Synthesis of Amines via Ionic or Radical Methods

Introduction

Amines as fundamental species or moieties are ubiquitous in natural products or pharmaceutical compounds. For instance, chlorpromazine is a dopamine antagonist of the typical antipsychotic class of medications possessing additional antiadrenergic, antiserotonergic, anticholinergic and antihistaminergic properties used to treat schizophrenia; chlorpheniramine (brand name: Chlorphen-12), as a first-generation alkylamine antihistamine is used to prevent the symptoms of allergic conditions such as rhinitis and urticarial. Alkaloids, a vast family of natural products, contain by definition at least one basic nitrogen. Swainsonine, an indolizidine alkaloid, is a potent inhibitor of Golgi α-mannosidase II, an immunomodulator, and a potential chemotherapy drug; recently, Igarashi and co-workers reported a new pyrrolidine alkaloid, preussin B, that was isolated from the culture extract of the fungus *Simplicillium lanosoniveum* TAMA 173 (Figure 2.1).

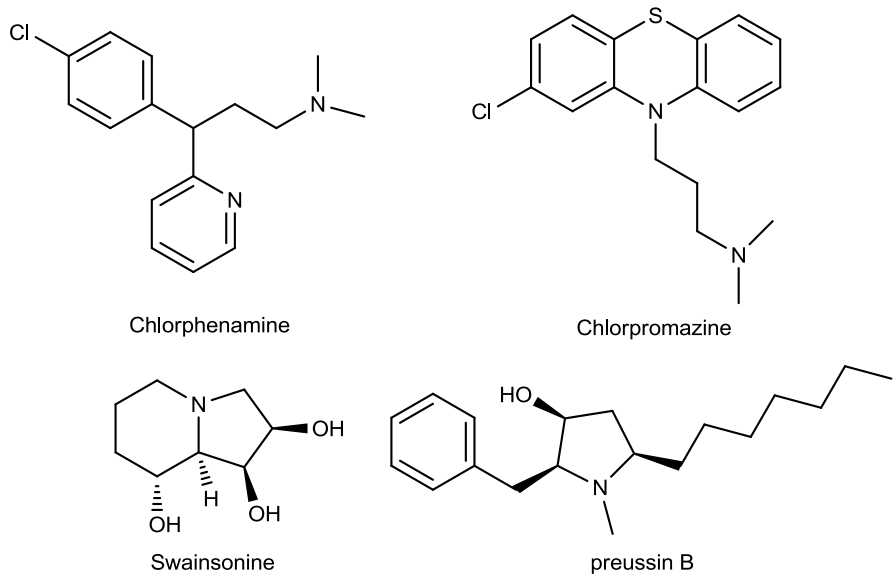
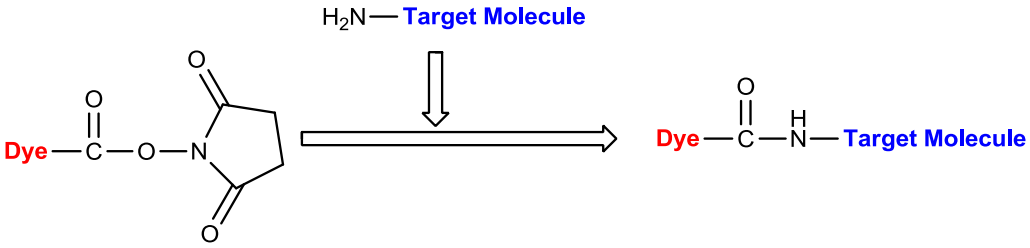


Figure 2.1 Examples of biologically active compounds containing amino-unit

In material science amines as starting materials are involved in the design of amine-reactive fluorescent dyes used to prepare bioconjugates for immunochemistry, fluorescence *in situ* hybridization (FISH), cell tracing, receptor labeling and

fluorescent analog cytochemistry. As illustrated in Scheme 2.1, there have been a large number of fluorescent amino-reactive dyes used to label various biomolecules.



Scheme 2.1 Label of biomolecules by fluorescent amino-reactive dye

While numerous methods for the preparation of functionalized amine have been reported over the decades, there is still a strong demand for new flexible routes to access complex amine derivatives. An observation made in our group demonstrated that a carbon radical can be stabilized by a phthalimido group, and thus the efficient intermolecular radical chain additions of phthalimido-substituted xanthates to various alkenes could be accomplished. As a result, we were encouraged us to apply this protocol in developing a more practical and general route to highly functionalized amines. In this chapter, our previous work on the preparation of phthalimido-substituted xanthates and xanthates containing other nitrogen group together with their applications in synthesis of functionalized amines will be briefly discussed.

