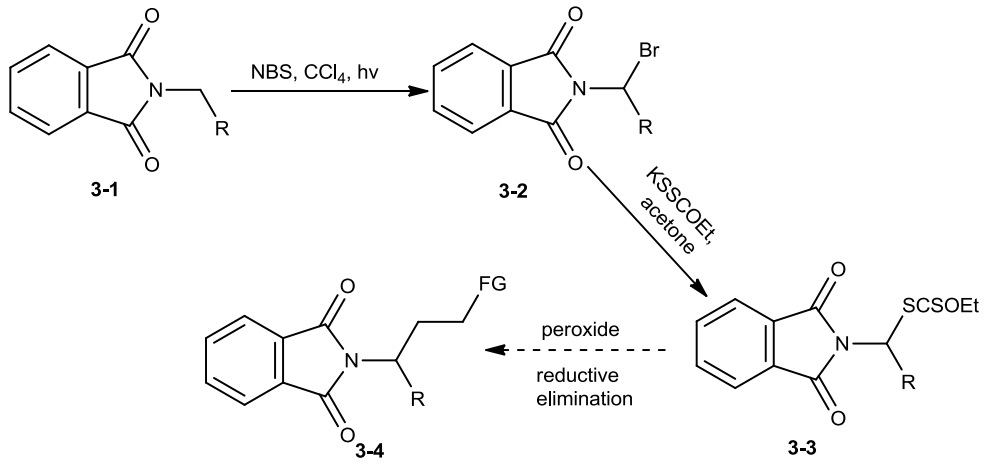
Amines synthesis via the Combination of the Wohl-Ziegler Reaction with Xanthate Chemistry

Introduction

Carbon radicals stabilized by a phthalimido group possesses a small but nevertheless significant allylic character, which allow the efficient intermolecular radical addition of phthalimido-substituted xanthates to various unactivated alkenes. Although we have applied this feature to the synthesis of numerous phthalimide protected amines, it was important to expand the pool of obtaining xanthates to members not readily available by the previous methods. We were therefore intrigued by the bromination of **3-1** to form bromide **3-2** via the classical Wohl-Ziegler allylic bromination process. Displacement of bromine by xanthate group would afford the corresponding xanthate **3-3,** which could then be employed in the typical radical additions to alkenes. This potentially flexible and general route for the construction of complex amines is generalized in Scheme 3.1.



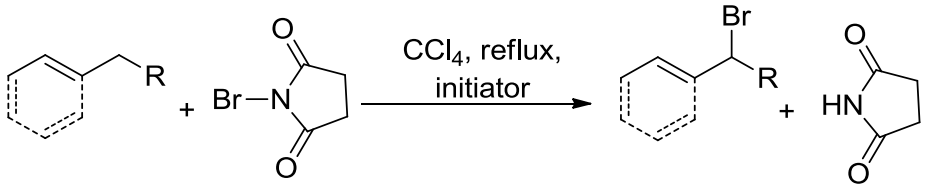
Scheme **3.1** The synthesis of xanthates via Wohl-Ziegler bromination

In view of the large pool of commercially available or easily accessible primary amines, success of the Wohl-Ziegler reaction in one case would considerably expand this approach to complex amines.

Ⅰ. Bromination of *N*-phthalimide protected amines via the Wohl-Ziegler reaction

1. The Wohl-Ziegler reaction

In 1942, Ziegler developed a bromination process by using *N*-bromosuccinimide as a convenient brominating agent. Several years later Karrer found that the addition of a small amount of dibenzoyl peroxide significantly increased the reaction rate and the scope of this reaction was greatly extended.[85] Quickly chemists recognized that this reaction proceeded by a free radical chain process. Nowadays, the Wohl–Ziegler reaction has been defined as a reaction between an allylic or benzylic substrate with *N*-bromosuccinimide (NBS) under radical initiating conditions which can provide the corresponding allylic or benzylic bromide (Scheme 3.2).[86]



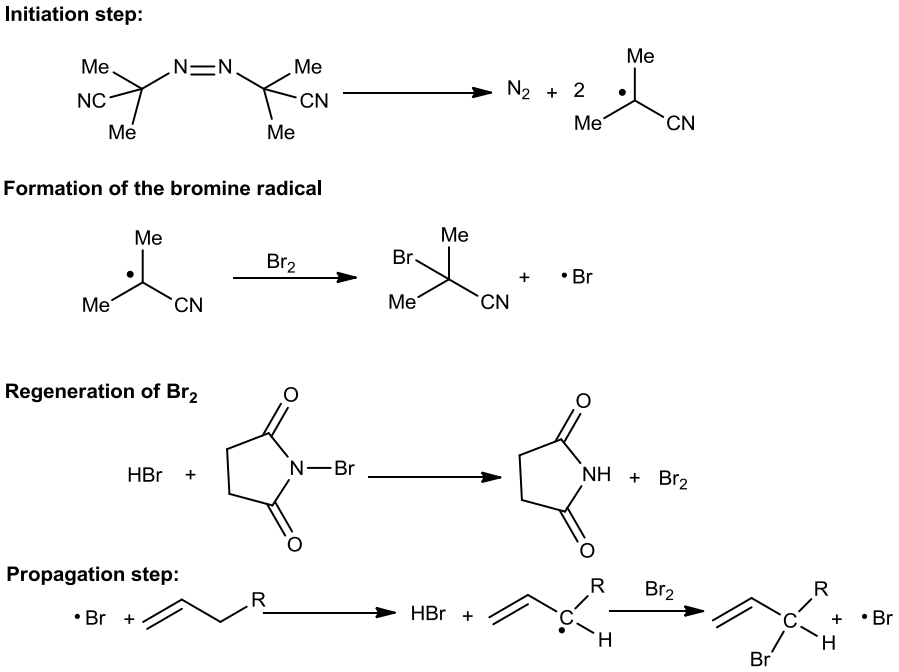
Scheme 3.2 Wohl-Ziegler reaction

As shown in the scheme 3.3, heating a solution of AIBN releases nitrogen gas and leads to the formation of two *tert*-butyronitrile radicals. These radicals readily react with the small amount of Br_2 present in the NBS to form a bromine atom. Light or heat may be used to initiate the reaction instead of AIBN or other initiators. In the following propagation step, the bromine atom abstracts an allylic hydrogen forming a stable allylic radical and HBr. This latter reacts immediately with NBS to maintain the low concentration of Br_2 which plays an essential role in sustaining the chain process.

[85] (a) Wohl, A. *Ber*. **1919**, *52*, 51. (b) Wohl, A.; Jaschinowski, K. *Ber.* **1921**, *54*, 476. (c) Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Ann*. **1942**, *551*, 80. (d) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1946**, *29*, 573.

[86] (a) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271. (b) Dauben, H. J.; McCoy, L. L. *J. Am. Chem. Soc.* **1959**, *81*, 4863.

Since a high concentration of Br_2 would lead to the bromination of the double bond, a low concentration of Br_2 is therefore critical for an efficient bromination.

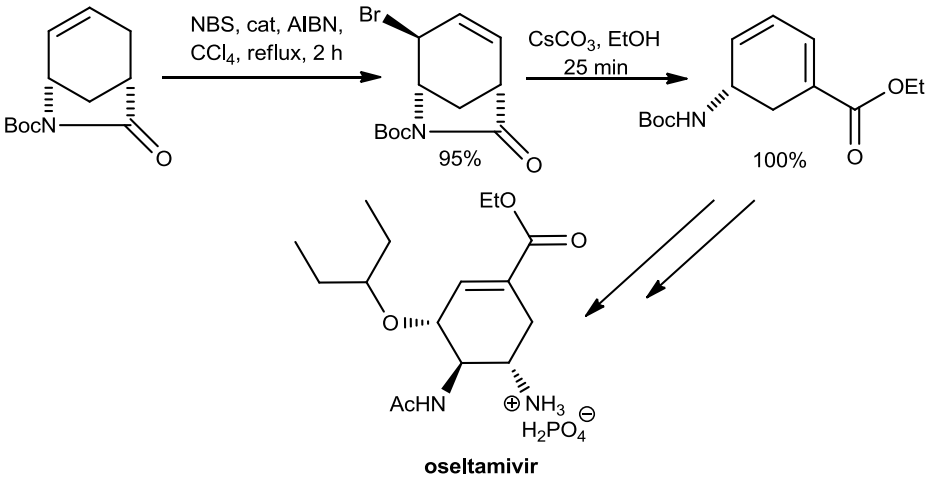


Scheme 3.3 Mechanism of Wohl-Ziegler reaction

2. The Wohl-Ziegler reaction in organic synthesis

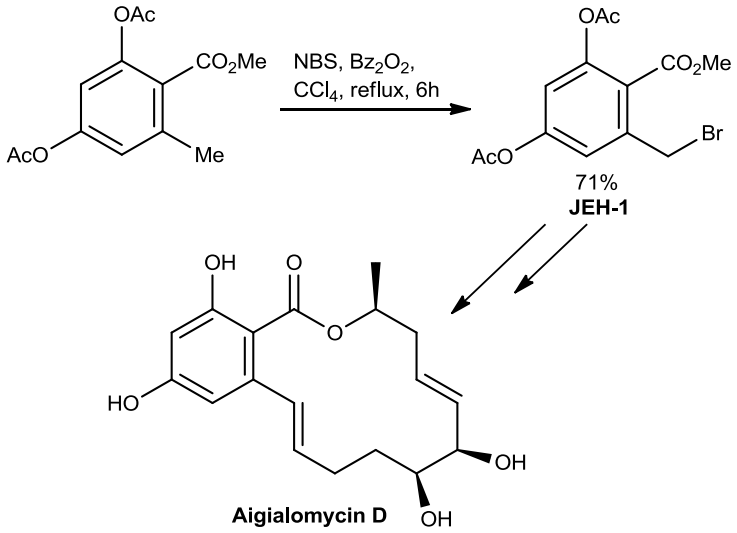
Numerous brominations have been reported over the past decades, using the Wohl-Ziegler. The following studies demonstrate the wide applicability of this reaction. In the synthesis of oseltamivir, an anti-influenza neuramidase inhibitor, Corey and co-workers constructed the 1,3-cyclohexadiene intermediate via a Wohl-Ziegler bromination and elimination (Scheme 3.4).[87] A 95% yield of the brominated product attests to the efficiency that can be attained by this reaction.

[87] Yeung, Y. Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* 2**006**, 12*8*, 6310.



Scheme 3.4 Total synthesis of the oseltamivir involving a Wohl-Ziegler bromination

Harvey and co-workers applied the Wohl-Ziegler bromination in the course of the total synthesis of aigialomycin D (Scheme 3.5).[88] The benzylic bromide **JEH-1** as a key intermediate was synthesized via a Wohl-Ziegler reaction. Instead of AIBN, benzoyl peroxide was used as an initiator in this reaction.

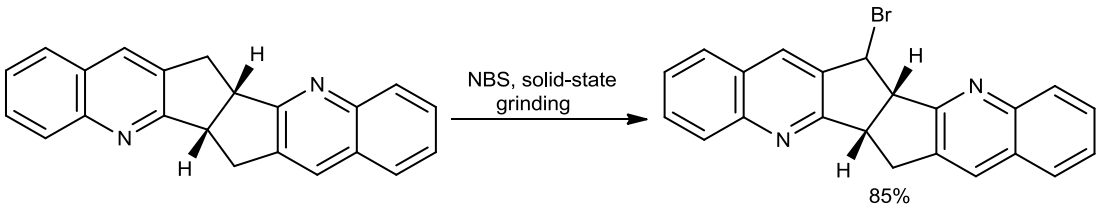


Scheme 3.5 Total synthesis of aigialomycin D involving a Wohl-Ziegler bromination

Despite many applications of Wohl-Ziegler reaction in organic synthesis, some unsolved problems have somewhat limited the further applications of this reaction. Carbon tetrachloride is the most commonly used solvent in the Wohl-Ziegler reaction, but the toxic and ozone-depleting properties of carbon tetrachloride have made it less

[88] Baird, L. J.; Timmer, M. S. M.; Teesdale-Spittle, P. H.; Harvey, J. E. *J. Org. Chem.* **2009**, *74*, 2271.

available and encouraged chemists to find alternative solvents. One solvent free Wohl-Ziegler reaction was developed by Rahman and co-workers as shown in Scheme 3.6. Using this solid-solid Wohl-Ziegler reaction, the bromination of diquinoline was completed in high yield.[89]



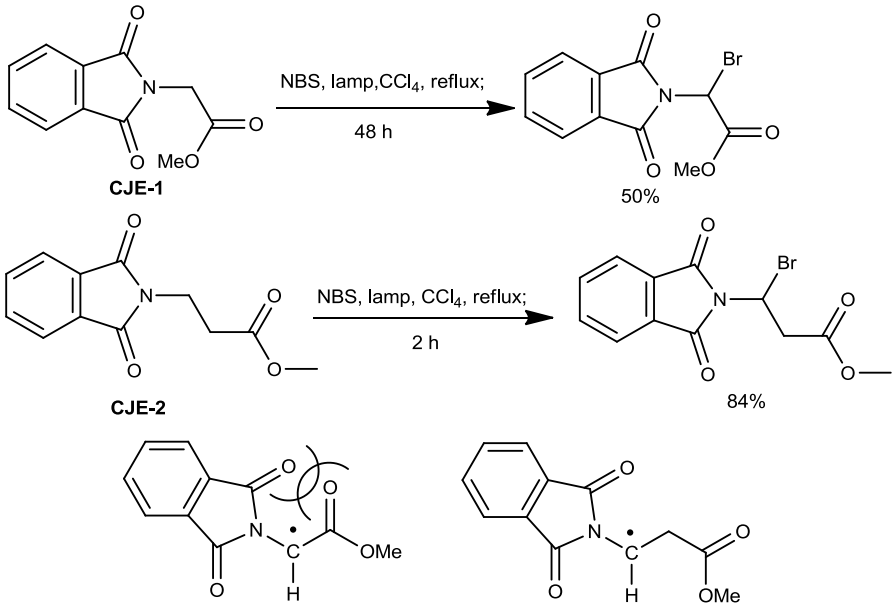
Scheme 3.6 Wohl-Ziegler reaction in the absence of solvent

