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UNIVERSITY OF ALBERTA

REDUCTIONS, DEBROMINATIONS AND ALLYLATIONS

BY

XIANFENG LI

A THESIS
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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

REDUCTIONS, DEBROMINATIONS AND ALLYLATIONS

submitted by XIANFENG LI in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

Professor D. D. Tanner

Professor W. A. Ayer

Professor W. A. G. Graham

Professor E. E. Knaus

DATED April 24 1992

ABSTRACT

Chapter 1

Efficient asymmetric syntheses of optically active NADH model compounds have been achieved by the reaction of a pinyl substituted Hantzsch ester with dimethylaluminum amide derived from (S)- or (R)-α-methylbenzylamine. By this approach, four diastereomeric (2,6)-dimethyl-3-ethoxycarbonyl-5-(N-α-methylbenzylcarbamoyl-1-propyl-4-[(2S)-pinyl]-1,4-dihydropyridines were prepared in good yields. Separation of these diastereomeric isomers was obtained very easily by chromatography on silica gel.

The reduction of (±)-3-bromocamphor to camphor by these dihydropyridines proceeds by a free radical chain mechanism involving an electron transfer process. An enantioselective electron transfer from these dihydropyridines to (±)-3-bromocamphor has been demonstrated.

The reduction of methyl benzoylformate with these model compounds was also carried out in the presence of magnesium perchlorate. Both enantiomers of methyl mandelate can be obtained using these NADH models. It appears that the configuration of the reduction product is determined mainly by the configuration of hydrogen at the 4-position of these optically active dihydropyridines.

Chapter 2

The reaction of *vic*-Dibromides with N-benzyl-1,4-dihydronicotinamide (BNAH) was studied in tetrahydrofuran and

acetonitrile. The thermodynamically more stable isomer of the alkene was produced as the major debromination product. Contrary to the original proposal, the reaction is shown to proceed via a free radical chain sequence. A chain propagating step in the sequence of these reductions is the bromine atom abstraction of a hydrogen from BNAH to generate a 4-dihydropyridyl radical.

Chapter 3

The reactions of α-haloketones and α-(carbonyloxy)acetophenone ($PhCOCR_1R_2X$, X=F, Cl, Br, OCOPh) with allyltributylstannane cleanly yield allylation products. The reaction was shown to proceed via a free radical chain sequence which contains an electron transfer process. The formation of trapping product provides direct evidence of the involvement of an enolyl radical, $PhCOCR_1R_2\cdot$. The observation that the reaction of α-bromoacetophenone with allyltributylstannane can be inhibited by the addition of one equivalent of α-bromoisobutyrophenone is consistent with the proposed chain sequence.

The reactions of α-arylsulfonyl ketones and α-phenylthio ketones ($PhCOCR_1R_2Y$, $Y=SO_2Tol$-*p* and SPh) with allyltributylstannane were also investigated. However, these reactions give a nearly 1:1 mixture of allyl tolylsulfone or allyl phenylsulfide and the corresponding ketone. The radical trapping product is not formed as a major product. The reaction is believed to proceed by the formation of a stannylketyl radical as an intermediate. Studies of the reactivity and steric effect of these compounds are in support of this proposal.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Professor Dennis D. Tanner for his guidance and supervision during the course of this work.

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Many thanks to the Chemistry Department and the University of Alberta for funding this work in the form of a teaching/research assistantship.

Finally my gratitude to my lovely wife for her encouragement, patience and support.

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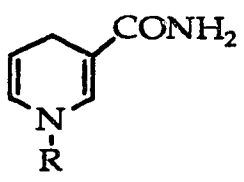
Preparation and Reactions of Optically Active 2, 6-Dimethyl-3-ethoxycarbonyl-5-(N-α-methylbenzylcarbamoyl)-1-propyl-4-[(2S)-pinyl]-1, 4-dihydropyridines

Introduction

During the past decade considerable interest has been expended designing model compounds to mimic the action of the natural enzym system.[1] As oxidation and reduction reactions are important biologi processes, those related to the NAD^+/NADH system have been extensiv investigated.[2] The design of readily accessible NADH model compou combining high reactivity and enantioselectivity has ranged through a hos structurally diverse 1,4-dihydropyridines. All the models contain the dihydropyridine ring of the nicotinamide part of the coenzyme as a comm feature and most of them have one of following three fundamer structures: a dihydronicotinamide **1**, a 3,5-disubstituted dihydropyridine **2** a Hantzsch ester **3**.



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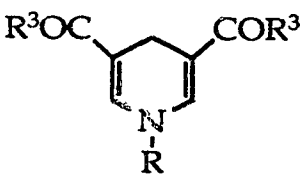

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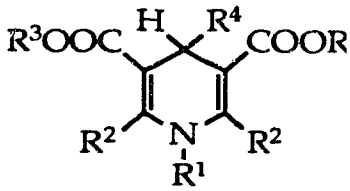


3

Biological transformations are highly stereospecific. To mimic t feature has been a major goal for organic chemists. In the reduction o highly electrophilic prochiral ketone such as methyl or ethyl benzoylform (**4**) to (R)- or (S)-mandelate (**5**), high enantiomeric excesses have b achieved with a variety of chiral NADH models. Most of the work on chi NADH models have been focused on models of type **1**, which exhibit closest similarity to the active part of the coenzyme.

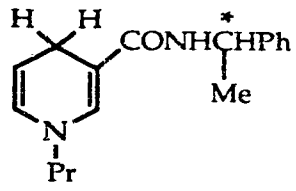
5, R=Me, Et

6, R=Me, Et

In the majority of the early models studied, the 1,4-dihydropyridines possessed a chiral N-substituted amide (type **1**) or a chiral moiety at R_3 (type **2** and **3**). The synthesis of the first optically active model, (R)- or (S)-N-(α-methylbenzyl)-1-propyl-1,4-dihydronicotinamide **7**, was reported by Ohno in 1975.[3] Since then, many structurally diverse 1,4-dihydropyridines have been synthesized and used in the reduction of prochiral ketones. Among these compounds are the dihydronicotinamides modified by chiral moieties on the nitrogen of the carbamoyl groups: **8**,[4] **9**,[5] **10**,[6] a dihydropyridine containing a chiral macrocycle, **11**,[7] a dihydropyridine containing a sulphinyl moiety, **12**,[8] and a chiral bis(NADH) model, **13**,[9]. A Hantzsch ester with chiral groups on the two alkoxycarbonyl groups, **14**,[10-11] was also investigated. It was found that the chirality at the position far away from the reaction center was effectively transferred to the reduction product.

Some NADH models substituted by a chiral moiety on the ring nitrogen, **15**[12] and **16**,[13] were also subjected to asymmetric reduction. However, the enantioselectivity demonstrated by these models was quite unsatisfactory (<30% ee).

The chirality at reaction center, C-4, of the dihydropyridine, is found to exert high enantioselectivity. Ohno developed several models by incorporating a chiral center at C-4 and maintaining a polar functional group at C-3.[14,15] Enantiomerically pure **17** was obtained as four distinct diastereomers by recrystallization of amides derived from (S)-and (R)-amine.



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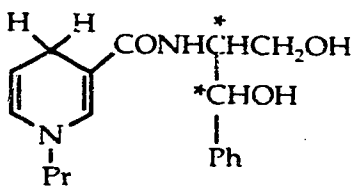

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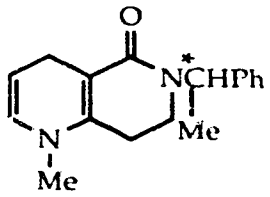

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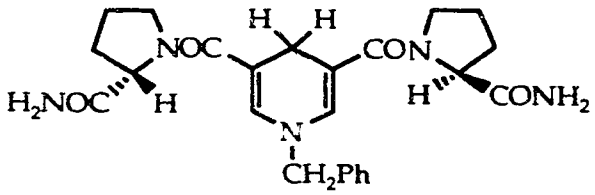

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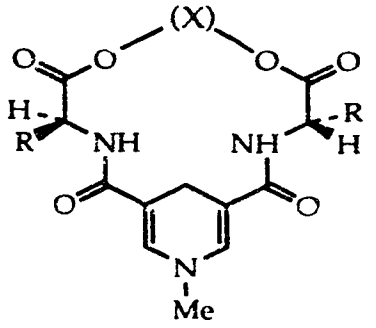

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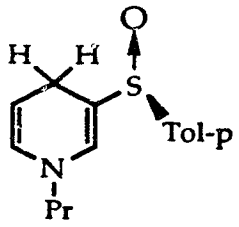

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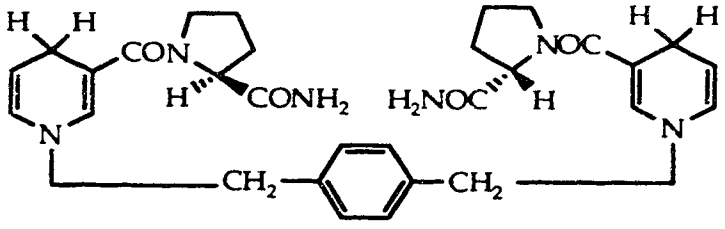

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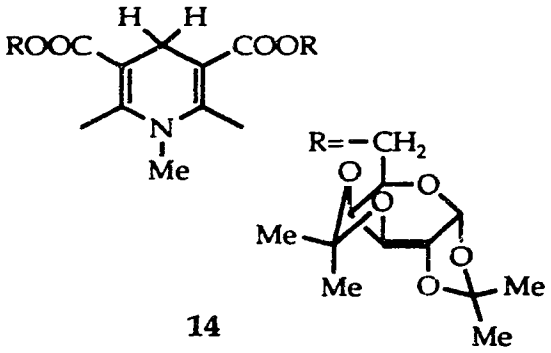

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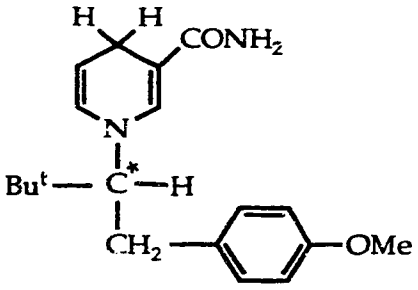

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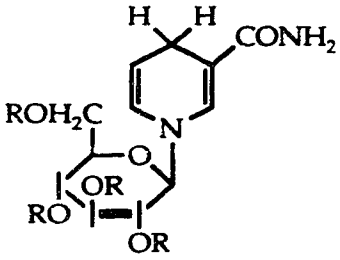

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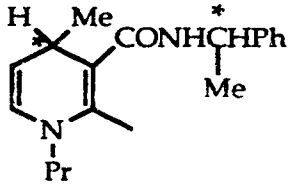

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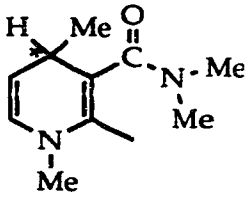

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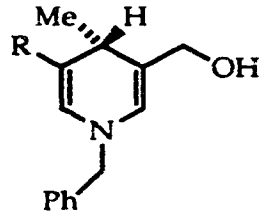

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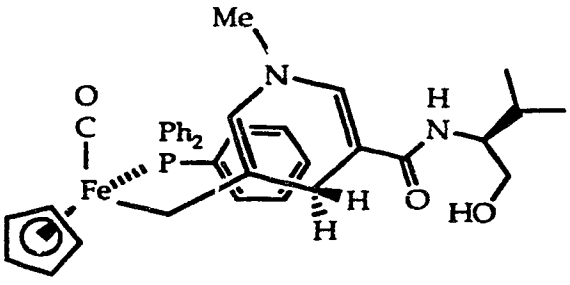
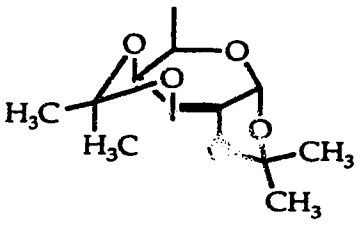


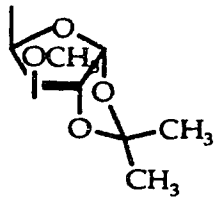
20

These chiral models reduced certain ketones in excellent chemical and optical yields.[14] The model **18** was prepared as a racemic mixture. The resolution of racemic **18** was accomplished by chromatography on a column packed with cellulose triacetate.[15] Meyers reported an efficient asymmetric synthesis of **19** with a chiral center at C-4 and hydroxymethyl moiety at C-3.[16] Recently, the synthesis of the chiral organometallic NADH mimics was described by Davies.[17] Resolution of the diastereomeric isomer was obtained by recrystallization. In this model, **20**, one face of the dihydronicotinoyl was effectively shielded by the the sterically demanding chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] so that only one face of the diastereotopic hydrogens at C-4 was available for reaction. The enantiomeric excesses of the reduction product in the reduction with these models ranged as high as 98% ee.

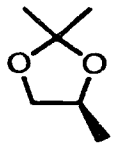
In addition, Gelbard reported the synthesis of a new type of chiral NADH model, a Hantzsch ester. The chiral substituent at C-4 is derived from a sugar.[11] The chiral substituent such as L-arabino, L-threo and (4S)-2,2-dimethyl-1,3-dioxolyl was incorporated into the C-4 position of the Hantzsch ester by a proper choice of a chiral aldehyde as a starting material.



L-arabino



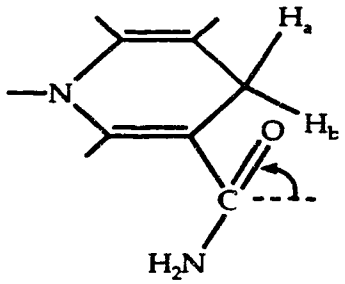
L-threo



(4S)-2,2-dimethyl-1,3-dioxolyl

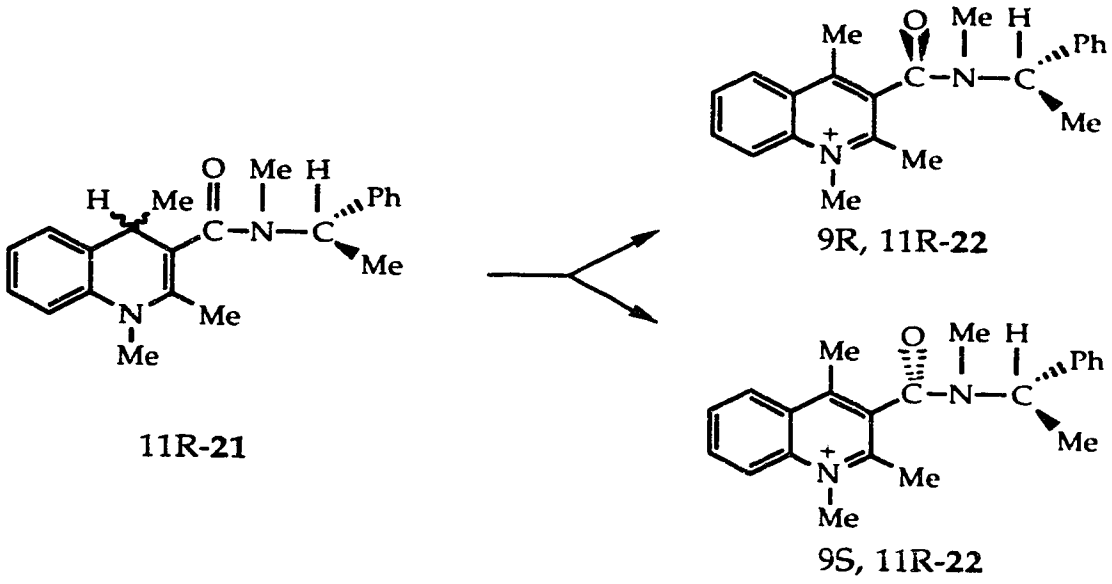
The x-ray crystal structure of (4R, 9R)-N-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (**17**) has been determined.[18] The structural analysis revealed a *syn*-orientation of the hydrogen at C-4 and the carbonyl

group. The out-of-plane orientation of the CONHR group is 65° with respect to the 1,4-dihydropyridine moiety. Based on semiempirical MINDO/3 calculations of models of pyridinium cation and dihydropyridine with a carbamoyl substituent, Buck and co-workers suggested that a low enthalpy transition state corresponds to the conformation in which the carbonyl dipole in dihydronicotinamide points towards the substrate.[19a,b] That is, at the transition state of the reaction, the migrating hydrogen (H_a) at C-4 and the carbonyl oxygen are set in *syn* configuration.



Although x-ray crystallography has revealed that model **17** in the crystalline state has a *syn*-conformation with respect to the C-4 hydrogen and the carbonyl group, the conformation is not stable in solution and free rotation is observed for the C_3-$C_{carbonyl}$ single bond. Ohno et al. developed a 1,4-dihydroquinoline (**21**) combining high reactivity and enantioselectivity.[20a] The model **21** has a central chirality at C-4 but its side-chain carbonyl group can rotate freely, however, the presence of a second N-substituted amide prevents the free rotation of the carbonyl group in its salt form (**22**). When (11R)-**21** was employed as a reducing agent, the resulting salt was found to be a mixture of two isomers.[20b,c,d] The carbonyl oxygen sticks out of the quinolinium plane in one isomer (9S, 11R-**22**), whereas it points under the plane in the other isomer (9R, 11R-**22**). These results are in support

of the proposed *syn*-orientation of the transferring hydrogen and the amide carbonyl dipole in the activated complex.

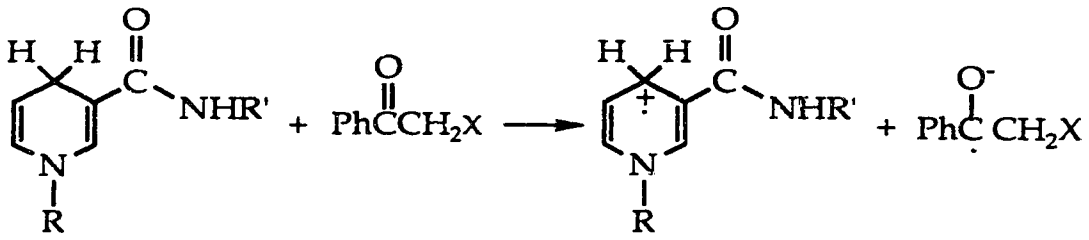


In these model systems, a divalent metal ion (Mg^{2+} or Zn^{2+}) is always employed to mimic the action of metal ion contained in NADH reductase enzymes. The metal ions catalyze the reactions and presumably facilitate stereocontrol by the formation of a complex between the dihydropyridine ring and the ketone during the hydride transfer step. However, whether the reduction with these model compounds proceeds through a single-step hydride transfer or a homolytic process still remains unclear.