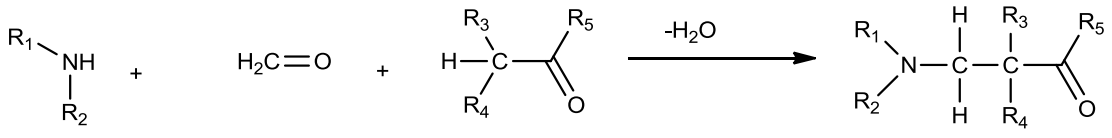
I. Amines synthesis

1. Named reactions in amine synthesis

Numerous classical named reactions are known for the synthesis of amines, such as the Mannich reaction, the Strecker Reaction, the Kabachnik-Fields reaction, the Buchwald-Hartwig cross-coupling, the Petasis boronic acid-Mannich Reaction, the Gabriel synthesis, the Delépine reaction, the Eschweiler-Clarke reaction, the Schmidt reaction, the Curtius rearrangement, the Sharpless asymmetric aminohydroxylation, and the Staudinger ketene cycloaddition.

1.1. The Mannich reaction

In 1903, Tollens and von Marle found that the reaction of acetophenone with formaldehyde and ammonium chloride resulted in the formation of a tertiary amine. Fourteen years later, Mannich studied the generality of this reaction.[42] The Mannich reaction can be considered as the addition a CH-activated compounds to iminium salts or imines which lead to the formation of a substituted β-amino-carbonyl compound known as a Mannich base (Scheme 2.2).[43] Nowadays, the Mannich-Reaction is widely applied in the synthesis of peptides, nucleotides, alkaloids and other amine related compounds.

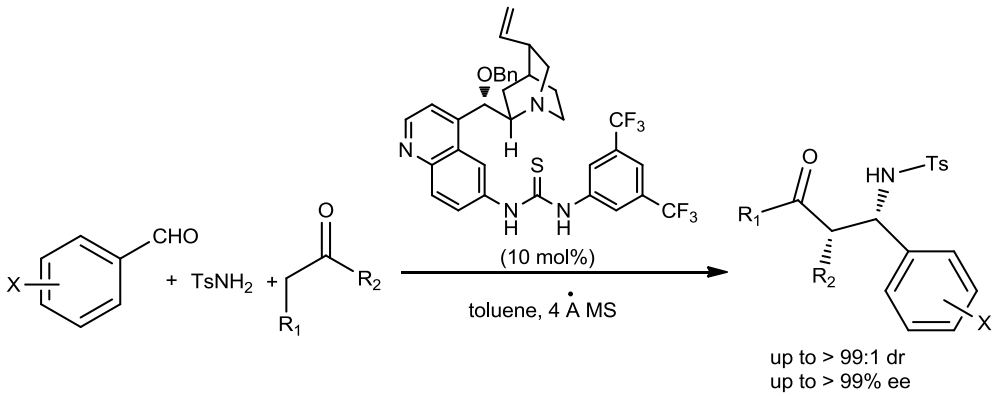


Scheme 2.2 Mannich reaction

Recently, Zhao and co-workers developed a highly enantioselective

[42] Mannich, C.; Krösche, W. *Arch. Pharm. Pharm. Med. Chem.* **1912**, *250*, 647.
[43] Cummings, T. F.; Shelton, J. R., *J. Org. Chem.* **1960**, *25*, 419.

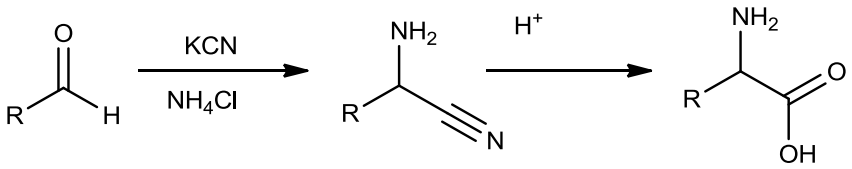
three-components directed Mannich reaction of unfunctionalized ketones.[44] As shown in Scheme 2.3, this multicomponent Mannich reaction consists of an aromatic aldehyde, *p*-toluenesulfonamide, and an unfunctionalized ketone. It was the first time a bifunctional quinidine thiourea was used as a Bronsted base catalyst to accomplish a highly diastereoselective and enantioselective Mannich reaction.