3. Bromination of *N*-phthalimide protected amines based on the Wohl-Ziegler reaction

The application of the phthalimido as a protecting group to assist the synthesis of amines is extensively documented in the literature. In 1898, Sachs prepared *N*-bromomethylphthalimide from *N*-methylphthalimide by using bromine as the brominating agent; however, under the same conditions, *N*-ethylphthalimide gave only *N*-tribromoethylphthalimide. [90] In 1954, Zaugg successfully obtained *N*-(2-bromoethyl)-phthalimide in high yield from *N*-ethylphthalimide via Wohl-Ziegler synthetic method, which was the first bromination of *N*-alkylphthalimide via Wohl-Ziegler synthesis.[91] In 1989, Easton and co-workers examined the bromination of a wide range of amino acid derivatives including *N*-phthalimide protected amino acid by using *N*-bromosuccinimide as the brominating agent.[92] By comparing the rates of bromination, they discovered how different substituents influenced the stability of the radical intermediates generated from the protected amine substrates.[93] Therefore, this study inspired us to synthesize novel phthalimide protected amine xanthates via the Wohl-Ziegler reaction. Furthermore,

[89] Rahman, A. N. M. M.; Bishop, R.; Tan, R.; Shan, N. *Green Chem.*, **2005**, *7*, 207.
[90] Sachs, F. *Ber*. **1898**, *31*, 1225.
[91] Zaugg, H. E. *J. Am. Chem. Soc.*, **1954**, *76*, 5818.
[92] Burgess, V. A., Easton, C. J., Hay, M. P. *J. Am. Chem. Soc.* **1989**, *111*, 1047.
[93] Easton, C. J., Hutton, C.A., Rositano, G., Tan, E. W. *J. Org. Chem.* **1991**, *56*, 5614.

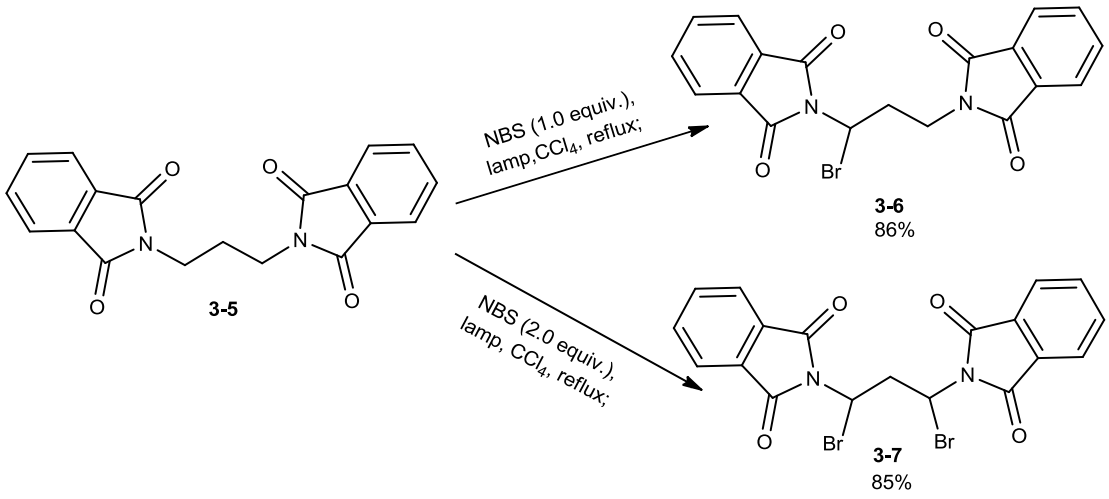
they described the bromination of phthalimide protected *α*-amino acid **CJE-1** was quite inefficient, and required 48 h to achieve 50% conversion; however, the bromination of *β*-amino acid **CJE-2** was completed with high efficiency in 84% yield (Scheme 3.7). A plausible explanation was then proposed. As described in Scheme 3.7, the steric effect arising from the interaction of the methoxycarbonyl and phthalimidyl group would destroy its planar configuration resulting in less efficient delocalization of the unpaired electron.



Scheme 3.7 Bromination of **CJE-1** and **CJE-2**

According to the literature procedure we prepared bromination product **CJE-2** and then extended this study to find other suitable amine substrates for the preparation of the corresponding xanthates via the same bromination approach. The decarboxylation process previously described was used to obtain the 1,4-diaminobutyl and 1,5-diaminopentyl xanthates but other synthetically interesting xanthates derived from 1,2-diaminoethane and 1,3-diaminopropane are not readily accessible by this route because the precursor aminoacids are not available. Thus, we tested the bromination of di-phthalimide protected 1,3-diaminopropane **3-5** which afforded the mono-bromo-product **3-6** in high yield. If a little more than exactly one equivalent

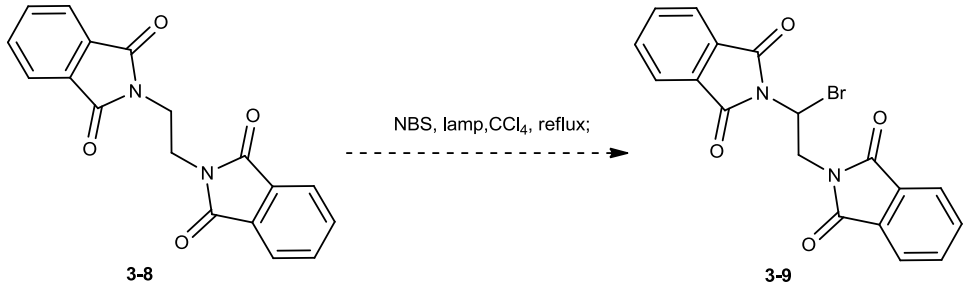
NBS with respect to the amine was added, then a small amount of the di-bromo-product **3-7** was observed (Scheme 3.8). To convert all the starting material **3-5** to di-bromo-product **3-7**, two equivalents of NBS were required.



Scheme 3.8 Bromination of **3-5**

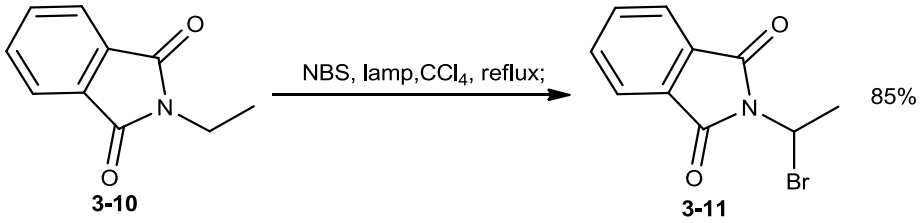
With compound **3-6** and **3-7** in hand, we tried to accomplish the synthesis of the mono-bromo 1,2-diaminoethane derivative in the same manner, but *N*-phthalimide protected 1,2-diamine **3-8** was only slightly soluble in CCl_4 which prevented the bromination process (Scheme 3.9). Even under quite dilute conditions, the starting material **3-8** still remained largely insoluble and then, in the presence of light and a small amount of AIBN, the starting material remained unaffected without any trace of bromination product observed, even after a quite long time. Since compound **3-8** was soluble in chloroform, we added dropwise chloroform to the refluxing CCl_4 mixture until all the starting material was totally dissolved. After 10 h, trace amounts of the desired bromide **3-9** were observed in the crude NMR spectrum. However, after an additional 10 h, the NMR spectrum showed that the ratio of **3-8** to **3-9** remained the same. Replacing totally the solvent with chloroform, again after 10 h starting material **3-8** remained unchanged. Probably, this unsuccessful bromination suffered from the same problem as the bromination of *N*-phthalimide protected glycine ester, but the exact reason is still unclear. It could also be due to a mismatch of polar effects, with

one phltalimide group acting as an electron-withdrawing (by induction) towards the adjacent position.



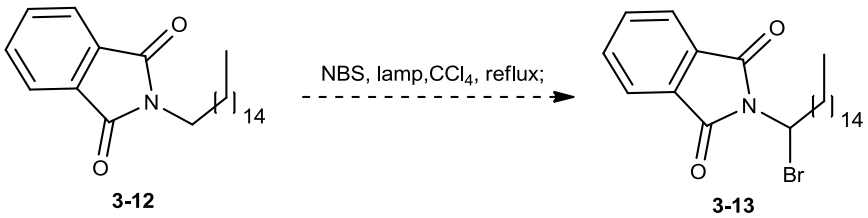
Scheme 3.9 Bromination of **3-8**

We next turned our attention to the bromination of the simple *N*-phthalimide protected alkyl amine like **3-10**, devoid of the unfavorable influence of other functional groups. The bromination was indeed completed as we expected in high yield (Scheme 3.10).



Scheme 3.10 Bromination of **3-10**

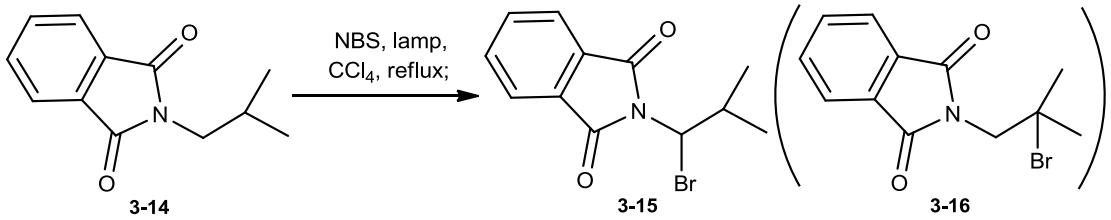
Then, we extended our study to *N*-phthalimide protected alkyl amines such as **3-12** bearing a long chain (Scheme 3.11). Although the starting material was partial consumed after 5 h, besides **3-12** a undetermined mixture was obtained. Zaugg attributed this to the non-specific substitution which meant that increasing length of the alkyl substituent made the bromination unselective. Thus, if the alkyl chain contains less than six carbons, then a high yield will be guaranteed, but longer chain will give mixtures.



3-12 **3-13**

Scheme 3.11 Bromination of **3-12**

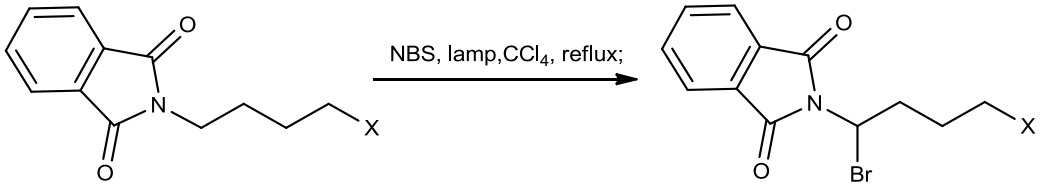
It is a great interesting to compare the stability of tertiary carbon radicals with carbon radicals geminal to phthalimido groups, and this encouraged us to test the bromination of **3-14** bearing a tertiary carbon (Scheme 3.12). Whereas **3-14** was totally consumed in 5 h, no desired product **3-15** was observed. The crude NMR spectrum indicated that probably a small part of the starting material was converted into **3-16**, which suggested that the tertiary carbon radical is more stable than the carbon radical stabilized by a phthalimido group.



3-14 **3-15** **3-16**

Scheme 3.12 Bromination of **3-14**

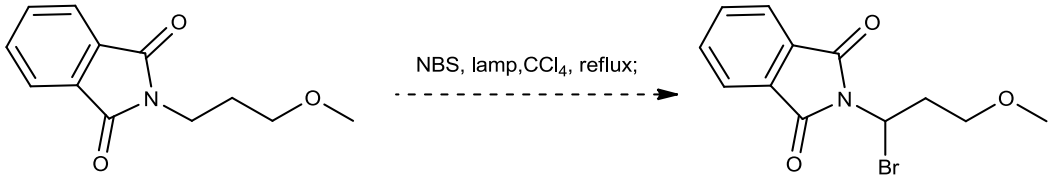
With better knowledge about bromination of *N*-alkyl substituted phthalimides, we examined phthalimides bearing other heteroatoms such as oxygens or halogens. As illustrated in Scheme 3.13, the bromination of substrates **3-17** containing a chlorine or a bromine atom proceeds smoothly to furnish the desired products **3-18** in good yield.



3-17 **3-18**

Scheme 3.13 Bromination of **3-17**

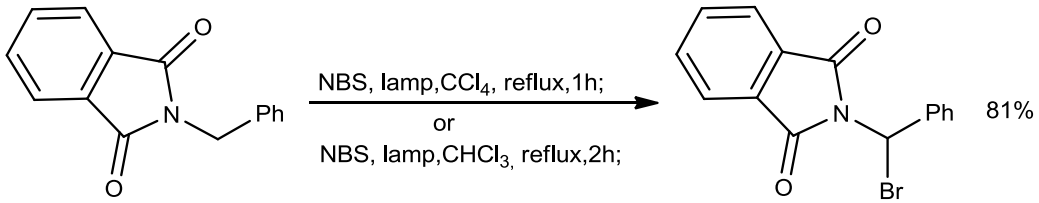
However, bromination of **3-18** did not give the desired product **3-19** (Scheme 3.14). After 7 h, the starting material **3-18** was totally consumed via the same approach, but the crude NMR spectrum showed only undetermined mixture. It is possible that the electrophilic bromine atom prefers to abstract a hydrogen from the carbon geminal to the oxygen atom leading to the formation of a nucleophilic radical.