The reduction of α-haloacetophenones by one of the most widely used NADH models, N-benzyl-1,4-dihydronicotinamide (BNAH)[21a] has also been studied. The reaction proceeds by a free radical chain mechanism which contains initiation and propagation steps involving single electron transfer (Scheme I-1). The ketyl intermediate in these reductions abstracts a hydrogen atom from the dihydronicotinamide and forms a 4-dihydropyridyl radical (eq 3), which carries the chain by subsequent electron transfer to another

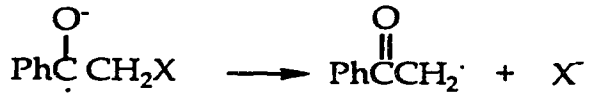
molecule of α-haloacetophenone. The reduction of α-haloacetophenones by NADH also proceeds by a free radical chain process.[21b]

initiation

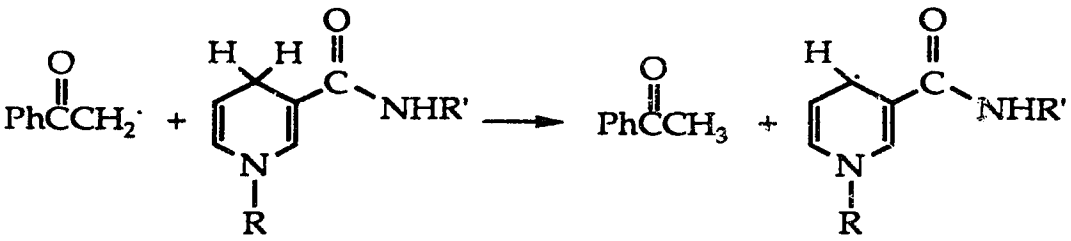


(1)

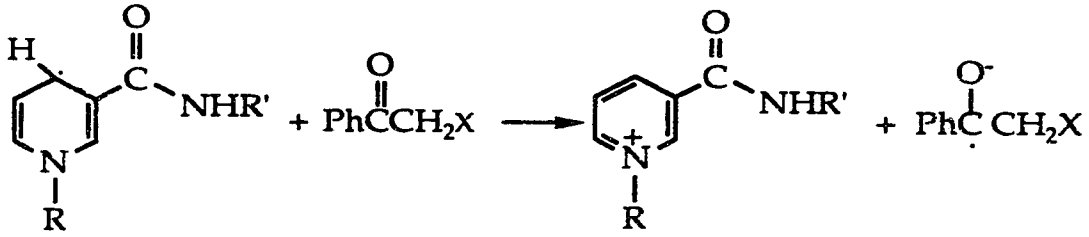
propagation



(2)



(3)



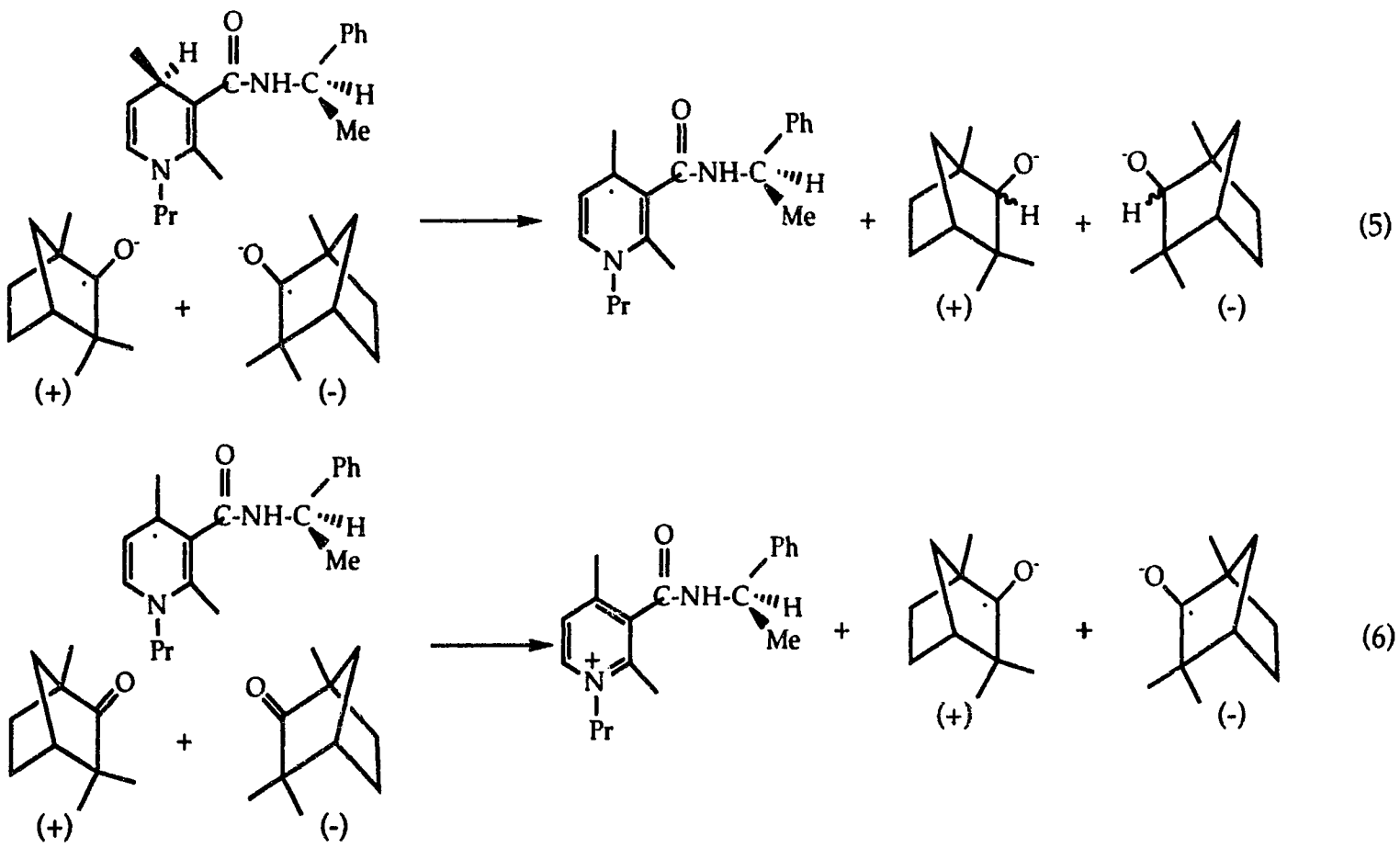
(4)

Scheme I-1. Mechanism for the Reduction of α-Haloacetophenones by BNAH

Although more and more stereoselective radical reactions have been reported[22-25], very few enantioselective radical reactions have been identified. Recently, Tanner reported a free radical reaction whose propagation step involves an enantioselective electron transfer reaction from the 4-dihydropyridyl radical to fenchone (eq 6, Scheme I-2).[26] When the (±)-

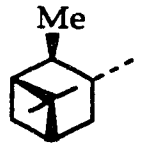
fenchone was selectively reduced by the optically active (4R, 9R)-N-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (17) or its (4S, 9R)-epimer, preferential enantioselective reduction of (+)-fenchone to a mixture of exo- and endo-(-)-fenchyl alcohols was observed with 16% ee. Meanwhile, the result showed a 10.6% ee for the recovered fenchone. When d,l-fenchone was reduced by using a mixture of (4R,9R)-(-)-and (4S,9R)-(+)-epimers, the same enantioselective reduction takes place. These results suggest the electron transfer reaction with these two diastereomeric models show the same enantioselectivity since the chirality of the radical center is the same whether it is produced from (4R, 9R)-dihydronicotinamide or its (4S, 9R)-epimer (eq 5, Scheme I-2).

Another example of an enantioselective radical reaction is that of an enantioselective α-hydrogen atom abstraction from an ester by an optically active amine-boryl radical.[27] When an oxirane solution of an amine-alkylborane complex, racemic methyl 2-phenylpropanoate, and di-*tert*-butyl peroxide was irradiated under UV light, the *tert*-butoxyl radical abstracted hydrogen from amine-alkylborane complex to produce the optically active amine-boryl radical (eq 7), which abstracted hydrogen from the (R)-methyl 2-phenylpropanoate 2.4 times faster than from its (S)-enantiomer (eq 8).



Scheme I-2. The Enantioselective Reduction of *d, l*-Fenchone by Optically Active (4R, 9R)-17

$$R'NMe_2 \rightarrow BH_2R \xrightarrow[- Bu^tOH]{Bu^tO\cdot} R'NMe_2 \rightarrow \dot{B}HR \qquad (7)$$

R= 

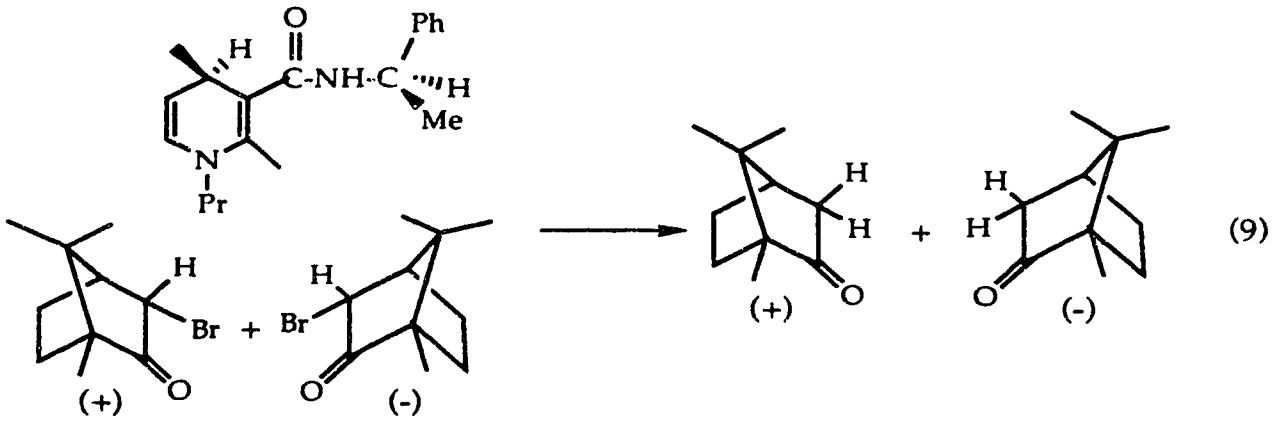
R'=Me, $CH_2CH_2NMe_2 \rightarrow BH_2R$

$$R'NMe_2 \rightarrow \dot{B}HR + PhMeCHCO_2Me \longrightarrow$$

$$PhMeC\dot{C}O_2Me + R'NMe_2 \rightarrow BH_2R \qquad (8)$$

Scheme I-3. The Enantioselective α-Hydrogen-Atom Abstraction by the Optically Active Amine-boryl Radical

As part of a continuing project directed towards the development of enantioselective electron transfer reactions, racemic α-bromocamphor was chosen as a substrate to test the possibility of enantioselective electron transfer reduction during the radical chain reactions with N-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (**17**). Preliminary results showed that reduction of α-bromocamphor by (4R, 9R)-**17** or its (4S, 9R)-epimer could be initiated (5% AIBN) to about 20% completion. The isolated camphor and α-bromocamphor, however, were racemic. This result suggests that the electron transfer of 4-dihydropyridyl radical to α-bromocamphor shows no enantioselectivity (eq 9). Therefore, one goal of this project is to design sterically more demanding optically active NADH models which exhibit improved chiral discrimination during the electron transfer process while still maintaining its ability to reduce the substrate.

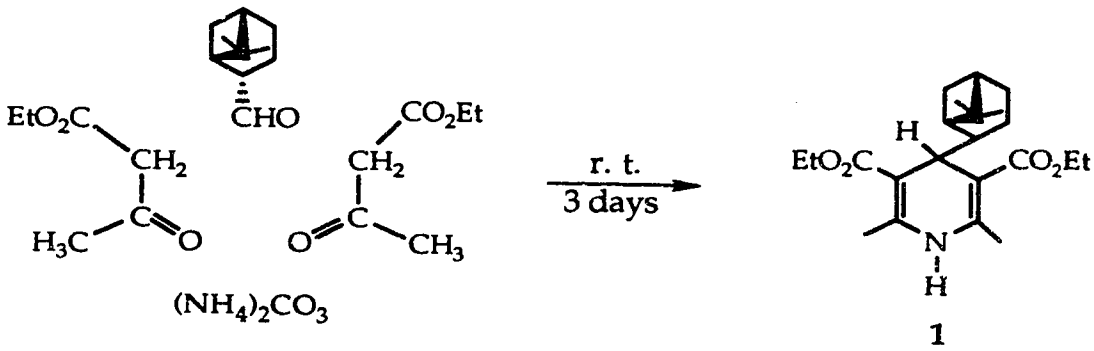


(9)

The system chosen are the models of type **3**. Although they show a lower reactivity than type **1**, these compounds can be synthesized easily using a one-pot condensation. Furthermore, it is possible to introduce a highly sterically hindered substituent into the 4-position of the dihydropyridine ring by a proper choice of an aldehyde as a starting material. For this purpose, Hantzsch esters **3** was chosen to be a precursor for the preparation of an optically pure NADH model. One would anticipate that if one of the two ester groups of the Hantzsch ester was modified properly, the molecule would become asymmetric and a new kind of optically pure NADH model would be produced.

Results and Discussion

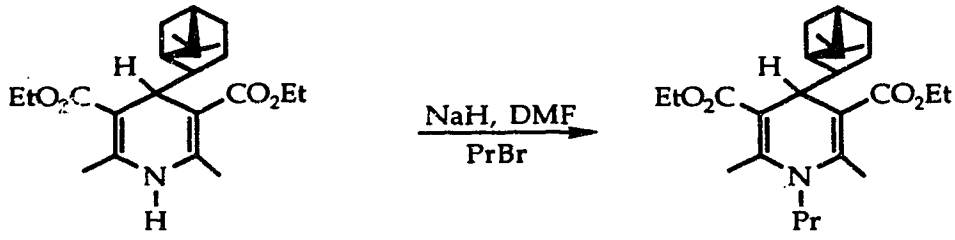
THE SYNTHESIS OF DIHYDROPYRIDINES 3a-d An efficient synthesis of these compounds is outlined in eq 10-11. Commercially available (-)-*trans*-myrtanol was oxidized with PCC to give (+)-*trans*-myrtanal,[28] an one-pot condensation of (+)-*trans* myrtanal with ethyl acetoacetate in ammonium carbonate solution produced Hantzsch ester **1** in 79% yield.[11] When (-)-*cis*-myrtanal was used for the condensation instead of (+)-*trans*-myrtanal under the same reaction condition, expected Hantzsch ester was not produced. On the basis of ^{1}H NMR, the major product isolated was an acyclic compound which did not have the pinyl group.



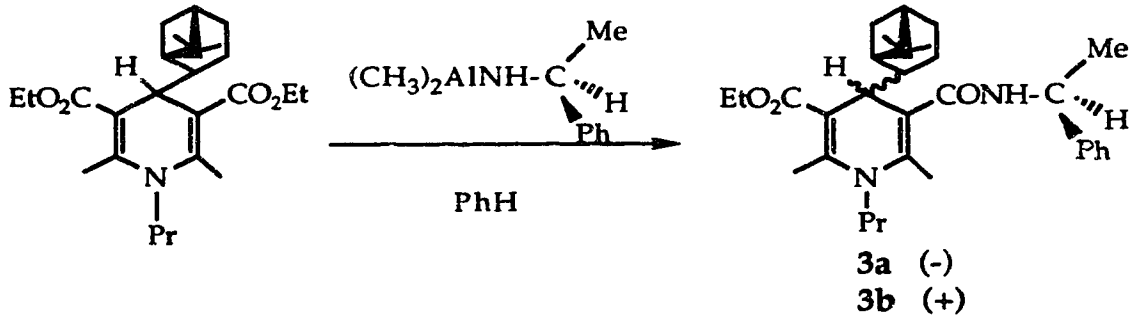
1 (10)

Hantzsch ester **1** was treated with sodium hydride in DMF, then allowed to react with 1-bromopropane to give Hantzsch ester **2** (eq 11).[29] Treatment of Hantzsch ester **2** with dimethylaluminum amide derived from (S)-(-)-α-methylbenzylamine[31] formed a mixture of diastereomeric compounds **3a** and **3b** (eq 12). A careful chromatographic separation on silica gel gave pure **3a** and **3b** in 44% and 28% yields respectively. Both diastereoisomers were characterized by ^{1}H NMR spectroscopy, and with the detection limits of the ^{1}H NMR, the isolated diastereoisomer **3a** and **3b** were

pure. The reaction can be followed by TLC until starting material **2** is completely consumed. Generally, the formation of **3a** and **3b** was complete in 14 h. It was found that the second ester was converted to diamide **4** with prolonged reaction. When the mixture was heated to reflux for over 20 h, a new product was slowly formed. This new compound was isolated and characterized as the diamide **4**.



2 (11)

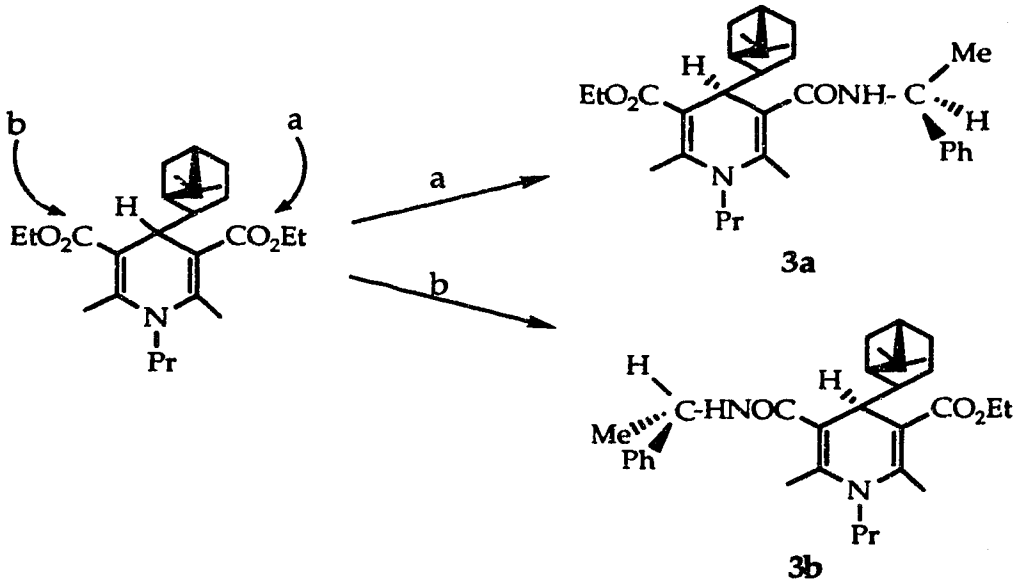


3a (-)
3b (+) (12)

When the reaction was followed by ^{1}H NMR the spectra also showed the formation of **3a** and **3b** with a relative ratio of 3:2. As shown in Scheme I-4, there are two possible pathways for the attack at an ester group by dimethylaluminum amide (pathway a and pathway b). It is not unreasonable to assume that attack by dimethylaluminum amide away from the bridge of the 4-pinyl group (pathway a) proceeds more rapidly than the attack from the bridge side (pathway b). As a result, **3a** is formed as the major product whose

configuration can tentatively be assigned to (4S,9S). Accordingly configuration of the minor isomer **3b** can be assigned to (4R,9S).

To further substantiate these assignments, an MM-2 calculation two structures shows that **3a** has the lowest energy. A model c minimized structure is given in Figure I-1. As expected, the bulky pinyl at C-4 forces the 1,4-dihydropyridine to adopt a flat-boat conformation result is consistent with that found for the crystal structure of imidazolyl)-1,4-dihydropyridine.[30] Structure **3a**, also shows that th hydrogen and the bridge of the pinyl group point in opposite direc However, the attempt to establish the absolute configuration o diastereomeric isomer by x-ray crystallography was not successful.



Scheme I-4. Possible Attacks at an Ester by Dimethylaluminum Amic Derived from (S)-α-Methylbenzylamine

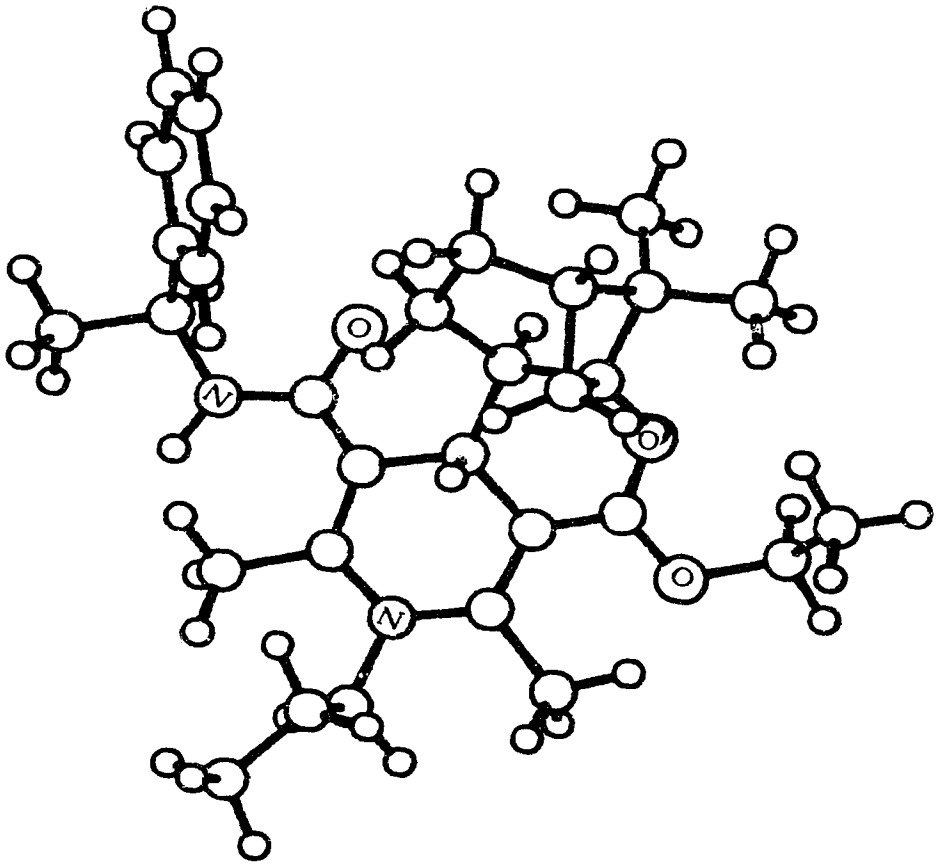
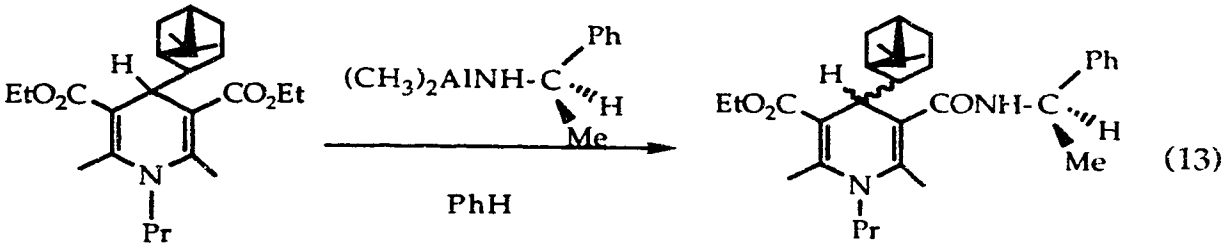


Figure I-1. A Graphic Representation of MM2-Minimized Structure of 3a

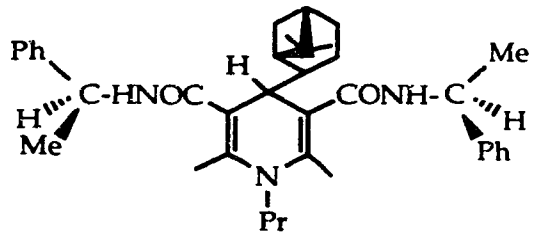
With the use of (R)-(+)-α-methylbenzylamine, **3c** and **3d** were prepared in good yields under the same reaction conditions as those used for the synthesis of **3a** and **3b**. However, the separation of **3c** and **3d** appeared to be more difficult than the separation of **3a** and **3b** because of the close polarity of **3c** and **3d** during the TLC analyses.



