protonated) basic nitrogen protects the indole ring towards protonation. A recent study of the reduction of indeno[1,2-*b*]quinoxalines and benzo[*b*]phenazines has been reported (e.g., equation 31) (*70*).



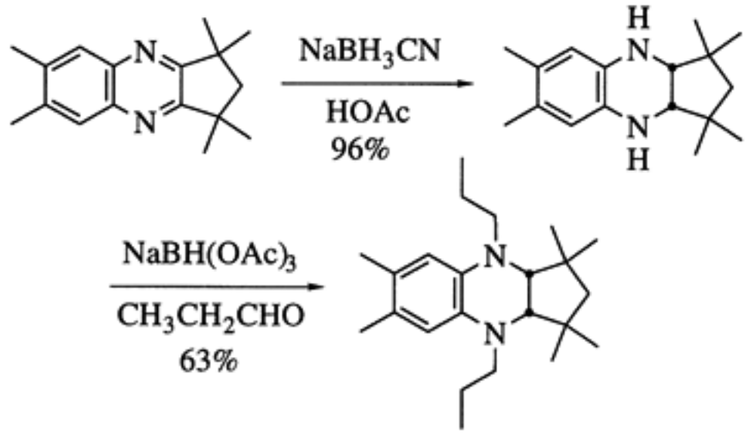
(28)



(29)

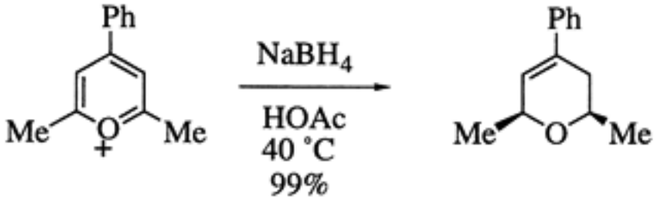


(30)



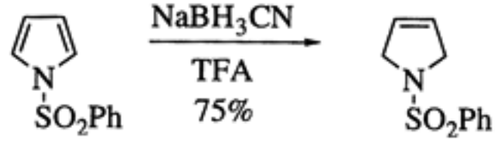
(31)

In a series of papers, Balaban and his colleagues have utilized $NaBH_4$/HOAc to reduce pyrylium salts (equation 32) (*71-74*).



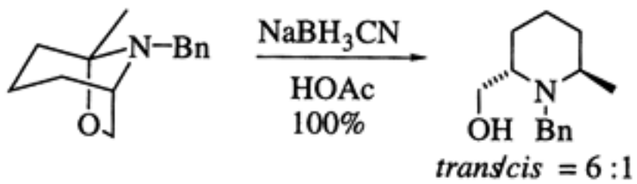
(32)

Although our early attempts to reduce simple pyrroles were unsuccessful (Gribble, G.W. Dartmouth College, unpublished results), Ketcha has succeeded in reducing *N*-(phenylsulfonyl)pyrroles with $NaBH_3CN$/TFA (equation 33) (*75*). The fully reduced compounds are minor products.

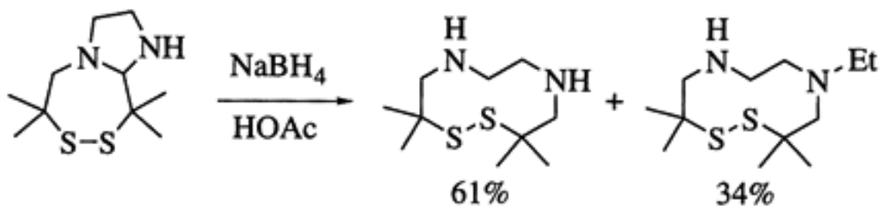


(33)

Saturated heterocycles are reductively cleaved under these conditions, analogous to the reaction of acetals (*vide infra*). Two examples are shown (equations 34, 35) (*76, 77*).



(34)

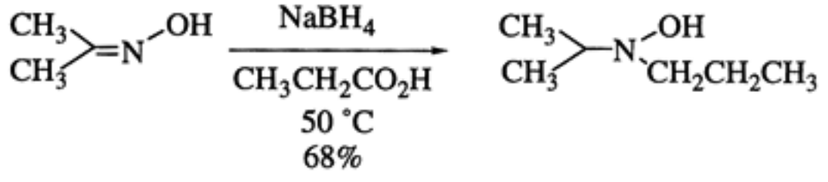


(35)

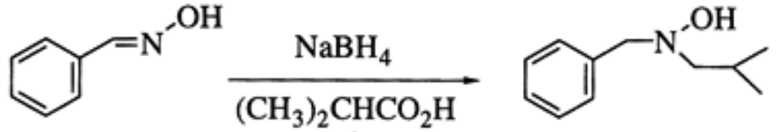
Reduction of Oximes, Imines, Enamines and Related Compounds.

Not surprisingly, in view of the facile reductions of indole, quinoline, and related heterocycles with $NaBH_4/RCO_2H$ (*vide supra*), a wide range of C=N compounds are also transformed with these reagents. Moreover, compounds, such as enamines and enamides that can be protonated to form iminium ions are also readily reduced. An earlier review documents many examples of this type (*9*).

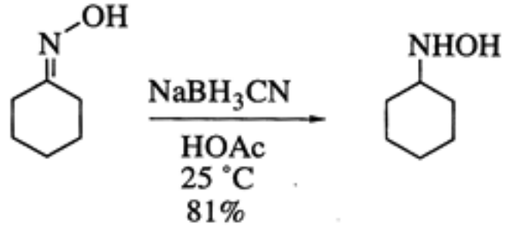
Oximes can be reduced and *N*-alkylated under the influence of $NaBH_4/RCO_2H$ and this procedure represents an excellent way to prepare unsymmetrical *N,N*-dialkylhydroxylamines (*78*). Three examples are shown (equations 36-38). Once again, alkylation can be suppressed by using $NaBH_3CN$ (equation 38).



(36)

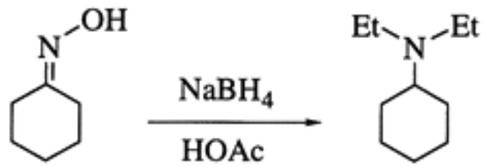


(37)

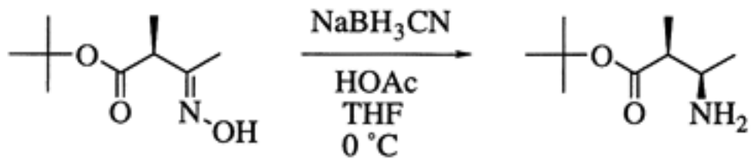


(38)

In some cases, over-reduction results (equations 39, 40) (*78, 79*).



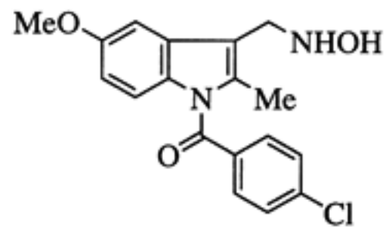
(39)



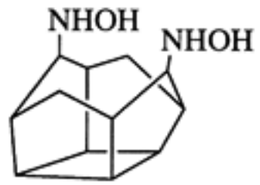
(40)

Several workers have exploited this methodology to reduce oximes or oxime ethers and the products of these reactions are summarized in Scheme 8.

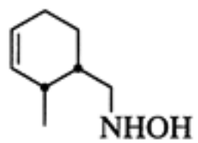
Scheme 8



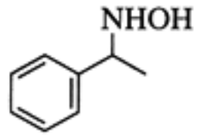
(*81*)



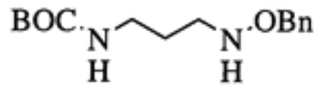
85% (*81*)



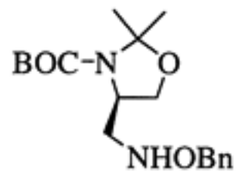
64% (*82*)



67% (*83*)

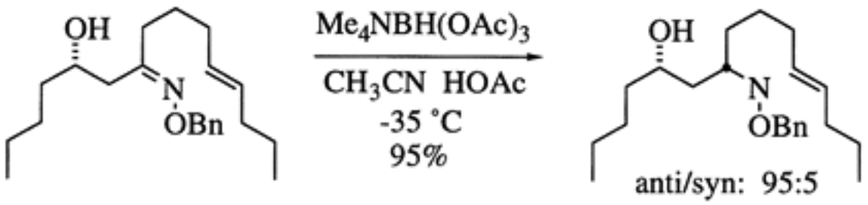


70% (*84*)



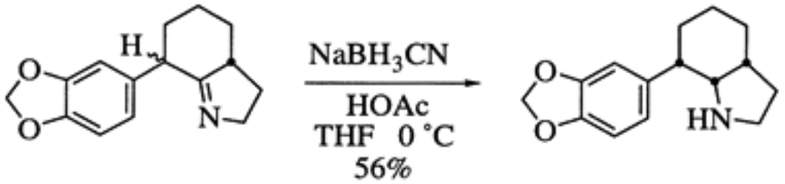
76% (*85*)

Furthermore, Williams has described the hydroxy-directed reduction of oxime ethers using the isolated reagent $NaBH(OAc)_3$ (equation 41) (*86*), a powerful tactic that will be discussed again in the reduction of β-hydroxy ketones.

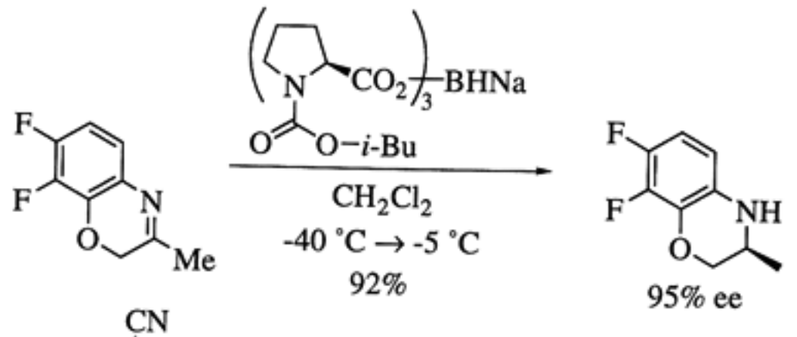


(41)

A number of simple imines are reduced with $NaBH_4$ or $NaBH_3CN$ in carboxylic acids, as tabulated in equations 42-44 (*87-89*).



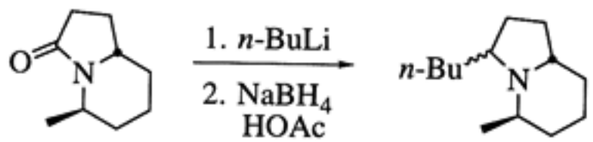
(42)



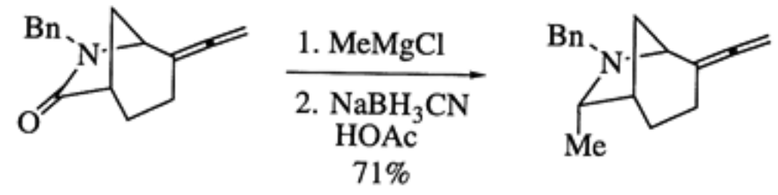
(43)

(44)

The imine-immonium ion can be generated *in situ* as illustrated by the examples in equations 45, 46 (*90*, *91*).



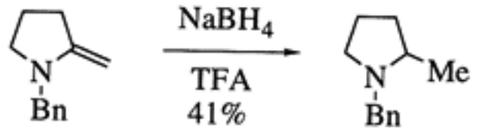
(45)



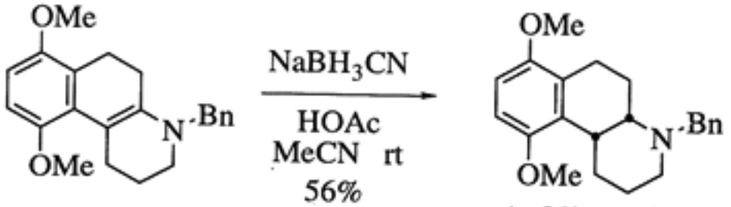
(46)

The combination of $NaBH_3CN$/TFA reduces all eight imine units in a four-fold bridged double-decker prophyrin (*92*).