3-18 **3-19**

Scheme 3.14 Bromination of **3-18**

We also attempted to prepare the xanthate from benzylamine in the same manner. The high stability of benzylic radical should promote the desired reaction. Indeed, the bromination of **3-20** was completed within one hour (Scheme 3.15). Furthermore, chloroform, as a more environmentally benign solvent, could be used for this bromination reaction instead of carbon tetrachloride, but a longer reaction time was required to consume all of phthalimide **3-20**.



3-20 **3-21**

Scheme 3.15 Bromination of **3-20**

The study of bromination of *N*-phthalimide protected amine derivatives to give geminal phthalimido-bromo derivatives improved our understanding of the stability of carbon radicals geminal to phthalimido groups. This knowledge is very useful in the context of the present xanthate chemistry.

Ⅱ. Radical synthesis of *β*-amino acids, alkylamines, 1,3-diamines and polyamines

1. Radical synthesis of *β*-amino acids

1.1. *β*-Amino acids

β-amino acids are highly valuable substances from a medicinal chemistry perspective, since they are often found in natural products and pharmaceuticals.[94] Several pharmaceutical products are displayed in Figure 3.1 Phenoxymethylpenicillin, commonly known as penicillin V, has a range of antimicrobial activity against Gram-positive bacteria; TAN-1057 A as a dipeptide antibiotic is specifically active against staphylococcus species including methicillin-resistant strains; Sitagliptin **(**trade name Januvia), an enzyme-inhibiting drug, is used either alone or in combination with other oral antihyperglycemic agents (such as metformin or a thiazolidinedione) for the treatment of diabetes mellitus type 2 with fewer side effects in the control of blood glucose levels.

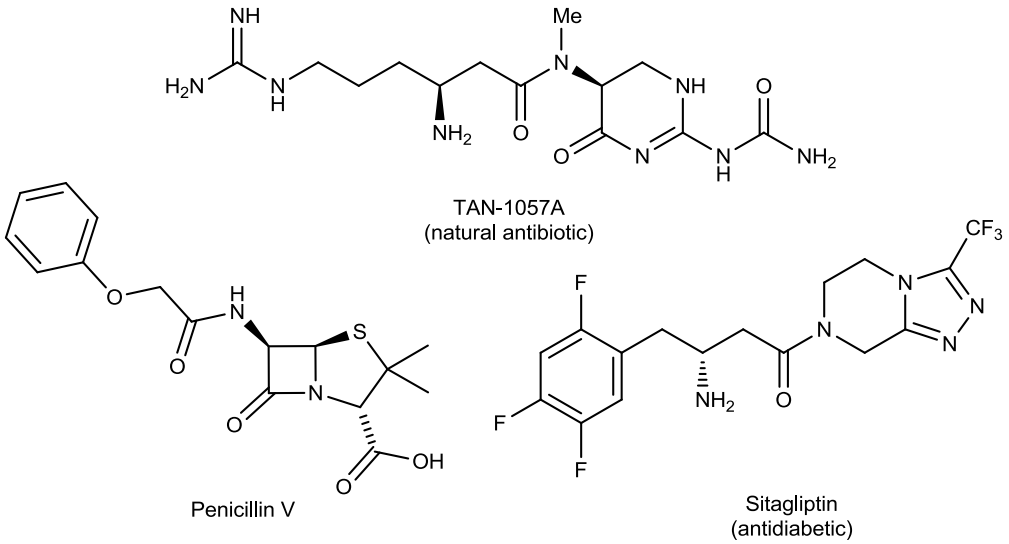
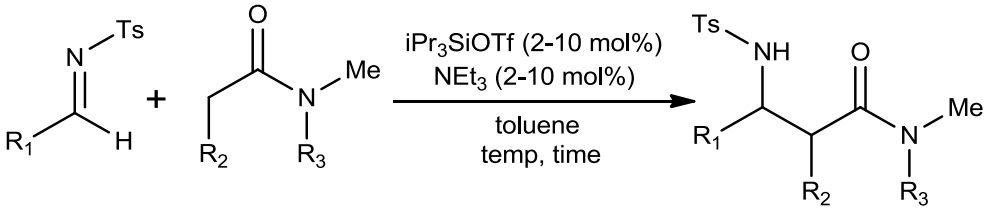


Figure 3.1 Examples of pharmaceutical products

[94] (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley: New York, 1997. (c) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V., Eds.; Wiley: Hoboken, NJ, 2005.

1.2. Recent approaches for the synthesis of *β*-aminoacids

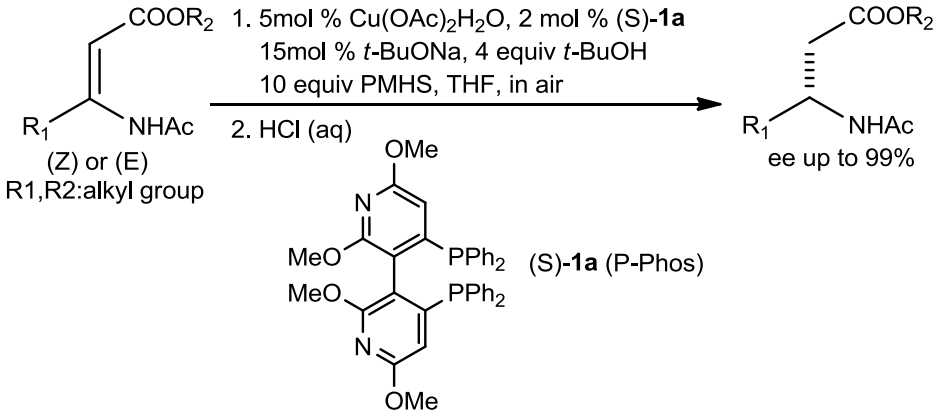
Traditionally, silicon enolates require stoichiometric amounts of the reactive silicon species, but Kobayashi and co-workers described a Mannich-type reaction to give various *β*-amino acids based on a silicon catalyzed process.[95] In the presence of a catalytic amount of trimethylsilyl triflate and triethylamine, this Mannich reaction with various imines occurs even with the less acidic *α*-position of amides to afford the corresponding *β*-amino acids (Scheme 3.16).



Scheme 3.16 The synthesis of *β*-amino acids via Mannich-type reaction

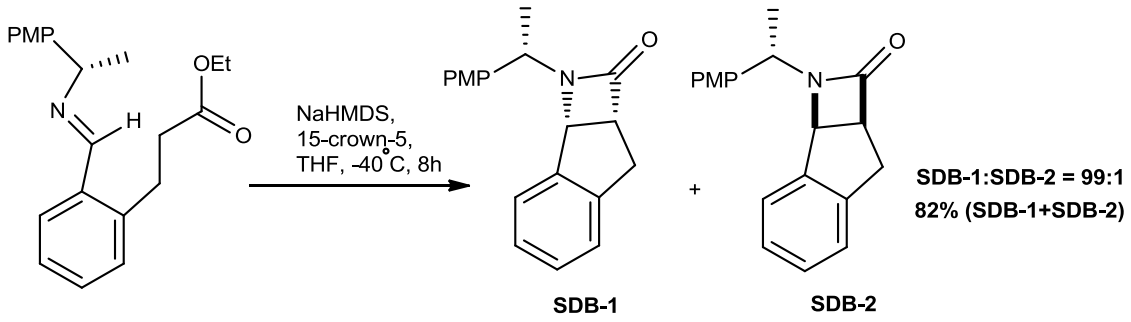
Recently, Chan and co-workers accomplished the synthesis of *β*-alkyl-*β*-amino acid derivatives via the asymmetric 1,4-reduction of *β*-(acylamino)acrylates using a copper-catalyzed process.[96] As shown in Scheme 3.17, in the presence of 5 mol% copper(II) acetate monohydrate ($Cu(OAc)_2H_2O$) together with 2 mol% *(S)*-**1a** as the catalyst, and 10 equiv of polymethylhydrosiloxane (PMHS), either (Z) or (E)-*β*-(acylamino) acrylates were reduced to the highly enantiopure *β*-alkyl-*β*-amino acids under mild conditions.

[95] Kobayashi, S.; Kiyohara, H.; Yamaguchi, M. *J. Am. Chem. Soc.* **2011**, *133*, 708.
[96] Wu, Y.; Qi, S.-B.; Wu, F. F.; Zhang, X.; Li, M.; Wu, J.; Chan, A. S. C. *Org. Lett.* **2011**, *13*, 1754.



Scheme 3.17 The synthesis of *β*-amino acids via copper-catalyzed process

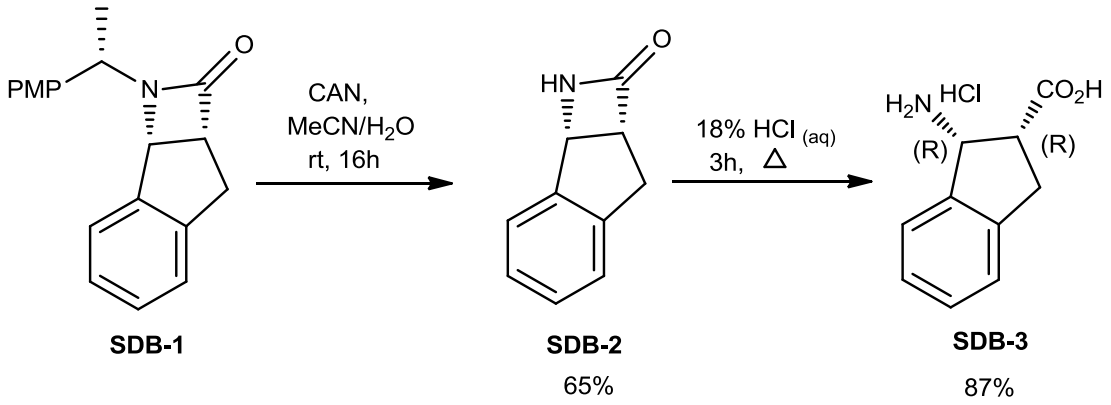
The ring opening of *β*-lactams provides another possibility for the synthesis of *β*-amino acids. Bull and co-workers described a highly diastereoselective intramolecular cyclization of imino-esters which afforded *β*-lactams **SDB-1** in the presence of base (Scheme 3.18).[97]



Scheme 3.18 Intramolecular cyclization of imino-esters

The deprotection of **SDB-1** was realized by using ceric ammonium nitrate (CAN) to afford corresponding *β*-lactam **SDB-2** which was then converted to *β*-amino acids **SDB-3** under acidic conditions in high yield.

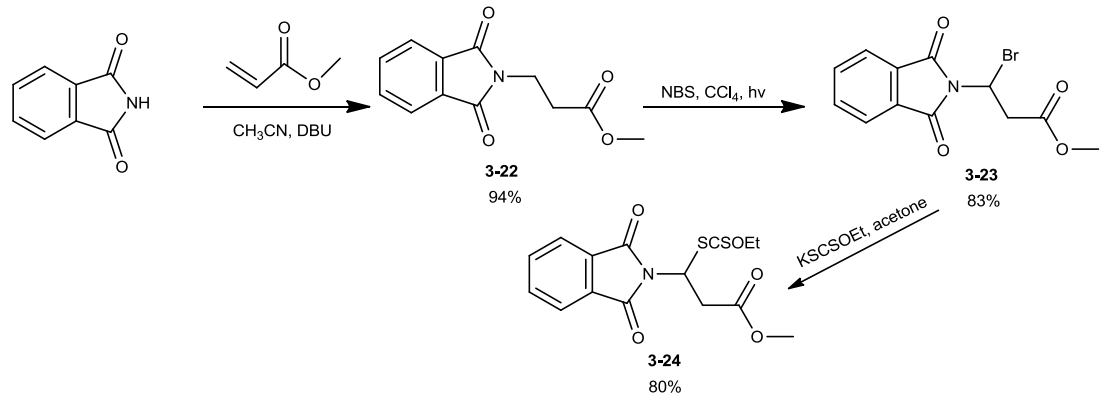
[97] Evans, C. D.; Mahon, M. F.; Andrews, P. C.; Muir, J.; Bull, S. D. *Org. Lett.* **2011**, *13*, 6276.



Scheme 3.19 Ring opening of **SDB-1**

1.3. Synthesis of *β*-amino acids based on xanthate chemistry[98]

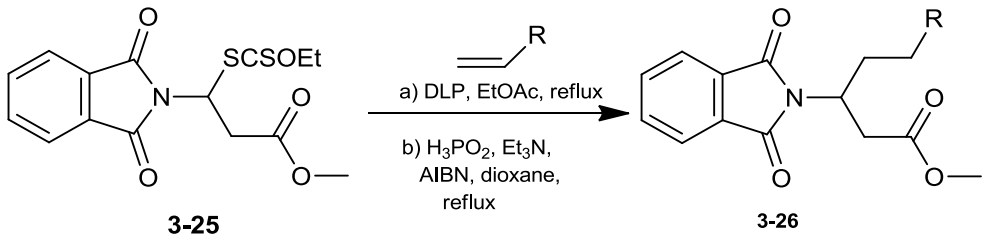
Based on previous studies on radical hydroaminomethylation of alkenes and bromination of the various phthalimido protected amines via the classical Wohl-Ziegler allylic bromination using *N*-bromosuccinimide (NBS), we extended this radical hydroaminomethylation approach to the synthesis of *β*-amino acid derivatives. As shown in the Scheme 3.20, the **3-22** was rapidly prepared via Michael addition of phthalimide with methyl acrylate in the presence of DBU.[99] Next, bromination of **3-22** gave **3-23** and then replacement of bromine by potassium ethyl xanthate furnished the desired xanthate product **3-24**.