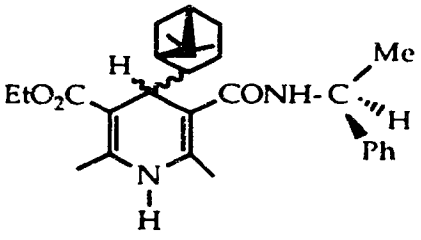
(13)

3c (-)
3d (+)

Upon the reaction of Hantzsch ester **1** with dimethylaluminum amide derived from (S)-(-)-α-methylbenzylamine, compound **5** was obtained as a mixture of diastereoisomers. These two compounds were isolated and were characterized by ^{1}H NMR.



4



5a (-)
5b (+)

The successful preparation of **3a-d** prompted the use of the same approach for the preparation of the optically active model compounds with a second amide N-substituent. When Hantzsch ester **2** was allowed to react with dimethylaluminum amide derived from (R)-(+)-N-methyl-α-

nethylbenzylamine, the expected secondary amide was not obtained. In all :ases, only starting material **2** was recovered. Similarly, the reaction of the Hantzsch ester **2** with dimethyl-aluminium amide derived from *tert*-)utylamine was unsuccessful. It appears that this method is only successful 'or the unhindered primary amine.

ENANTIOSELECTIVE ELECTION TRANSFER REACTION OF (±)-3-3ROMOCAMPHOR WITH DIHYDROPYRIDINES 3a-d The reduction of α-ıaloacetophenone by the N-alkyl or N-aryl-1,4-dihydronicotinamides)roceeds via a free radical chain reaction.[20] Similarly, a radical chain pathway vas established for the reduction of α-haloacetophenone with lihydropyridines **1-3**. For example, the reduction of α-haloacetophenone with **)a** gave 17% of acetophenone at 91 °C in methanol for 4 days. With initiation)y 5% *tert*-butyl peroxybenzoate, the reduction gave 37% of acetophenone.

In c der to demonstrate the possibile involvement of enantioselective :lection transfer reduction with dihydropyridines **1-3,** reactions were carried)ut on racemic 3-bromocamphor (α=0.000). There was no appreciable reaction <5%) in the absence of a radical initiator. With a small amount of an added nitiator, the reaction yielded camphor as the only product (Table I-1). Qualitatively, the reactivity followed the order **1≈2>3.**

The reduction by **1** and **2** can be initiated with *tert*-butyl peroxybenzoate ıt 91 °C to about 20% completion (Table I-1, entries 1 and 2), the camphor and 'ecovered bromocamphor were isolated. Polarimeric results showed both the solated camphor and the recovered bromocamphor were racemic, the 'eaction showed no enantioselectivity. Under the same conditions, only trace

Table I-1. The Reduction of (±)-3-Bromocamphor by Dihydropyridines 1-3[a]

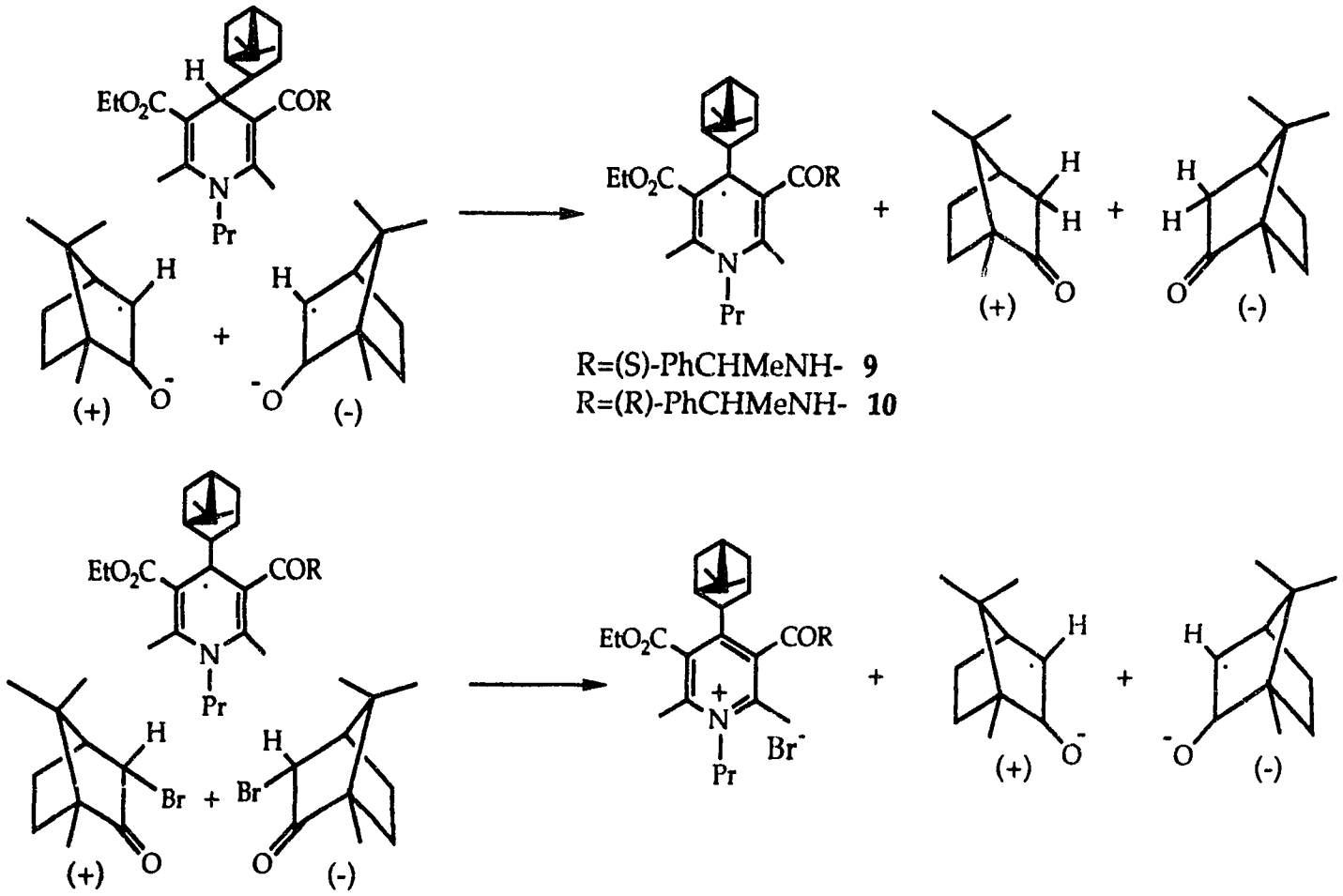
	model		bromocamphor			camphor		
reaction	compd.	additive	yield%[b]	ee%[c]	config.	yield%[b]	ee%[c]	config.
1	**1**	4% $PhCO_3Bu^t$	85.2	0		17.8	0	
2	**2**	4% $PhCO_3Bu^t$	76.3	0		27.4	0	
3	**3a**	4% $(Bu^tO)_2$	76.3	4.3	(+)-1R	22.3	3.7	(-)-1S
4	**3b**	4% $(Bu^tO)_2$	80.3	4.0	(+)-1R	18.5	4.1	(-)-1S
5	**3c**	4% $(Bu^tO)_2$	79.7	4.2	(-)-1S	22.0	3.3	(+)-1R
6	**3d**	4% $(Bu^tO)_2$	76.0	4.5	(-)-1S	21.0	3.7	(+)-1R

[a] Reductions were performed at 91 °C (reaction 1-2) or 120 °C (reaction 3-6) for 4 days in MeOH. [b] Determined by GC, in two runs. [c] Based on the optical rotations of pure 3-bromocamphor $[\alpha]_D^{19}$=+129° or $[\alpha]_D^{20}$=-127° (MeOH) and camphor $[\alpha]_D^{25}$=+44° or $[\alpha]_D^{25}$=-43 ° (EtOH). (Aldrich).

amount of camphor was detected in the reduction of 3-bromocamphor with **3a-d**. Initiation with *tert*-butyl peroxide at 120 °C, however, gave about 20% reduction (Table I-1, entries 3-6). These reactions showed some enantioselectivity, although the ee was very low.

The reductions by **3a** and **3b** were shown to be enriched in (1S)-(-)-camphor (4.3% ee; 4.0% ee), leaving the remaining starting material enriched in (1R)-(+)-3-bromocamphor (3.7% ee; 4.1% ee). Meanwhile, the reductions by **3c** and **3d** were shown to be enriched in (1R)-(+)-camphor (4.2% ee; 4.5% ee), and leaving the recovered starting material enriched in (1S)-(-)-3-bromocamphor (3.3% ee; 3.7% ee). These results indicate that the same radical **9** formed from **3a** and **3b** undergoes electron transfer slightly faster to (1S)-(-)-3-bromocamphor whereas radical **10** from **3c** and **3d** undergoes electron transfer slightly faster to the other enantiomer, (1R)-(+)-3-bromocamphor (see Scheme I-5). Moreover, electron transfer from **3a** and **3b** shows the same enantioselectivity since the chirality of the radical is the same. Similarly, electron transfer from **3c** and **3d** also shows the same enantioselectivity.

Although enantioselective electron transfer from these dihydropyridines **3a-d** to (±)-3-bromocamphor has been demonstrated, the ee obtained so far is very low. Since these reductions could only be initiated at very high temperature (120 °C), chiral discrimination during electron transfer from asymmetric 4-dihydropyridyl radical (**9** or **10**) to (+) and (-)-3-bromocamphor seemed to be disappointing.



Scheme I-5. The Enantioselective Reduction of 3-Bromocamphor by 3a-d

ASYMMETRIC REDUCTION OF METHYL BENZOYLFORMATE WITH DIHYDROPYRIDINES 3a-d The reduction of methyl benzoylformate were performed in the presence of 1 equivalent of magnesium perchlorate. No reduction products are detected in the absence of the salt, magnesium perchlorate. The results (Table I-2) show that Hantzsch esters **1** and **2** with bulky pinyl group in the 4-position show poor reactivity, which are consistent with those reported by Kellogg.[30] The reduction with **3a** and **3c** proceeded quite well in 83% and 61% yields. However, the reduction with **3b** and **3d** gave less satisfactory yields. In all cases, the yields of the reductions were not affected either by the presence of a radical initiator (AIBN) or an inhibitor (*m*-DNB).

Table I-2. The Reduction of Methyl Benzoylformate by Dihydropyridines 1-3[a]

	model	products		
reaction	compound	yield%[b]	ee%[c]	config.
7	**1**	<10	d	-
8	**2**	<10	d	-
9	**3a**	83	72	(+)-S
10	**3b**	25	31	(-)-R
11	**3c**	61	42	(+)-S
12	**3d**	19	7	(-)-R

[a] Reductions were performed in acetonitrile at 61 °C with 1 eq. of $Mg(ClO_4)_2$ for 20 days. [b] Determined by GC, in two runs. [c] Based on the optical rotation of pure methyl mandelate, $[\alpha]_D$=141.4° (lit.[16]). [d] Not determined.

Dihydropyridines **3a** and **3c** gave S-(+)-methyl mandelate whereas **3b** and **3d** gave R-(-)-methyl mandelate. Both enantiomers of methyl mandelate can be obtained using these NADH models. Although the enantiomeric excesses from **3b** and **3d** were not promising (Table I-1, entries 10 and 12), the reduction of methyl benzoylformate with **3a** and **3c** were obtained in moderate to good enantiomeric excesses (Table I-1, entries 10 and 12). It appears that the configuration of the reduction product is determined mainly by the configuration of hydrogen at the 4-position of these optically active dihydropyridines.

Based on previous models,[14,16,17] the transition state for the reduction of **3a** can be depicted as a magnesium complex, see Figure I-2. One can anticipate that the magnesium is complexed to both the C-3 carbonyl oxygen and the C-5 carbonyl oxygen and to ester carbonyl oxygen of methyl benzoylformate. This conformation produces the (S)-mandelate as the major enantiomer. An examination of Dreiding-Stereomodels of the proposed transition state indicates that the formation of the other enantiomer, (R)-mandelate is energetically disfavored because of the steric interactions between the benzoyl phenyl and amide group of the model.

High reactivity of **3a** or **3c** and the good ee obtained from these reactions appear to be achieved through a transition state in which chelation of the substrate and the dihydropyridine is efficient. Although the bridge of the pinyl group exists in the molecule, it is away from the hydrogen at C-4 (Figure I-1). However, in model **3b** and **3d**, the hydrogen at C-4 and the bridge of the pinyl group are on the same side. The complex would be forced to adopt a conformation in which the bridge of the pinyl group prevents efficient chelation of the substrate and the dihydropyridine. Both the

reactivity of **3b** and **3d** and the ee% produced from these reactions are much lower than those from corresponding dihydropyridines **3a** and **3c**.

Since the absolute configuration of these model compounds has not been being determined, further studies are required to establish the precise orientation of chelation of magnesium ion with these dihydropyridines and ketone.

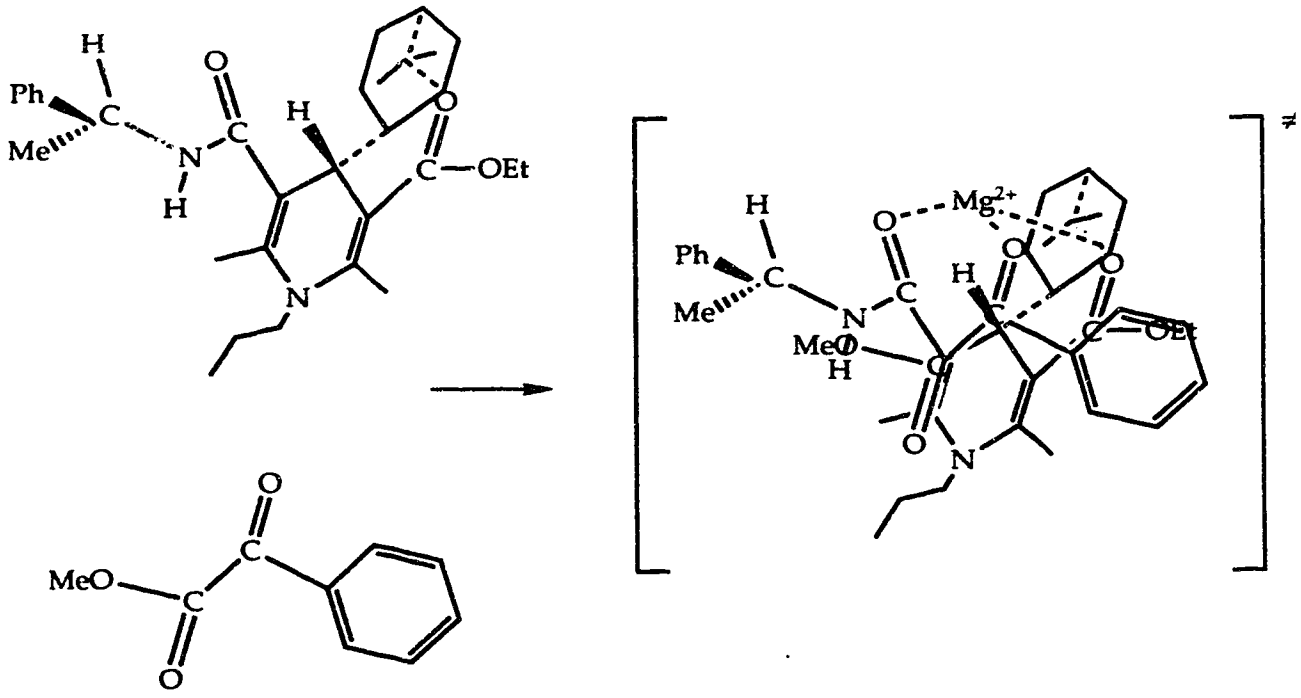


Figure I-2. Proposed Transition State for the Reaction of Model 3a

Conclusions

We have shown that the efficient asymmetric synthesis of optically active NADH model compounds can be achieved by the reaction of Hantzsch ester with the dimethylaluminum amide derived from (S)- or (R)-α-methylbenzylamine. By this approach, four diastereomeric 2,6-dimethyl-3-ethoxycarbonyl-5-(N-α-methylbenzylcarbamoyl-1-propyl-4-[(2S)-pinyl]-1,4-dihydropyridines (**3a-d**) were prepared in very good yields. Seperation of the diastereomeric isomers was obtained very easily by chromatographic separation on silica gel.

The reduction of (±)-3-bromocamphor to camphor by these dihydropyridines proceeds by a free radical chain mechanism involving electron transfer reaction. When the chiral NADH models (**3a-d**) were used, electron transfer step showed very low enantioselectivity.

The reduction of methyl benzoylformate with these model compounds (**3a-d**) was also carried out in the presence of magnesium perchlorate. It was found that **3a** and **3c** gave (S)-methyl mandelate whereas **3a** and **3c** gave (R)-methyl mandelate. In addition, the dihydropyridines **3a** and **3c** showed good reactivity and enantioselectivity.

Experimental

1. Materials

Reagent (Caledon, HPLC grade) **acetonitrile** was used after distillation over calcium hydride. **Methanol** (Caledon, HPLC grade) was distilled over calcium hydride.

The preparation or purification of ***p*-di-*tert*-butylbenzene**, **α,α-azoisobutyronitrile (AIBN) and m-dinitrobenzene (*m*-DNB)** has been described previously[20].

***tert*-Butylperbenzoate** (K & K laboratory), ***tert*-butyl peroxide** (Aldrich, 98%), **magnesium perchlorate** (B.D.H. Laboratory Chemicals Division), **1-bromopropane** (Aldrich, 99%) and **trimethylaluminium** (Aldrich, 2.0 M solution in toluene), ***tert*-butylamine** (Aldrich, 98%), **methyl benzoylformate** (Aldrich, 95%), (R)-(+)-**α-methylbenzylamine** (Aldrich, 98%, $[\alpha]_D^{23}$=+38° (neat)), (S)-(-)-**α-methylbenzylamine** (Aldrich, 98%, $[\alpha]_D^{20}$=-39° (neat)), ***trans*-myrtanol** (Fluka, $[\alpha]_D^{20}$=-29° ($CHCl_3$)), ***cis*-myrtanol** (Fluka, $[\alpha]_D^{20}$=-19.5° ($CHCl_3$)) and S-(+)-**methyl mandelate** (Aldrich, 99%, $[\alpha]_D^{20}$=+141.4° (MeOH)) were used as purchased.

(±)-Camphor (Eastman) was purified by sublimation, mp 174-175 °C (lit.[32] 175-177 °C)

(1R)-*endo*-(+)-3-bromocamphor (Aldrich, 98%, $[\alpha]_D^{19}$=+129° (MeOH)) and **(1S)-*endo*-(-)-3-bromocamphor** (Aldrich, 98%, $[\alpha]_D^{20}$=-127° (MeOH)) were purchased separately. **(±)-3-Bromocamphor** was made by mixing (1R)-*endo*-(+)-3-bromocamphor and (1S)-*endo*-3-bromocamphor until a rotation of [α]=0.000 was obtained.

(R)-(+)-N-Methyl-α-methylbenzylamine was prepared by Dr. Jian J. Chen in this laboratory according to the literature procedure,[33] $[\alpha]_D^{23}$=+60.6° (EtOH) [lit.[33] $[\alpha]_D^{23}$=+62.7±0.5° (EtOH)]; ^{1}H NMR ($CDCl_3$) δ: 1.33 (d, 3H), 2.30(s, 3H), 3.65 (q, 1H), 7.30 (m, 5H).

2. Methods

1) Physical Constants and Microanalyses

All melting point values were measured on a Fisher-Johns hot stage instrument or on a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at room temperature. Thin-layer chromatography was performed by using precoated sheets of silica gel IB2-F (Baker-Flex), and flash column chromatography was carried out with silica gel 1918 (20-45 microns, Terochem). Microanalyses were performed in the Microanalytic Laboratory, Department of Chemistry, University of Alberta.

2) Spectral Measurements

^{1}H NMR spectra were recorded on a Bruker WP-200 (200 MHz) or WP-300 (300 MHz) spectrometers with deuterio-chloroform as solvent and residual chloroform (δ 7.26 ppm) as the standard. Chemical shifts are expressed in ppm. Mass spectra were obtained using an A.E.I. MS-50 high resolution mass spectrometer coupled to a Data General Nova 2DS-50. Gas chromatograph-mass spectra (GC/MS) were recorded on a VG-70 E mass

spectrometer with a 1125 data system. The products of the reactions were separated on a Varian Vista 6000 gas chromatograph fitted with a gas capillary column (DB-5, 30 m × 0.25 mm × 0.25 μ, J & W Scientific). Gas chromatograph-infrared spectra (GC/IR) were obtained with a HP 5965A IRD spectrometer interfaced to a HP 5890 gas chromatograph (Hewlett-Packard) that was fitted with a glass capillary column (ultra 2, 25 m × 0.32 mm × 0.52 μ, Hewlett-Packard).

3) Quantitative gas chromatograph (GC) analyses

GC analyses with packed columns were carried out using a Hewlett Packard 5840 A gas chromatograph equipped with a flame ionization detector. The detector was coupled to a Hewlett Packard 5840 A terminal integrator.

In order to calculate the yields of the reaction products by GC analyses, a standard solution of known concentrations of the authentic products and internal standard was made and analyzed by GC. The concentration of the standard mixture is as close to that of the real reaction mixture as possible. The initial concentrations of the substrate (RX) and internal standard (S) are C_{RX} and C_S. A standard mixture of substrate (C^f_{RX}), internal standard (C^f_S), and product (P, C^f_P) was analyzed to give the relative area ratios: P, A^f_P/A^f_S; RX, A^f_{RX}/A^f_S. The reaction was then analyzed to give the relative area ratios: P, A_P/A_S; RX, A_{RX}/A_S. The yields of the product P and the recovered RX were calculated using the following equations:

$$P\% = [(A_P/A_S)/(A^f_P/A^f_S)][C^f_P/C^f_S][C_S/C_{RX}] \times 100\%$$

$$RX\% = [(A_{RX}/A_S)/(A^f_{RX}/A^f_S)][C^f_{RX}/C^f_S][C_S/C_{RX}] \times 100\%$$

Several injections of the solutions were carried out to obtain tl average relative area ratios. The specifications of the columns use throughout the course of the work are given in the individual experiments.