Scheme 2.3 Bronsted base catalyzed Mannich reaction

1.2. The Strecker Reaction

In 1850, A. Strecker devised the first laboratory method to access α-amino acids. The condensation of an aldehyde with ammonium chloride in the presence of cyanide generates an α-aminonitrile and hydrolysis finishes the desired α-amino-acid (Scheme 2.4).[45] The development of the Strecker reaction allows the use of ammonia, primary, or secondary amines and both ketones and aldehydes as substrates. The Strecker reaction has proved to be a powerful tool for the synthesis of amino acids.

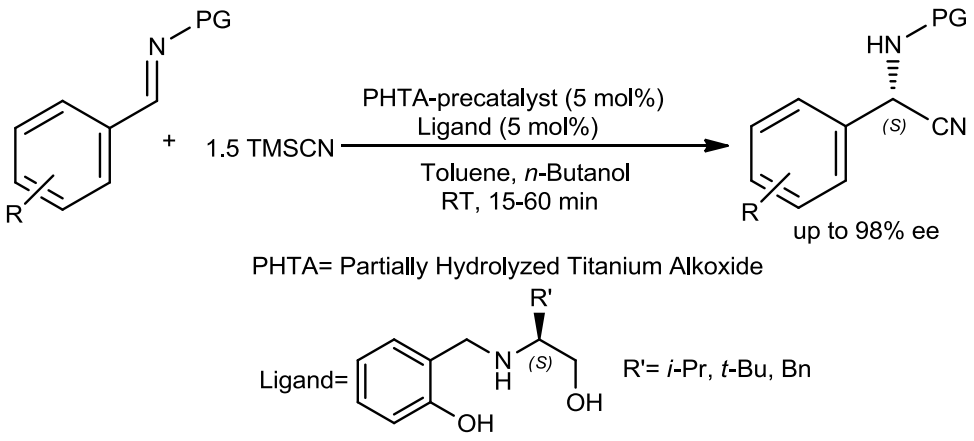


Scheme 2.4 Strecker reaction

[44] Guo, Q.; Zhao, J. C.-G. *Org. Lett.*, **2013**, *15*, 508.

[45] (a) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27. (b) Strecker, A. *Ann. Chem. Pharm.* **1854**, *91*, 349.

However, the enantioselective synthesis of aminonitriles remains a quite challenging issue. A highly enantioselective titanium-catalyzed cyanation of imines at room temperature was recently described by Chai and co-workers (Scheme 2.5).[46] The reaction of various *N*-protected imines with TMSCN was catalyzed by a partially hydrolyzed titanium alkoxide precatalyst together with a readily available *N*-salicyl-*β*-aminoalcohol ligand to form the corresponding aminonitrile with high enantioselectivity.



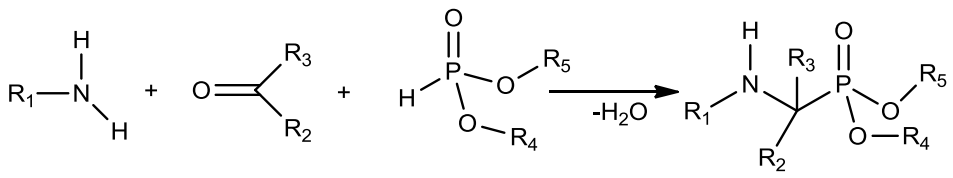
Scheme 2.5 Titanium-catalyzed Strecker reaction

1.3. The Kabachnik-Fields reaction

This multi-component reaction was concurrently reported by Kabachnik and Fields in 1952 (Scheme 2.6). This one pot process involves the reaction of amines, carbonyl compounds and dialkyl phosphonates to form α-amino phosphonates and their derivatives, which are useful as chelating agents.[47]