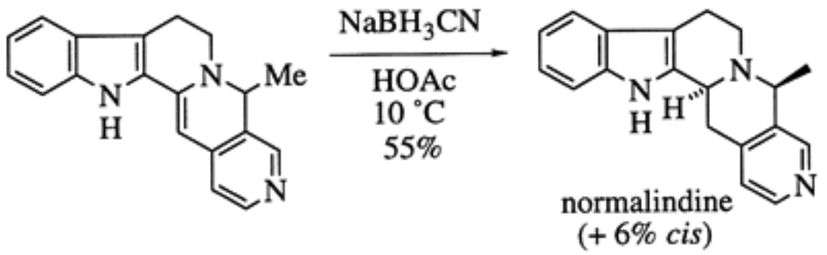
Following the early studies of Marshall and Johnson (*4-6*) and the subsequent exhaustive study by Hutchins (*93*), several recent examples of enamine reduction using $NaBH_4$ or $NaBH_3CN$ in carboxylic acids have been described (equations 47-50) (*94-98*). Normalindine (equation 49) can also be reached via the same reduction from the exocyclic enamine (*97*).



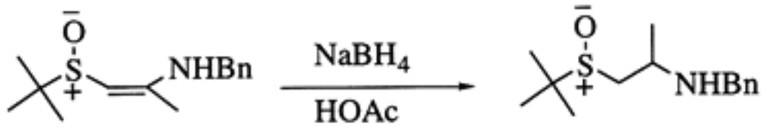
(47)



(48)

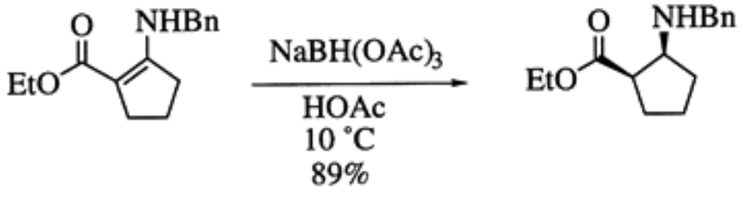


(49)

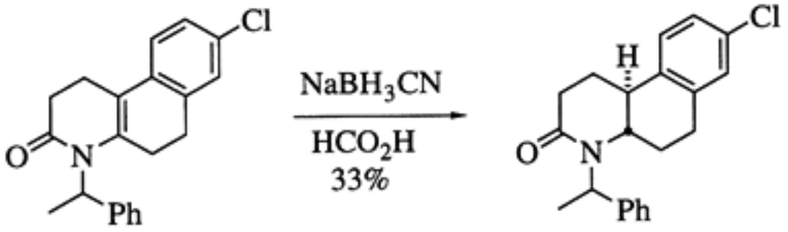


(50)

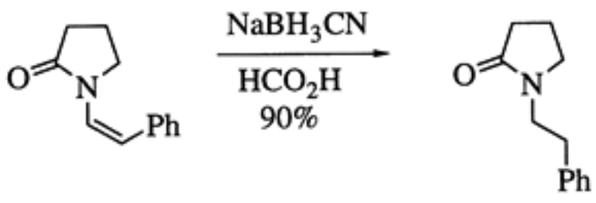
Similarly, enamides, vinylogous amides, and related compounds are generally smoothly reduced to their saturated analogues, and some recent cases are depicted in equations 51-55 (*99-103*). The Bartoli chemistry (equation 51) is highly diastereoselective (*99*), and the reaction shown in equation 52 was actually performed on a homochiral substrate to give diastereomers (*100*).



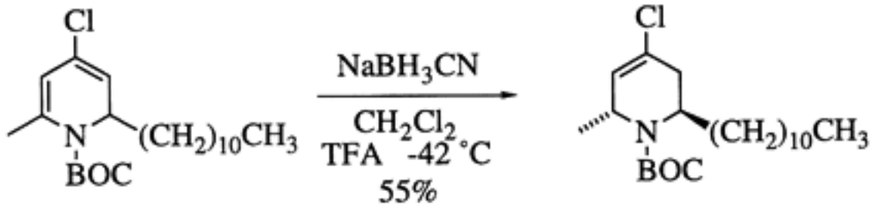
(51)



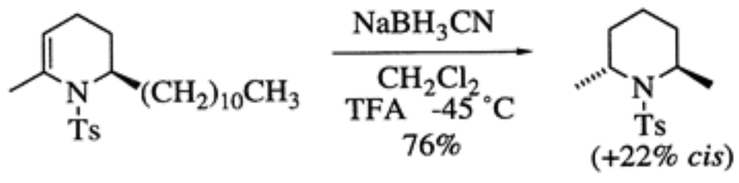
(52)



(53)

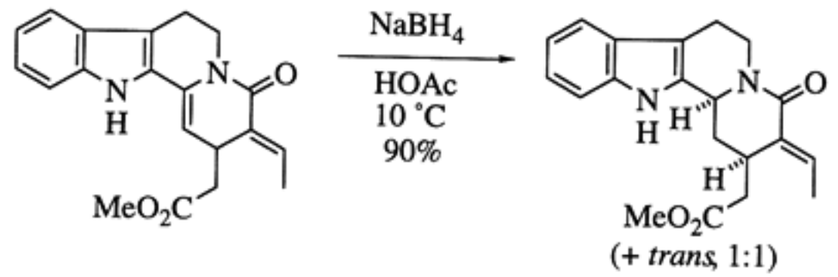


(54)

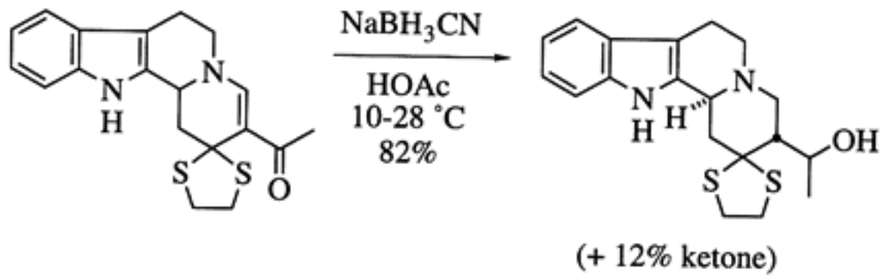


(55)

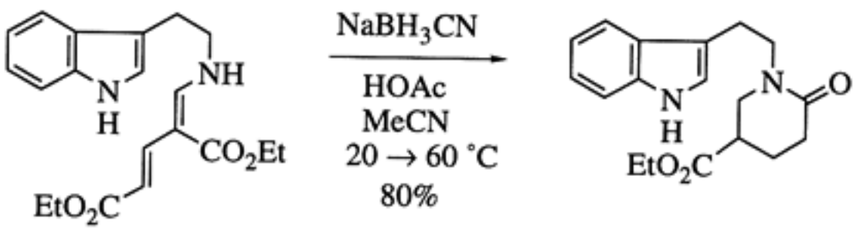
Several such reductions are known from the indole field (equations 56-59) (*104-107*), including Djerassi's original observation (equation 7) (*28*). As expected, the indole double bond is impervious to these reduction conditions.



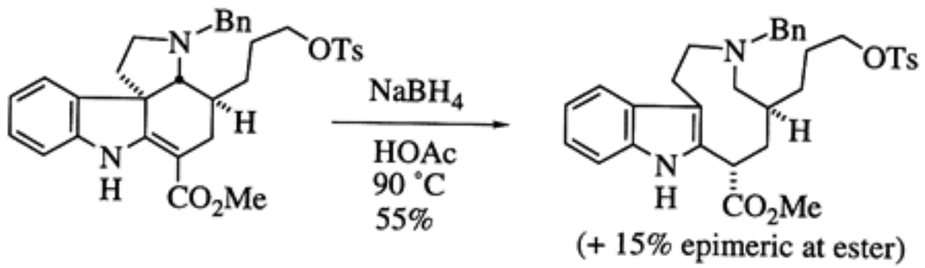
(56)



(57)



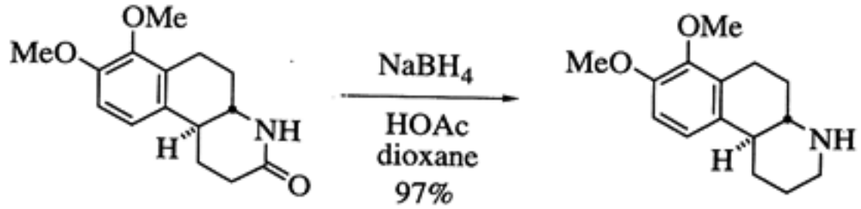
(58)



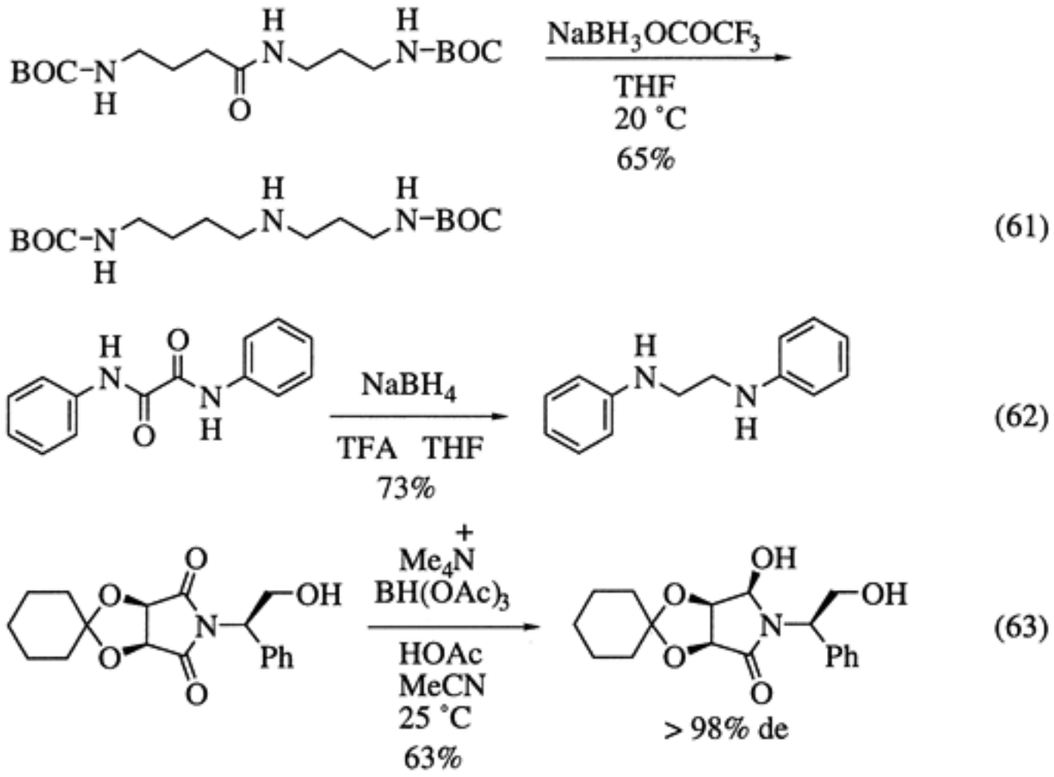
(59)

Reduction of Amides.

It has been seen that amides survive unscathed in the reaction medium presented thus far, which generates $NaBH(OCOR)_3$ species (excess RCO_2H). Umino and his colleagues discovered that amides are, in fact, reduced to amines under conditions that generate the more reactive $NaBH_3OCOR$ species (*108*). This important extension of the $NaBH_4/RCO_2H$ technology has been utilized by several groups to reduce amides and lactams (*9*). A few recent examples are tabulated in equations 60-63 (*109-112*). The selectivity in equations 61 and 63 is noteworthy, and the latter reduction is thought to involve hydroxyl participation since the OTBS ether is not reduced (*112*).