3. Preparations of Compounds 1-5

(-)-2,6-Dimethyl-3,5-diethoxycarbonyl-4-[(2S)-pinyl]-1,4-dihydropyridin 1. Ethyl acetoacetate (12.5 g, 0.096 mol), (+)-trans-myrtanal (7.6 g, 0.05 mo were dissolved in 250 mL of 10% ammonium carbonate solution. Th mixture was allowed to stir at room temperature for 3 days. A large crop crystals was obtained. The crystals was dissolved in diethyl ether and resultir mixture was extracted three times with diethyl ether. The combined organ extract was washed with water and brine and dried over anhydrous MgSC Filtration and evaporation of the solvent from the filtrate gave a sticky yello solid. The residue was purified by flash chromatography (dieth ether/petroleum ether=1/4) to give **1** (14.9 g, 79%). Recrystallization fro ether and hexane gave yellowish crystals: m.p. 118 °C $[\alpha]_D^{22}$=-36.0° (c 0.8 EtOH). ^{1}H NMR ($CDCl_3$) δ: 0.68 (s, 3H), 1.13 (s, 3H), 1.27 (t, 3H), 1.30 (t, 3H 1.35-2.02 (m, 9H), 2.30 (s, 6H), 3.98 (d, 1H), 4.00-4.32 (m, 4H), 5.62 (s, 1H). Ana Calcd. for $C_{22}H_{33}NO_4$: C,70.37; H, 8.86; N,3.73. found: C, 70.09; H, 9.04; N, 3.6 The (+)-*trans* -myrtanal was obtained by oxidation of *trans*-myrtanol (Fluk $[\alpha]_D^{20}$=-29° ($CHCl_3$)) with PCC according to the literature procedure,[28] bp 9 100 °C/8 mmHg (lit.[28] 89-91 °C/12 mmHg); $[\alpha]_D^{20}$=+71.9° (EtOH), (lit.[3 $[\alpha]_D^{20}$=+53.2° (EtOH)).

(-)-2,6-Dimethyl-3,5-diethoxycarbonyl-1-propyl-4-[(2S)-pinyl]-1,4-dihydropyridine, 2. Under a nitrogen atmosphere, sodium hydride (60% i

mineral oil, 1.34 g, 0.02 mol) was added slowly to a cooled solution (0 °C) of **1** (6.0 g, 0.016 mol) in DMF (20 mL). The solution was allowed to warm to room temperature and PrBr (11.8 g, 0.097 mol) was added gradually over 10 min. The mixture was stirred for 3 hr and treated with water. The solution was extracted three times with diethyl ether. The combined organic extract was washed with water and brine and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent from the filtrate gave a sticky yellow solid. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether=1/1) provided **2** (6.2 g, 93%). Recrystallization from ether and hexane gave yellowish crystals: m.p. 82 °C; $[\alpha]_D^{22}$=-39.0° (c 2.28, EtOH). ^1H NMR ($CDCl_3$) 0.56 (s, 3H) 0.85 (t, 3H) 1.22 (dt, 6H) 1.24-1.96 (m, 11H) 2.39 (s, 3H) 2.42 (s, 3H) 3.55 (t, 2H) 3.93 (d, 1H) 4.13 (m, 4H). Anal Calcd for $C_{25}H_{39}NO_4$ C, 71.91; H 9.41 N, 3.35 Found: C, 71.74; H, 9.47; N, 3.28.

(±)-2,6-Dimethyl-3-ethoxycarbonyl-5-[(S)-N-α-methylbenzylcarbamoyl]-1-propyl-4-[(2S)-pinyl]-1,4-dihydropyridines, 3a-b. A dry 100 mL three-necked round bottom flask was equipped with a reflux condenser fitted with a nitrogen inlet, a rubber septum and a magnetic stirrer. Under a nitrogen atmosphere, a toluene solution (2.85 mL) of $Al(CH_3)_3$ (0.0057 mol, 2 M) was added slowly to 10 mL of benzene. The solution was stirred and cooled in an ice-salt bath at -10 °C. (S)-α-Methylbenzylamine (1.38 g, 0.0114 mol) was added slowly over 30 min. When the addition was complete, 3 mL of benzene solution of **2** (1.07 g, 0.00256 mol) was injected into the flask. The solution was heated under reflux for 20 hr. After the reaction was complete, as determined by TLC analysis, 10 mL (0.6 M) HCl was added. The mixture was stirred for 30 min and extracted three times with 50 mL ethyl acetate. The combined organic extract was washed with water and brine and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent from the filtrate gave a

sticky yellow solid. The residue was purified by flash chromatography (ethyl acetate/ether/petroleum ether=1/1/2) to give each diastereomer of **3**. The product with higher R_f value, **3a** (5.5 g , 44%): m.p. 99 °C; $[\alpha]_D^{22}$=-176.8° (c 1.38, EtOH); ^{1}H NMR ($CDCl_3$) δ: 0.65 (s, 3H), 0.92 (t, 3H) 1.17 (s, 3H), 1.25 (t, 3H), 1.50 (d, 3H), 1.35-2.08 (m, 11H), 2.30 (s, 3H), 2.41 (s, 3H), 3.53 (d,1H), 3.60 (t, 2H), 4.15 (m, 2H), 5.17 (m, 1H), 5.84 (d,1H), 7.30 (m, 5H); Anal Calcd for $C_{31}H_{44}N_2O_3$:C, 75.57; H 9.00. N, 5.69. Found: C, 75.57; H, 9.14; N, 5.56; The product with lower R_f value, **3b** (3.5 g , 28%): m.p. 78 °C; $[\alpha]_D^{22}$=+149.1° (c 0.87, EtOH); ^{1}H NMR ($CDCl_3$) δ: 0.59 (s, 3H), 0.90 (t,3H) 1.10 (s, 3H), 1.23 (t, 3H), 1.49 (d, 3H), 1.35-2.00 (m, 11H), 2.20 (s, 3H), 2.44 (s, 3H), 3.46 (d, 1H), 3.60 (t, 2H), 4.12 (m, 2H), 5.22 (m, 1H), 5.80 (d,1H), 7.33 (m, 5H) Anal Calcd for $C_{31}H_{44}N_2O_3$: C, 75.57; H 9.00; N, 5.69. Found: C, 75.40; H, 9.23; N, 5.58.

(-)-2,6-Dimethyl-3,5-bis-[(S)-N-α-methylbenzylcarbamoyl]-1-propyl-4-[(2S)-pinyl]-1,4-dihydropyridines, 4. When the above solution was heated to reflux for 30 hr, a new product was formed. This polar product was isolated by flash chromatography (ethyl acetate/ether=1/1) to give a yellowish solid. m.p. 70 °C; $[\alpha]_D^{22}$=-6.8° (c 0.95, EtOH); ^{1}H NMR ($CDCl_3$) δ: 0.61 (s, 3H), 0.88 (t,3H) 1.11 (s, 3H), 1.51 (d, 3H), 1.22-1.98 (m, 11H), 2.14 (s, 3H), 2.24 (s, 3H), 3.12 (d, 1H), 3.50 (m, 2H), 5.20 (m, 2H), 5.83 (d,1H), 5.90 (d, 1H), 7.30 (m, 5H); mass spectrum m/e (rel intensity) 567 (M^+, 3), 419 (100), 297 (47), 272 (3), 147 (5), 120 (20), 105 (59), 91 (4), 77 (10).

(±)-2,6-Dimethyl-3-ethoxycarbonyl-5-[(R)-N-α-methylbenzylcarbamoyl]-1-propyl-4-[(2S)-pinyl]-1,4-dihydropyridines, 3c-d. A dry 100 mL three-necked round bottom flask was equipped with a reflux condenser fitted a nitrogen inlet, a rubber septum and a magnetic stirrer. Under a nitrogen atmosphere, a toluene solution (2.85 mL) of $Al(CH_3)_3$ (0.0057 mol, 2 M) was added slowly to 10 mL of benzene. The solution was stirred and cooled in an ice-salt bath at

-10 °C. (R)-α-Methylbenzylamine (1.38 g, 0.0114 mol) was added slowly over 30 min. When the addition was complete, **2** (1.07 g, 0.00256 mol) in 3 mL benzene was injected into the flask. The solution was heated to reflux for 20 hr. After the reaction was complete, as determined by TLC analysis, 10 mL (0.6 M) HCl was added. The mixture was stirred for 30 min and extracted three times with 50 mL ethyl acetate. The combined organic extract was washed with water and brine and dried over anhydrous $MgSO_4$. Filtration and Evaporation of the solvent from the filtrate gave a sticky yellow solid. The residue was purified by column chromatography (ethyl acetate/ether/petroleum ether=1/1/3) to give each diastereomer of **3**. The product with higher R_f value, **3c** (2.9 g , 31%): m.p.100 °C; $[\alpha]_D^{22}$=-165.4° (c 0.91, EtOH); ^1H NMR ($CDCl_3$).δ: 0.59 (s, 3H), 0.90 (t, 3H) 1.10 (s, 3H), 1.23 (t, 3H), 1.49 (d, 3H), 1.35-2.00 (m, 11H), 2.20 (s, 3H), 2.44 (s, 3H), 3.46 (d, 1H), 3.60 (t, 2H), 4.12 (m, 2H), 5.22 (m, 1H), 5.80 (d, 1H), 7.33 (m, 5H); Anal Calcd for $C_{31}H_{44}N_2O_3$: C, 75.57; H 9.00; N, 5.69 ; Found: C, 75.69; H, 9.09; N, 5.64. The product with lower R_f value, **3d** (3.2 g , 25%): m.p. 106 °C; $[\alpha]_D^{22}$=+167.3° (c 0.9, EtOH); ^1H NMR ($CDCl_3$).δ: 0.63 (s, 3H), 0.90 (t, 3H) 1.12 (s, 3H), 1.23 (t, 3H), 1.54 (d, 3H), 1.15-2.01 (m, 11H), 2.17 (s, 3H), 2.42 (s, 3H), 3.53 (d, 1H), 3.60 (t, 2H), 4.10 (m, 2H), 5.20 (m, 1H), 5.78 (d, 1H), 7.36 (m, 5H); Anal Calcd for $C_{31}H_{44}N_2O_3$: C, 75.57; H 9.00; N, 5.69 ; Found: C, 75.51; H, 9.14; N, 5.68. In addition, some unresolved mixture **3c-d** (2.1 g, 17%) were obtained.

(±)-2,6-Dimethyl-3-ethoxycarbonyl-5-[(S)-N-α-methylbenzylcarbamoyl]-4-[(2S)-pinyl]-1.4-dihydropyridines, 5a-b. Hantzsch ester **1** was treated with dimethyl-aluminium amide derived from (S)-(-)-α-methylbenzylamine in benzene according to the procedure described for the preparation of **3a-b** (reaction time 21 hr) to give a sticky yellow solid. The residue was purified by flash chromatography (ethyl acetate/ether/petroleum ether=2/1/2) to give

each diastereomer of **5**. The product with higher R_f value, **5a**: m.p.137 °C; $[\alpha]_D^{22}$=-59.5° (c 0.75, EtOH); ^{1}H NMR ($CDCl_3$) δ: 0.67 (s, 3H), 1.13 (s, 3H), 1.25 (t, 3H), 1.49 (d, 2H), 1.20-2.10 (m, 7H), 2.22 (s, 3H), 2.27 (s, 3H), 3.57 (d,1H), 4.13 (dq, 2H), 5.17 (t, 2H), 5.65 (s,1H), 5.83(d, 1H), 7.27 (m, 5H); Anal Calcd for $C_{28}H_{38}N_2O_3$: C, 74,63; H, 8.50. N, 6.22 Found: C, 74.61; H, 8.44; N,6.22. The product with lower R_f value, **5b**: m.p.175 °C; $[\alpha]_D^{22}$=+138.3° (c 0.74, EtOH); ^{1}H NMR ($CDCl_3$) δ: 0.62 (s, 3H), 1.06 (s, 3H), 1.27 (t, 3H), 1.50 (d, 2H), 1.20-1.90 (m, 7H), 2.20 (s, 3H), 2.29 (s, 3H), 3.54 (d,1H), 4.15 (dq, 2H), 5.21 (t, 2H), 5.54 (s,1H), 5.83(d, 1H), 7.33 (m, 5H); Anal Calcd for $C_{28}H_{38}N_2O_3$: C, 74,63; H, 8.50. N, 6.22 Found: C, 74.45; H, 8.64; N, 6.17.

4. Reaction Procedures

General Procedure for the reduction of (±)-3-bromocamphor to camphor Reaction ampules were Pyrex tubes joined to 10/30 joints. The ampules were cleaned with chromic acid solution, water, concentrated ammonium hydroxide, and distilled water, then oven dried at 120 °C. The reactants were placed in the ampules, degassed by three freeze-thaw cycles at -198 °C, and sealed under vacuum. The degassed mixtures were subsequently allowed to react under the desired conditions.

An aliquot of an acetonitrile solution of (±) 3-bromocamphor (0.05 M), 1,4-di-*tert*-butylbenzene (0.02 M), dihydropyridine **1-3** (0.1 M) was placed in a degassed ampoules with or without additives. The initiator (*tert*-butyl peroxybenzoate or *tert*-butyl peroxide) or inhibitor *m*-DNB was added before the reaction mixture was degassed The reaction ampoules were thermostated in an oil bath at 91 °C (*tert* -butyl peroxybenzoate) or 120 °C (*tert*-butyl peroxide) for 4 days. The ampoules were opened and the mixtures were

analyzed by GC using a 20 ft × 1/8 in glass column packed with 10% SE-30 on chromosorb WAW DMCS 80-100 mesh. The isolation of the products and unreacted dihydropyridines was carried out by preparative GC (Varian 90P) using a 10 ft × 1/4 in SS column packed with 10% SE-30 on chromosorb WAW DMCS 100-120 mesh. After dissolving the material in 1.0 mL methanol (3-bromocamphor) or ethanol (camphor), the specific rotation of the sample was measured. The ee's were calculated from the values given for the optically pure compounds. For the recovered 3-bromocamphor, the ee's were calibrated according to the conversion determined by GC (Table I-1)

General Procedure for Asymmetric Reduction of Methyl Benzoylformate to (S)- or (R)-Methyl Mandelate An aliquot of an acetonitrile solution of methyl benzoylformate **1-3** (0.1 M), *p*-di-*tert*-butylbenzene (0.033 M), dihydropyridine (0.1 M) was placed in a degassed ampoule. The reaction ampoules were thermostated in an oil bath at 61 °C for 20 days. The ampoules were opened and the mixtures were analyzed by GC using a 20 ft. × 1/8 in glass column packed with 10% carbowax 20 m on chromosorb P 80-100 mesh. After removing the unreacted dihydropyridine by flash column chromatography, the products were isolated by preparative GC (Varian 90P) on a 10 ft 1/4 in SS column packed with 20% QF-1 on chromosorb PAW 100-120 mesh. After dissolving this material in 1.0-1.5 mL of methanol, the specific rotation of the sample was measured. The ee's were calculated from the values given for the optically pure compounds (Table I-2).

Products were identified by a comparison of their retention times, GC/MS, GC/IR and ^{1}H NMR spectra with those of authentic samples. Duplicate experiments were run in each case.

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CHAPTER 2

On the Mechanism of the Debromination of *vic*-Dibromides with N-Benzyl-1, 4-dihydronicotinamide

Introduction

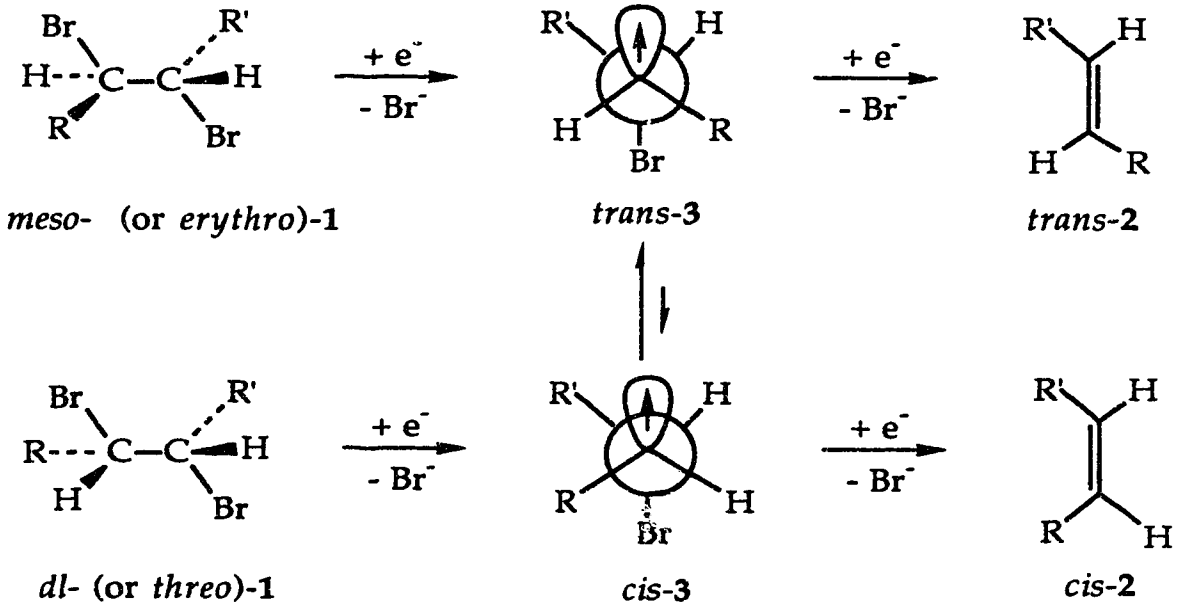
The dehalogenation of *vic*-dihalides to alkenes has been a subject of interest due to its importance in organic synthesis, especially for its usefulness in the purification of olefins and in the protection of the C=C bond through their dibromides. A variety of reagents have been reported to accomplish this transformation under a variety of reaction conditions.[1-7]

Both stereospecific and stereoselective dehalogenations of *vic*-dihalides have been reported.[7] Studies on the stereochemistry of the reductions of these *vic*-dibromides have shown some valuable mechanistic details in the reaction with different reducing agents. For example, reduction of *vic*-dibromide by a two-electron reducing agent such as iodide and thiosulfate gives mainly concerted anti-elimination products, which result in stereoselective formations of *trans*- and *cis*-alkenes, respectively. On the other hand, reduction by a one-electron reducing agent such as copper (I) and iron (II) generates free radical species, which then give thermodynamically more stable alkenes as major products. As a result, the reductive debromination of *vic*-dibromides can be used as a useful stereochemical probe to detect whether the radical intermediate is involved in the reaction system.

The reduction with NADH model compounds have been intensively studied from a mechanistic point of view because of their importance in biochemical oxidation and reduction transformations.[9] However, whether the reduction with NADH proceeds through heterolytic hydride transfer[10] or homolytic processes involving the electron transfer[11] is still controversial. The most widely studied NADH models is the N-benzyl-1,4-dihydronicotinamide (BNAH). Ohno and co-workers have studied the

reduction of several *vic*-dibromides with BNAH. They found that the thermodynamically more stable isomers of the alkene was formed predominantly[12]. A mechanism involving the intermediacy of free radicals was proposed in Scheme II-1. *vic*-Dibromide, **1**, accepts one electron from BNAH and eliminates a bromide ion to generate free radical species **3**. Since *trans*-**3** is more stable than *cis*-**3**, *cis*-**3** can rotate around the C-C bond to form radical intermediate with a more favorable conformation. The *trans*-**3** then accepts a second electron from BNAH and eliminates another bromide ion to produce the thermodynamically more stable alkene, in a non-chain process.

Scheme II-1.