Scheme 3.20 The synthesis of xanthate **3-24**

[98] Preliminary results were attained by Rachel A. Jones.
[99] Yeom, C.-E.; Kim, M. J.; Kim, B. M.; *Tetrahedron*, **2007**, *63*, 904.

Addition of xanthate **3-25** to various alkenes gave various adducts which underwent reductive removal of the xanthate group by triethylammonium hypophosphite to furnish the corresponding *N*-phthalimide protected *β*-amino acid derivatives (Scheme 3.21).

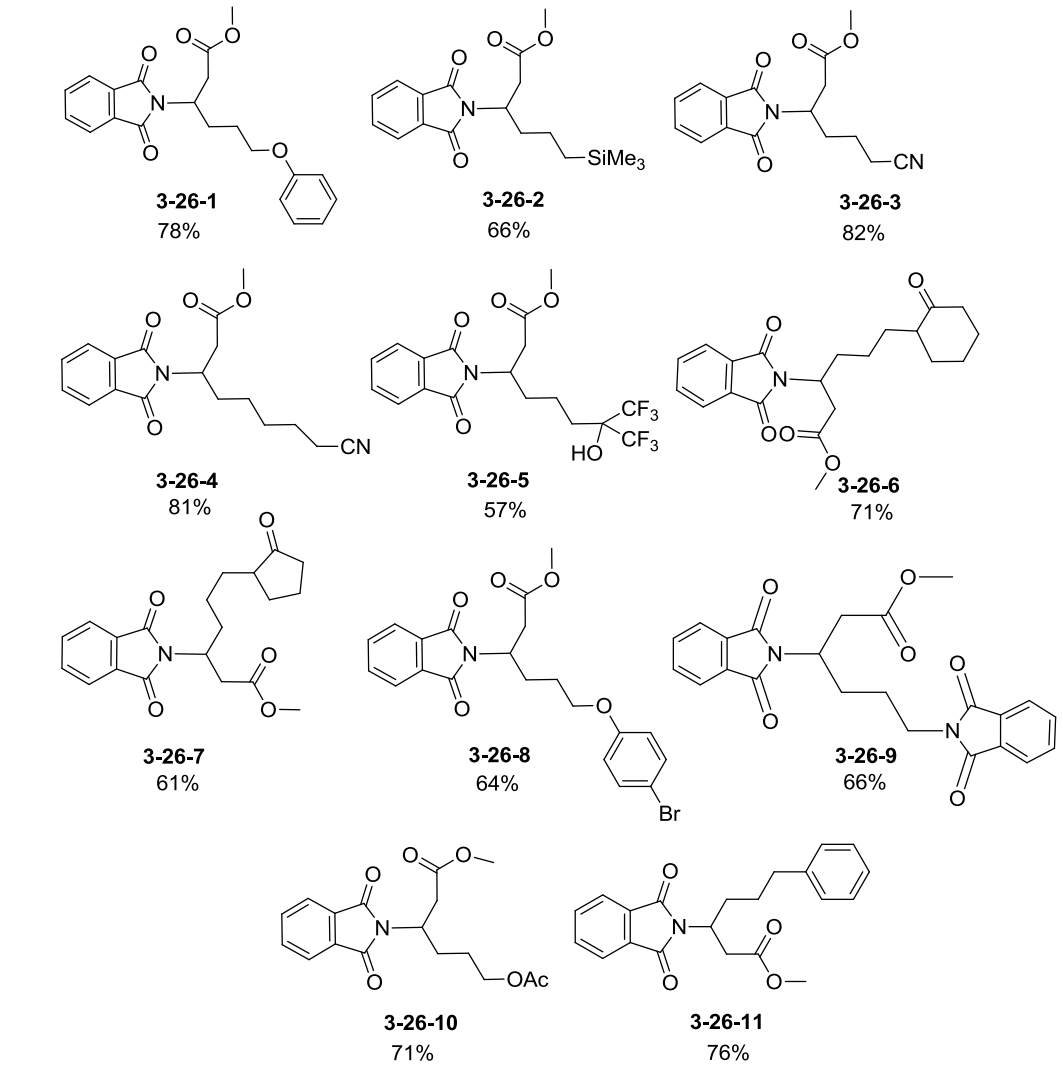


Scheme 3.21 Radical addition of **3-25** to olefins

A wide range of functional groups, such as trimethylsilyl, cyano, ketonyl, trifluoromethyl, ester or alicyclic groups like cyclohexanyl and cyclopentanyl, or aromatic rings like phenoxy or phenyl are incorporated into the *N*-phthalimide protected amino acids, as illustrated in Scheme 3.22. It is worthwhile to note that **3-26-9** corresponds to methyl *β*-lysinate with the two amino groups protected as phthalimides. *β*-Lysine (or isolysine) is present in blood platelets during coagulation and in tears, and acts as an antibiotic by causing lysis of numerous Gram-positive bacteria.[100] It has been found as key components in a range of antibiotics such as streptothrycin F, racemomycins and viomycin.[101] There has therefore been an increasing interest for its synthesis, and our approach provides a quite concise and efficient route to access phthalimido protected *β*-lysine in two steps.

[100] Spiteller, P.; von Nussbaum, F. *β*-Amino Acids in Natural Products. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E.; Soloshonok, V. Eds.; Wiley: Hoboken, NJ, 2005; pp 19-91.

[101] (a) Gould, S. J.; Thiruvengadam, T. K. *J. Am. Chem. Soc.* **1981**, *103*, 6752. (b) Thiruvengadam, T. K.; Gould, S. J.; Aberhart, D. J.; Liu, H.-J.; *J. Am. Chem. Soc.* **1983**, *105*, 5470. (c) Y. Sawada and H. Taniyama, *Chem. Pharm. Bull.* **1977**, *25*, 1302.

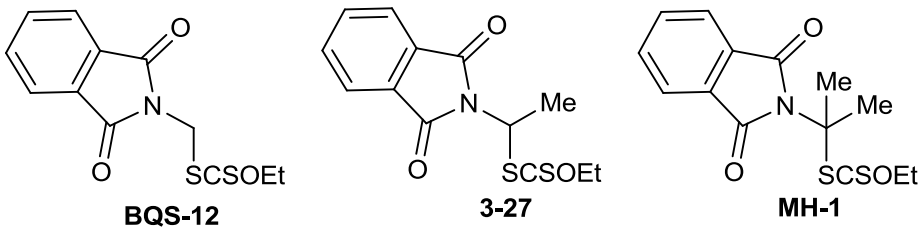


Scheme 3.22 *N*-Phthalimide protected *β*-amino acids

2. Radical synthesis of alkylamine

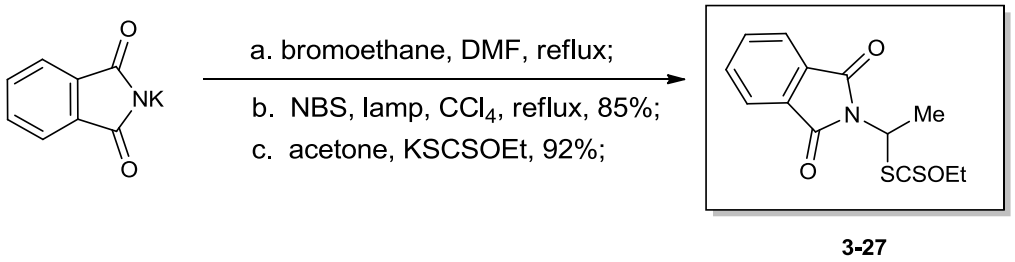
In chapter 2 we have already discussed the radical addition of phthalimido-substituted amine xanthate **BQS-12** to various alkenes. In another previous study we examined the addition of xanthate **MH-1**.[102] In these cases a primary and a tertiary carbon radical is generated. To better understand the difference in their behaviours, xanthate **3-27** was therefore prepared and its radical addition to unactivated olefins investigated (Scheme 3.23).

[102] Heinrich, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 4969.



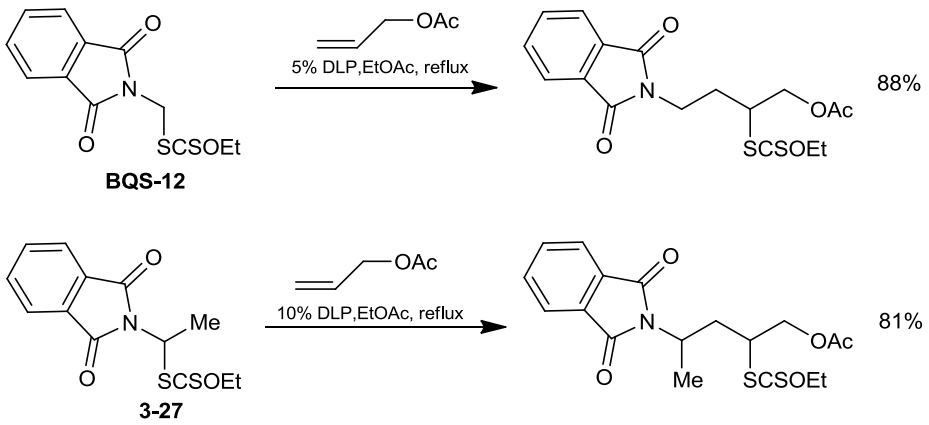
Scheme 3.23 Primary, secondary and tertiary phthalimido-substituted xanthates

As illustrated in Scheme 3.24, the preparation of xanthate **3-27** was quite straightforward. The *N*-phthalimide protected amine was prepared by Gabriel synthesis and then it would proceed to afford xanthate **3-27** via Wohl-Ziegler bromination and replacement of bromine by xanthate group.



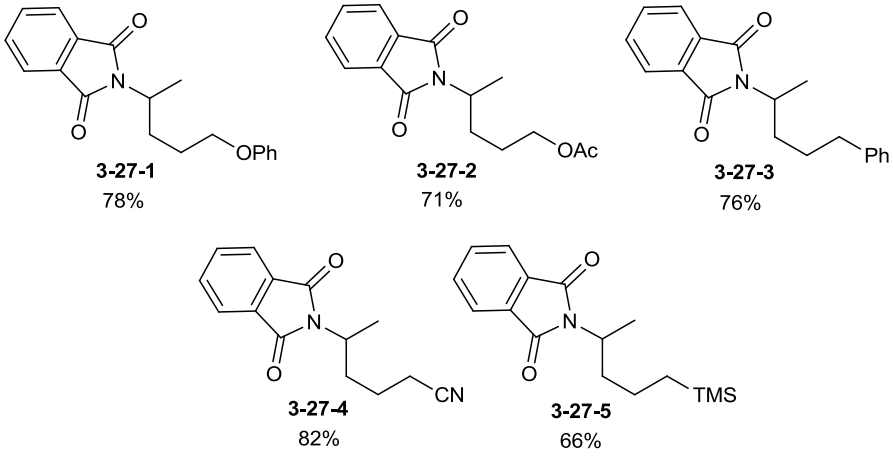
Scheme 3.24 The preparation of xanthate **3-27**

As we expected, the addition of **3-27** to olefins gave adducts in high yield and only10-15 mol% DLP was required for complete conversion. To compare the difference between xanthate **BQS-12** and **3-27**, the addition of **3-27** to allylacetate was examined (Scheme 3.25). The yield was 81% compared with 88% using xanthate **BQS-12** under the same conditions. There was therefore no apparent difference as far as yields were concealed. However, in the case of xanthate **BQS-12** only 5 mol% of DLP was needed to complete the reaction but 10 mol% DLP for xanthate **3-27**. A possible explanation might be attributed to the steric effect which would lower the efficiency of radical addition step.



Scheme 3.25 Radical addition of xanthates **BQS-12** and **3-27** to allyl acetate

As shown in Scheme 3.26, we have also tested the radical addition of xanthate **3-27** to other olefins such as 4-allylanisole, allylbenzene, allylcyanide and allyltrimethylsilane.

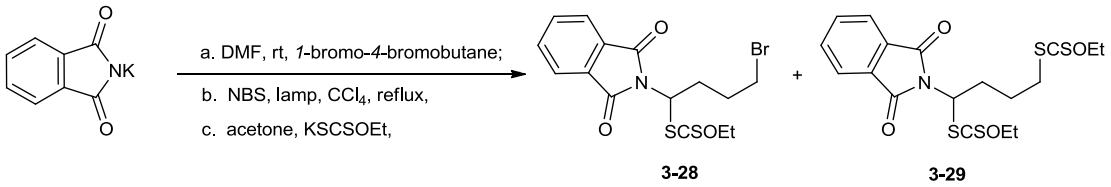


Scheme 3.26 *N*-phthalimide protected alkyamines

3. Radical synthesis of chloroalkylamines and pyrrolidines

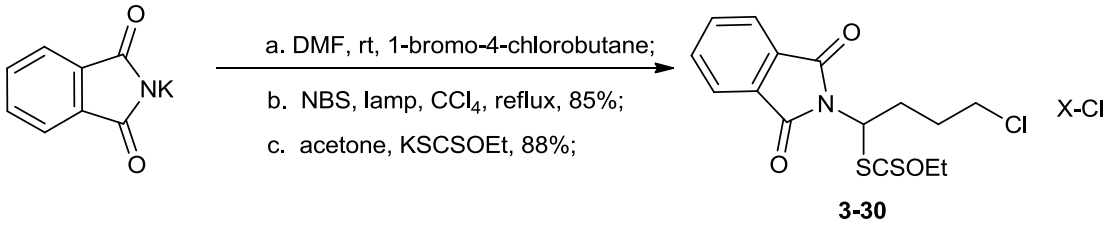
1,4-Dibromobutane was next employed to prepare the corresponding xanthate. The replacement of bromine by potassium ethyl xanthate led to the formation of xanthate **3-28**, but a small amount of byproduct **3-29** was also observed, even when

using less than one equivalent of the xanthate salt (Scheme 3.27). Although xanthate **3-28** was the major product, it couldn't be separated from the mixture. Therefore, the mixture of xanthate **3-28** and byproduct **3-29** was used directly for the radical addition to olefins. 50 mol% DLP was required to totally consume the starting material but, instead of the desired adduct, only an undetermined mixture and a small amount of the reduced product were observed.