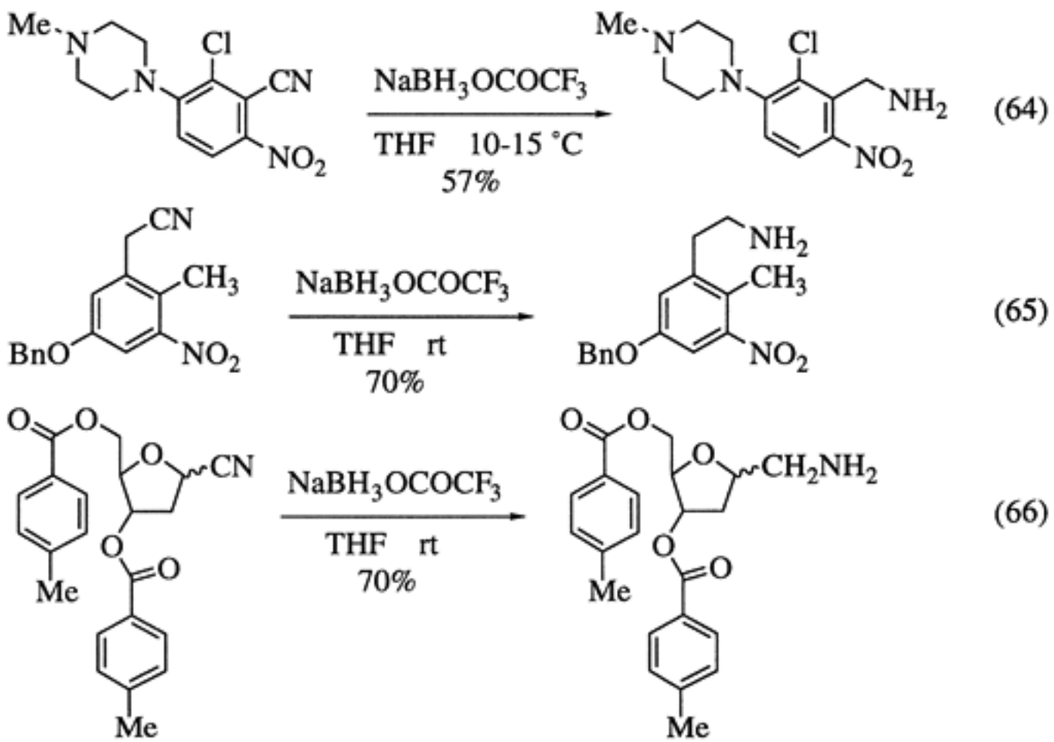


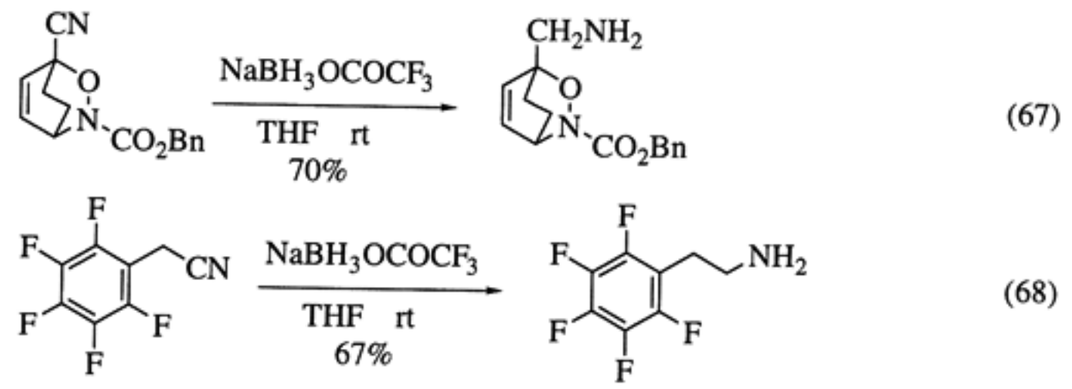
(60)



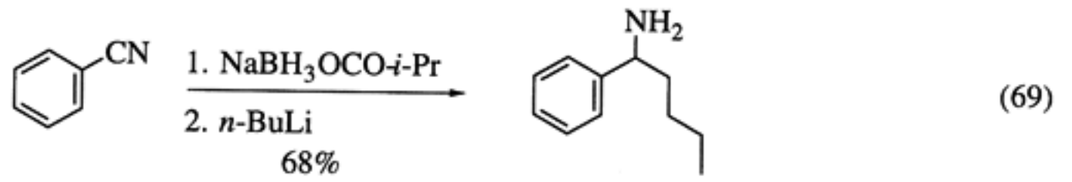
Reduction of Nitriles.

Umino also discovered that nitriles can be reduced to primary amines with $NaBH_3OCOCF_3$, but poorly with $NaBH_3OAc$ (*113*). A few recent cases are shown here (equations 64-68) (*114-117*, Gribble, G.W. Dartmouth College, unpublished results). The lack of nitro group reduction is particularly noteworthy since conventional reduction methods would invariably reduce the nitro group before the cyano group.



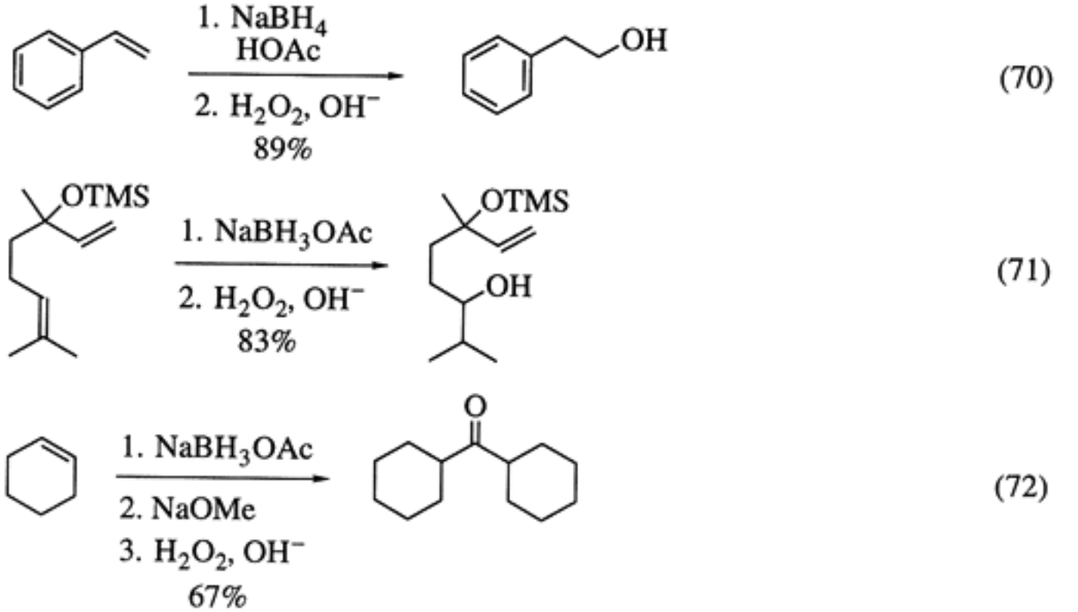


Itsuno has been able to trap the *N*-boryl imines, generated from nitriles and $NaBH_3OCOR$, with alkyllithium reagents to give amines (e.g., equation 69) (*118*).



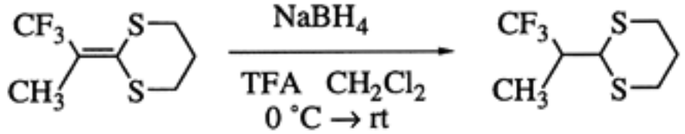
Hydroboration of Alkenes.

Marshall and Johnson also described the use of $NaBH_4$/HOAc to hydroborate alkenes (*119*), and several recent examples and variations have been reported (*9*). A few recent examples are illustrated in equations 70-72 (*120-122*). The $NaBH_3OAc$ in equations 70 and 71 can also be generated from $NaBH_4$ and $Hg(OAc)_2$ (*120, 121*). In related chemistry, organomercurials can be reduced with $NaBH(OAc)_3$ (*123*).

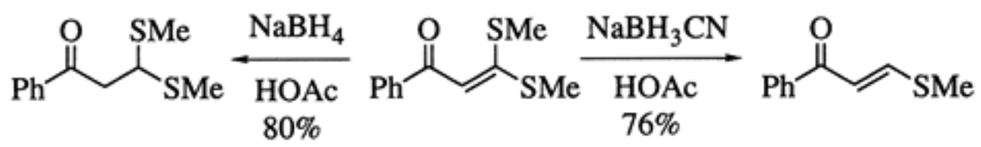


Reduction of Alkenes.

In addition to hydroboration, alkenes can be reduced to alkanes in a few cases. The first such example was our observation that 1,1-diphenylethylene was reduced to 1,1-diphenylethane with $NaBH_4$/TFA in 93% yield, undoubtedly via the highly stabilized carbocation (*124*). However, only a few other examples of alkene reductions with $NaBH_4/RCO_2H$ have been reported (e.g., equations 73, 74) (*125, 126*).



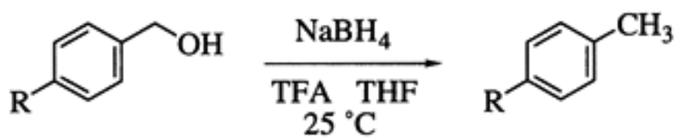
(73)



(74)

Reduction of Alcohols.

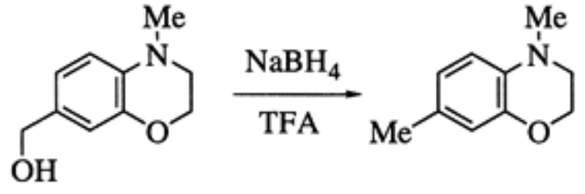
Early in our research program, when we realized that trifluoroacetic acid (TFA) and $NaBH_4$ were reasonably compatible, we thought that benzylic alcohols would be reduced to hydrocarbons under these conditions, since TFA is an excellent solvent for solvolysis and other S_N1 reactions (ionizing power Y value = 1.84). Indeed, diphenylmethanol and triphenylmethanol are reduced to diphenylmethane and triphenylmethane in 93% and 99% yields, respectively (*124*). The reaction is very general for di- and triarylcarbinols but is poorer for monobenzylic alcohols (*9*, *124*) where the more reactive intermediate carbocations undergo side reactions (*9*). However, Nutaitis has found that the more reactive $NaBH_3OCOCF_3$ can reduce certain monobenzylic alcohols (equation 75) (*127*). Secondary and tertiary monobenzylic alcohols give higher yields.



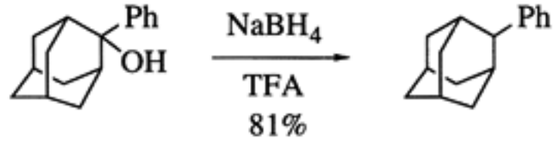
(75)

R	%
Me_2N	78%
OH	45%
SMe	41%
OMe	19%
Me	0%
Ph	0%

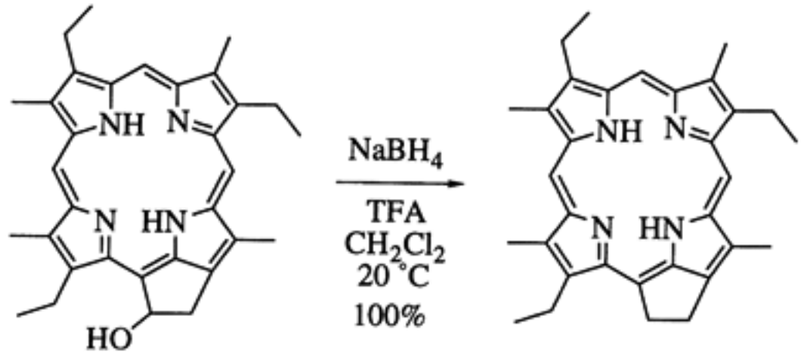
Some other recent examples of the reduction of monobenzylic alcohols are cited in equations 76-78 (*128-130*). Interestingly, Olah has found that $NaBH_4/CF_3SO_3H$ is even more effective (98%) in reducing the alcohol shown in equation 77 (*129*). The selective deoxygenation shown in equation 78 is remarkable indeed (*130*).