1a; R=R'=COOEt
1b; R=Ph, R'=COOEt
1c; R=R'=Ph

Recently, the photoreduction of *vic*-styrene dibromide (**1d**) with BNAH has been studied by Ohkubo and co-workers.[13] The reaction was carried out in aqueous solution to form styrene and (1-bromoethyl)benzene. Based on quantum efficiency higher than unity, a radical chain mechanism was proposed for the formation of styrene. As shown in Scheme II-2, the initial step proceeds via the photoexcitation of BNAH to form a radical anion, followed by the elimination of bromide ion from the radical anion (eq 1). The resulting radical undergoes elimination to yield a bromine radical (eq 2) which initiates a radical chain process by abstraction of hydrogen from BNAH (eq 3). A similar radical chain pathway has been suggested for the photosensitized reduction of vic-dibromides by zinc porphyrin[14] and ruthenium (II) tris(bipyridine) ($Ru(bpy)_3^{2+}$).[15]

Scheme II-2

$$BNAH^* + PhCHBrCH_2Br \longrightarrow [BNAH^{\cdot+}\ PhCHBrCH_2Br^{\cdot-}] \xrightarrow{-Br^-} BNAH^{\cdot+} + PhCHCH_2Br \quad (1)$$

$$PhCHCH_2Br \longrightarrow PhCH{=}CH_2 + Br^{\cdot} \quad (2)$$

$$Br^{\cdot} + BNAH \longrightarrow HBr + BNA^{\cdot} \quad (3)$$

$$BNA^{\cdot} + PhCHBrCH_2Br \longrightarrow PhCHBrCH_2Br^{\cdot-} \quad (4)$$

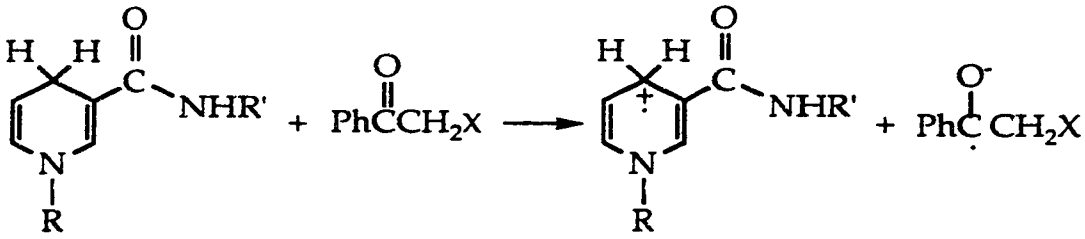
$$PhCHBrCH_2Br^{\cdot-} \longrightarrow PhCHCH_2Br + Br^- \quad (5)$$

During the course of our studies BNAH is found to reduce a series of monohalides such as α-fluoro-, α-chloro- and α-bromoacetophenone to give

the dehalogenation product, acetophenone.[16] The reaction proceeds by a free radical chain mechanism whose initiation step and propagation step contain an electron transfer. As shown in Scheme II-3, the initiation step is the electron transfer from the reducing agent, BNAH to α-haloacetophenone (eq 6). The ketyl radical formed subsequently eliminates a bromine ion to generate the enolyl radical (eq 7). The enolyl radical abstracts a hydrogen atom

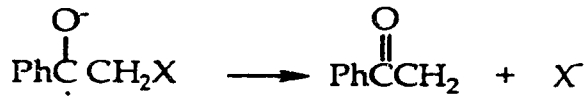
Scheme II-3

initiation



(6)

propagation



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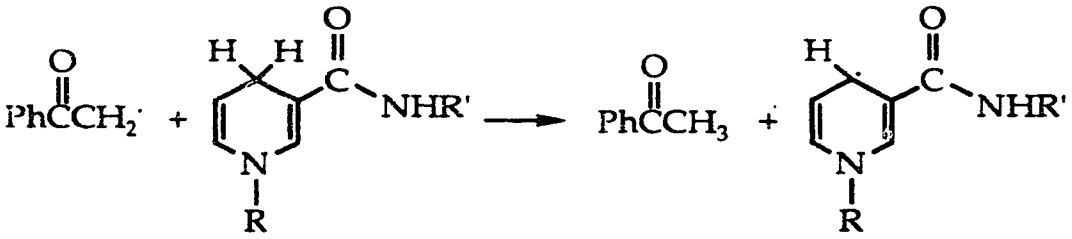

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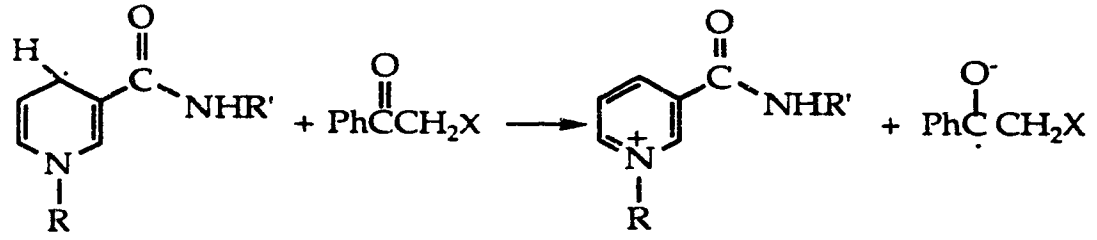


(9)

from the dihydronicotinamide to form a dihydropyridyl radical (eq 8), which carries the chain by subsequent electron transfer to another molecule of α-haloacetophenone (eq 9).

Since the photoreduction of *vic*-dibromides by BNAH proceeds by a radical chain process, and since the proposed initiation step in the reduction of a *vic*-dibromide is the same as that of the reduction of monohalides, it is of interest to reinvestigate in some mechanistic detail the thermal reduction of *vic*-dibromides with BNAH. One can expect that the free radical chain mechanism would be energetically more favorable than the proposed two electron transfer process for this reaction. For this purpose, initiation and inhibition studies were carried out for the BNAH reduction of a series of *vic*-dibromides in organic solvent.

Results and Discussion

The compounds studied in this work are

RCHBrCHBrR'

meso- or *dl-* **1a**; R=R'=COOEt

erythro- **1b**; R=Ph, R'=COOEt

meso- or *dl-* **1c**; R=R'=Ph

1d; R=Ph, R'=H

The reduction of *vic*-dibromides with one equivalent of BNAH was carried out at 61℃ in tetrahydrofuran (THF) or acetonitrile (AN) solution. Radical initiation (AIBN) and inhibition (*m*-DNB) were studied to establish whether a free radical chain mechanism was involved in the BNAH reduction of these dibromides. The reaction yields were not optimized since conditions were chosen so that initiation and/or inhibition could be observed clearly. The results of the reactions are listed in Table II.

During the BNAH reduction of diethyl *meso*-dibromosuccinate (*meso*-**1a**) or diethyl *dl*-dibromosuccinate (*dl*-**1a**), diethyl fumarate was formed as the only debromination product (Table II-1, entries 1, 4, 7 and 10). Diethyl maleate, was not detected in the reaction mixture. In addition, appreciate amount of an elimination product, diethyl 2-bromofumarate (*trans*-**4**) and diethyl 2-bromomaleate (*cis*-**4**), were produced. Interestingly, when the reaction was carried out in THF, a small amount of a 1:1 mixture of diastereomeric product, compounds **6**, was formed (Table II-1,entries 1 and 4).

Table II-1. The Reductive Debromination of *vic*-Dibromides with BNAH[a]

			products (%)[b,c,d]				
reaction	dibromides	conditions	*trans*-**2**	*cis*-**2**	*trans*-**4**	*cis*-**4**	**6**
1	*meso*-**1a**	THF, 24 h	38.4±0.3	-	trace	trace	3.0±0.2
2	*meso*-**1a**	THF, 24 h, 4% AIBN	51.0±2.4	-	0	0	49.9±7.6
3	*meso*-**1a**	THF, 24 h, 3% DNB	15.0±0.6	-	2.4±0.1	4.6±0.3	0
4	*dl*-**1a**	THF, 24 h	12.9±1.9	-	37.6 ±2.7	trace	1.1±0.5
5	*dl*-**1a**	THF, 24 h, 4% AIBN	22.5±1.2	-	12.9±0.2	trace	30.3±0.6
6	*dl*-**1a**	THF, 24 h, 3% DNB	0.4±0.0	-	44.7±1.2	trace	0
7	*meso*-**1a**	AN, 24 h	36.9±4.1	-	6.2±0.1	10.0±4.1	-
8	*meso*-**1a**	AN, 24 h, 4% AIBN	52.3±0.6	-	4.4±0.1	7.0±0.4	-
9	*meso*-**1a**	AN, 24 h, 3% DNB	16.0±2.9	-	7.0±0.1	18.4±0.6	-
10	*dl*-**1a**	AN, 24 h	9.9±0.3	-	66.1±0.3	1.1±0.1	-
11	*dl*-**1a**	AN, 24 h, 4% AIBN	55.0±5.2	-	48.0±1.2	1.4±0.2	-
12	*dl*-**1a**	AN, 24 h, 3% DNB	0.6±0.1	-	71.4±2.1	1.9±0	-

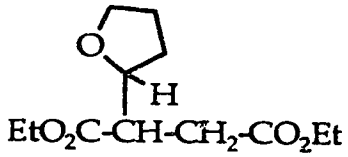
[a] All reactions were carried out at 61 °C with a mole ratio of 1:1 of dibromide to BNAH. [b] Errors are the mean deviation from the average value obtained from two or more independent experiments. [c] Yields determined by GC. [d] Recovered dibromide accounts for the material balance.

Table II-2. The Reductive Debromination of *vic*-Dibromides with BNAH[a]

reaction	dibromide	conditions	products (%)[b,c,d] *trans*-2	*cis*-2
13	*erythro*-**1b**	THF, 8 h	49.4±10.1	-
14	*erythro*-**1b**	THF, 8 h, 4% AIBN	83.7±3.6	-
15	*erythro*-**1b**	THF, 8 h, 3% DNB	47.2±2.3	-
16	*meso*-**1c**	THF, 20 h	58.7±8.9	-
17	*meso*-**1c**	THF, 20 h, 4% AIBN	96.7±5.8	-
18	*meso*-**1c**	THF, 20 h, 3% DNB	42.8±8.9	-
19	*dl*-**1c**	THF, 20 h	46.8±5.9	10.0±0.1
20	*dl*-**1c**	THF, 20 h, 4% AIBN	96.1±0.6	3.3±0.2
21	*dl*-**1c**	THF, 20 h, 3% DNB	47.0±2.9	10.5±0.8
22	**1d**	THF, 48 h	8.5±2.2	
23	**1d**	THF, 48 h, 4% AIBN	28.0±0.1	
24	**1d**	THF, 48 h, 3% DNB	0.6±0.2	

[a] All reactions were carried out at 61 °C with a mole ratio of 1:1 of dibromide to BNAH. [b] Errors are the mean deviation from the average value obtained from two or more independent experiments. [c] Yields determined by GC. [d] Recovered dibromide accounts for the material balance.

However, this compound was not produced when the reaction was carried out in acetonitrile. The mixture was isolated by preparative TLC. The structural analyses by ^1H NMR spectra, GC-IR and GC-MS indicate that this compound is a mixture of diastereomers of diethyl (tetrahydro-2-furyl)succinate (**6**).



6

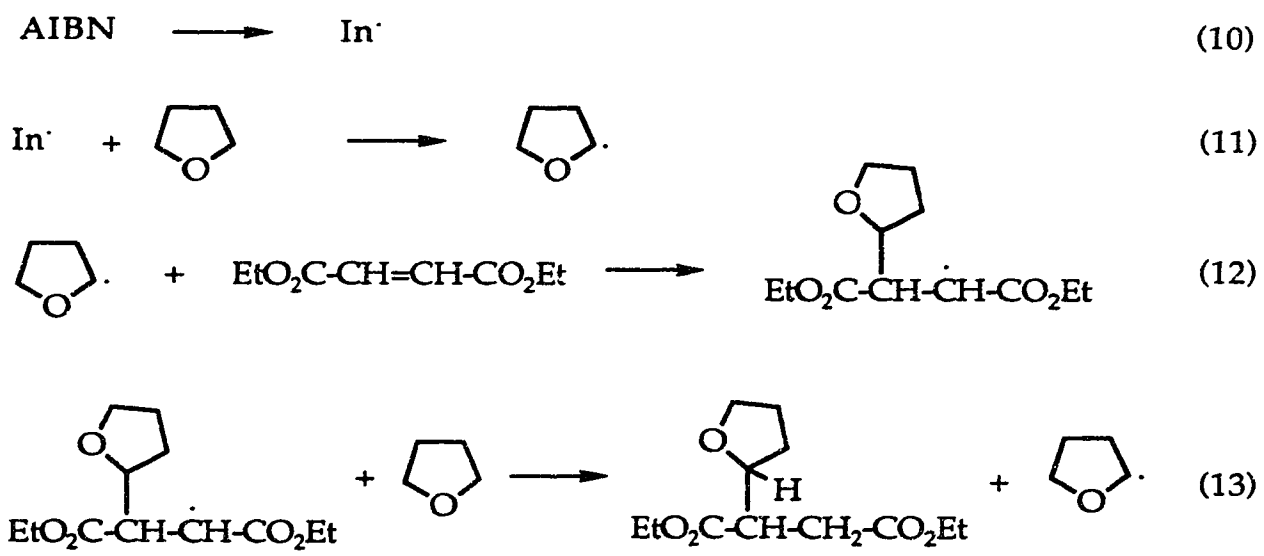
Ethyl *erythro*-α,β-dibromo-β-phenylpropionate (*erythro*-**1b**) was reduced by BNAH to give a single product, ethyl cinnamate, in 49% yield (Table II-2, entry 13). *meso*-1,2-Dibromo-1,2-diphenylethane (*meso*-**1c**) reacted with BNAH to give trans-stilbene as the only product in 59% yield (Table II-2, entry 16), while *dl*-1,2-dibromo-1,2-diphenylethane (*dl*-**1c**) reacted with BNAH to give 47% of *trans*-stilbene and 10.0% of *cis*-stilbene (Table, entry 19). (±)-1, 2-Dibromoethylbenzene appeared to be less reactive towards BNAH, since only 8.5% of styrene was formed (Table II-2, entry 22).

These results obtained are consistent with those reported previously.[12] *meso*- (*erythro*-)-Dibromide gives trans-alkene as the only debromination product, while *dl*-dibromide gives a mixture of *trans*-alkene (the major debromination product) and *cis*-alkene (the minor debromination product).

The reduction of *vic*-dibromides **1a** with BNAH was initiated by the addition of AIBN (Table II-1, entries 2, 5, 8 and 11) and inhibited by the addition of small amounts of *m*-DNB (Table II-1, entries 3, 6, 9 and 12). When the BNAH reduction of *meso*- or *dl*-**1a** was carryed out in THF in the presence

of AIBN, a large amount of diethyl (tetrahydro-2-furyl)succinate (**6**) was also formed (Table II-1, entries 2 and 5). Obviously, this compound was formed by a radical chain process from furyl radical addition to diethyl fumarate produced in the reaction (Scheme II-4).[17] As expected, when diethyl fumarate was allowed to reflux in THF in the presence of 5% AIBN for 30 hr, diethyl (tetrahydro-2-furyl)succinate was produced in a 63% yield as a 1:1 adduct.

Scheme II-4



The reduction of dibromide **1d** gave 28% of styrene with AIBN initiation (Table II-2, entries 23). When 3% of *m*-DNB was added, the reaction was completely inhibited (Table II-2, entry 24). Although no obvious inhibition with *m*-DNB was observed in the reduction of *vic*-dibromide **1b** and **1c**, the yields of the products were substantially increased when the reaction was repeated in the presence of 4% of AIBN (Table II-2, entries 14, 17 and 20).

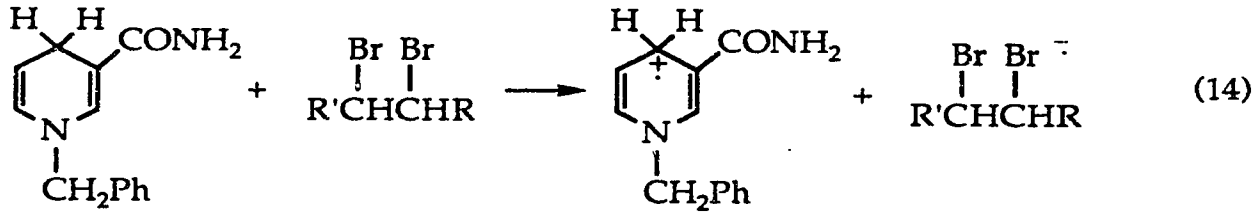
The initiation and inhibition studies clearly establish that the reduction of these *vic*-dibromides by BNAH proceed by a free radical chain process. Based on the above results, a free radical chain mechanism is proposed as shown in Scheme II-5.

As had been proposed for the BNAH reduction of α-haloacetophenone (eq 6, Scheme II-3),[15] the initiation step is an electron transfer from BNAH to the dibromide to form radical anion which cleaves to give a bromide ion and the radical intermediate (eq 14). When radical intermediate **3** is formed (eq 15), the radical intermediate cleaves to give the alkene and a bromine atom (eq 16). Since the addition of bromine radical to the double bond is reversible process,[18] the cleavage of radical to alkene and a bromine atom is anticipated when the alkene can be stabilized by the presence of the ester or phenyl groups.

It is well known from the mechanism of bromination of N-bromosuccinimide (NBS), that the bromine atom undergoes allylic hydrogen abstraction in preference to the addition to the double bond.[19] The bromine atom generated from the cleavage of radical anion abstracts a hydrogen atom from the 4-position of the dihydropyridine (eq 17), and the 4-dihydropyridyl radical then undergoes an electron transfer to the *vic*-dibromide (eq 18), which again furnishes the chain propagating species. When the substituted alkene is stabilized by one or two phenyl groups, the cleavage into alkene and bromine radical should be more favorable. As expected, the initiated reaction of dibromide **1b**, or **1c** takes place much more efficiently than the initiated reaction of dibromide **1a**. In addition, with AIBN initiation, the reduction can be completed with 1 equivalent of BNAH. This observation indicates that a second electron transfer from BNAH to dibromide is not involved.

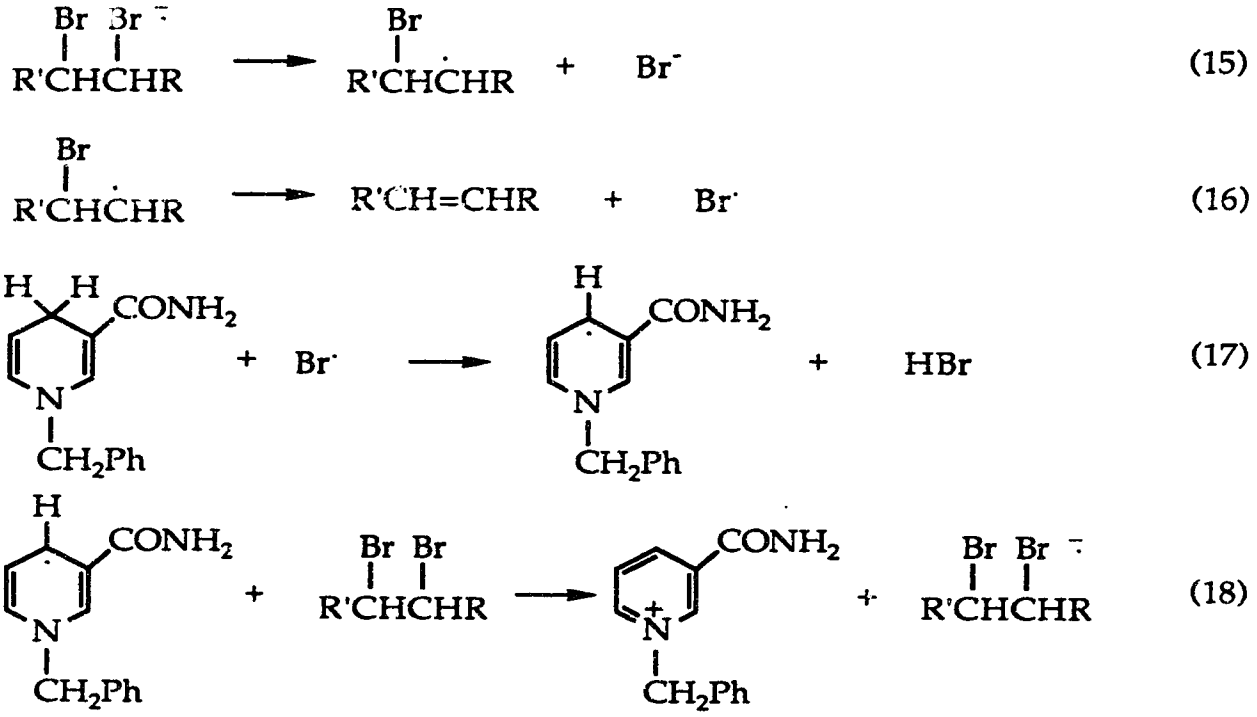
Scheme II-5

initiation



(14)

propagation

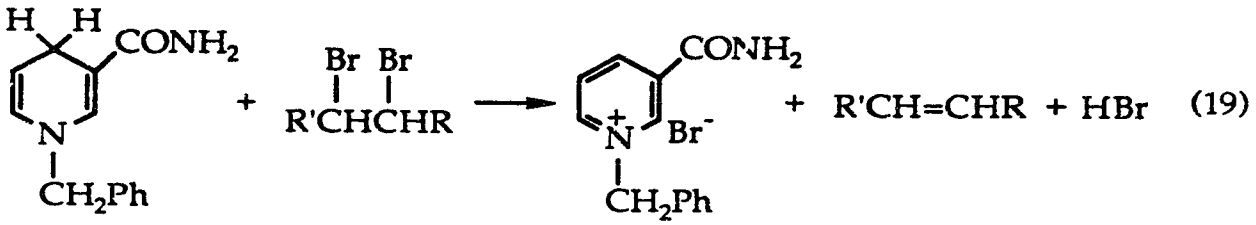


(15)

(16)

(17)

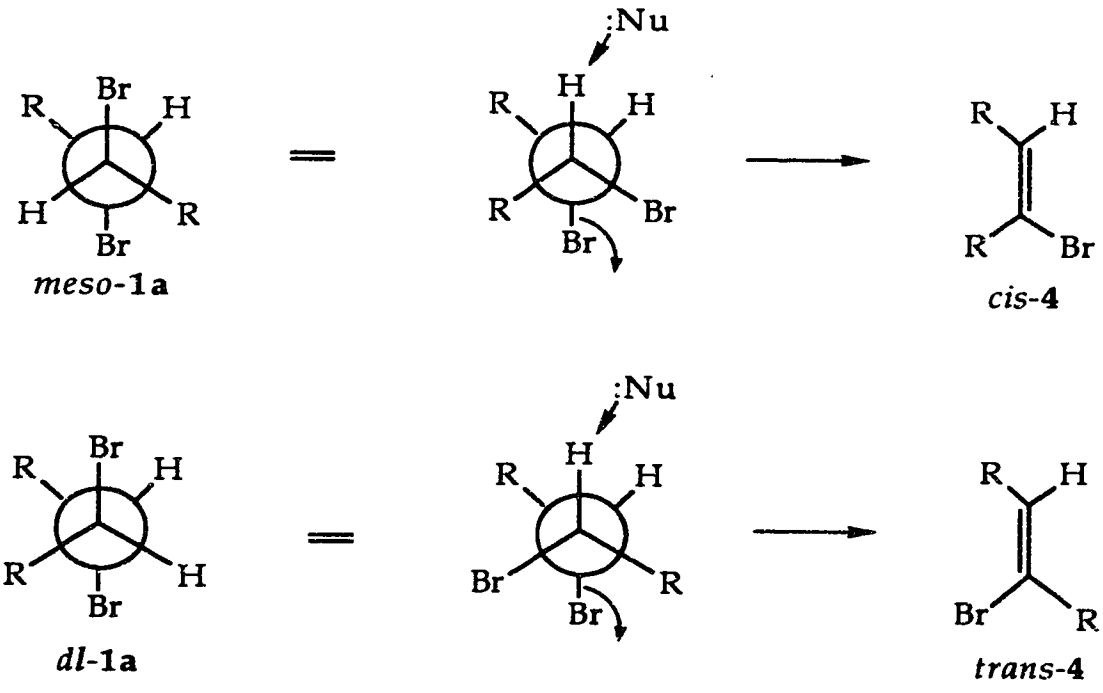
(18)



(19)

When a THF solution of *vic*-dibromide **1a** was allowed to react with BNAH, *trans*-elimination of hydrogen bromide took place to give an appreciable amount of α-bromoalkene (**4**). In the more polar solvent acetonitrile, the amount of α-bromoalkene increased. cis-α-Bromoalkene (*cis*-**4**) was formed as a major product for *meso*-dibromide **1a**, whereas *trans*-α-bromoalkene (*trans*-**4**) was formed as a major product in the reaction of *dl*-dibromide **1a**. The products are most likely formed by the competitive β-elimination of hydrogen bromide (see Scheme II-6).