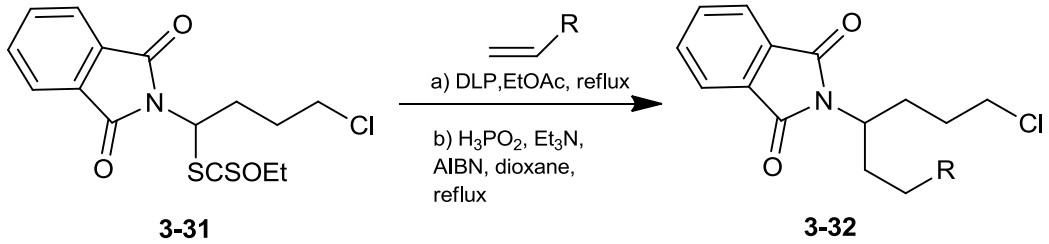
Scheme 3.27 Synthesis of xanthate **3-28**

Since even trace amounts of impurity such as **3-29** might prevent the radical chain process, we reexamined this process by replacing 1,4-dibromobutane by 1-bromo-4-chlorobutane (Scheme 3.28). 0.9 Equivalent of potassium O-ethyl xanthate was used, and only the desired xanthate **3-30** was obtained.



Scheme 3.28 Synthesis of xanthate **3-30**

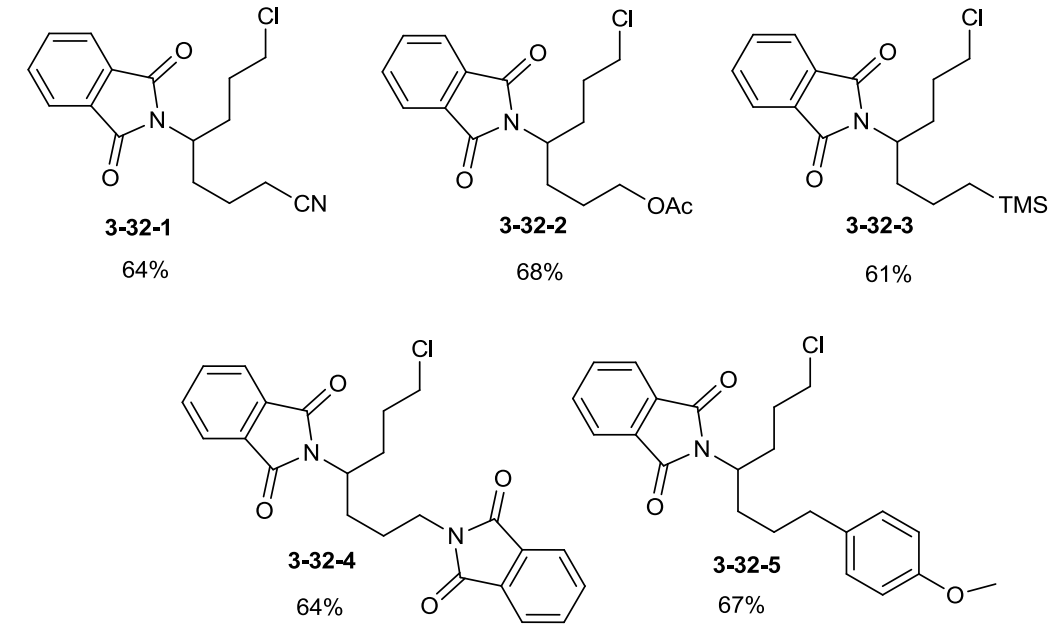
To our delight, the addition of xanthate **3-30** to various olefins gave the desired adducts. Next, the xanthate was reduced off by action of the triethylammonium salt of hypophosphorus acid to afford the corresponding phthalimides **3-32** in generally good yields (Scheme 3.29).



3-31 **3-32**

Scheme 3.29 Synthesis of **3-32**

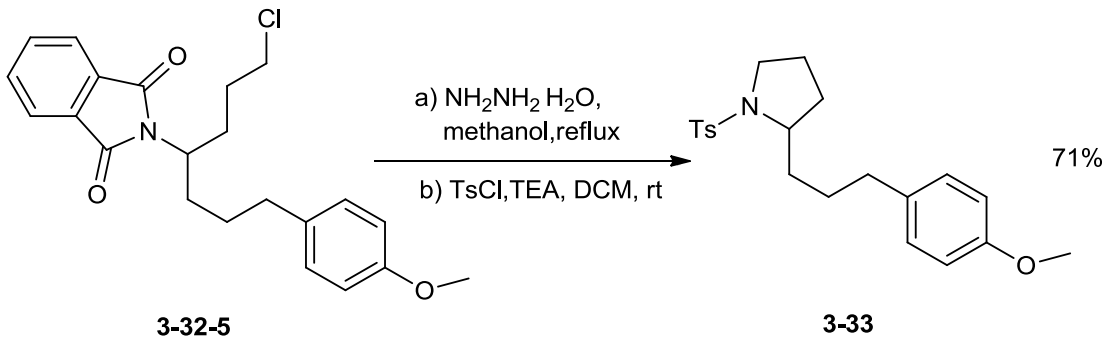
Besides the various functional groups that are incorporated into these products, the presence of the chlorine atom four carbons away in these adducts is especially useful for the construction of heterocyclic rings or for other extensions through the intermolecular substitutions (Scheme 3.30).



Scheme 3.30 *N*-phthalimide protected chloroalkylamine **3-32**

We have illustrated one such possibility in the case of **3-32-5** as shown in Scheme 3.31. To unmask the amine, we added hydrazine hydrate to a refluxing methanol solution of **3-32-5**, and this treatment furnished the corresponding cyclopentylamine directly. After concentration of the solution, the residue was dissolved in DCM without purification followed by addition of triethylamine and 4-toluenesulfonyl chloride in a 1:1 ratio. This afforded the easy to isolate derivative

3-33 in 71% yield for the two steps. Therefore, this concise and highly efficient route can be exploited to construct substituted pyrrolidines, especially by modification at their position 2.[103]



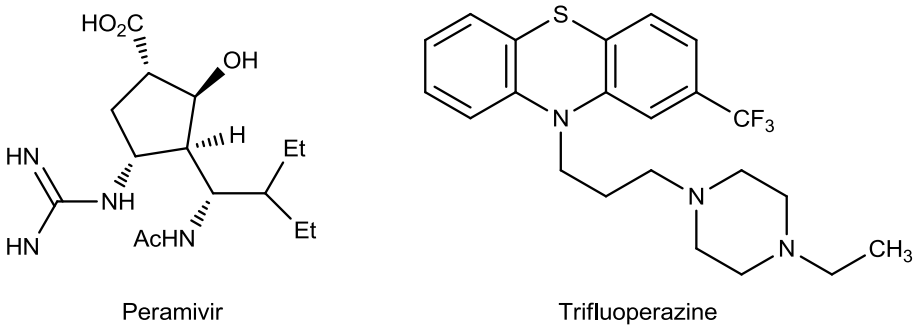
Scheme 3.31 Synthesis of pyrrolidines **3-33**

4. Radical synthesis of 1,3-diamines and polyamines

4.1. 1,3-diamines

1,3-diamines are highly versatile species, which have been used in acid-base catalysis, as molecular recognition devices, as metal-chelating moieties, and as functional group in the synthesis of macrocycles and other larger molecular.[104] As shown in Figure 3.2, peramivir is an antiviral drug developed by BioCryst Pharmaceuticals, Inc. for the treatment of influenza;[105] trifluoperazine has been used for patients with behavioural problems, severe nausea and vomiting, and its activity is attributed to its central antiadrenergic, antidopaminergic, and minimal anticholinergic effects.[106] Furthermore, there have been numerous applications of chiral 1,3-diamines as chiral auxiliaries, chiral catalysts and chiral ligands in enantioselective synthesis.

[103] (a) Enders, D.; Goddertz, D. P.; Beceno, C.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 2863. (b) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (c) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400.
[104] Bender, J.; Meanwell, N. A.; Wang, T. *Tetrahedron* **2002**, *58*, 3111.
[105] Shetty, A. K.; Peek, L. A. *Expert Rev. Anti Infect. Ther.* **2012**, *10*, 123.
[106] Post, A.; Warren, R. J.; Zarembo, J. E. *Anal. Profiles Drug Subst.* **1980**, *9*, 543.



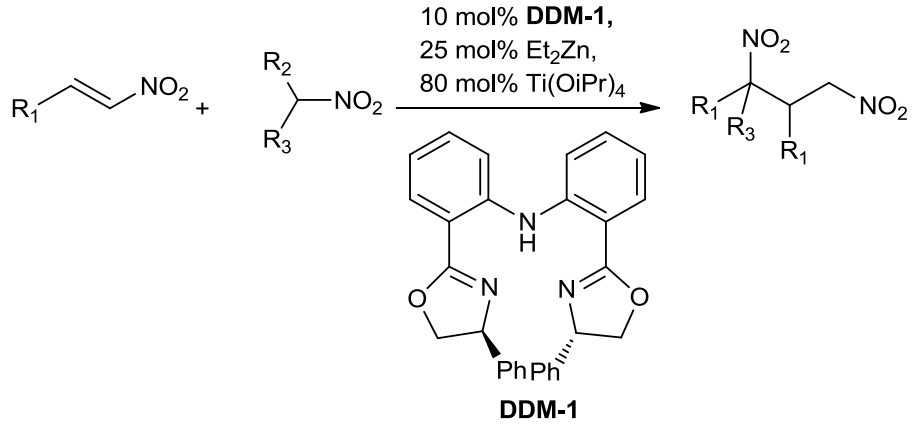
Peramivir Trifluoperazine

Figure 3.2 Examples of pharmaceutical products

4.2. Synthesis of 1,3-diamines

4.2.1. Reduction of 1,3-dinitro compounds to 1,3-diamines

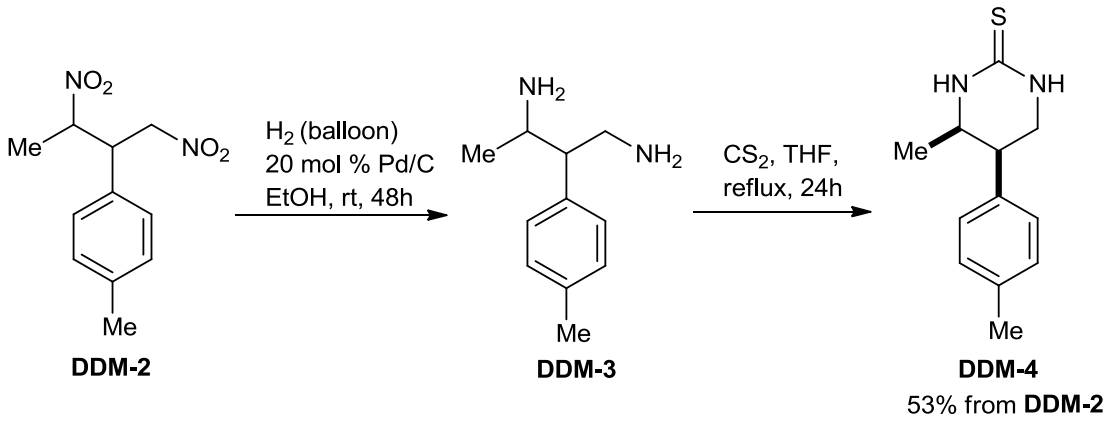
An investigation undertaken by Du and co-workers disclosed that the bis(oxazoline) ligand such as **DDM-1** or bis(thiazoline) ligand would promote the Zn (II)-catalyzed stereoselective addition of nitroalkanes to a wide range of nitroalkenes, in a highly stereoselective approach to 1,3-nitroamines (Scheme 3.32).[107]



Scheme 3.32 Synthesis of 1,3-nitroamines

Like the example shown in Scheme 3.33, these 1,3-dinitroalkanes **DDM-2** can be converted into the corresponding enantioenriched 1,3-diamines **DDM-3** via simple reduction of their nitro groups.