(76)

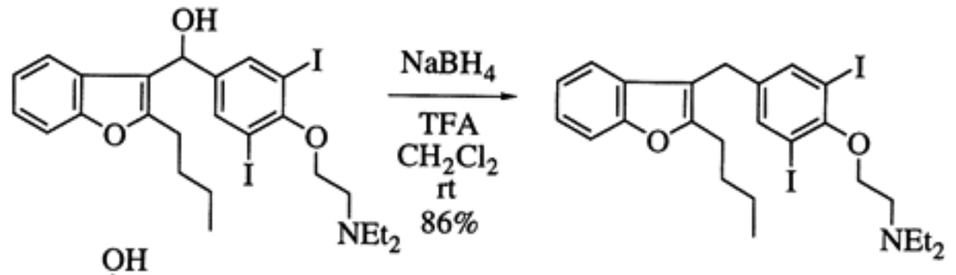


(77)

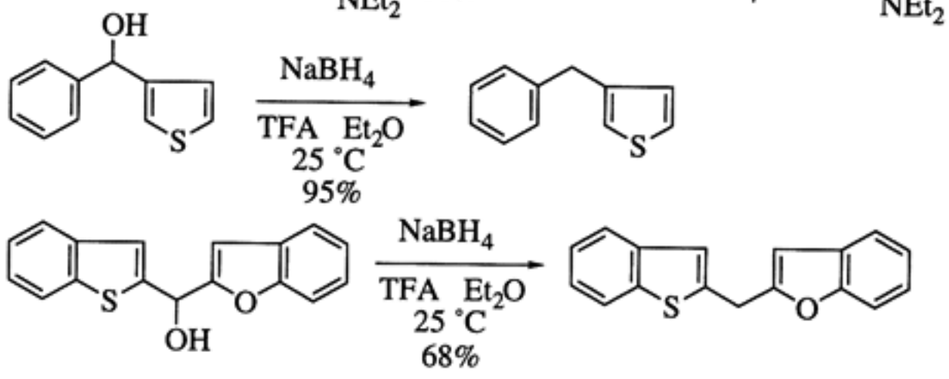


(78)

Following an initial result by Kabalka (*131*), Nutaitis and his coworkers have shown that a wide range of doubly-benzylic heterocyclic alcohols are reduced by $NaBH_4$/TFA to the corresponding hydrocarbons (equations 79-81) (*131*, *132*).



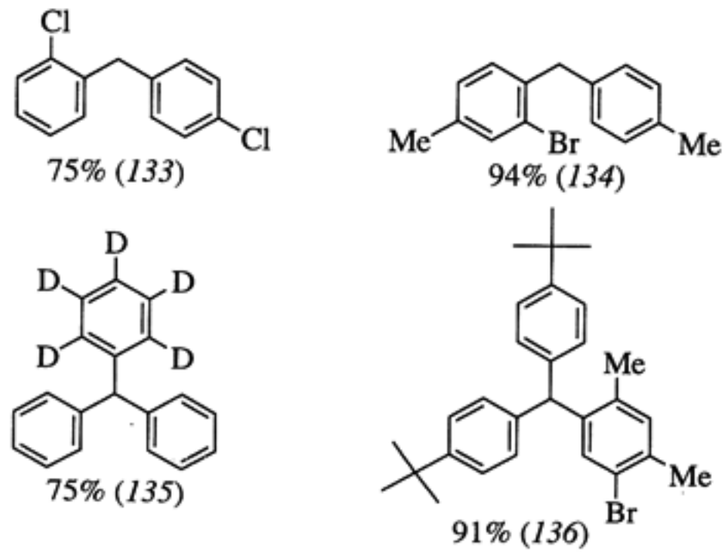
(79)



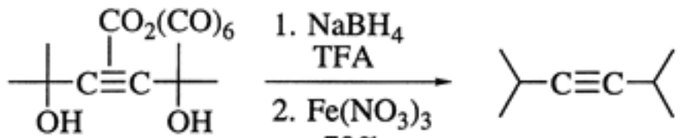
(80) (81)

Other substrates that have been recently synthesized from the corresponding benzyl alcohols and $NaBH_4$/TFA are listed in Scheme 9 (see also *137*).

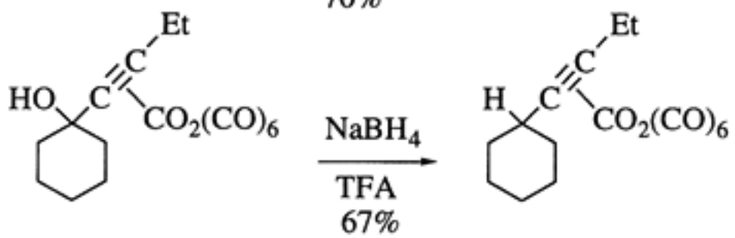
Scheme 9



Nicholas has shown that acetylenic diol cobalt complexes are smoothly deoxygenated with $NaBH_4$/TFA (equations 82, 83) (*138*, *139*).

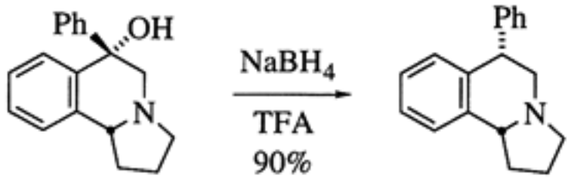


(82)

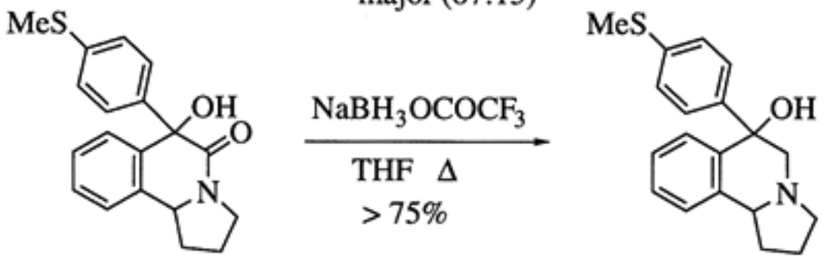


(83)

The enormous power and versatility of the $NaBH_4$/TFA reducing system is beautifully revealed by the companion reactions discovered by Maryanoff and his colleagues (equations 84, 85) (*140*). In the first reaction, the alcohol is reduced by $NaBH(OCOCF_3)_3$ in the presence of excess TFA, but, in the second reaction, the more reactive $NaBH_3OCOCF_3$ reduces only the lactam since excess TFA is not present.



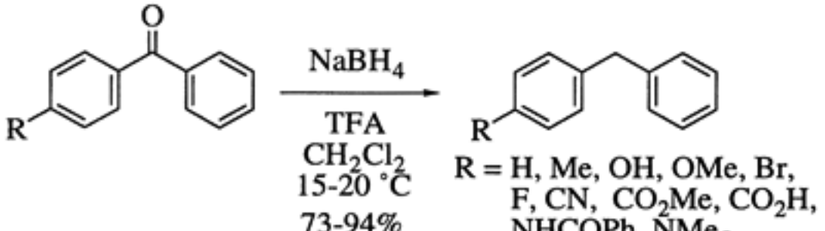
(84)



(85)

Reduction of Ketones to Hydrocarbons.

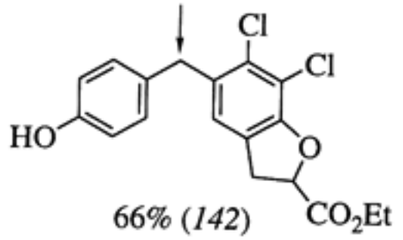
During our early research on the reduction of diarylmethanols to diarylmethanes (*124*) (*vide supra*), we also discovered that benzophenone is reduced to diphenylmethane with $NaBH_4$/TFA in 92% distilled yield (*124*). Subsequent studies in our laboratory revealed the generality of this novel and efficient reduction method (equation 86) (*141*). A range of functional groups tolerates these reaction conditions and the reaction only fails or fares poorly when the ketone is highly hindered (dimesityl ketone) or contains a nitro group (*141*, *9*).



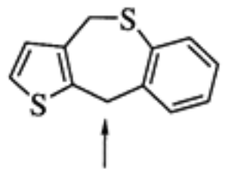
(86)

Some recent compounds that have been synthesized by the action of $NaBH_4$/TFA on the corresponding ketone (indicated by an arrow) are listed in Scheme 10. The $NaBH_3CN$/TFA reaction leading to the pyrrole imide (*147*) appears to be the first reduction of a formyl group to a methyl group using this methodology.

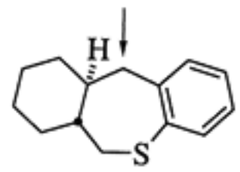
Scheme 10



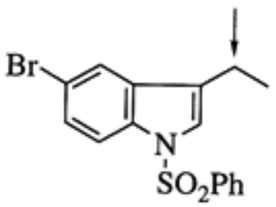
66% (*142*)



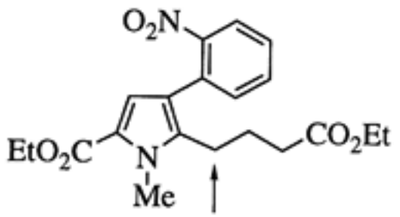
89% (*143*)



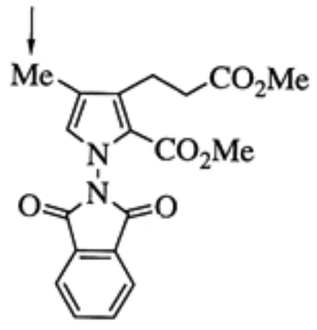
74% (*144*)



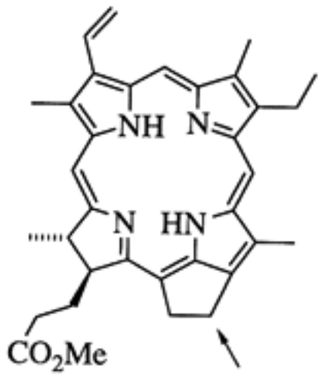
94% (*145*)



88% (*146*)



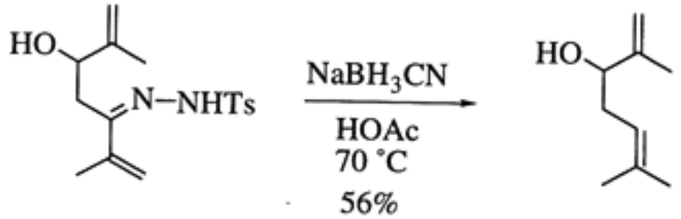
60% (*147*)



86% (*148*)

The reaction of 2-iodo-3-acetyl-*N*-(phenylsulfonyl)indole with $NaBH_4$/TFA gives 3-ethyl-*N*-(phenylsulfonyl)indole (75% yield) (*145*). This appears to be the first example of dehalogenation with $NaBH_4/RCO_2H$.

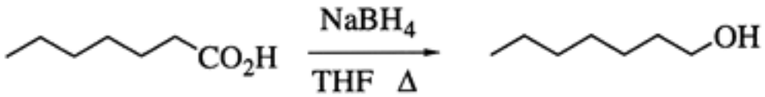
In related chemistry discovered sometime ago, Hutchins utilized $NaBH_4$/HOAc to reduce the tosylhydrazones of aldehydes and ketones to hydrocarbons (*149*). A recent example of this reaction is shown in equation 87 (*150*).



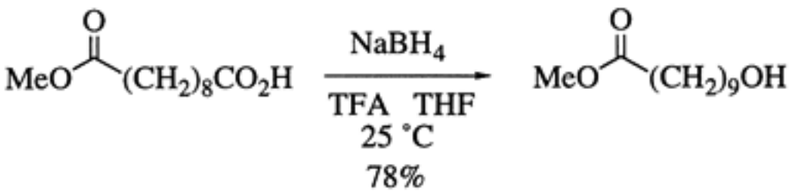
(87)

Reduction of Carboxylic Acids and Esters.

In view of the facile reduction of carboxylic acids to aldehydes with $NaBH_4$, via acyloxyborohydrides, it is not surprising that complete reduction to primary alcohols has been observed by two groups (equations 88, 89) (*151*, *152*), following the pioneering work by Liberatore and colleagues (*40*).