Scheme II-6



Since BNAH is a weak base, it can abstract the proton from the favored conformation of these dibromides. So *cis*-alkene is the major product from *meso*-dibromide whereas *trans*-alkene is the major product from *dl*-dibromide. This proposal is supported by the fact that *meso*- or *dl*-dibromide

1a react with triethylamine[11] to give β-elimination product instead of reductive debromination. When the reduction were carried out in acetonitrile, more β-elimination product was formed than in THF. However, no β-elimination products were detected from the reaction of BNAH with *vic*-dibromides **1b, 1c** and **1d**. A plausible explanation for this result is that the α-hydrogen atoms of dibromides **1b** , **1c** and **1d** are less acidic than that of dibromide-**1a**.

Conclusions

The reaction of *vic*-dibromides with BNAH yields the thermodynamically more stable isomer of the alkene as the major debromination product. Contrary to the original proposal,[11] the reaction proceeds by a free radical chain sequence. The initiation step is an electron transfer from BNAH to the dibromide. The radical intermediate formed then cleaves to give the thermodynamically more stable alkene and a bromine atom. A chain propagating step in the sequence of these reductions is the abstraction of a hydrogen from BNAH by bromine atom, which generates a 4-dihydropyridyl radical.

Experimental

1. Materials

Tetrahydrofuran (THF) (Aldrich, HPLC grade) was distilled from $LiAlH_4$. Reagent **acetonitrile (AN)** (Caledon, HPLC grade) was purified by distillation from calcium hydride.

The preparation or purification of **N-benzyl-1,4-dihydronicotinamide (BNAH)**, ***p*-di-*tert*-butylbenzene**, **α,α-azobisisobutyronitrile (AIBN)** and **m-dinitrobenzene (*m*-DNB)** has been described previously.[16]

Diethyl fumarate (Aldrich, 98%), **diethyl maleate** (Aldrich, 97%), **ethyl cinnamate** (Aldrich, 96%), ***cis*-stilbene** (Aldrich, 97%), ***trans*-stilbene** (Aldrich, 96%), **styrene** (Aldrich, 99%), ***meso*-1,2-dibromo-1,2-diphenylethane (*meso*-1c)** (Aldrich, 96%) and **(±)-1,2-dibromoethylbenzene (1d)** (Aldrich, 99%) were used as supplied.

Diethyl *dl*-dibromosuccinate (*dl*-1a) was prepared by bromination of diethyl meleate,[21] bp 132-133 °C/5.5 mmHg (lit.[21] 137-138 °C/11 mmHg). ^1H NMR ($CDCl_3$) δ: 1.26 (t, 6H), 4.21(q, 4H), 4.58 (s, 2H).

Diethyl *meso*-dibromosuccinate (*meso*-1a) was prepared by bromination of diethyl fumarate[21] and recrystallized from methanol, mp 57 °C (lit.[21] 58 °C). ^1H NMR ($CDCl_3$) δ: 1.32 (t, 6H), 4.30(q, 4H), 4.64 (s, 2H).

Ethyl *erythro*-α,β-dibromo-β-phenylpropionate (*erythro*-1b) was prepared by bromination of ethyl cinnamate[22] and recrystallized from petroleum ether, mp 76 °C (lit.[22] 74-75 °C). ^1H NMR ($CDCl_3$) δ: 1.40 (t, 3H), 4.36 (q, 2H), 4.38 (d, 1H), 5.36 (d, 1H), 7.49(m, 5H).

***dl*-1,2-dibromo-1,2-diphenylethane (*dl*-1c)** was prepared by bromination of cis-stilbene [23] and recrystallized from ethanol, mp 112 °C (lit.[23] 110-111 °C). ^{1}H NMR ($CDCl_3$) δ: 5.48 (s, 1H), 7.20 (s, 5H).

2. General Procedure for Reactions

Measurements of physical constants, microanalyses, spectral measurements, and GC analyses were carried out using the same instrumentation described in Chapter 1.

Reaction ampules were Pyrex tubes joined to 10/30 joints. The ampules were cleaned with chromic acid solution, water, concentrated ammonium hydroxide, and distilled water, then oven dried at 120 °C.

An aliquot of a solution (THF or AN) of the dibromide (0.05 M), BNAH (0.05 M) and the internal standard (*p*-di-*tert*-butylbenzene, 0.02 M) was placed in a pyrex ampule with or without additives. The initiator AIBN or inhibitor *m*-DNB was added before the reaction mixture was degassed. The ampule was degassed by three freeze-thaw cycles and sealed under vacuum. The degassed mixtures were subsequently thermostated at 61 °C for the specified time. After the desired reaction time, the ampule was opened and analyzed by GC using a 20 ft × 1/8 in glass column packed with 10% SE-30 on chromosorb WAW DMCS 80-100 mesh.

For each reaction the products were identified by a comparison of their GC retention times, GC-IR spectra and GC-MS spectra with those of authentic samples. All reactions were run in duplicate and the average yield of the products is reported.

Isolation and identification of **diethyl(tetrahydro-2-furyl)succinate (6** A solution of diethyl fumarate (860.9 mg , 5 mmol), AIBN (24.9 mg, 3%) wa heated to reflux in 100 mL of tetrahydrofuran for 24 hr under a nitroge atmosphere. GC analyses showed that a 61% yield of a 1:1 mixture o diastereomeric products was produced. Evaporation of the solvent gave a yellowish oil. The residue was purified using preparative TLC (ethy acetate/hexane=1/2). ^{1}H NMR ($CDCl_3$) δ: 1.28 (m, 6H), 1.88 (m, 4H), 2.4-3.5 (m 3H), 3.72-4.10 (m, 3H), 4.11 (m, 4H). Anal. Calcd. for $C_{12}H_{20}O_5$ (a mixture o diastereomers): C,59.00; H, 8.25. found: C, 58.73; H, 8.38.

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CHAPTER 3

On the Mechanism of the Reaction of α-Substituted Ketones with Allyltributylstannane

Introduction

The radical allylation of organic halides and related precursors by allylstannanes is a powerful and selective method to form C-C bonds, which introduce allyl groups into organic molecules.

The radical allylation of organic halides with allylstannanes was originally discovered and studied by Pereyre[1] and Migita.[2] They found that the reactions could be initiated with benzoyl peroxide and inhibited with a small amounts of a radical scavenger, *p*-quinone. The order of reactivity in a series of organic halides was found to be F<Cl<Br<I. The evidence of a carbon-centered free radical intermediate was adduced from the fact that reaction of an optically active halide with allylstannane gives racemic product. In addition, rearrangement product from the unstable intermediate free radical was observed. Based on these facts, the free radical chain mechanism was proposed, see Scheme III-1. The radical chain transfer agent was the $Bu_3Sn\cdot$ radical.

Scheme III-1

(1)

$$RX + \cdot SnBu_3 \longrightarrow XSnBu_3 + R\cdot \qquad (2)$$

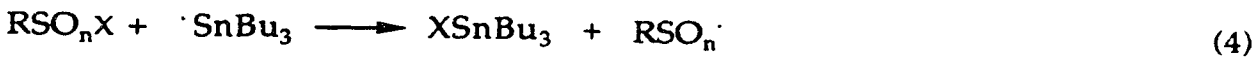
Subsequently, Keck found that this free radical allylation provided a valuable synthetic method.[3] A variety of alkyl halides could be used, including less reactive aryl halides and activated aryl halides. The reaction is

initiated either with AIBN or photochemically with a tungsten lamp. Yields are generally very high. Since then, this allylation has been applied[4] in approaches to the synthesis of many compounds such as pseudomonic acid,[5] perhydrohistrionicotoxin,[6] and in construction of β-lactam side chains. [7, 8]

The potential of allylstannanes to provide efficient free radical pathways for intermolecular C-C bond formation has been extended to intramolecular ring cyclizations.[9] Allylstannanes also show promise as reagents that will permit the planned sequencing of radical reactions.[10] In addition, this free radical chain substitution has been extended to include propargyl and alkenyloxy tin derivatives.[11-12]

Replacement of tin by other heteroatoms such as sulfur is also possible. Russell reported the free radical chain reactions of allylstannanes with $PhSO_2Cl$ or PhSSPh.[12] The reactions did not occur in the dark but could initiated by AIBN or light. In these reactions, the attacking radicals leading to allylic rearrangement with displacement of $Bu_3Sn\cdot$ were hetero-centered radicals such as $PhSO_2\cdot$ (n=2) and PhS· (n=0).

(3)



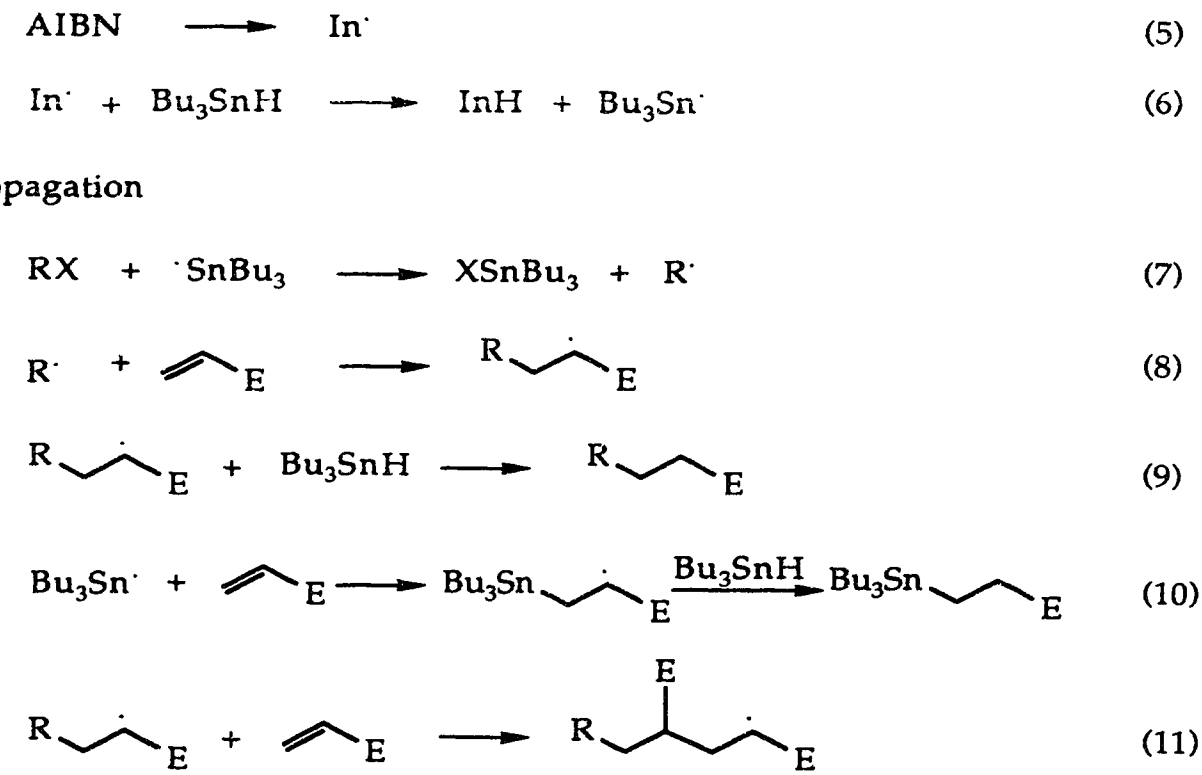
(4)

The free radical addition of tin hydride to alkene is well documented.[13] As shown in Scheme III-2, the trialkyltin radical ($Bu_3Sn\cdot$) abstracts a halogen atom to generate the alkyl radical R (eq 7). The alkyl radical now has two reasonable options. It can undergo either hydrogen atom abstraction from tin hydride to form a reduction product or addition to the electron-deficient alkene to form addition product (eq 8). Both reactions are second-order

reactions with similar rate constants $k_H \approx k_a \approx 10^6\ M^{-1}\ s^{-1}$. (at ambient temperature). From a synthetic perspective, addition to alkene is the desired pathway. The yield of the allylation product is increased by using an excess of alkene and/or by keeping tin hydride in high-dilution. Detailed guidelines on experimental conditions for a variety of substance are available.[14]

Scheme III-2

initiation



propagation

However, a balance must be maintained. If a large excess of alkene is used, side reactions such as hydrostannation (eq 10) and telomerization (eq 11) can compete with radical addition. The hydrostannation by-product can be minimized by the use of most reactive radical precursors possible. Alkyl

iodines are prefered for this purpose. Less reactive bromides and chlorides can not generally be employed.

Although the chain propagating species ($SnBu_3\cdot$) in the free radical allylation reaction is the same as in the tin hydride method, there are significant advantages to allylation. Since no tin hydride is involved in the reaction, intermediate radicals generated are not intercepted by hydrogen atom abstraction, and high-dilution techniques are not required. The intermediate radicals generated in the reaction have enough lifetime to undergo addition, followed by rapid fragmentation to provide the allyl product and the chain carrying radical. Since it is very easy for the β-stannyl radical to undergo fragmentation, the formation of side-products from telomerization and hydrostannation is unlikely.

Recently, rate constants for the addition of alkyl radicals to allylstannanes were estimated to be in the range of 10^4-10^5 M^{-1} s^{-1} at 50-80 °C.[15] Although the allylstannanes are not as reactive as electron-deficient alkenes toward alkyl radical, they are at least one order of magnitude more reactive than simple alkenes towards alkyl radicals. This modest activation insures the starting allylstannane is more reactive than the allylated product and it aids in promoting propagation. Since allylstannanes propagate tin-radical based chains without using tin hydride, they are powerful synthetic reagents.

Electron transfer is one of the most thoroughly investigated chemical reactions. Recently, much attention has been focused on identifying electron transfer pathways in many classical organic reactions believed to proceed by polar ionic reactions. For example, electron transfer reactions are now believed to be involved in some of the reductions with metal hydrides.[16]

Organotin hydride are a class of organometallics of particular interest and their value is now widely recognized among organic chemists. Since the discovery of the reduction of the alkyl halide with triphenyltin hydride,[17-18] the reduction of a variety of alkyl or aryl halides with different organotin hydrides has been studied extensively from the synthetic and mechanistic point of view.

Kuivila[18] has extensively studied the mechanism for the reduction of alkyl halides with triaryl- and alkyltin hydrides. He found that reaction showed catalysis by AIBN and light, and inhibition by small amounts of hydroquinone. Additional evidence of a radical intermediate can be adduced from the fact optically active α-phenylethyl chloride on treatment with triphenyltin deuteride yields racemic α-deuterioethylbenzene. A radical chain mechanism involving direct halogen atom abstraction from benzyl halides to the stannyl radical was proposed. The tin radical abstracts the halogen by direct halogen atom transfer to give the carbon-centered radical (eq 12) which then abstracts hydrogen from tin hydride to give the reduction product (eq 13).

$$R'X + {}^{\cdot}SnR_3 \longrightarrow \left[R' \cdots X \cdots SnR_3 \right]^{\cdot \neq} \longrightarrow XSnR_3 + R'^{\cdot} \qquad (12)$$

$$R'^{\cdot} + HSnR_3 \longrightarrow {}^{\cdot}SnR_3 + R'H \qquad (13)$$

This radical chain mechanism involving the halogen abstraction was supported by the studies of other workers. Carlson and Ingold found that either the X abstraction or the H abstraction could be rate-determining step.[19] Coates and Tedder studied the reduction of alkyl halides by trimethyltin in the gas phase and found that the rate of halogen abstraction followed the

order: F<Cl<Br.[20] These results indicated the involvement of direct halogen abstraction.

Tanner examined the reduction of a series of substituted benzyl halides with tributyltin hydride.[21a] It was found that the order of reactivity was shown to be Cl<Br<I, the same as reported previously. The benzyl halide reductions showed excellent Hammett correlations with positive p values. However, the magnitudes of the ρ values were not found to be in the inverse order of the relative reactivities. This result suggested the benzyl iodides underwent reduction by a different mechanism than the chlorides and bromides. The anomalously high ρ value observed for the benzyl iodide was considered to be indicative of a greater charge separation which would be the case for the electron transfer process. Consistent with this hypothesis was the large solvent effect when the reduction of the iodide was carried out in acetonitrile. Based on these observations, a free radical chain mechanism involving an electron transfer in the propagation step was suggested for the reduction of benzyl iodides with tributyltin hydride (eq 14, 15).

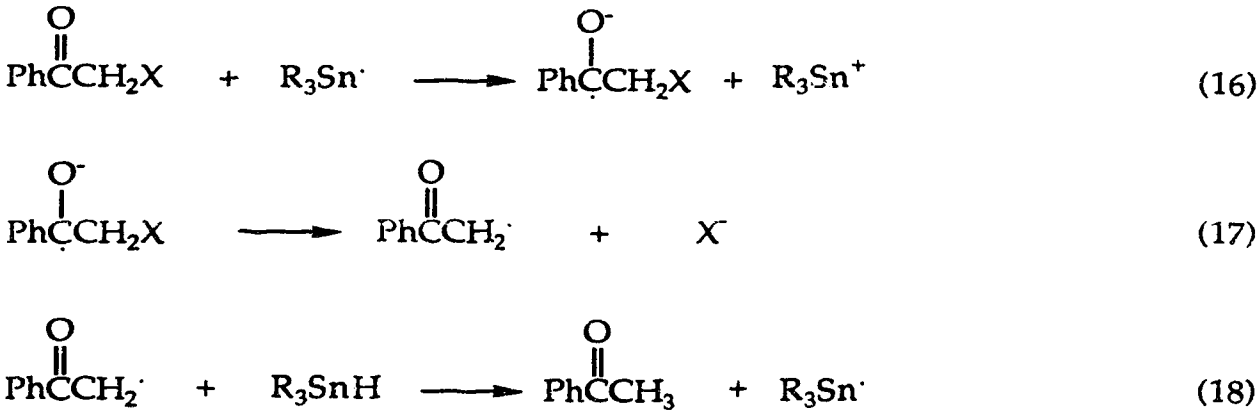
$$R_3Sn^{\cdot} + ICH_2Ar \longrightarrow R_3Sn^{+} + {}^{\cdot}CH_2Ar + I^{-} \qquad (14)$$

$$ArCH_2^{\cdot} + R_3SnH \longrightarrow ArCH_3 + R_3Sn^{\cdot} \qquad (15)$$

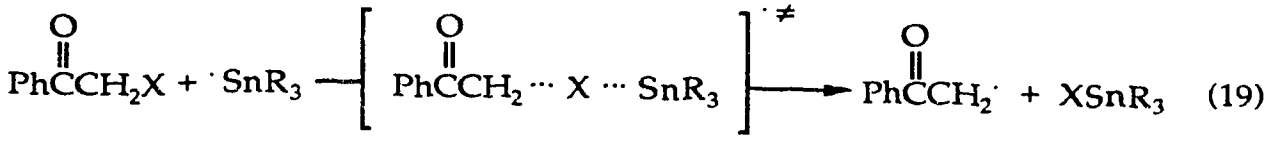
Subsequently, the reductions of some tertiary nitro compounds[21b,21c] and methyl iodide[22] by trialkyltin hydride were shown to proceed by an electron transfer mechanism. The reduction of α-haloacetophenones by organotin hydrides has also been studied by Tanner.[23] Both homolytic and heterolytic reactions could be recognized since the homolytic reactions yield acetophenone and heterolytic reactions yield α-(halomethyl)benzyl alcohol.

The homolytic pathways of the dehalogenation are either the direct halogen abstraction or electron transfer (eq 16), followed by a rapid fragmentation to form the radical with the elimination of the halide anion (eq 17).