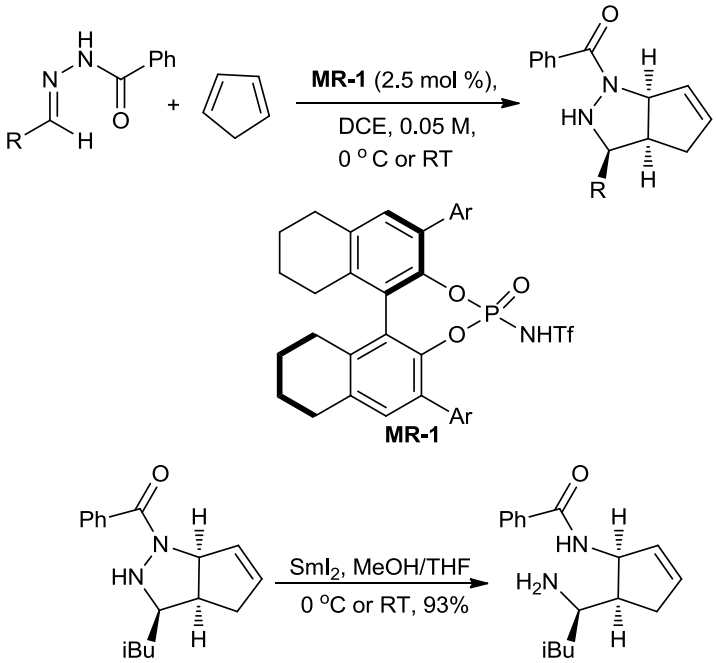
[107] Lu, S.-F.; Du, D.-M.; Xu, J.; Zhang, S.-W. *J. Am. Chem. Soc.* **2006**, *128*, 7418.



Scheme 3.33 Reduction of 1,3-dinitroalkanes

4.2.2. 1,3-Diamines from pyrazolidine derivatives

Rueping and co-workers developed a general and highly enantioselective approach to access optically active pyrazolidine derivatives.[108] As shown in Scheme 3.34, the cycloaddition occurred between various alkenes and *N*-benzoylhydrazones and was catalyzed by Bronsted acid **MR-1**. Cleavage of the N-N bond provided the corresponding 1,3-diamines in high yield.

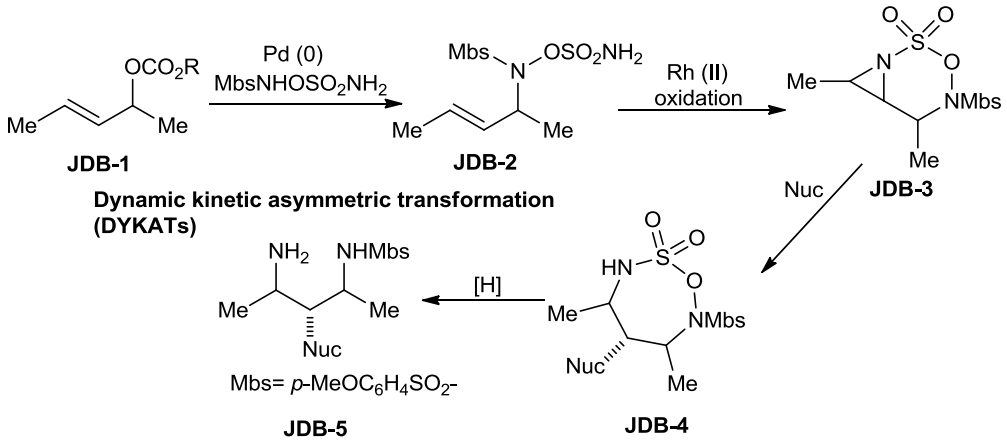


Scheme 3.34 Synthesis of 1,3-diamines from pyrazolidine derivatives

[108] Rueping, M.; Maji, M. S.; Kucuk, H. B.; Atodiresei, I. *Angew. Chem. Int. Ed.* **2012**, *51*, 12864.

4.2.3. Asymmetric synthesis of diamine derivatives based on organocatalysis

Recently Trost and co-workers described a route to 1,3-diamines involving a rhodium catalyzed cyclization step (Scheme 3.35).[109] Palladium-catalyzed allylic amination of **JDB-1** gave the allylic hydroxylamine-derived sulfamate esters **JDB-2** via a dynamic kinetic asymmetric transformation. Intermediate **JDB-2** was then subjected to a rhodium catalyzed intramolecular amination process to afford aziridine **JDB-3**. Finally, ring opening of the latter furnished compound **JDB-4,** which was reduced to afford the corresponding 1,3-diamine **JDB-5**.



Scheme 3.35 Synthesis of diamine based on rhodium catalyzed proccess

4.3. Xanthate chemistry based approach to access 1,3-diamines

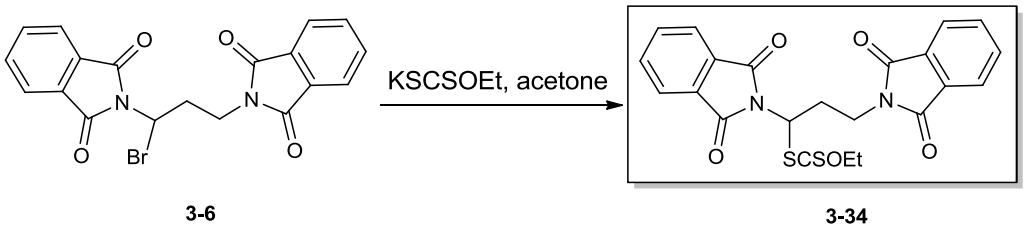
Although numerous methods to access 1,3-diamines have been reported, due to their broad applications in organic synthesis and medicinal chemistry, there has remained an interest in investigating other synthetic routes, especially modular approaches and metal free methods.

4.3.1. Radical synthesis of 1,3-diamines using xanthate **3-34**

As we mentioned in chapter 2, the synthesis of 1,4- and 1,5-diamines was developed in our group based on the decarbonylation of α-amino acid to prepare the

[109] Trost, B. M.; Malhotra, S.; Olson, D. E.; Maruniak, A.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 4190.

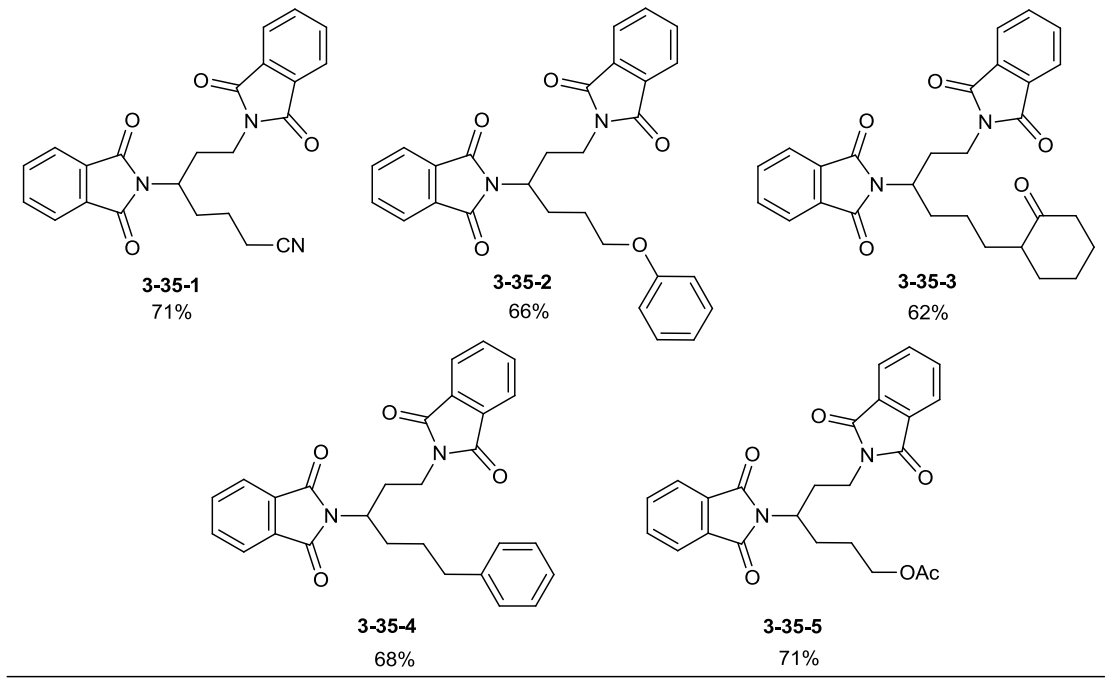
corresponding xanthates. However, 2,4-diaminobutanoic acid as the starting material for synthesis of 1,3-diamine is much more expensive in comparison with starting with 1,3-diaminopropane via the bromination reaction. We thus converted 1,3-diaminopropane into xanthate **3-34** in nearly quantitative yield (Scheme 3.36).



3-6 **3-34**

Scheme 3.36 Synthesis of xanthate **3-34**

The addition of xanthate **3-34** to several unactivated olefins proceeded in generally high yield needing 10-15 mol% DLP for completion. The examples are collected in Scheme 3.37. As before, these adducts were reduced by the Barton reagent to give compound **3-35** bearing various side chains in a total yield ranging from 62% to 71%.

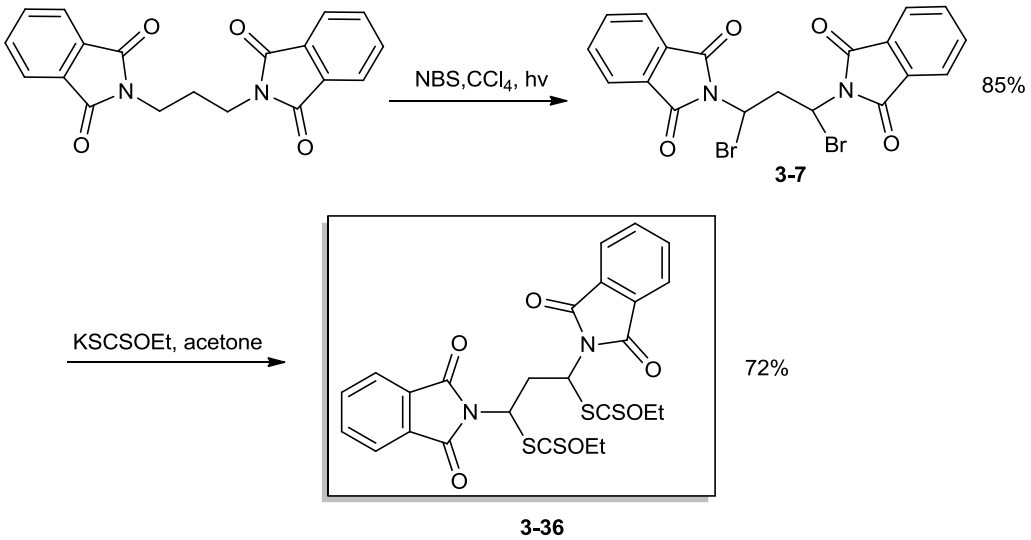


3-35-1 71%
3-35-2 66%
3-35-3 62%
3-35-4 68%
3-35-5 71%

Scheme 3.37 Examples of 1,3-diamines **3-35**

4.3.2. Radical synthesis of 1,3-diamines by using xanthate **3-36**

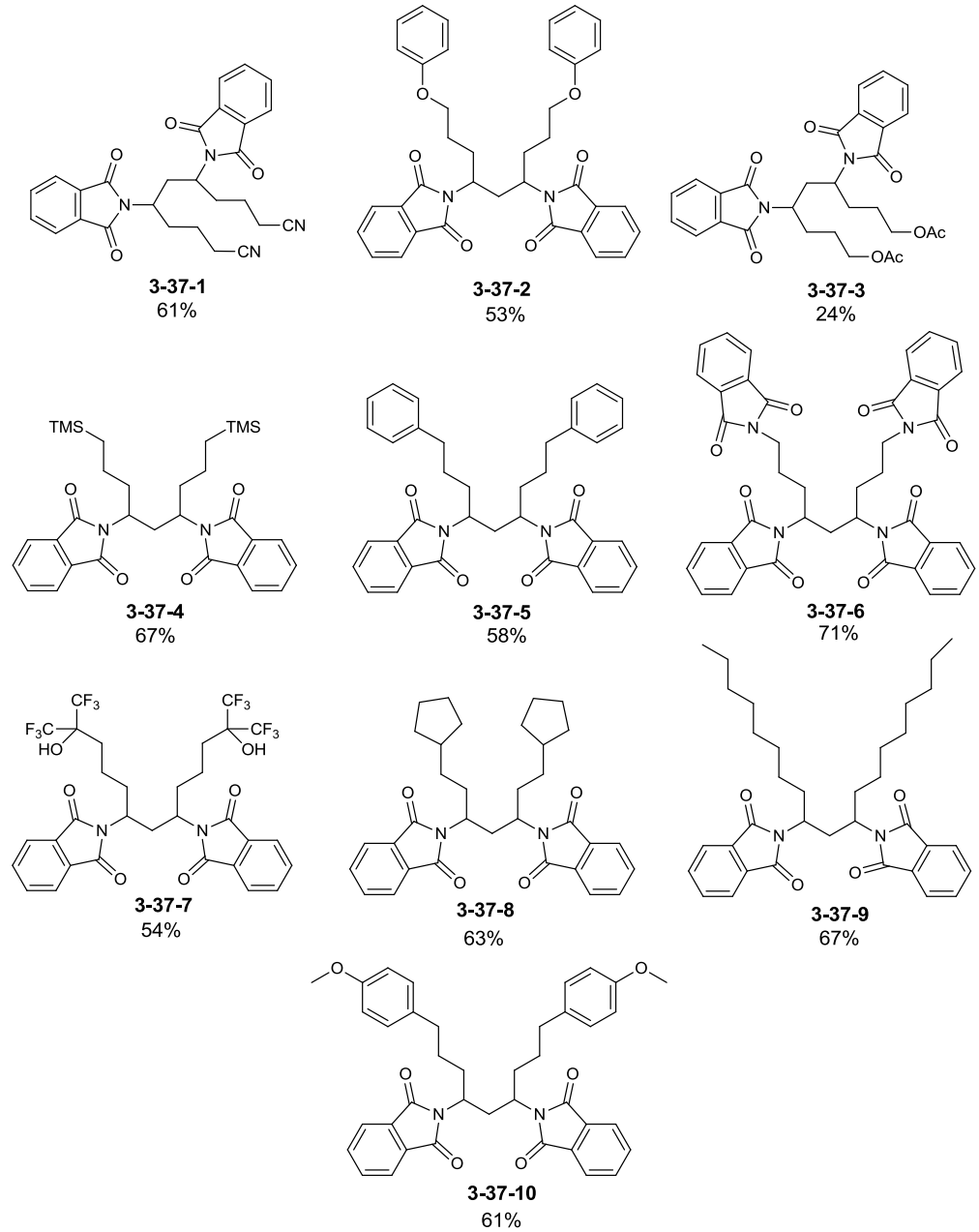
Adding more than one equivalent of *N*-bromosuccinimide with respect to the substrate, a small amount of dibrominated product was formed in the mixture. Thus, we repeated this process by adding two equivalents of *N*-bromosuccinimide and obtained dibrominated product **3-7** along with a small amount of monobrominated product **3-6**. To secure the total transformation of **3-5** into **3-7**, 2.5 equivalents of *N*-bromosuccinimide were needed. Replacement of the bromine by the xanthate group furnished xanthate **3-36** in quantitative yield (Scheme 3.38). The radical addition of xanthate **3-36** to various olefins was then investigated and the corresponding double addition products were observed. Usually, but depending on the boiling points of olefins more than one equivalent or even four equivalents olefins were added to accomplish a complete transformation. We found it was quite difficult to control the radical addition to afford only mono-addition products. The double addition products from xanthate **3-36** are particularly interesting. Reductive removal of the xanthate groups simplified considerably the mixture, since now only *meso* and *dl* modifications of these diamines remained in approximately 2:1 ratio.