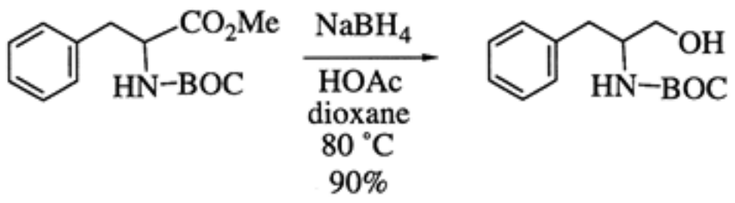


(88)



(89)

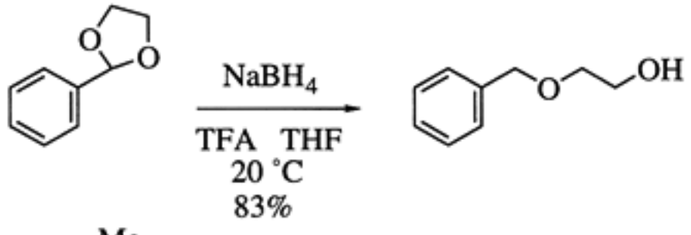
The only report of the $NaBH_4/RCO_2H$ reduction of an ester group appears to be that shown in equation 90 (and related examples) (*153*).



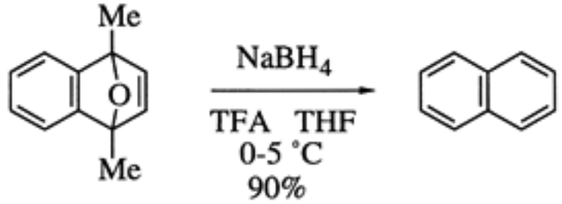
(90)

Reductive Cleavage of Acetals, Ketals and Ethers.

As might be anticipated, the action of $NaBH_4/RCO_2H$ effects the cleavage of acetals, ketals, ethers and related compounds (*9*). We have reported both the reductive cleavage of cyclic acetals and ketals (e.g., equation 91) (*154*) and the reductive deoxygenation of 1,4-epoxy-1,4-dihydronaphthalenes (e.g., equation 92) (*155*). We utilized the latter reaction in the synthesis of a dimethylbenzo[*b*]carbazole (equation 93) (*156*).



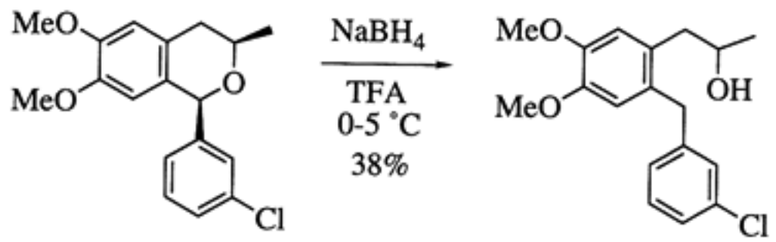
(91)



(92)

(93)

The reductive cleavage of isochromanes with $NaBH_4$/TFA has recently been described (equation 94) (*157*).



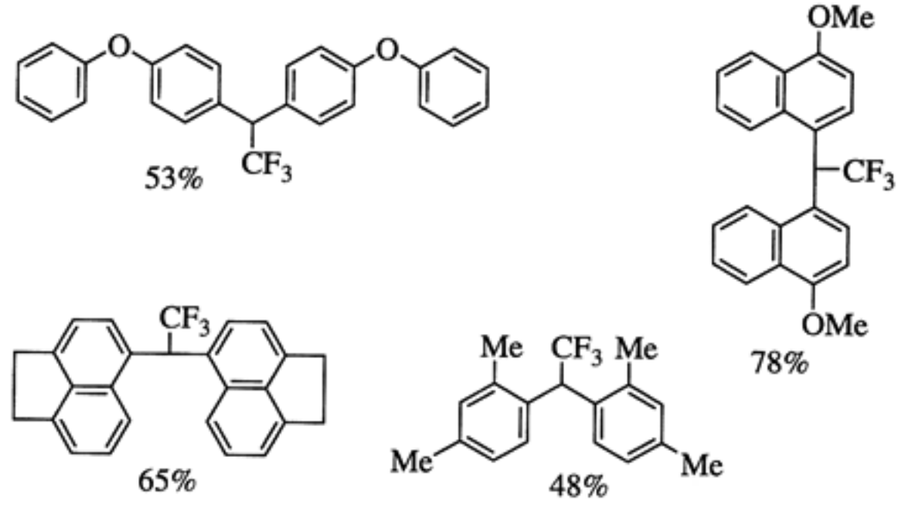
(94)

Friedel-Crafts Alkylation of Arenes.

During our investigation of the reaction of indole with $NaBH_4$/TFA, we observed the formation of the interesting "Baeyer condensation" product **10** (*9*, *12*). This compound presumably arises from the reaction between indoline and trifluoroacetaldehyde, analogous to the synthesis of DDT from chlorobenzene, trichloroacetaldehyde, and H_2SO_4.

This reaction is reasonably general and the products shown in Scheme 11 have been prepared using this method (arene/$NaBH_4$/TFA) (*158*). With sterically congested arenes (e.g., mesitylene, durene), the reaction stops at the carbinol stage (34% and 15%, respectively).

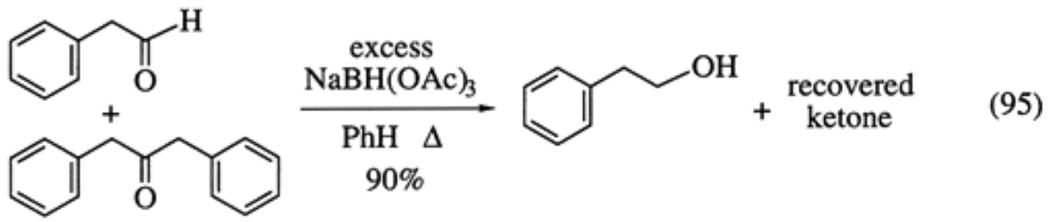
Scheme 11



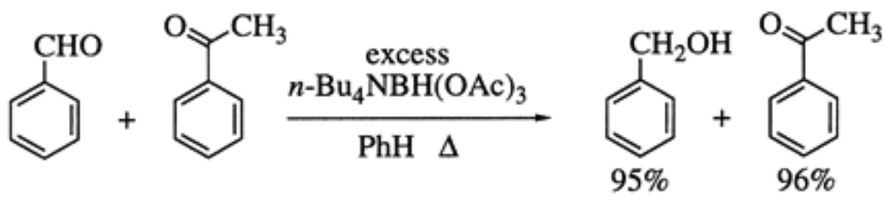
Selective Aldehyde Reduction

Early in our work with $NaBH_4/RCO_2H$, we observed that aldehydes and, especially, ketones are reduced much more slowly to alcohols by $NaBH_4$/HOAc than in conventional alcoholic or aqueous media. Indeed, this is why the *N*-alkylation of amines in this medium is successful! For example, although benzaldehyde is completely reduced to benzyl alcohol after 1 hr at 15 °C with a large excess of $NaBH_4$ in glacial HOAc, acetophenone is only reduced to the extent of 60% at 25 °C after 40 hr (*9*, Gribble, G.W. Dartmouth College, unpublished results).

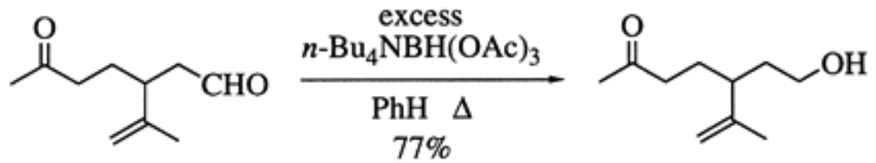
These and related observations paved the way for the chemoselective reduction of aldehydes, in the presence of ketones. We found that the isolated reagents ($NaBH(OAc)_3$ (*56*) or *n*-$Bu_4NBH(OAc)_3$ (*159*) in benzene worked extremely well in this regard (equations 95-97). For other examples, see ref. *9*.



(95)



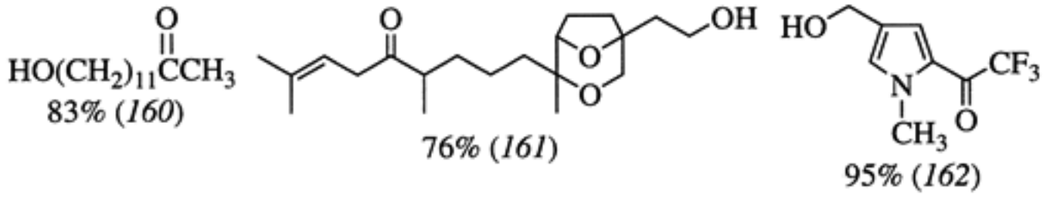
(96)



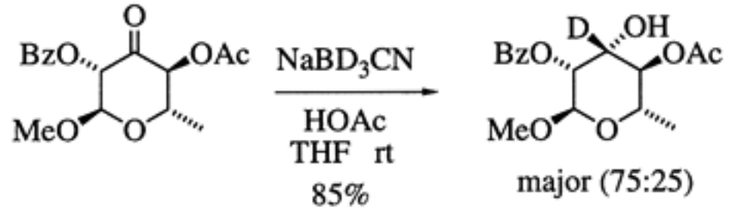
(97)

More recently, other workers have exploited this method for the selective reduction of aldehydes in the presence of ketones (Scheme 12). In each case, the primary alcohol was derived from the corresponding ketoaldehyde using $NaBH(OAc)_3$ in benzene.

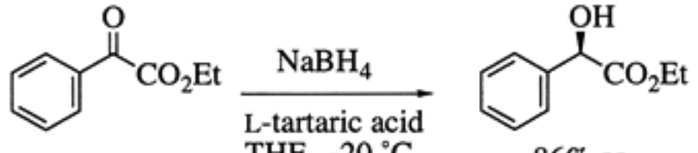
Scheme 12



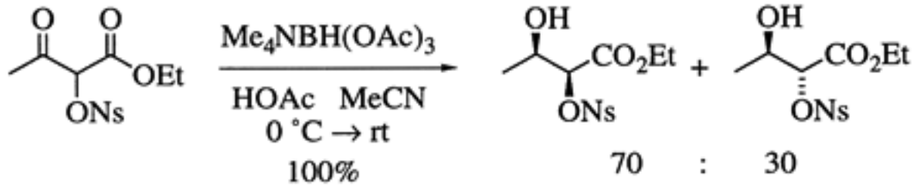
Intrinsically more reactive ketones (cyclic, α- and β-keto) are reduced by $NaBH_4/RCO_2H$ and some recent examples are shown in equations 98-100 (*163-165*).



(98)

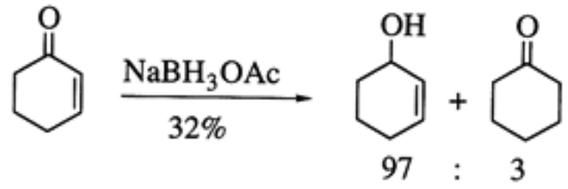


(99)

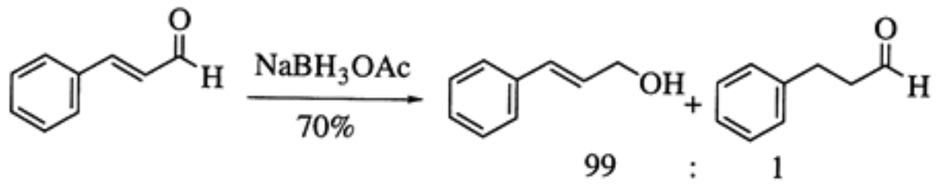


(100)

Nutaitis has studied the reduction of enones with $NaBH_4$/HOAc, conditions which give 1,2-reduction (equations 101-102) (*166*).



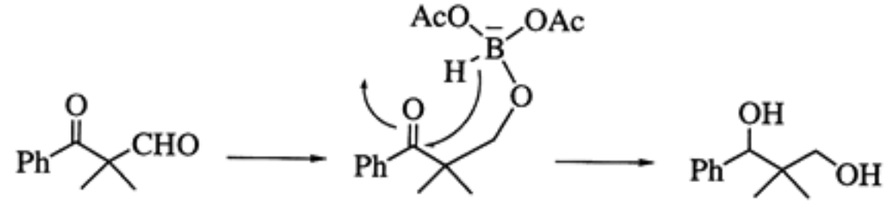
(101)



(102)

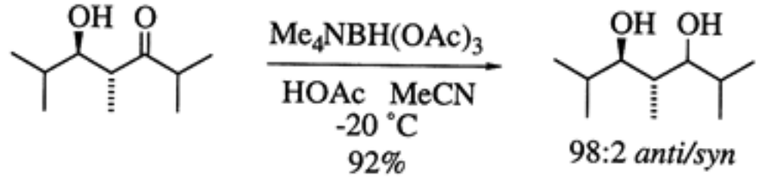
Hydroxyl-Directed Carbonyl Reduction.