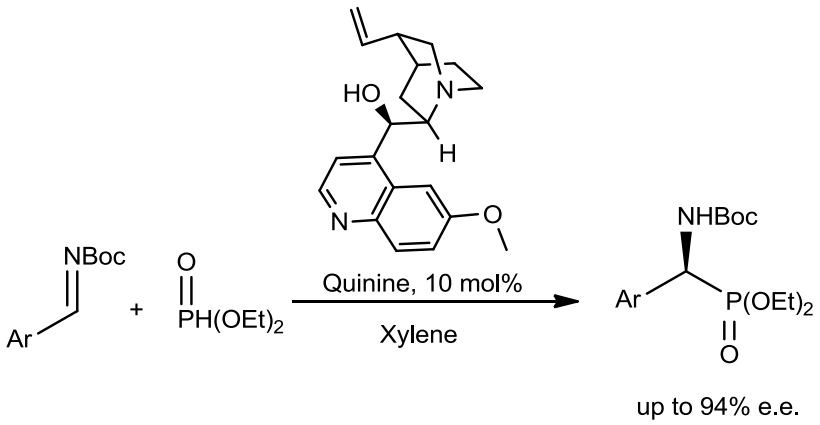
[46] Seayad, A. M.; Ramalingam, B.; Yushinaga, K.; Nagata, T.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 264.

[47] (a) Kabachnik, M.I.; Medved, T.Y. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 689. (b) Fields, E.K. *J.Am. Chem. Soc*. **1952**, *74*, 1528.



Scheme 2.6 Kabachnik-Fields reaction

A recent study of the organocatalytic asymmetric hydrophosphonylation of imines by Ricci and co-workers resulted in the synthesis of enantiomerically enriched *α*-amino phosphonic acid derivatives in a simple and efficient manner (Scheme 2.7).[48] The readily available quinine (10 mol%) as the catalyst for the addition of diethyl phosphate to *N*-Boc protected imines ensured the high enantioselectivity.



Scheme 2.7 Organocatalytic asymmetric hydrophosphonylation of imines

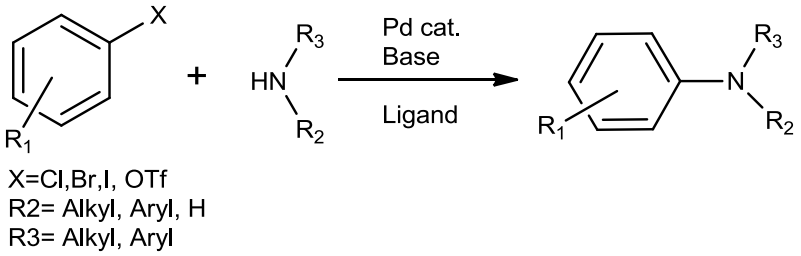
1.4. The Buchwald-Hartwig Cross-Coupling

C-N bond formation via palladium-catalyzed cross-coupling of aryl halides or trifluoromethanesulfonates with amines in the presence of base is known as the Buchwald-Harwig cross-coupling (Scheme 2.8).[49] Between 1994 and the late 2000s Buchwald and Hartwig established the scope of this aromatic C-N bond formation.

[48] Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.*, **2006**, *71*, 6269.

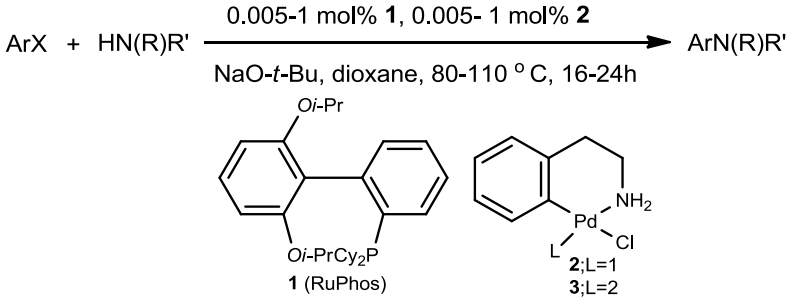
[49] (a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

Indeed, the Buchwald-Harwig cross-coupling has been widely applied for the formation of aryl C-N bonds in the synthesis of pharmaceuticals and natural products.



Scheme 2.8 Buchwald-Hartwig cross-coupling

Recently, a multiligand based Pd catalyst for the C−N cross-coupling reaction was investigated by Buchwald and co-workers (Scheme 2.9). This Pd catalyst system was based on two biarylphosphine ligands, which demonstrated that two ligands together could display higher reactivity than either of them exhibited separately.[50] This multiligand based Pd catalyst system opens up an interesting approach for catalyst development.