Scheme 3.38 Synthesis of xanthate **3-36**

The examples displayed in Scheme 3.39 give an idea of the scope and the

tolerance for the various functional groups.To best of our knowledge, this is the first bidirectional approach to access 1,3-disubstituted diaminopropanes with a C_{2v} symmetry. It is worthwhile noting that tetramine **3-37-6** is synthesized in two steps. Such compounds are difficult to obtain by current methods. In the case of **3-37-7**, four trifluoromethyl groups are incorporated into the *N*-phthalimide protected diamine.



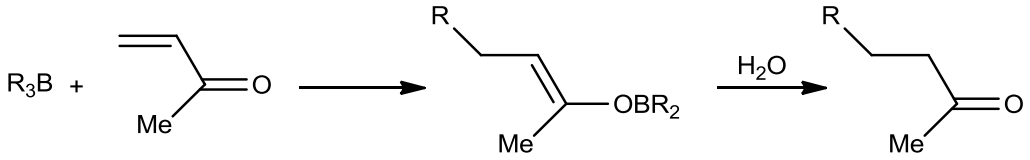
Scheme 3.39 Examples of **3-37**

5. Radical synthesis of amines involving the autoxidation of triethylborane

5.1. Organoboranes

Brown received the Noble Prize in chemistry in 1979 for his pioneering research on the applications of organoborane compounds in organic synthesis. In the following decades, due to the rich and varied chemistry of organoboranes, there has been an enormous increase in the applications of organoboranes in organic synthesis.

The first organoborane induced radical reactions were reported in 1967. Brown and co-workers found that trialkylboranes underwent 1,4-conjugate addition with unsaturated ketones followed by hydrolysis to furnish the corresponding ketones (Scheme 3.40). However, they did not immediately realize that it was a free radical process until they found that a small amount of oxygen in the nitrogen gas was the key to a successful addition.[110]



Scheme 3.40 1,4-conjugate addition of trialkylboranes to unsaturated ketones

Later, the use of boron alkyls in combination with oxygen was developed by Oshima and co-workers and experienced a fast growth in interest and popularity.[111] In 2001, Ollivier and Renaud described many applications of boron alkyls in free radical initiated syntheses and discussed the now accepted mechanism for the autoxidation of organoboranes in their review.[112]

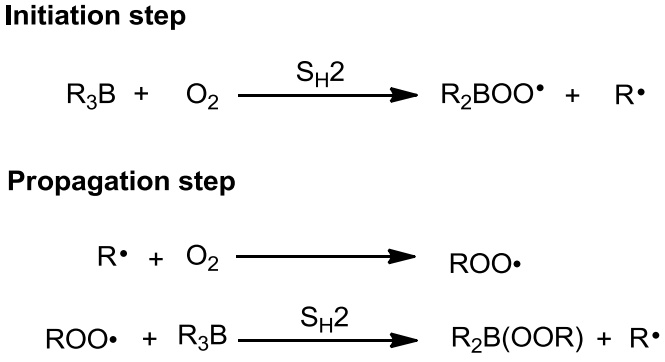
As shown in Scheme 3.41, in the initiation step, trialkylborane liberates a free alkyl radical upon exposure even to trace amounts of oxygen. In the propagation step, this free alkyl radical combines with another molecule of oxygen to generate a peroxy

[110] (a) Suzuki, A.; Arase, A.; Matsumoto, H.; Itoh, M.; Brown, H. C.; Rogic, M. M.; Rathke, M. W.; *J. Am. Chem. Soc.* **1967**, *89*, 5708. (b) Brown, H. C.; Midland, M. M. *Angew. Chem. Int. Ed.* **1972**, *11*, 692.

[111] Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143.

[112] Ollivier, C.; Renaud, P.; *Chem. Rev.* **2001**, *121*, 3543.

radical which is readily captured by trialkylboranes to generate another alkyl radical, and so on.

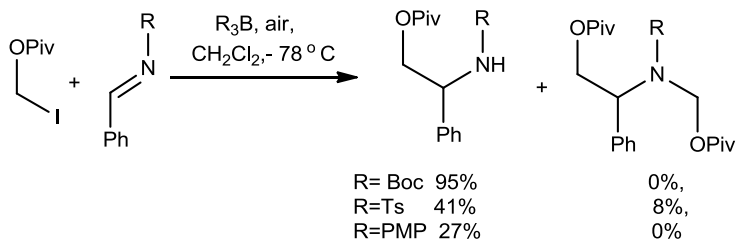


Scheme 3.41 Autoxidation of organoborane

5.2. Applications of organoborane in radical synthesis

Currently, organoboranes have been applied to a wide range of free-radical reactions, such as additions to alkynes, alkenes, ethynyloxiranes, azidoalkenes and imines or conjugate addition to unsaturated ketones and aldehydes or hydroxylation, azidation and halogenation.[113]

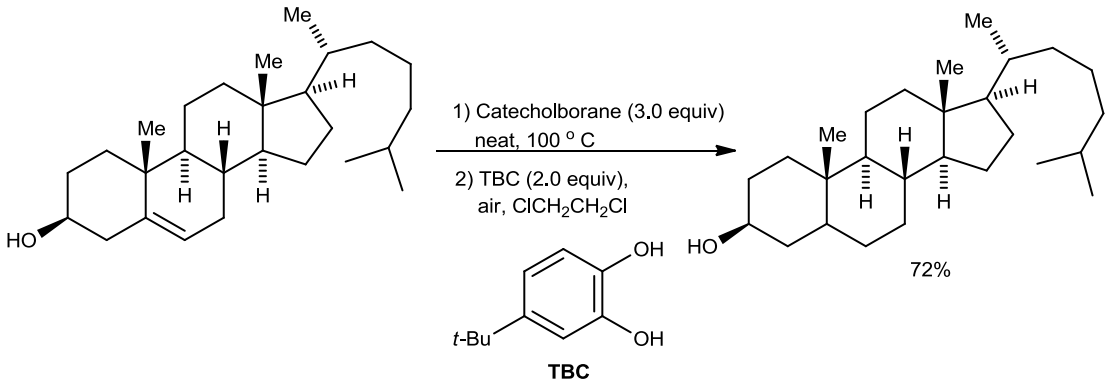
Recently, Yamada and co-workers described a triethylborane-induced tin-free radical alkylation of *N*-protected imines with iodomethylpivalate to give the corresponding amine products (Scheme 3.42).[114] Since the autoxidation of triethylborane with a small amount of oxygen proceeds smoothly even at -78 ℃, this reaction could be completed at low temperature (-78 to -20 ℃), a great advantage when using triethylborane-air as the initiator.



Scheme 3.42 Triethylborane-induced radical alkylation of *N*-protected imines

[113] Darmency, V.; Renaud, P. *Top. Curr. Chem.* **2006**, *263*, 71.
[114] Yamada, K.; Konishi, T.; Nakano, M.; Fujii, S.; Cadou, R.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2012**, *77*, 1547.

The conversion of alkenes to alkanes relies mainly on metal catalyzed hydrogenation. Recently, Renaud and co-workers reported the reduction of alkylboron compounds with catechols via a radical chain process (Scheme 3.43).[115] The hydroboration of the alkene gives the *B*-alkycatecholborane intermediate and then by using catechols as the reducing agent *B*-alkycatecholborane is reduced to form corresponding alkane in the presence of air via a free radical chain process.

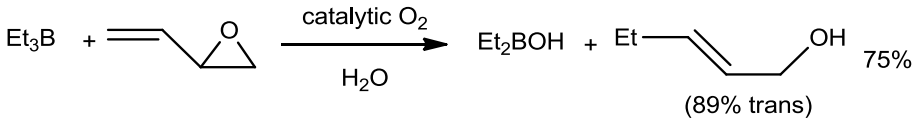


Scheme 3.43 Reduction of alkylboron compounds with catechols

5.3. Organoboranes in combination with xanthate chemistry

5.3.1. Radical addition of trialkyboranes to 1,3-butadiene monoxide

In 1971, Brown and co-workers initially reported the addition of trialkyboranes to 1,3-butadiene monoxide in the presence of trace amounts of oxygen via a free radical chain process (Scheme 3.44).[116]

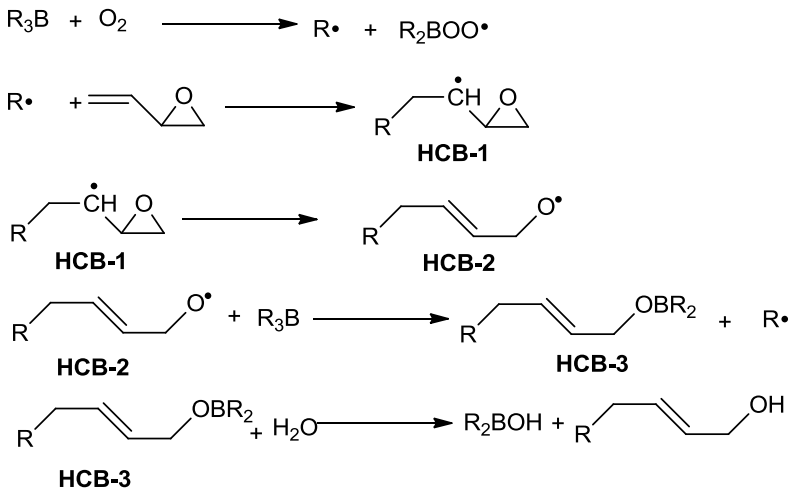


Scheme 3.44 Addition of trialkyboranes to 1,3-butadiene monoxide

A plausible mechanism of this radical process is outlined in Scheme 3.45. The autoxidation of trialkyborane gives an alkyl radical which adds to the double bond to

[115] Villa, G.; Povie, G.; Renaud, P. *J. Am. Chem. Soc.* **2011**, *133*, 5913.
[116] Suzuki, A.; Miyaura, N.; Itoh, M.; Brown, H. C.; Holland, G.W.; Negishi, E. Rogic, *J. Am. Chem. Soc.* **1971**, *93*, 2792.

generate a radical intermediate **HCB-1**. The opening of the epoxide ring leads to another radical intermediate **HCB-2** which is readily trapped by trialkyborane to generate intermediate **HCB-3** and another alkyl radical. Finally, the hydrolysis of intermediate **HCB-3** provides the corresponding allylic alcohol products.

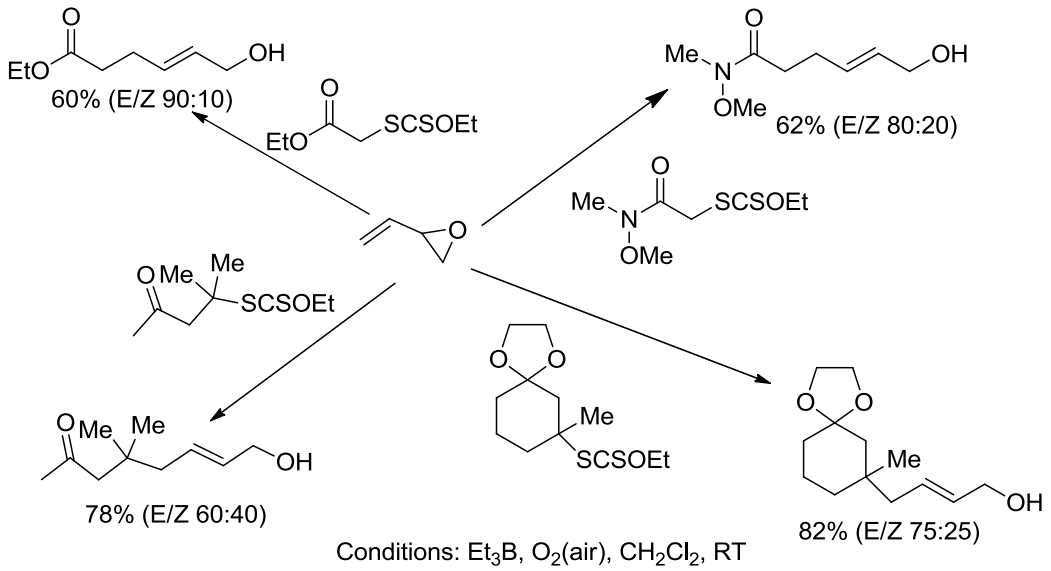


Scheme 3.45

5.3.2. Radical additions of xanthates to vinyl epoxides and related derivatives

The radical addition of xanthate to vinyl epoxides using triethylborane-air as the radical initiator was accomplished in our group.[117] As illustrated in Scheme 3.46, the addition of various xanthates to butadiene monoepoxide gave the corresponding allylic alcohols bearing a wide range of functional groups.