During our studies on the chemoselective reduction of aldehydes, we reported the reduction of the ketoaldehyde shown in equation 103 with n-$Bu_4NBH(OAc)_3$ and postulated an intramolecular hydride delivery as illustrated (*159*).

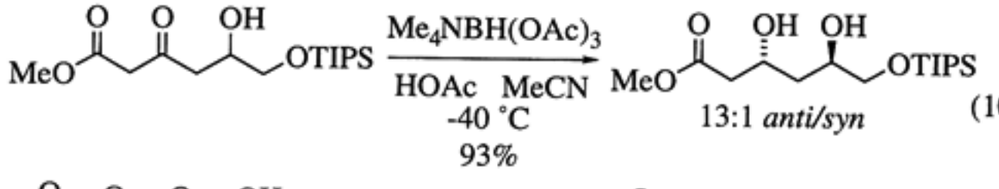


(103)

During our studies, Saksena reported the same reaction of $NaBH(OAc)_3$ with β-hydroxyketones in steroidal systems (*167*). In particular, he observed excellent stereoselectivities of this (intramolecular) hydride reduction. Subsequently, Evans developed this novel reduction into an extraordinarily useful stereoselective reduction method of β-hydroxyketones (*168, 57*), and he fully characterized several of the $MBH(OAc)_3$ reagents for the first time. Examples of this reduction procedure are listed in equations 104-110 (*168-174*).



(104)



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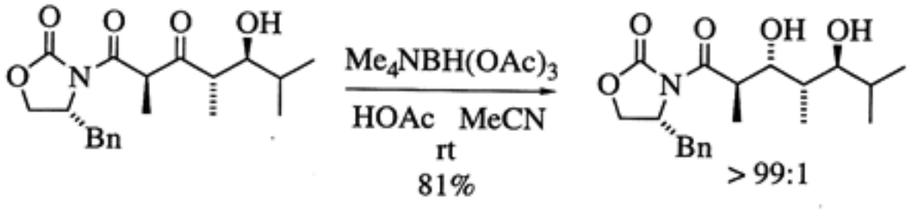
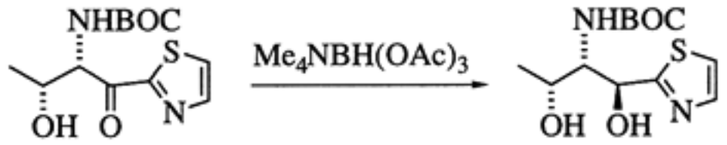
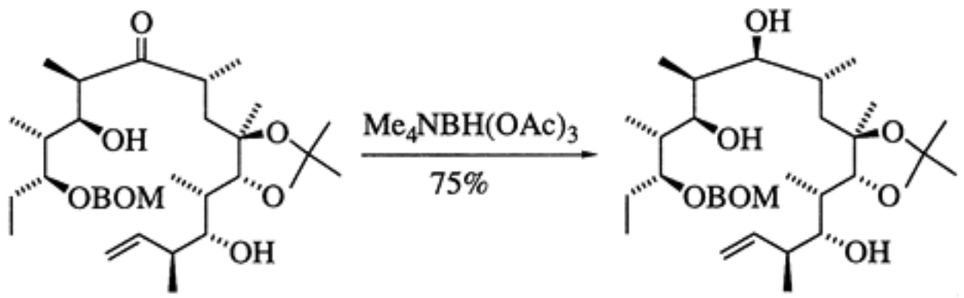


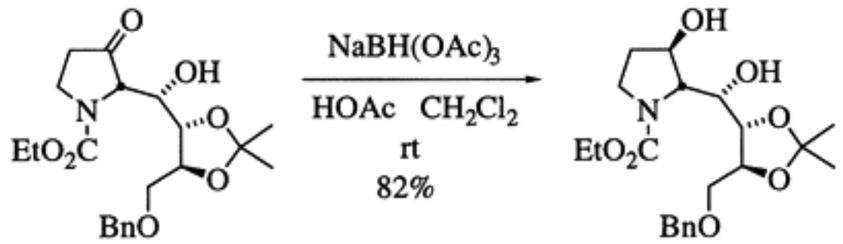
(106)



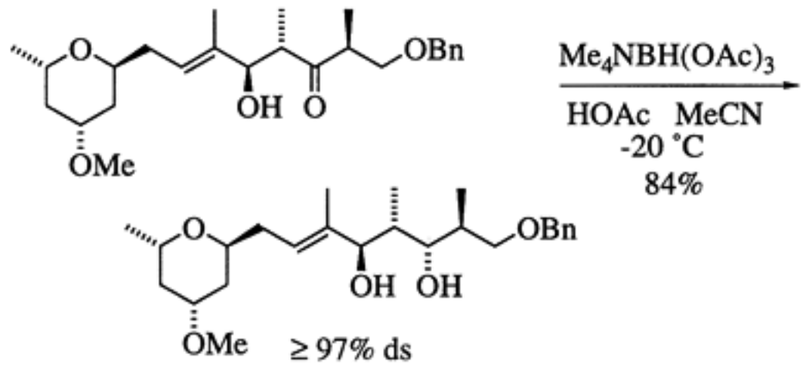
(107)



(108)



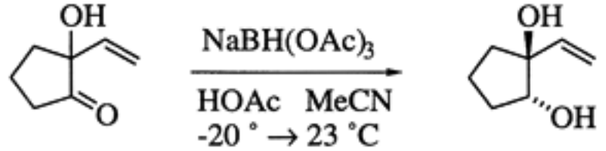
(109)



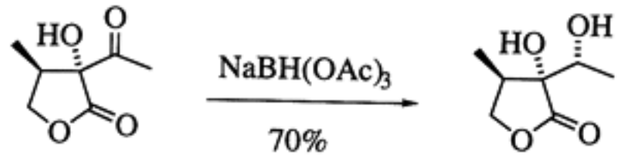
(110)

Numerous other examples of this stereoselective β-hydroxyketone reduction have been described in recent years (*175-193*), including the use of $MBH(OAc)_3$ in syntheses or synthetic approaches to verrucosidin (*194*), phorbol (*195*), streptenol B (*196*), calyculin A (*197*), lepicidin (*198*), muamvatin (*199*), mintlactone (*200*), rhizoxin (*201*, *202*), *myo*-inositol derivatives (*203*), discodermolide (*204*), acutiphycin (*205*), and FK-506 (*206*, *207*). Despite the enormous success of this β-hydroxyketone stereoselective reduction, $Me_4NBH(OAc)_3$ showed no improvement over conventional methods in at least one case (*208*).

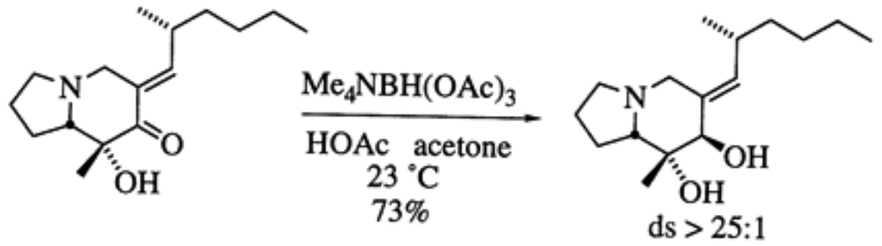
Interestingly, several examples of apparent stereoselective hydroxyl-mediated reductions of α-hydroxyketones have been reported (equations 111-113) (*209-211*).



(111)



(112)



(113)

Other notable examples of the stereoselective reduction of α-hydroxyketones with $MBH(OAc)_3$ include the final step in the total syntheses of rocaglamide (*212*, *213*) and pancracine (*214*).

Conclusions.

Over the past 20 years, the combination of $NaBH_4$ and RCO_2H has developed into an amazingly versatile and efficient set of reducing and amine alkylating agents. These acyloxyborohydride species have rapidly emerged as the preeminent reagents of choice for many chemical transformations. The ability to control chemoselectivity, regioselectivity, and stereoselectivity by adjusting the carboxylic acid, hydride reagent, stoichiometry, solvent, temperature and time has no parallel in the arsenal of chemical reagents available to the organic chemist. Nevertheless, despite the extraordinary scope of acyloxyborohydrides in organic transformations, much work remains to be done in understanding the mechanisms of some of the reactions, such as *N*-alkylation, and in applying these reagents to asymmetric synthesis.

References

1. Dolby, L.J.; Gribble, G.W. *J. Heterocycl. Chem.* **1966**, *3*, 124.
2. Moore, M.L. *Org. React. V* **1949**, 301.
3. Hinman, R.L.; Whipple, E.B. *J. Am. Chem. Soc.* **1962**, *84*, 2534.
4. Marshall, J.A.; Johnson, W.S. *J. Am. Chem. Soc.* **1962**, *84*, 1485.
5. Marshall, J.A.; Johnson, W.S. *J. Org. Chem.* **1963**, *28*, 421.
6. Billman, J.H.; McDowell, J.W. *J. Org. Chem.* **1961**, *26*, 1437.
7. Gribble, G.W.; Lord, P.D.; Skotnicki, J.; Dietz, S.E.; Eaton, J.T.; Johnson, J.L. *J. Am. Chem. Soc.* **1974**, *96*, 7812.
8. Gribble, G.W. *Eastman Organic Chemical Bulletin* **1979**, *51*, No. 1, 1.
9. Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proc. Int.* **1985**, *17*, 317.
10. Nutaitis, C.F. *J. Chem. Ed.* **1989**, *66*, 673.
11. Gribble, G.W.; Wright, S.W. *Heterocycles* **1982**, *19*, 229.
12. Gribble, G.W.; Nutaitis, C.F.; Leese, R.M. *Heterocycles* **1984**, *22*, 379.
13. Gribble,G.W.; Hoffman, J.H. *Synthesis* **1977**, 859.
14. Kumar, Y.; Florvall, L. *Synth. Commun.* **1983**, *13*, 489.
15. Siddiqui, M.A.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1523.
16. Toyota, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 547.
17. Rawal, V.H.; Jones, R.J.; Cava, M.P. *J. Org. Chem.* **1987**, *52*, 19.
18. Brown, D.W.; Graupner, P.R.; Sainsbury, M.; Shertzer, H.G. *Tetrahedron* **1991**, *47*, 4383.
19. Yao, X.L.; Nishiyama, S.; Yamamura, S. *Chem. Lett.* **1991**, 1785.
20. Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031.
21. Dhanoa, D.S., *et al.*, *J. Med. Chem.* **1993**, *36*, 4232.