Scheme III-3



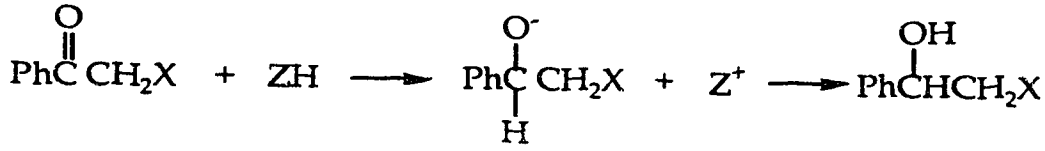
The direct halogen abstraction mechanism involves breaking of a carbon halogen bond (eq 19), and accordingly show a substantial secondary deuterium isotope effect. However, no secondary deuterium isotope effect was observed during the reduction of α, α-dideuterio-α-haloacetophenone. This experiment suggests that the direct halogen abstraction mechanism can be ruled out. As a result, the homolytic reductions proceeds by a free radical chain process whose propagation step involved a single electron transfer. Therefore, α-haloacetophenones can be used as probes to differentiate the heterolytic hydride transfer and homolytic electron transfer mechanism in the reductions of ketones by tin hydride.



(19)

Scheme III-4

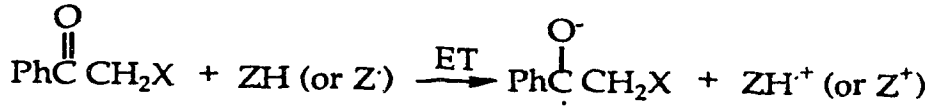
Hydride Transfer Mechanism:



(20)

Electron Transfer-Hydrogen Atom Abstraction Chain Mechanism:

initiation



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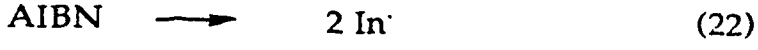

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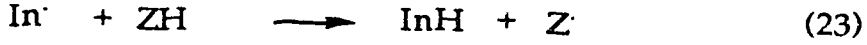
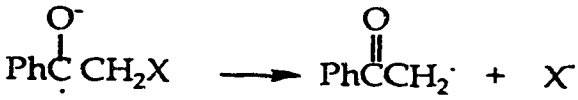


(23)

propagation



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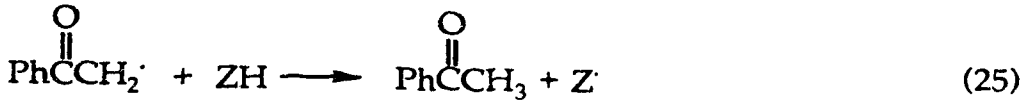

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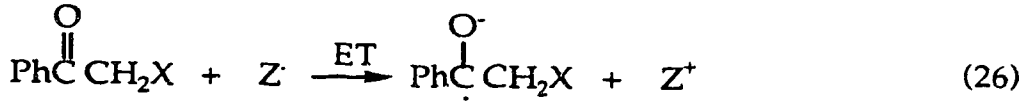


(26)

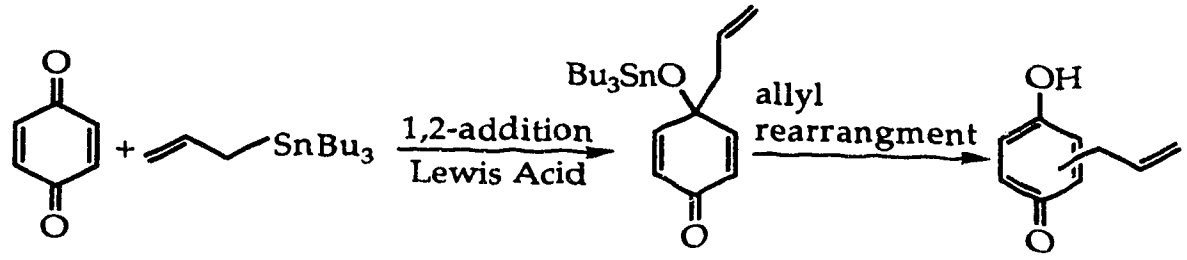
X=F, Cl, Br, OCOPh, OPh, SPh, SO_2Ar

ZH=R_3SnH, R_3SiH, BNAH, NADH, DMBI, etc.

α-Haloacetophenones have also been used as fragmentation probes to differentiate the hydride transfer and electron transfer mechanism in the reductions of ketones by other reducing reagents including 1,4-dihydropyridines,[24a] enzyme (HLADE) NADH[24b] and 1,3-dimethyl-2-phenylbenzimidazoline (DMBI).[24c] The two mechanisms can be easily distinguished on the basis of the products formed. Acetophenone is the product of an electron transfer chain pathway (eq 24) whereas the halohydrin is the product of a hydride transfer pathway (eq 19). For the reductions of α–haloacetophenones by these reducing agent, the major pathway is the electron transfer process since the major product formed is generally acetophenone (eq 21-26).

More recently, these fragmentation probes have been extended to include compounds such as α-carbonyloxy, α-arylsulfonyl and α-phenylthio ketones.[24d] The results indicate that a change of the leaving group of the α-substituted acetophenones does not change the reaction pathway. Therefore, these α-substituted acetophenone probes can be generally employed for the study of the electron transfer reactions of ketones with a variety of nucleophiles. The advantages to their use include the convenience of analyzing the products and the possibility of systematic study of the steric and electronic effects on electron transfer reactions.

The thermal allylation of quinones[25-26] or simple carbonyl compounds[27] by allylstannanes proceeded in the presence of a Lewis acid (eq 27). The products are believed to be formed by an ionic process (1,2-addition). however, systemetic studies on the thermal reaction of simple carbonyl compounds or α-substituted carbonyl compounds under neutral conditions have not been reported.[28]



(27)

In the free radical allylation with allylstannanes, the chain transfer species is the tin radical $R_3Sn\cdot$. Since the tin radical undergoes electron transfer to α-substituted acetophenones, it was of interest to investigate the mechanism of the thermal reaction of these α-substituted acetophenones with allylstannanes. One would anticipate that if a free radical intermediate was involved in the reaction, trapping products could be formed.

Although the reaction of α-haloacetophenones with tin radicals has been studied and the mechanism is well accepted,[23a,b] the mechanistic pathways for the reaction of α-arylsulfonyl or α–phenylthioacetophenone with the tin radical is still controversial.[29-32] More information is required to gain mechanistic insight into the nature of the reactions of these fragmentation probes with tin species. Therefore, the reaction of a series of α-arylsulfonyl or α–phenylthioacetophenone with allyltributylstannane was also investigated in more detail.

Results and Discussion

The compounds studied in this work were easily prepared by methods described previously (see Experimental Section).

$C_6H_5COCR_1R_2X$

Ia-g

a, X=F, R_1=R_2=H

b, X=Cl, R_1=R_2=H

c, X=Br, R_1=R_2=H

d, X=Br, R_1=Me, R_2=H

e, X=Br, R_1=R_2=Me

$C_6H_5COCH_2X$

IIa-b

a, X=OCOPh

b, X=OPh

$C_6H_5COCR_1R_2SO_2Tol$-p

IIIa-c

a, R_1=R_2=H

b, R_1=Me, R_2=H

c, R_1=R_2=Me

$C_6H_5COR_1R_2SPh$

IVa-b

a, R_1=R_2=H

b, R_1=R_2=Me

The reactions of the α-substituted ketones with allyltributylstannane were carried out at 61 °C in dry benzene. Radical initiation (AIBN) and inhibition (*m*-DNB) were studied to establish whether a free radical chain mechanism is involved in these reactions. The results of the reactions are summarized in Table III.

1. The Reactions of α-Halo Ketones, α-(Benzoyloxy)acetophenone and α-Phenoxyacetophenone with Allyltributylstannane

The reaction of the α-haloacetophenones (**Ia-c**) with allyltributylstannane gave 4-pentenophenone as the only product in 0-39% yields in the absence of AIBN (Table III-1, entries 1, 3 and 6). Qualitatively, the reactivity of these compounds followed the order $PhCOCH_2Br$ > $PhCOCH_2Cl$ > $PhCOCH_2F$, obtained previously for the reductions by organotin hydrides, dihydropyridines and 1,3-dimethyl-2-phenylbenzimidazoline. The addition of small amounts of AIBN initiated the reactions to yield near quantitative amount of allylation product (Table III-1, entries 2, 4 and 7). The uninitiated reaction could be inhibited completely by the addition of *m*-DNB (Table III-1, entries 5 and 8).

Similarly, the reaction of α-(benzoyloxy)acetophenone (**IIa**) with allyltributylstannane was initiated by the addition of AIBN (5%) to give 4-pentenophenone in 82.8% yield (Table III-2, entry 14), although the mixture of **IIa** and allyltributylstannane was completely unreactive at 61 °C (Table III-2, entry 13). However, the reaction of α-phenoxyacetophenone (**IIb**) with allyltributylstannane seemed to be much slower than the reaction of **IIa**. The reaction of **IIb** gave only trace amount of 4-pentenophenone even in the presence of AIBN (Table III-2, entry 16).

Initiation and inhibition of the reaction of these α-substituted acetophenone with allyltributylstannane clearly establishes that the reaction proceeds via a free radical chain mechanism. The results obtained in the uninitiated reactions at 61 °C suggest a key question about the nature of the initiation in these processes. It was reported that $Bu_3Sn\cdot$ radicals could not be

Table III-1. The Reaction of α-Substituted Ketones with Allyltributylstannane[a,b]

reaction	compound $PhCOCR_1R_2X$	additive	products (%) $PhCOCR_1R_2CH_2CH=CH_2$	unreacted ketone (%)
1	**Ia**	-	0	99.6±0.1
2	**Ia**	AIBN (5%)	94.7±0.1	6.1±1.0
3	**Ib**	-	29.6±5.6	62.4±6.2
4	**Ib**	AIBN (5%)	95.0±0.5	0
5	**Ib**	*m*-DNB (5%)	0	98.2±0.0
6	**Ic**	-	38.9±13.2	47.1±10.0
7	**Ic**	AIBN (5%)	95.4±0.4	0.9±0.9
8	**Ic**	*m*-DNB (5%)	0	102±0.0
9	**Id**	-	0	93.6±1.1
10	**Id**	AIBN (5%)	99.5±6.3	0
11	**Ie**	-	0	90.3±0.9
12	**Ie**	AIBN (5%)	trace	80.2±2.1

[a] All reactions were carried out at 61 °C in benzene for 53 h with a mole ratio of 1:2 of ketone to allyltributylstannane. [b] Yields determined by GC.

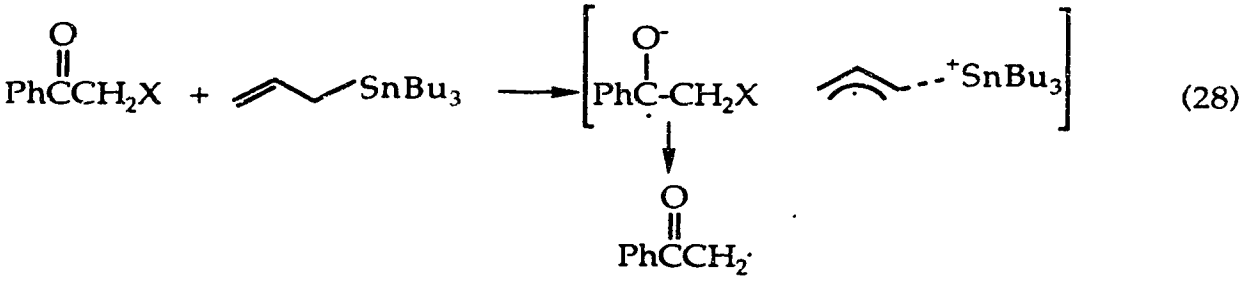
Table III-2 The Reaction of α-Substituted Ketones with Allyltributylstannane[a,b]

	compound		products (%)	unreacted
reaction	$PhCOCH_2X$	additives	$PhCOCH_2CH_2CH=CH_2$	ketone (%)
13	**IIa**	-	14.2±0.5	80.9±1.0
14	**IIa**	AIBN (4%)	82.8±1.1	0
15	**IIb**	-	0	>95.0
16	**IIb**	AIBN (4%)	0	>95.0

[a] All reactions were carried out at 61 °C in benzene for 53 h with a mole ratio of 1:2 of ketone to allyltributylstannane. [b] Yields determined by GC.

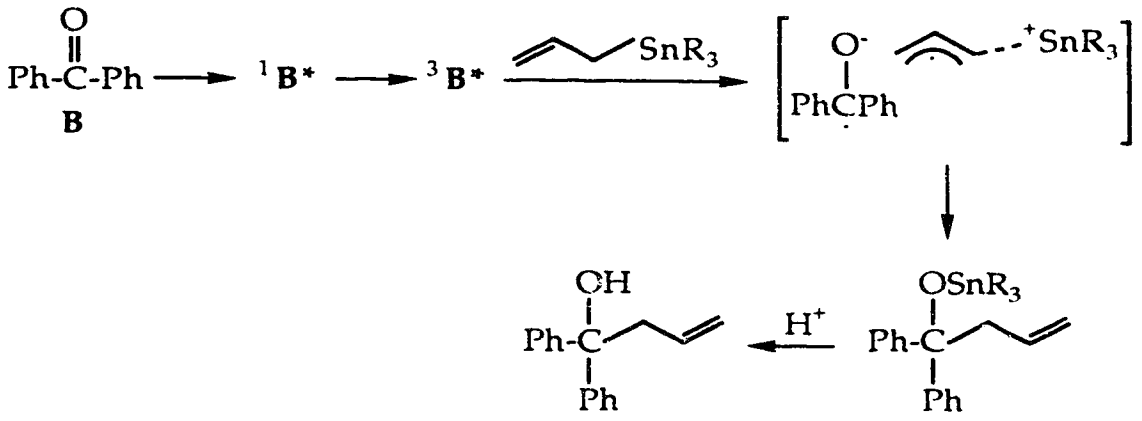
generated from hexabutyldistannane (Bu_3Sn-$SnBu_3$) at 61 °C. The thermal homolysis of the Sn-C bond, therefore, is not highly likely under the same reaction conditions (61 °C) since the bond dissociation energy for Sn-Sn are lower (46.7 kcal/mole)[33] than that for Sn-C (52.0 kcal/mole).[34]

The initiation step which can be considered presumably occurs by an electron transfer from allyltributylstannane to these ketones. The occurrence of the initiation suggests the possibility that tin hydride itself can act as the electron transfer reagent in the same manner as proposed for tin hydride.[23a,b] As a result, the reactants are in equilibrium with their charge transfer complexes which can dissociate to radical anion either thermally or photochemically promoted (eq 28).



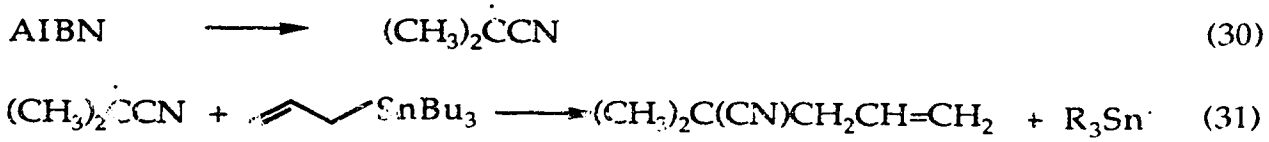
(28)

Photoinduced electron transfer reaction from allylstannanes to electron-acceptors such as quinones,[35] aromatic ketones,[36a] α-diketones[36b] and α, β-epoxy ketones[37] have been reported recently. For example, photoallylation of benzophenone (**B**) with allylstannane gave homoallyl alcohol. The mechanism was proposed to involve an electron transfer as shown in eq 29. The initial step is the electron transfer from allylstannane to excited triplet benzophenone to produce the radical ion pair. The electron transfer process in the photochemical reaction of quinones with allylstannanes has been confirmed by the absorbed spectra (^{1}H-CIDNP) generated during the reaction.[35]



(29)

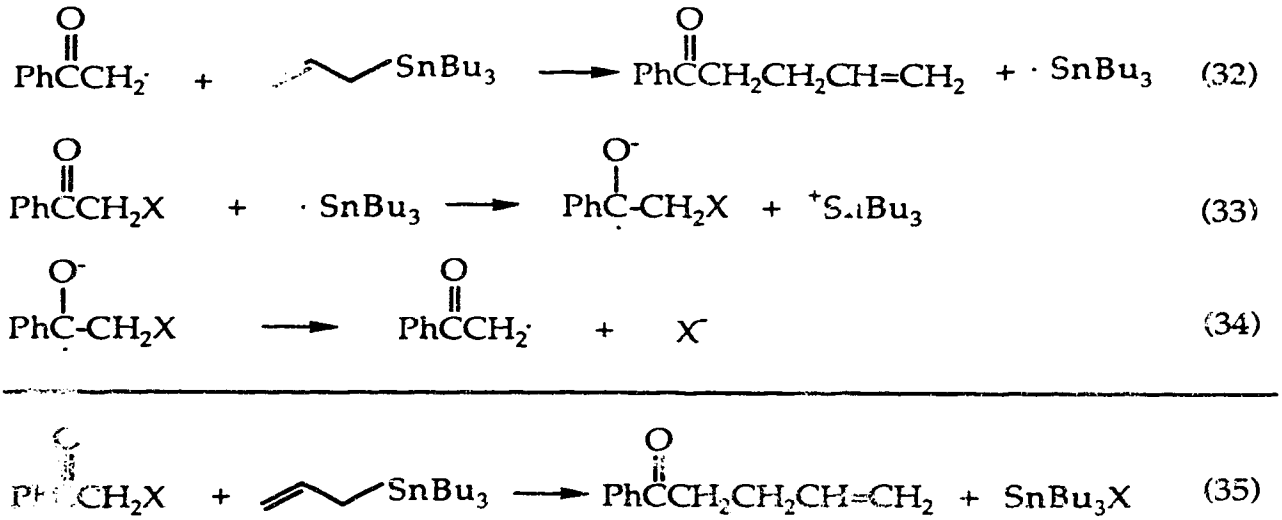
In the presence of radical initiator AIBN, the initiation step is more efficient. The thermal decomposition of AIBN gives two alkyl radicals (eq 30). The alkyl radical then undergoes addition to allyltributylstannane to generate tributyltin radical (eq 31), which acts as the chain transfer species.



(30)

(31)

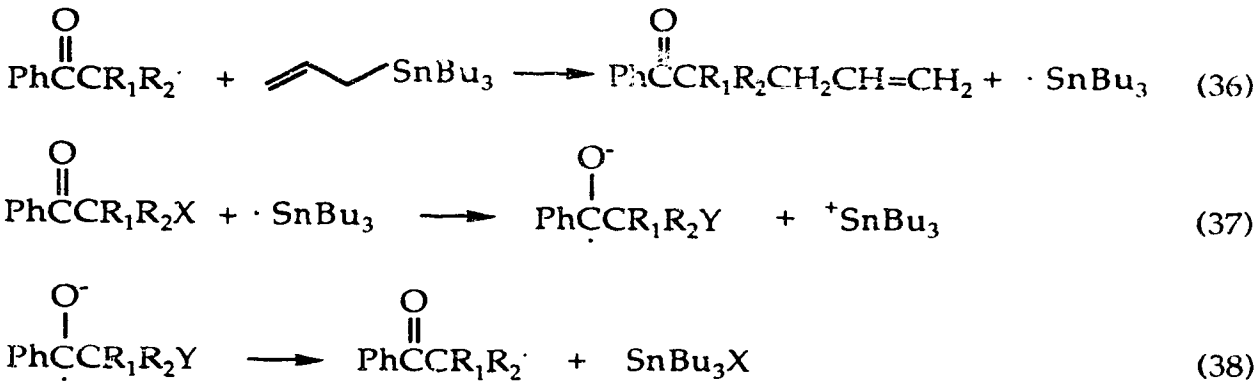
On the basis of these findings, an electron transfer chain mechanism is proposed to account for the formation of addition product. As shown in eq 33, the electron transfer from allyltributylstannane or tin radical to **I-II** to form the radical anion was reported previously.[24] The radical anion rapidly cleaves to form enoyl radical $PhCOCH_2\cdot$ (eq 34), which then adds to allyltributylstannane to give 4-pentenophenone with the elimination of the tributyltin radical (eq 32). The tributyltin radical transfers an electron to **I-II**, continuing the chain process The formation of the trapping product, 4-pentenophenone, clearly demonstrates the involvement of the $PhCOCH_2\cdot$ intermediate in the reaction.



The slow reactivity of α-phenoxyacetophenone is consistent with the slow cleavage of the radical anion of **Ie**.[24d] The absence of chain reaction for **Ie** is no doubt due to the low rate of its ketyl fragmentation. Since the radical anion of **Ie** ($PhCOCH_2OPh^{\cdot -}$) cleaves approximately 10^3 times slower than the radical anion of **Id** ($PhCOCH_2OCOPh^{\cdot -}$),[24d] the formation of radical $PhCOCH_2\cdot$ is slow and the radical chain is not propagating efficiently.

A remarkable steric effect was observed for the allylation reactions of a serial of α-bromo ketones. In the absence of AIBN, the reaction of α-bromoacetophenone (**Ic**) with allyltributylstannane gave 4-pentenophenone in 39% yield (Table III-1, entry 6), however, the reaction of α-bromopropiophenone (**Id**) required AIBN initiation. With AIBN initiation, the reaction of **Id** with allyltributylstannane gave 2-methyl-4-pentenophenone in 81% yield (Table III-1, entry 10). No expected allylation product, 2,2-dimethyl-4-pentenophenone, was produced from the reaction of α-bromoisobutyrophenone (**Ie**) (Table III-1, entry 12). These results are quite consistent with the proposed electron transfer free radical chain mechanism. More revealing, however, was the observation that the reaction of **Ic** with

allyltributylstannane could be inhibited by the addition of 1 equivalent of **Ie**. For example, **Ic** reacted with allyltributylstannane to give a 24% yield of 4-pentenophenone in 1 hr, but only 0.4% of 4-pentenophenone was formed when one equivalent of **Ie** was added. This result could be explained by a comparison of the difference in the rate of the chain propagation steps.