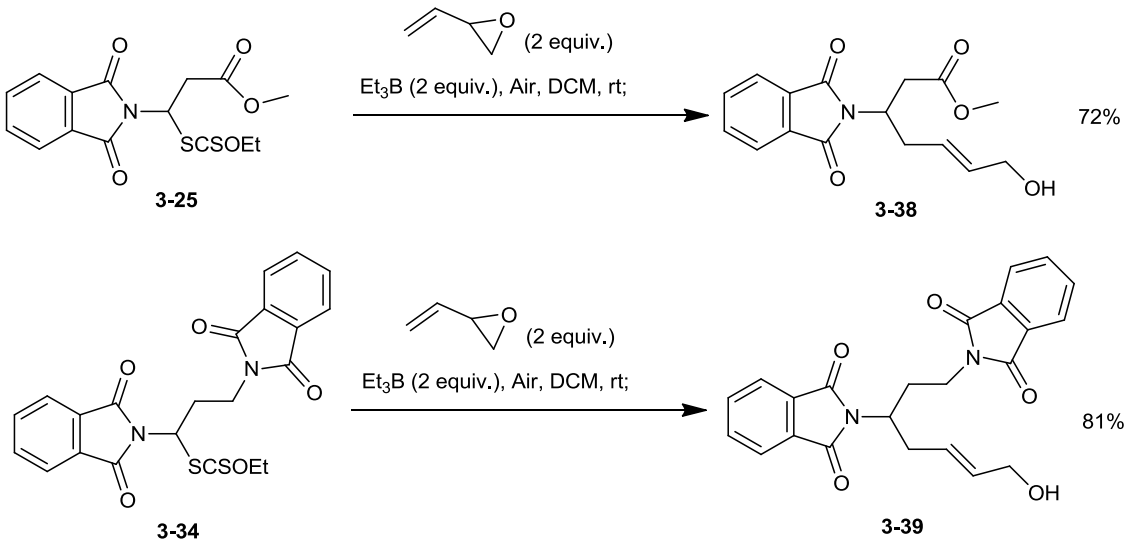
[117] Charrier, N.; Gravestock, D.; Zard, S. Z. *Angew. Chem. Int. Ed. Eng.* **2006**, *45*, 6520.



Scheme 3.46 Addition of various xanthates to butadiene monoepoxide

5.3.3. Radical synthesis of cyclic diamines

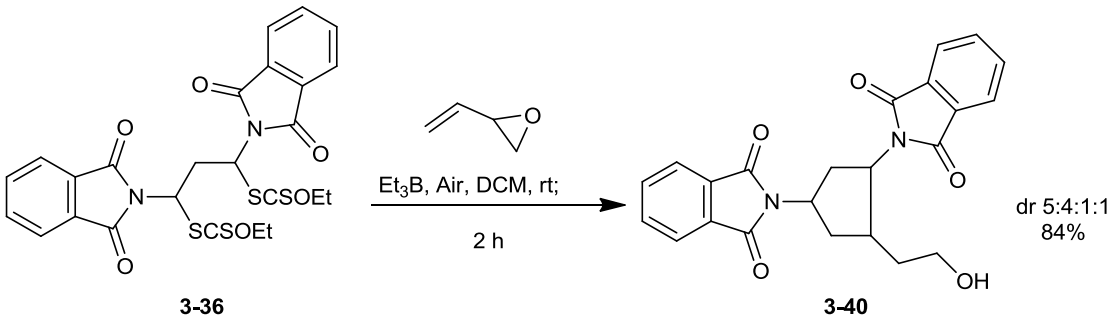
Based on this previous study, we tested the addition of xanthates **3-25** and **3-34** to butadiene monoepoxide via the same approach. The desired products **3-38** and **3-39** were obtained in high yield within two hours (Scheme 3.47).



Scheme 3.47 Radical addition of xanthate **3-25** and **3-34** to butadiene monoepoxide

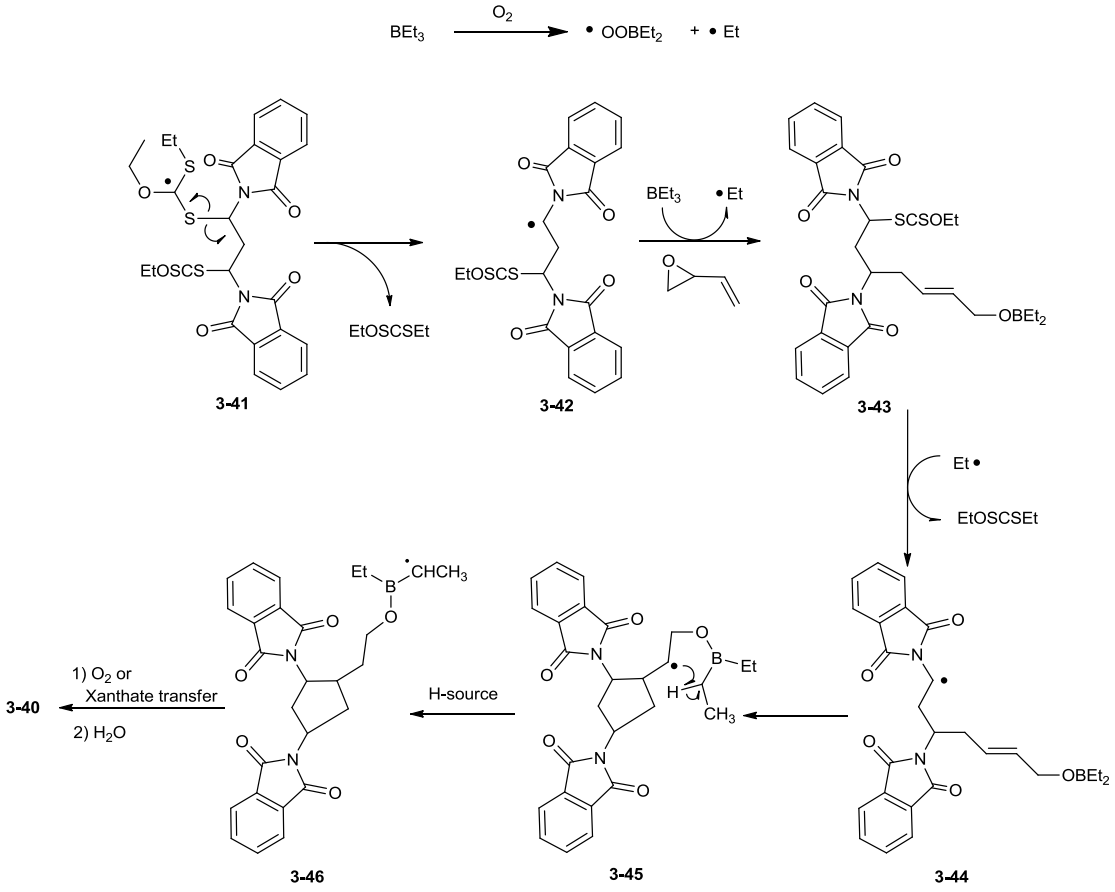
It should be more interesting to apply this protocol for the synthesis of cyclopentane-1,3-diamine derivatives such as **3-40** by using xanthate **3-36**, which may undergo an intermolecular addition followed by a cyclization step. Surprisingly,

radical reaction between xanthate **3-36** with butadiene monoepoxide quickly gave the cyclized reduced product directly in 84% yield (Scheme 3.48).



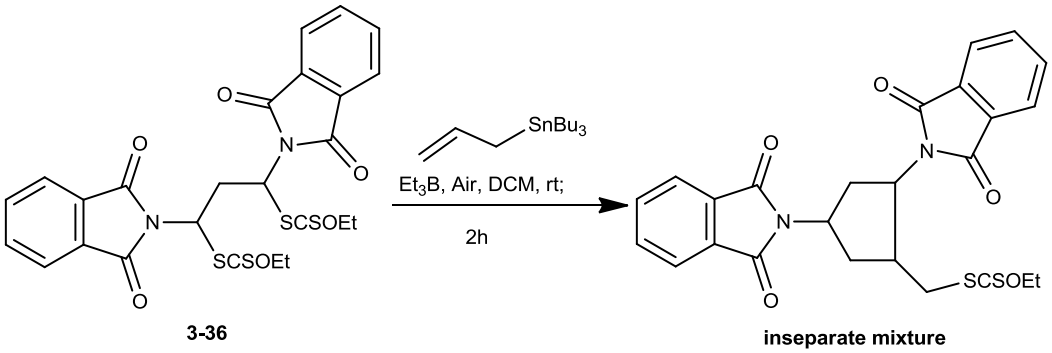
Scheme 3.48 Radical addition of xanthate **3-36** to butadiene monoepoxide

A plausible mechanism is proposed in Scheme 3.49. The autoxidation of triethylborane generates an ethyl radical which adds to the xanthate to give intermediate **3-41**. This then collapses to radical **3-42**, which is readily trapped by the butadiene monoepoxide to form a ring opened product **3-43** and another ethyl radical which ultimately exchanges the xanthate group to form radical intermediate **3-44**. The cyclization of the latter leads to **3-45** which then abstracts a hydrogen α to the boron. The resulting radical **3-46** either readily reacts with oxygen or exchanges a xanthate group. In either case, hydrolysis finally leads to the observed alcohol **3-40**. Radical **3-46** is stabilized by delocalization into the empty orbital on boron.



Scheme 3.49 Mechanism of radical addition between xanthate **3-36** and butadiene--monoepoxide

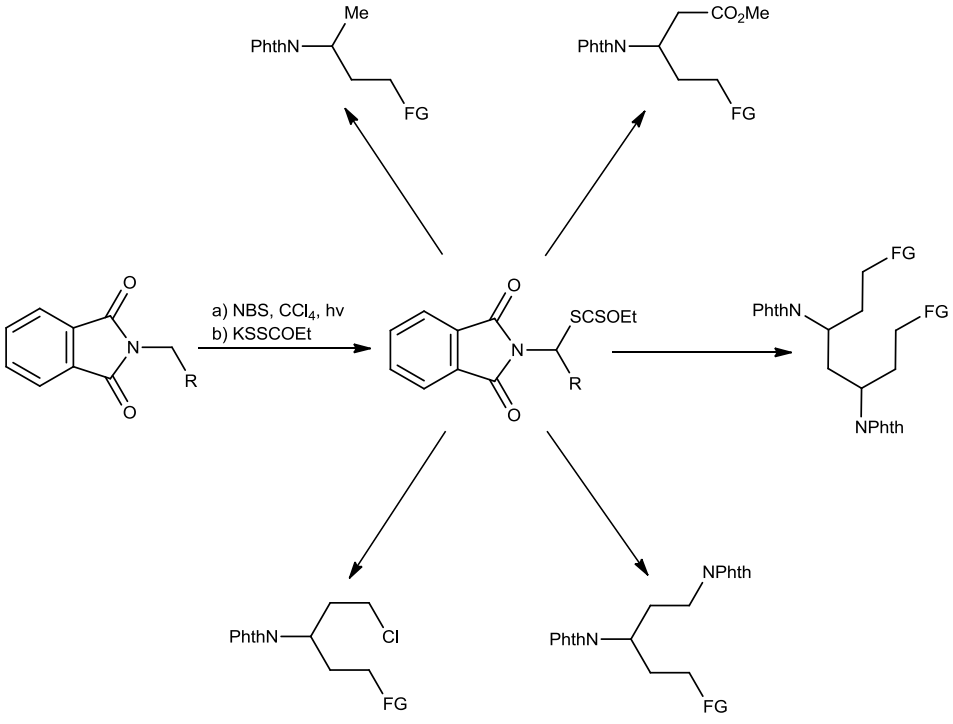
We expected that a similar radical reaction would occur between xanthate **3-36** and allyltributylstannane. Over the same period xanthate **3-36** was totally consumed, but only an inseparable mixture was obtained (Scheme 3.50). Therefore, it was difficult to tell what exactly occurred during this radical process from the NMR spectrum of the crude mixture.



Scheme 3.50 Addition of xanthate **3-36** to allyltributylstannane

Conclusion

In conclusion, this radical hydroaminomethylation process is based on an increasing stabilising effect provided by the phthalimido group. In previous studies, we have applied this feature to the synthesis of other amine derivatives, such as *β*-lactams, 1,4- and 1,5-diamines, *γ*-amino acids, *β*-aminoalcohols, 2-aminotetralines and triamines. In this study, by exploiting yet another radical reaction, the classical Wohl-Ziegler allylic bromination, the bromination of *N*-phthalimide protected amines has significantly extended the scope of this radical hydroaminoalkylation method. These novel xanthates derived from easily accessible primary amines have proved to be powerful tools for the preparation of *β*-aminoacids, alkylamines, 1,3-diamines and polyamines (Scheme 3.51). The present approach, in association with those of the previous studies, constitutes an extremely powerful, general and modular strategy for the fast preparation of highly functionalised amines.



Scheme 3.51