22. Bolton, R.E.; Moody, C.J.; Rees, C.W.; Tojo, G. *Tetrahedron Lett.* **1987**, *28*, 3163.
23. Boger, D.L.; Coleman, R.S.; Invergo, B.J. *J. Org. Chem.* **1987**, *52*, 1521.
24. Bolton, R.E.; Moody, C.J.; Rees, C.W.; Tojo, G. *Tetrahedron Lett.* **1987**, *28*, 3163.
25. Meghani, P.; Street, J.D.; Joule, J.A. *J. Chem. Soc., Chem. Commun.* **1987**, 1406.
26. Sundberg, R.J.; Hamilton, G.S.; Laurino, J.P. *J. Org. Chem.* **1988**, *53*, 976.
27. Martin, P. *Helv. Chim. Acta* **1989**, *72*, 1554.
28. Djerassi, C.; Monteiro, H.J.; Walser, A.; Durham, L.J. *J. Am. Chem. Soc.* **1966**, *88*, 1792.
29. Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron* **1973**, *29*, 2015.
30. Thielke, D.; Wegener, J.; Winterfeldt, E. *Chem. Ber.* **1975**, *108*, 1791.
31. Wanner, M.J.; Koomen, G.J.; Pandit, U.K. *Tetrahedron* **1983**, *39*, 3673.
32. Gribble, G.W.; Johnson, J.L.; Saulnier, M.G. *Heterocycles* **1981**, *16*, 2109.
33. Takayama, H.; Seki, N.; Kitajima, M.; Aimi, N.; Seki, H.; Sakai, S. *Heterocycles* **1992**, *33*, 121.
34. Kucherova, N.F.; Sipilina, N.M.; Novikova, N.N.; Silenko, I.D.; Rozenberg, S.G.; Zagorevski, V.A. *Khim. Getero. Soed.* **1980**, 1383.
35. Lanzilotti, A.E.; Littel, R.; Fanshawe, W.J.; McKenzie,T.C.; Lovell, F.M. *J. Org. Chem.* **1979**, *44*, 4809.
36. Repic, O.; Long, D.J. *Tetrahedron Lett.* **1983**, *24*, 1115.
37. Maryanoff, B.E.; McComsey, D.F. *J. Org. Chem.* **1978**, *43*, 2733.
38. Maryanoff, B.E.; McComsey, D.F.; Nortey, S.O. *J. Org. Chem.* **1981**, *46*, 355.
39. Ketcha, D.M.; Lieurance, B.A. *Tetrahedron Lett.* **1989**, *30*, 6833.
40. Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, F.M. *J. Org. Chem.* **1975**, *40*, 3453.
41. Oklobdzija, M.; Fajdiga, T.; Kovac, T.; Zonno, F.; Sega, A.; Sunjic, V. *Acta Pharm. Jugosl.* **1980**, *30*, 131; *Chem. Abstr.* **1981**, *94*, 121481.
42. Raftery, M.J.; Bowie, J.H. *Aust. J. Chem.* **1988**, *41*, 1477.
43. Thomas, E.W.; Nishizawa, E.E.; Zimmermann, D.C.; Williams, D.J. *J. Med. Chem.* **1985**, *28*, 442.
44. Fischer, J.W.; Nissan, R.A.; Lowe-Ma, C.K. *J. Heterocycl. Chem.* **1991**, *28*, 1677.
45. Gunzenhauser, S.; Balli, H. *Helv. Chim. Acta* **1989**, *72*, 1186.
46. Labaudiniére, R.; Dereu, N.; Cavy, F.; Guillet, M.-C.; Marquis, O.; Terlain, B. *J. Med. Chem.* **1992**, *35*, 4315.
47. Gribble, G.W.; Jasinski, J.M.; Pellicone, J.T.; Panetta, J.A. *Synthesis* **1978**, 766.
48. Thomas, E.W.; Cudahy, M.M.; Spilman, C.H.; Dinh, D.M.; Watkins,T.L.; Vidmar, T.J. *J. Med. Chem.* **1992**, *35*, 1233.
49. Katritzky, A.R.; Davis, T.L.; Rewcastle, G.W.; Rubel, G.O.; Pike, M.T. *Langmuir* **1988**, *4*, 732.
50. Cannon, J.G.; Walker, K.A.; Montanari, A.; Long, J.P.; Flynn, J.R. *J. Med. Chem.* **1990**, *33*, 2000.
51. James, L.J.; Parfitt, R.T. *J. Med. Chem.* **1986**, *29*, 1783.
52. Cannon, J.G.; Dushin, R.G.; Long, J.P.; Ilhan, M.; Jones, N.D.; Swartzendruber, J.K. *J. Med. Chem.* **1985**, *28*, 515.
53. Connor, D.T.; Unangst, P.C.; Schwender, C.F.; Sorenson, R.J.; Carethers, M.E.; Puchalski, C.; Brown, R.E.; Finkel, M.P. *J. Med. Chem.* **1989**, *32*, 683.
54. Cannon, J.G.; Jackson, H.; Long, J.P.; Leonard, P.; Bhatnagar, R.K. *J. Med. Chem.* **1989**, *32*, 1959.
55. Gribble, G.W.; Nutaitis, C.F. *Synthesis* **1987**, 709.
56. Gribble, G.W.; Ferguson, D.C. *J. Chem. Soc., Chem. Commun.* **1975**, 535.
57. Evans, D.A.; Chapman, K.T.; Carreira, E.M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
58. Rao, K.V.; Jackman, D. *J. Heterocycl. Chem.* **1973**, *10*, 213.

59. Gribble, G.W.; Heald, P.W. *Synthesis* **1975**, 650.
60. Johnson, J.V.; Rauckman, B.S.; Baccanari, D.P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942.
61. Vigante, B.A.; Ozols, Ya.Ya.; Dubur, G.Ya. *Khim. Geter. Soed.* **1991**, 1680.
62. Carling, R.W.; Leeson, P.D.; Moseley, A.M.; Baker, R.; Foster, A.C.; Grimwood, S.; Kemp, J.A.; Marshall, G.R. *J. Med. Chem.* **1992**, *35*, 1942.
63. Uchida, M.; Chihiro, M.; Morita, S.; Yamashita, H.; Yamasaki, K.; Kanbe, T.; Yabuuchi, Y.; Nakagawa, K. *Chem. Pharm. Bull. Jpn.* **1990**, *38*, 534.
64. Ishii, H.; Ishikawa, T.; Ichikawa, Y.; Sakamoto, M.; Ishikawa, M.; Takahashi, T. *Chem. Pharm. Bull. Jpn.* **1984**, *32*, 2984.
65. Bergman, J.; Tilstam, U.; Törnroos, K.-W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 519.
66. Bock, M.G.; DiPardo, R.M.; Rittle, K.E.; Evans, B.E.; Freidinger, R.M.; Veber, D.F.; Chang, R.S.L.; Chen, T.; Keegan, M.E.; Lotti, V.J. *J. Med. Chem.* **1986**, *29*, 1941.
67. Yadagiri, B.; Lown, J.W. *Synth. Commun.* **1990**, *20*, 175.
68. Moody, C.J.; Warrellow, G.J. *Tetrahedron Lett.* **1987**, *28*, 6089.
69. Evans, B.E., *et al.*, *J. Med. Chem.* **1987**, *30*, 1229.
70. Brown, D.W.; Mahon, M.F.; Ninan, A.; Sainsbury, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 3117.
71. Balaban, T.-S.; Balaban, A.T. *Tetrahedron Lett.* **1987**, *28*, 1341.
72. Balaban, T.-S.; Balaban, A.T. *Org. Prep. Proc. Int.* **1988**, *20*, 231.
73. Balaban, A.T.; Balaban, T.-S. *Rev. Roumaine Chim.* **1989**, *34*, 41.
74. Dinculescu, A.; Balaban, T.S.; Popescu, C.; Toader, D.; Balaban, A.T. *Bull. Soc. Chim. Belg.* **1991**, *100*, 665.
75. Ketcha, D.M.; Carpenter, K.P.; Zhou, Q. *J. Org. Chem.* **1991**, *56*, 1318.
76. Wasserman, H.H.; Rusiecki, V. *Tetrahedron Lett.* **1988**, *29*, 4977.
77. Bodar, N.; Koltai, E.; Pròkai, L. *Tetrahedron* **1992**, *48*, 4767.
78. Gribble, G.W.; Leiby, R.W.; Sheehan, M.N. *Synthesis* **1977**, 856.
79. Chiba, T.; Ishizawa, T.; Sakaki, J.; Kaneko, C. *Chem. Pharm. Bull. Jpn.* **1987**, *35*, 4672.
80. Kramer, J.B., *et al.*, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1655.
81. Waykole, L.M.; Shen, C.-C.; Paquette, L.A. *J. Org. Chem.* **1988**, *53*, 4969.
82. Wu, P.-L.; Chu, M.; Fowler, F.W. *J. Org. Chem.* **1988**, *53*, 963.
83. Cliffe, I.A.; Ifill, A.D.; Mansell, H.L.; Todd, R.S.; White, A.C. *Tetrahedron Lett.* **1991**, *32*, 6789.
84. Chaubet, F.; Duong, M.N.V.; Courtieu, J.; Gaudemer, A.; Gref, A.; Crumbliss, A.L. *Cand. J. Chem.* **1991**, *69*, 1107.
85. Guibourdenche, C.; Roumestant, M.L.; Viallefont, Ph. *Tetrahedron: Asym.* **1993**, *4*, 2041.
86. Williams, D.R.; Osterhout, M.H. *J. Am. Chem. Soc.* **1992**, *114*, 8750.
87. Pearson, W.H.; Schkeryantz, J.M. *J. Org. Chem.* **1992**, *57*, 6783.
88. Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, I. *J. Heterocycl. Chem.* **1991**, *28*, 329.
89. Lewin, G.; Atassi, G.; Pierré, A.; Rolland, Y.; Schaeffer, C.; Poisson, J. *J. Nat. Prod.* **1995**, *58*, 1089.
90. Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. *J. Org. Chem.* **1985**, *50*, 3243.
91. Klaver, W.J.; Hiemstra, H.; Speckamp, W.N. *J. Am. Chem. Soc.* **1989**, *111*, 2588.
92. Kreysel, M.; Vögtle, F. *Synthesis* **1992**, 733.
93. Hutchins, R.O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y.P. *J. Org. Chem.* **1983**, *48*, 3412.
94. Petasis, N.A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393.
95. Cannon, J.G.; Amoo, V.E.D.; Long, J.P.; Bhatnagar, R.K.; Flynn, J.R. *J. Med. Chem.* **1986**, *29*, 2529.
96. Maiti, B.C.; Giri, V.S.; Pakrashi, S.C. *Heterocycles* **1990**, *31*, 847.

97. Rey, A.W.; Szarek, W.A.; MacLean, D.B. *Heterocycles* **1991**, *32*, 1143.
98. Kawecki, R.; Kozerski, L.; Urbánczyk-Lipkowska, Z.; Bocelli, G. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2255.
99. Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328.
100. Audia, J.E.; Lawhorn, D.E.; Deeter, J.B. *Tetrahedron Lett.* **1993**, *34*, 7001.
101. Ainscow, R.B.; Brettle, R.; Shibib, S.M. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1781.
102. Comins, D.L.; Weglarz, M.A. *J. Org. Chem.* **1991**, *56*, 2506.
103. Jefford, C.W.; Wang, J.B. *Tetrahedron Lett.* **1993**, *34*, 2911.
104. Naito, T.; Shinada, T.; Miyata, O.; Ninomiya, I.; Ishida, T. *Heterocycles* **1988**, *27*, 1603.
105. Sankar, P.J.; Das, S.K.; Giri, V.S. *Heterocycles* **1991**, *32*, 1109.
106. Stoit, A.R.; Pandit, U.K. *Tetrahedron* **1988**, *44*, 6187.
107. Kuehne, M.E.; Zebovitz, T.C. *J. Org. Chem.* **1987**, *52*, 4331.
108. Umino, N.; Iwakuma, T.; Itoh, M. *Tetrahedron Lett.* **1976**, 763.
109. Cannon, J.G.; Chang, Y.; Amoo, V.E.; Walker, K.A. *Synthesis* **1986**, 494.
110. Sundaramoorthi, R.; Marazano, C.; Fourrey, J.-L.; Das, B.C. *Tetrahedron Lett.* **1984**, *25*, 3191.
111. Nutaitis, C.F. *Synth. Commun.* **1992**, *22*, 1081.
112. Miller, S.A.; Chamberlin, A.R. *J. Org. Chem.* **1989**, *54*, 2502.
113. Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, 2875.
114. Ishikawa, F.; Saegusa, J.; Inamura, K.; Sakuma, K.; Ashida, S. *J. Med. Chem.* **1985**, *28*, 1387.
115. Mayer, J.P.; Cassady, J.M.; Nichols, D.E. *Heterocycles* **1990**, *31*, 1035.
116. Iyer, R.P.; Phillips, L.R.; Egan, W. *Synth. Commun.* **1991**, *21*, 2053.
117. Baldwin, J.E.; Otsuka, M.; Wallace, P.M. *Tetrahedron* **1986**, *42*, 3097.
118. Itsuno, S.; Hachisuka, C.; Ushijima, Y.; Ito, K. *Synth. Commun.* **1992**, *22*, 3229.
119. Marshall, J.A.; Johnson, W.S. *J. Org. Chem.* **1963**, *28*, 595.
120. Narayana, C.; Periasamy, M. *Tetrahedron Lett.* **1985**, *26*, 1757.
121. Gautam, V.K.; Singh, J.; Dhillon, R.S. *J. Org. Chem.* **1988**, *53*, 187.
122. Narayana, C.; Periasamy, M. *Tetrahedron Lett.* **1985**, *26*, 6361.
123. Gouzoules, F.H.; Whitney, R.A. *J. Org. Chem.* **1986**, *51*, 2024.
124. Gribble, G.W.; Leese, R.M.; Evans, B.E. *Synthesis* **1977**, 172.
125. Solberg, J.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1989**, *43*, 69.
126. Rao, C.S.; Chakrasali, R.T.; Ila, H.; Junjappa, H. *Tetrahedron* **1990**, *46*, 2195.
127. Nutaitis, C.F.; Bernardo, J.E. *Synth. Commun.* **1990**, *20*, 487.
128. Kotha, S.; Kuki, A. *J. Chem. Soc., Chem. Commun.* **1992**, 404.
129. Olah, G.A.; Wu, A.; Farooq, O. *J. Org. Chem.* **1988**, *53*, 5143.
130. Bauder, C.; Ocampo, R.; Callot, H.J. *Tetrahedron* **1992**, *48*, 5135.
131. Kabalka, G.W.; Kennedy, T.P. *Org. Prep. Proc. Int.* **1989**, *21*, 348.
132. Nutaitis, C.F.; Patragnoni, R.; Goodkin, G.; Neighbour, B.; Obaza-Nutaitis, J. *Org. Prep. Proc. Int.* **1991**, *23*, 403.
133. Jensen, B.L.; Caldwell, M.W.; French, L.G.; Briggs, D.G. *Toxicol. Appl. Pharmacol.* **1987**, *87*, 1.
134. Lai, Y.-H.; Peck, T.-G. *Aust. J. Chem.* **1992**, *45*, 2067.
135. Currie, G.J.; Bowie, J.H.; Massy-Westropp, R.A.; Adams, G.W. *J. Chem. Soc., Perkin Trans. II* **1988**, 403.
136. Rajca, A.; Janicki, S. *J. Org. Chem.* **1994**, *59*, 7099.
137. Osuka, A.; Zhang, R.P.; Maruyama, K.; Yamazaki, I.; Nishimura, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2807.
138. Nicholas, K.M.; Siegel, J. *J. Am. Chem. Soc.* **1985**, *107*, 4999.
139. McComsey, D.F.; Reitz, A.B.; Maryanoff, C.A.; Maryanoff, B.E. *Synth. Commun.* **1986**, *16*, 1535.
140. Sorgi, K.L.; Maryanoff, C.A.; McComsey, D.F.; Graden, D.W.; Maryanoff, B.E. *J. Am. Chem. Soc.* **1990**, *112*, 3567.