Although an electron transfer from the tin radical to α-bromoisobutyrophenone (**Ie**) (eq 37, 38) would be expected to be more favorable than to α-bromoacetophenone (**Ic**), the radical addition to the allyltributylstannane is much more favorable for the primary radical than for the tertiary radical. As a result, the addition of the tertiary radical to the allylstannane is slow (eq 36) and no tin radical is generated to carry the chain. The α-bromoacetophenone would then appear to be unreactive. A similar argument has been used for the reduction of α-halo ketones by 1,3-dimethyl-2-phenylbenzimidazoline (DMBI).[24c]

2. The Reaction of α-Arylsulfonyl and α–Phenylthio Ketones with Allyltributylstannane

The reactions of α-arylsulfonyl ketones (**IIIa-c**) or α-phenylthio ketones (**IVa-b**) with allyltributylstannane were examined under the same reaction conditions as for the reactions of **I** and **II**. The initiation-inhibition studies of the reaction of **III-IV** show that the reaction also proceeds via a free radical chain mechanism. It was expected that the reaction of these compounds with allyltributylstannane would afford the same product as the reaction of **I** and **II**. However, the radical trapping product, is not formed as a major product in these reactions, but a nearly 1:1 mixture of allyl tosylsulfone or allyl phenylsulfide and the ketone is obtained.

The uninitiated reaction of α-arylsulfonylacetophenone (**IIIa**) with allyltributylstannane gave acetophenone and allyl tolylsulfone in 32% and 31% yields (Table III-3, entry 19). The reactions were initiated by AIBN to give products in high yields (Table III-3, entry 20) and completely inhibited by *m*-DNB (Table III-3, entry 21). α-Phenylthioacetophenone (**IVa**) appears to be less reactive than α-arylsulfonylacetophenone. For the reaction of **IVa** with allyltributylstannane, there was a small amount of product (<4%) in the absence of AIBN (Table III-4, entry 28). When AIBN was added, a 41% yield of acetophenone and a 39% yield of allyl phenylsulfide was produced. In addition, 6.2% of 4-pentenophenone was also formed (Table III-4, entry 29).

The reactions of the compounds **I-II** with allyltributylstannane gave free radical trapping product, whereas the reaction of the structurally similar compounds **III-IV** with allyltributylstannane gave quite different products. Since radical trapping products are not formed in the chain reaction of **III-IV**,

Table III-3. The Reaction of α-Substituted Ketones with Allyltributylstannane[a]

	compound		products (%)[c,d]	
reaction	$PhCOCR_1R_2SO_2Tol$-*p*	additive	$PhCOCHR_1R_2$	*p*-$TolSO_2CH_2CH{=}CH_2$
19	**IIIa**	-	32.3±10.4	31.4±8.5
20	**IIIa**	AIBN (5%)	89.4±3.2	89.1±1.9
21	**IIIa**	*m*-DNB (5%)	0	0
22[b]	**IIIa**	-	1.3±0.7	2.5±1.3
23[b]	**IIIa**	AIBN (5%)	77.9±2.5	77.8±1.3
24	**IIIb**	-	3.7±3.7	3.0±3.0
25	**IIIb**	AIBN (5%)	79.1±1.0	86.9±0.2
26	**IIIc**	-	4.4±4.0	7.9±7.9
27	**IIIc**	AIBN (5%)	36.8±2.7	91.5±1.0

[a] All reactions were carried out at 61 °C in benzene for 48 h with a mole ratio of 2 of ketone to allyltributylstannane except noted. [b] with a mole ratio of 1:1 ketone to allyltributylstannane. [c] Yields determined by GC. [d] Recovered ketone accounts for the material balance.

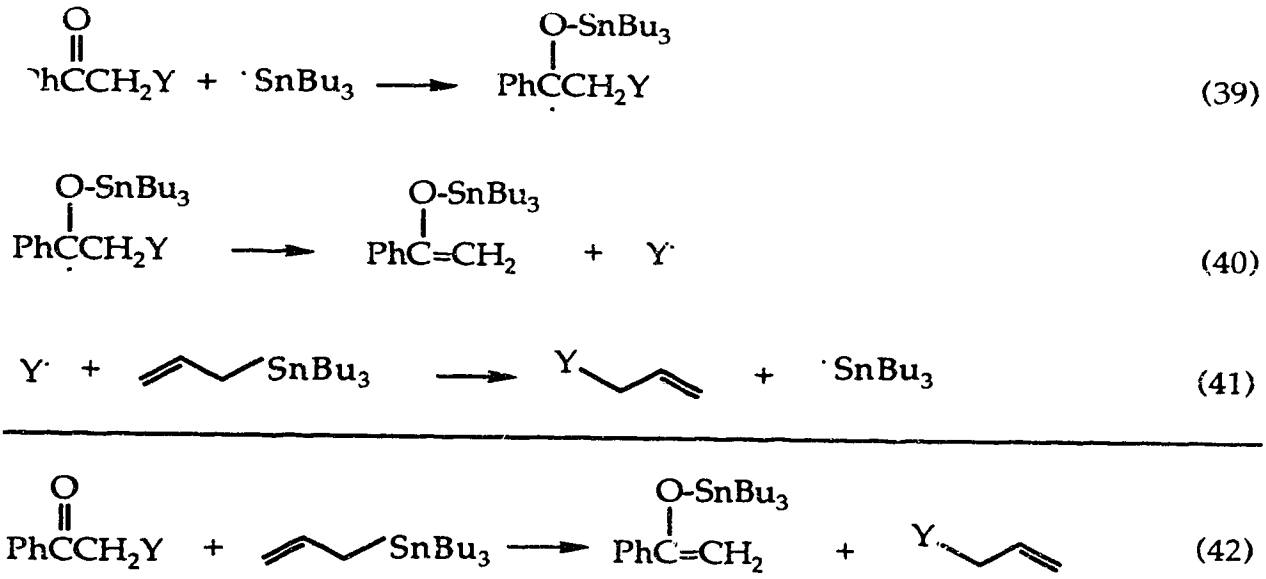
Table III-4. The Reaction of α-Substituted Ketones with Allyltributylstannane[a,b]

	compound		products (%)[c]		
reaction	$PhCOCR_1R_2SPh$	additive	$PhCOCR_1R_2CH_2CH{=}CH_2$	$PhCOCHR_1R_2$	$PhSCH_2CH{=}CH_2$
28	**IVa**	-	0	2.4±0.7	3.6±1.5
29	**IVa**	AIBN (5%)	6.2±1.0	41.0±1.8	38.7±0.4
30	**IVb**	-	-	-	-
31	**IVb**	AIBN (5%)	-	trace	trace

[a] All reactions were carried out at 61 °C in benzene for 48 h with a mole ratio of 1:2 of ketone to allyltributylstannane. [b] Yields determined by GC. [c] Recovered ketones accounts for the material balance.

a different pathway that does not involve the enolyl radical $PhCOCR_1R_2\cdot$ appears to be operative. A reaction pathway involving the attack by the tin radical at either the oxygen[38] or sulfur atom[30] of the sulfonyl or thio group can be ruled out, since one of the chain propagating species must be enolyl radical $PhCOCR_1R_2\cdot$ in all these free radical chain reactions. Alternatively, a radical addition-elimination process can be envisioned to account for the formation of the products formed in the reaction of **III-IV** with allyltributylstannane (Scheme III-6).

Scheme III-6



As shown in Scheme III-6, the addition of the tin radical to ketones (**III-IV**) generates a stannylketyl radical as had been proposed by Uneo (eq 39).[39] The stannylketyl radical undergoes rapid fragmentation to give the tin enolate with the elimination of the arylsulfonyl radical ($Y\cdot=ArSO_2\cdot$) or phenylthio radical ($Y\cdot=PhS\cdot$) (eq 40). The arylsulfonyl radical or phenylthio radical adds to the allylstannane leading to allyl tolylsulfone or allyl

phenylsulfide and $Bu_3Sn\cdot$ (eq 41).[12] The initially formed tin enolate is presumably hydrolyzed by adventitious water to afford the corresponding ketone.

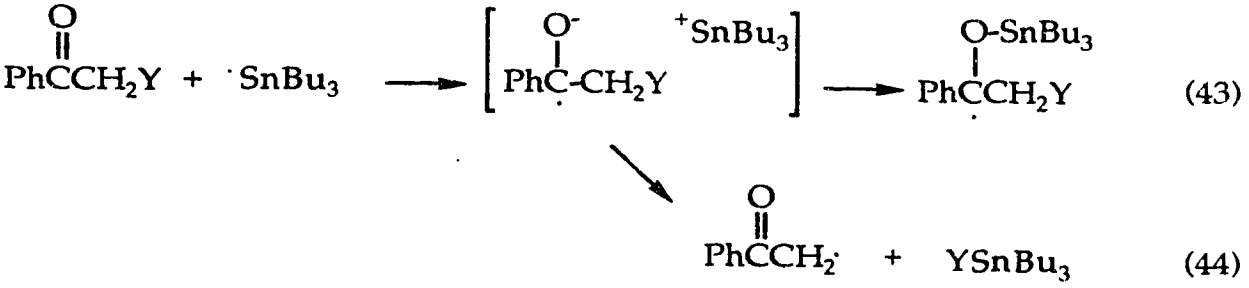
The tin hydride reductions of α-substituted acetophenones have been shown to proceed via an electron transfer process where the ketyl formed fragments to give the enolyl radical and the anion of the leaving group.[23] This sequence appears to be operative in the allylation reaction of **I-II**, however, the reactions of **III-IV** do not proceed by this chain sequence since the allylation products are not formed as major products.

In the allylation reactions of **I-II** the chain carrying species is the enolyl radical $PhCOCR_1R_2\cdot$ and the rate of the reaction is proportional to the concentration of this enolyl radical (eq 34). However, with **III** and **IV**, the enolyl radical is not formed rapidly, since fragmentation is relatively slow and the enolyl radical can not carry the chain. This radical addition-elimination pathway does not depend on the concentration of the enolyl radical but the addition to the ketone. Once the stannylketyl radical is formed, it is forced to fragment and give the leaving group as a radical.

The rate constants of a series of α-substituted acetophenone ketyls has been determined.[24d] The results are consistent with our experimental observations. Although all of these α-substituted acetophenone ketyls ($PhCOCH_2Y\cdot^-$) undergo fast cleavage ($k_{fy} > 10^6\ s^{-1}$) to form the the enolyl radical ($PhCOCH_2\cdot$), k_{fy} decreases in the order Br, Cl > F ≈ OCOPh > *p*-TolSO2 > SPh. Due to the slower fragmentation of α-arylsulfonyl or α-phenylthioacetophenone ketyls, the [illegible] of the stannylketyl radical becomes competitive with the cleavage of these ketyl radical anions.

Although the proposed radical addition-elimination mechanism can rationalize the experimental results of the reaction for **III-IV**, the stannylketyl

radical could also be formed by the electron transfer process as represented in eq 43. This pathway cannot be distinguished from the radical addition process at this stage. All efforts to isolate or intercept the tin enolate so far have been unsuccessful.[26,30,37] Therefore, further experiments are required to substantiate its involvement as an intermediate in the reaction.



(43)

(44)

When **IIIa-c** were allowed to react with allyltributylstannane in the presence of AIBN, all reactions gave allyl tolylsulfone in excellent yields (Table III-3, entries 20, 24 and 26). No steric effects were observed for the reactions of **IIIa-c**. These results are consistent with the proposed addition-elimination mechanism. When the tributyltin radical adds to the carbonyl oxygen of **IIIa**, **IIIb** or **IIIc**, the rate would not be much effected by the bulky of the group R_1 or R_2.

When **IIIc** reacted with allyltributylstannane, 92% of allyl tolylsulfone was formed. However, only 37% of isobutyrophenone was produced (Table III-3, entry 27). Presumably the intermediate, the tin enolate from **IIIc**, is not very susceptible to hydrolysis by adventitious water.

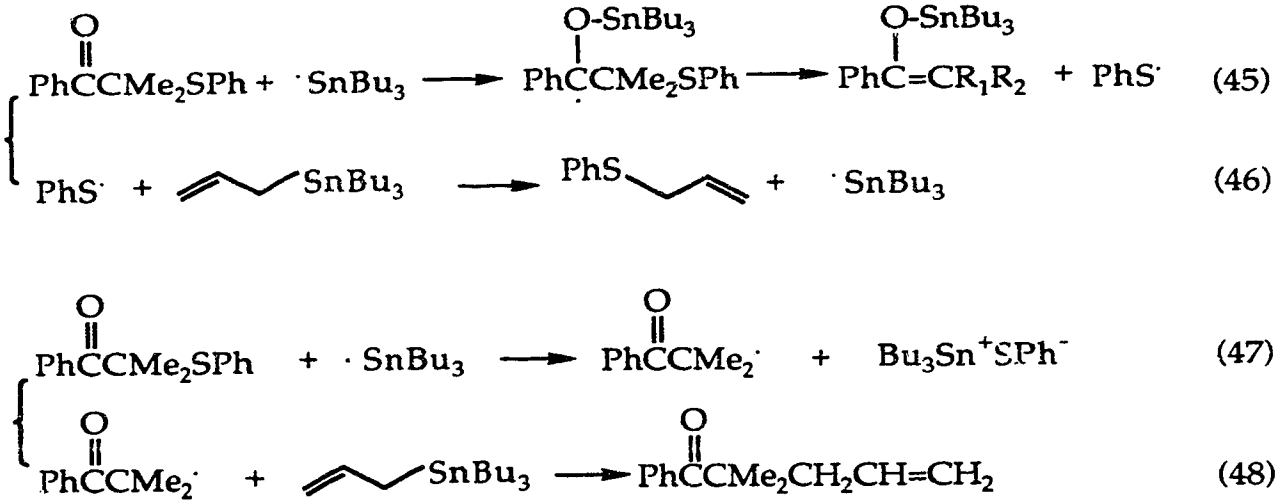
In order to substantiate this proposal, the reaction of **IIIc** with allyltributylstannane was carried out with added water. When 0.02 mL of water was added to the reaction mixture of **IIIc** before the reaction tube was degassed, both isobutyrophenone and allyl tolylsulfone were formed in 96%

yields. This result indicates that the tin enolate formed can be hydrolyzed to isobutyrophenone with sufficient water.

The reactivity of α-phenylthioacetophenone (**IVa**) appears to be much slower than that of α-arylsulfonylacetophenone (**IIIa**) towards allylstannane. This observation presumably reflects the slower cleavage of the α-phenylthiostannylketyl radical compared with that of α-arylsulfonylstannylketyl radical (Scheme III-6, eq 40). Although the cleavage rate of these stannylketyl is not available, the α-phenylthioacetophenone ketyl ($PhCOCH_2SPh^{\cdot -}$) cleaves at least 50 times slower than the α-arylsulfonylacetophenone ketyl ($PhCOCH_2SO_2Tol\text{-}p^{\cdot -}$).[24d] Because of the slow fragmentation of the α-phenylthiostannylketyl radical, the radical chain for the reaction of **IV** is not propagated efficiently.

Contrary to the results obtained during the reaction of **III**, a steric effect was observed for the reaction α-phenylthio ketones (**IV**) with allyltributylstannane. The initiated reaction of α-phenylthioacetophenone (**IVa**) with allyltributylstannane gave acetophenone and allyl phenylsulfide in moderate yields. When α-phenylthioisobutyrophenone (**IVb**) was allowed to react with allyltributylstannane under the same conditions, no products was detected (Table III-4, entries 30 and 31). Since the cleavage of the α-phenylthiostannylketyl radical is presumable slow (eq 45), the enolyl radical addition to allyltributylstannane (eq 47, 48) becomes competitive with the tributyltin radical addition to the ketone. The overall products of the reaction formed depends on the competitive reaction between these two processes. Since an electron transfer process would favor **IVb** compared with **IVa**, the tributyltin radical mainly undergoes electron transfer to form $PhCOCMe_2^{\cdot}$ (eq 47) for the reaction of **IVb**. However, the tertiary radical $PhCOCMe_2^{\cdot}$ can not

add to allyltributylstannane to carry the chain by addition (eq 48). As a result, **IVb** appears to be unreactive.



Conclusions

The reaction of α-haloacetophenones (**Ia-c**), α-(carbonyloxy)acetophenone (**IIa**) and α-phenoxyacetophenone (**IIb**) with allyltributylstannane yields 4-pentenophenone as the only product. The reaction proceeds by a free radical chain sequence which contains an electron transfer process. These ketones accept an electron from allyltributylstannane to generate the ketyls which cleave to give an enolyl radical and an anion. The formation of trapping product provides direct evidence of the involvement of an enolyl radical, $PhCOCH_2\cdot$. The reaction of α-bromopropiophenone (**Id**) with allyltributylstannane also gives the radical trapping product, 2-methyl-4-pentenophenone. However, the α-bromoisobutylphenone (**Ie**) appears to be unreactive. The observation that the

reaction of α-bromoacetophenone with allyltributylstannane can be inhibited by the addition of one equivalent of **Ie** is consistent with the proposed chain sequence since **Ie** reacts faster but the tertiary radical $PhCOCMe_2\cdot$ cannot carry the chain by addition.

The reaction of the α-arylsulfonyl ketones (**IIIa-c**) or α-phenylthio ketones (**IVa-b**) with allyltributylstannane was also carried out. However, these reactions give a nearly 1:1 mixture of allyl tolylsulfone or allyl phenylsulfide and the corresponding ketone. The radical trapping product is not formed as a major product. The reaction is believed to proceed by the formation of a stannylketyl radical as an intermediate. Studies of the reactivity and steric effect of these compounds are in support of this proposal.

Experimental

1. Materials

Commercial **benzene** (Fischer Scientific) was shaken with concentrated sulfuric acid (10% V/V) several times, washed with water three times, 10% sodium carbonate solution, water, and then dried over anhydrous calcium chloride. **Benzene** was fractionally distilled from CaH_2 and the middle fraction was collected.

The preparation or purification of **acetophenone, α-fluoroacetophenone (Ia), α-chloroacetophenone (Ib), α-bromoacetophenone (Ic), α-bromopropiophenone (Id), α-(benzoyloxy)acetophenone (IIa), α-phenoxyacetophenone (IIb), α-(*p*-methylbenzenesulfonyl)acetophenone (IIIa), α-(*p*-methylbenzenesulfonyl)propiophenone (IIIb), α-(*p*-methylbenzenesulfonyl)isobutyrophenone (IIIc), α-(phenylthio)acetophenone (IVa), *p*-di-*tert*-butylbenzene, α,α-azobisisobutyronitrile (AIBN) and *m*-dinitrobenzene (*m*-DNB)** has been described previously.[23,24]

α-Bromoisobutyrophenone (Ie) (Aldrich, 98%), **propiophenone** (Aldrich, 99%), and **isobutyrophenone** (Aldrich, 97%) were redistilled and their purity was found to be >99% by GC.

Allyltributylstannane (Aldrich, 97%) was used as supplied.

α-(Phenylthio)isobutyrophenone (IVb) was prepared according to the literature procedure,[40] bp 160-170 °C (3.5 mmHg) [lit.[40] 141 °C (0.45 mmHg)]; ^{1}H NMR δ 1.6 (s, 6H), 7.25-7.6 (m, 8H), 8.2-8.32 (m, 2H).

4-Pentenophenone was isolated from the reaction mixture (Table III-1, reaction 7) by flash chromatography as a colorless oil (ether/petroleum

ether=1/4),[41] ^{1}H NMR δ 2.53 (m, 2H), 3.08 (t, 2H), 5.05 (m, 2H), 5.75 (m, 1H), 7.40-7.96 (m, 5H).

2-Methyl-4-pentenophenone was isolated from the reaction mixture (Table III-1, reaction 10) by flash chromatography as a colorless oil (ether/petroleum ether=1/4),[42] ^{1}H NMR δ 1.13 (d, 3H), 2.13 (m, 1H), 2.48 (m, 1H), 3.47 (m, 1H), 4.96 (m, 2H), 5.71 (m, 1H), 7.32-7.90 (m, 5H).

Allyl tolylsulfone was prepared according to the literature procedure[41] and recrystallized from ether and petroleum ether, mp 50.5 °C (lit.[44] 50.5-51 °C). ^{1}H NMR δ 2.44 (s, 3H), 3.78 (d, 2H), 5.12 (m, 2H), 5.78 (m, 1H), 7.24-7.76 (m, 4H).

Allyl phenylsulfide was prepared according to the literature procedure,[45] bp 102-105 °C (25 mmHg) [lit.[45] 104-106 °C (25 mmHg)]; ^{1}H NMR δ 3.59 (d, 2H), 5.15 (m, 2H), 5.93 (m, 1H), 7.220-7.44 (m, 5H).

2. Methods and Procedures

Measurements of physical constants, microanalyses, spectral measurements, and GC analyses were carried out using the same instrumentation described in Chapter 1.

Reaction ampules were Pyrex tubes joined to 10/30 joints. The ampules were cleaned with chromic acid solution, water, concentrated ammonium hydroxide, and distilled water, then oven dried at 120 °C.

An aliquot of the ketones (0.05 M), allyltributylstannane (0.10 M), the internal standard (*p*-di-*tert*-butylbenzene, 0.02 M) was placed in a pyrex ampule with or without additives. The initiator AIBN or inhibitor *m*-DNB was added before the reaction mixture was degassed. The ampule was degassed and sealed using the high vacuum procedure, and thermostated at

61 °C for the specified time. After the required reaction time, the ampule was opened and analyzed by GC using a 20 ft × 1/8 in glass column packed with 10% QF-1 on chromosorb WAW DMCS 80-100 mesh.

For each reaction the products were identified by the comparison of their GC retention times, GC-IR spectra and GC-MS spectra with those of authentic samples. All reactions were run in duplicate and the average yields of the products are reported in Table III.

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