141. Gribble, G.W.; Kelly, W.J.; Emery, S.E. *Synthesis* **1978**, 763.
142. Lee, C.-M.; Parks, J.A.; Bunnell, P.R.; Plattner, J.J.; Field, M.J.; Giebisch, G.H. *J. Med. Chem.* **1985**, *28*, 589.
143. Daich, A.; Decroix, B. *J. Heterocycl. Chem.* **1992**, *29*, 1789.
144. Kurokawa, M.; Uno, H.; Itogawa, A.; Sato, F.; Naruto, S.; Matsumoto, J. *J. Heterocycl. Chem.* **1991**, *28*, 1891.
145. Ketcha, D.M.; Lieurance, B.A.; Homan, D.F.J.; Gribble, G.W. *J. Org. Chem.* **1989**, *54*, 4350.
146. Alazard, J.-P.; M.-Paillusson, C.; Boyé, O.; Guénard, D.; Chiaroni, A.; Riche, C.; Thal, C. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 725.
147. Jacobi, P.A.; Cai, G. *Heterocycles* **1993**, *35*, 1103.
148. Jeandon, C.; Ocampo, R.; Callot, H.J. *Tetrahedron Lett.* **1993**, *34*, 1791.
149. Hutchins, R.O.; Natale, N.R. *J. Org. Chem.* **1978**, *43*, 2299.
150. Baeckström, P.; Li, L. *Synth. Commun.* **1990**, *20*, 1481.
151. Cho, B.T.; Yoon, N.M. *Synth. Commun.* **1985**, *15*, 917.
152. Suseela, Y.; Periasamy, M. *Tetrahedron* **1992**, *48*, 371.
153. Soucek, M.; Urban, J.; Saman, D. *Coll. Czech. Chem. Commun.* **1990**, *55*, 761.
154. Nutaitis, C.F.; Gribble, G.W. *Org. Prep. Proc. Int.* 1985, *17*, 11.
155. Gribble, G.W.; Kelly, W.J.; Sibi, M.P. *Synthesis* **1982**, 143.
156. Gribble, G.W.; Saulnier, M.G.; Sibi, M.P.; Obaza-Nutaitis, J.A. *J. Org. Chem.* **1984**, *49*, 4518.
157. Koltai, E.; Horváth, G.; Botka, P.; Kórösi, J.; Tóth, G. *Acta Chim. Hung.* **1990**, *127*, 3.
158. Nutaitis, C.F.; Gribble, G.W. *Synthesis* **1985**, 756.
159. Nutaitis, C.F.; Gribble, G.W. *Tetrahedron Lett.* **1983**, *24*, 4287.
160. Odinokov, V.N.; Ishmuratov, G.Yu.; Ladenkova, I.M.; Tolstikov, G.A. *Chem. Nat. Cpds.* **1992**, 235.
161. Kanojia, R.M.; Chin, E.; Smith, C.; Chen, R.; Rowand, D.; Levine, S.D.; Wachter, M.P.; Adams, R.E.; Hahn, D. *J. Med. Chem.* **1985**, *28*, 796.
162. Barker, P.L.; Bahia, C. *Tetrahedron* **1990**, *46*, 2691.
163. Han, O.; Liu, H. *Tetrahedron Lett.* **1987**, *28*, 1073.
164. Yatagi, M.; Ohnuki, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1826.
165. Hoffman, R.V.; Kim, H.-O. *J. Org. Chem.* **1991**, *56*, 6759.
166. Nutaitis, C.F.; Bernardo, J.E. *J. Org. Chem.* **1989**, *54*, 5629.
167. Saksena, A.K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273.
168. Evans, D.A.; Chapman, K.T. *Tetrahedron Lett.* **1986**, *27*, 5939.
169. Evans, D.A.; Gauchet-Prunet, J.A.; Carreira, E.M.; Charette, A.B. *J. Org. Chem.* **1991**, *56*, 741.
170. Evans, D.A.; Ng, H.P.; Clark, J.S.; Rieger, D.L. *Tetrahedron* **1992**, *48*, 2127.
171. Dondoni, A.; Perrone, D.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 1313.
172. Martin, S.F.; Pacofsky, G.J.; Gist, R.P.; Lee, W.-C. *J. Am. Chem. Soc.* **1989**, *111*, 7634.
173. Thompson, S.H.J.; Subramanian, R.S.; Roberts, J.K.; Hadley, M.S.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1994**, 933.
174. Paterson, I.; Cumming, J.G. *Tetrahedron Lett.* **1992**, *33*, 2847.
175. Farr, R.N.; Kwok, D.-I.; Daves, G.D., Jr. *J. Org. Chem.* **1992**, *57*, 2093.
176. Zhang, H.-C.; Daves, G.D., Jr. *J. Org. Chem.* **1992**, *57*, 4690.
177. Mori, Y.; Kohchi, Y.; Suzuki, M.; Furukawa, H. *Chem. Pharm. Bull. Jpn.* **1992**, *40*, 1934.
178. Sato, M.; Sugita, Y.; Abiko, Y.; Kaneko, C. *Tetrahedron: Asym.* **1992**, *3*, 1157.
179. Paterson, I.; Channon, J.A. *Tetrahedron Lett.* **1992**, *33*, 797.
180. Solladié, G.; Ghiatou, N. *Tetrahedron Lett.* **1992**, *33*, 1605.
181. Chen, C.; Crich, D. *Tetrahedron Lett.* **1992**, *33*, 1945.
182. Paterson, I.; Tillyer, R.D. *Tetrahedron Lett.* **1992**, *33*, 4233.
183. Casy, G. *Tetrahedron Lett.* **1992**, *33*, 8159.
184. Mori, Y.; Asai, M.; Furukawa, H. *Heterocycles* **1992**, *34*, 1281.

185. Shao, L.; Seki, T.; Kawano, H.; Saburi, M. *Tetrahedron Lett.* **1991**, *32*, 7699.
186. Paterson, I.; Lister, M.A.; Ryan, G.R. *Tetrahedron Lett.* **1991**, *32*, 1749.
187. Grabley, S.; Hammann, P.; Kluge, H.; Wink, J.; Kricke, P.; Zeeck, A. *J. Antibiot.* **1991**, *44*, 797.
188. Turner, N.J.; Whitesides, G.M. *J. Am. Chem. Soc.* **1989**, *111*, 624.
189. Gu, R.; Sih, C.J. *Tetrahedron Lett.* **1990**, *31*, 3283.
190. Robins, M.J.; Samano, V.; Johnson, M.D. *J. Org. Chem.* **1990**, *55*, 410.
191. Hill, R.K.; Nugara, P.N.; Holt, E.M.; Holland, K.P. *J. Org. Chem.* **1992**, *57*, 1045.
192. Shao, L.; Kawano, H.; Saburi, M.; Uchida, Y. *Tetrahedron* **1993**, *49*, 1997.
193. Enders, D.; Osborne, S. *J. Chem. Soc., Chem. Commun.* **1993**, 424.
194. Whang, K.; Cooke, R.J.; Okay, G.; Cha, J.K. *J. Am. Chem. Soc.* **1990**, *112*, 8985.
195. Wender, P.A.; Kogen, H.; Lee, H.Y.; Munger, J.D., Jr.; Wilhelm, R.S.; Williams, P.D. *J. Am. Chem. Soc.* **1989**, *111*, 8957.
196. Romeyke, Y.; Keller, M.; Kluge, H.; Grabley, S.; Hammann, P. *Tetrahedron* **1991**, *47*, 3335.
197. Evans, D.A.; Gage, J.R.; Leighton, J.L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.
198. Evans, D.A.; Black, W.C. *J. Am. Chem. Soc.* **1992**, *114*, 2260.
199. Paterson, I.; Perkins, M.V. *J. Am. Chem. Soc.* **1993**, *115*, 1608.
200. Shishido, K.; Irie, O.; Shibuya, M. *Tetrahedron Lett.* **1992**, *33*, 4589.
201. Boger, D.L.; Curran, T.T. *J. Org. Chem.* **1992**, *57*, 2235.
202. Nakada, M.; Kobayashi, S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1035.
203. Estevez, V.A.; Prestwich, G.D. *J. Am. Chem. Soc.* **1991**, *113*, 9885.
204. Smith, A.B., III; Qiu, Y.; Jones, D.R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011.
205. Smith, A.B., III; Chen, S. S.-Y.; Nelson, F.C.; Reichert, J.M.; Salvatore, B.A. *J. Am. Chem. Soc.* **1995**, *117*, 12013.
206. Jones, T.K.; Reamer, R.A.; Desmond, R.; Mills, S.G. *J. Am. Chem. Soc.* **1990**, *112*, 2998.
207. Fisher, M.J.; Chow, K.; Villalobos, A.; Danishefsky, S.J. *J. Org. Chem.* **1991**, *56*, 2900.
208. Burke, S.D.; Shankaran, K.; Helber, M.J. *Tetrahedron Lett.* **1991**, *32*, 4655.
209. Brown, M.J.; Harrison, T.; Herrinton, P.M.; Hopkins, M.H.; Hutchinson, K.D.; Mishra, P.; Overman, L.E. *J. Am. Chem. Soc.* **1991**, *113*, 5365.
210. Schulz, S. *Ann.* **1992**, 829.
211. Goldstein, S.W.; Overman, L.E.; Rabinowitz, M.H. *J. Org. Chem.* **1992**, *57*, 1179.
212. Trost, B.M.; Greenspan, P.D.; Yang, B.V.; Saulnier, M.G. *J. Am. Chem. Soc.* **1990**, *112*, 9022.
213. Davey, A.E.; Schaeffer, M.J.; Taylor, R.J.K. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2657.
214. Overman, L.E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005.