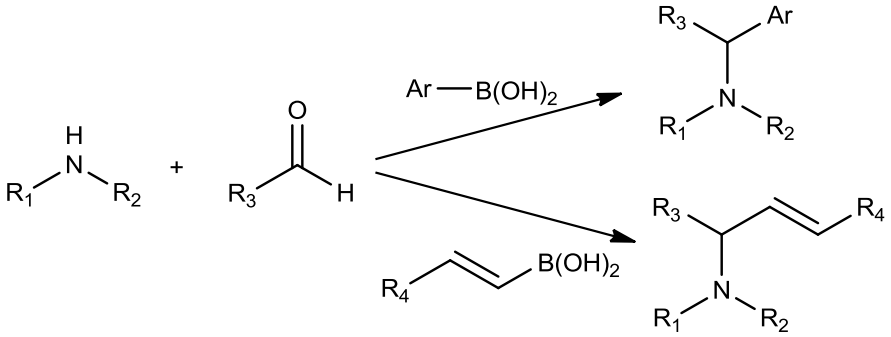
Scheme 2.9 Multiligand based Pd catalyst system

1.5. The Petasis Boronic Acid-Mannich reaction

In 1993, Petasis and co-workers reported a practical way towards the synthesis of allylic amines or amino-acids which may be considered as a variation of Mannich

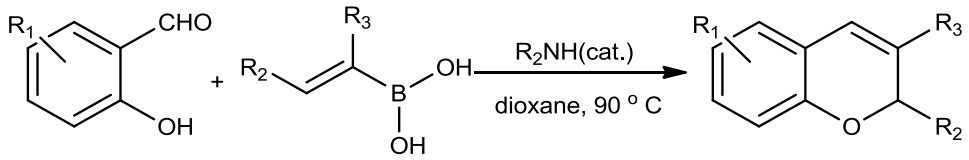
[50] Fors, B. P., Buchwald, S. L. *J. Am. Chem. Soc.*, **2010**, *132*, 15914.

reaction (Scheme 2.10).[51] In this multicomponent reaction, the boronic acid serves as the nucleophile and plays the same role as the enolizable ketone component in the Mannich reaction.



Scheme 2.10 Petasis Boronic Acid-Mannich Reaction

One application of the Petasis reaction for the synthesis of 2*H*-chromenes was studied by Finn and co-workers (Scheme 2.11).[52] Vinylic or aromatic boronic acids, o-phenolic aldehydes, and amines together underwent condensation and cyclization to form highly diverse 2*H*-chromenes. It appears that the successful condensation is assisted by the hydroxyl group adjacent to the aldehyde moiety.



Scheme 2.11 Synthesis of 2*H*-chromenes

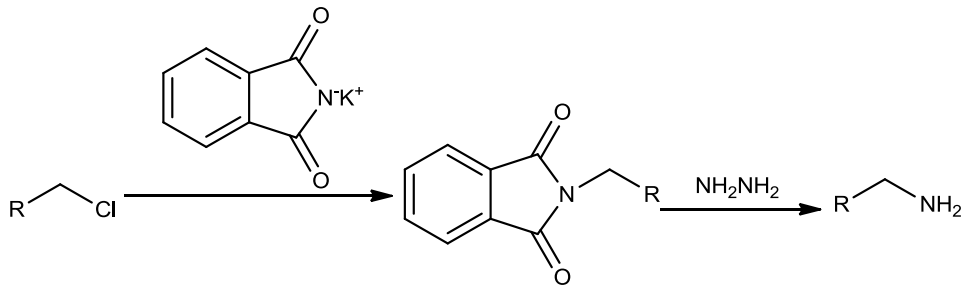
1.6. The Gabriel synthesis

The use of potassium phthalimide as the nitrogen source and nucleophile to react with alkyl halides was initially described in 1884, but later, in 1887, Gabriel studied

[51] (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett*. **1993**, *34*, 583–586. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1997**, *119*, 445–446. (c) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463–16470. (d) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1998**, *120*, 11798.

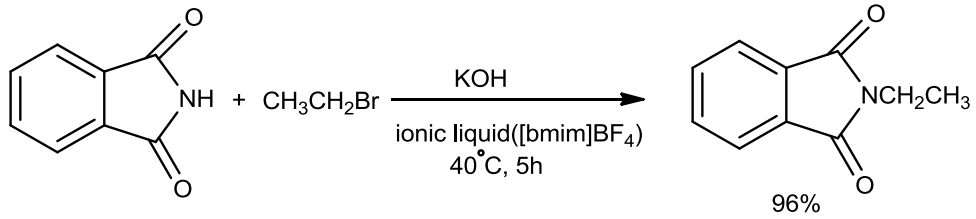
[52] Wang, Q.; Finn, M. G. *Org. Lett.*, **2000**, *2*, 4063.

the generality of this process (Scheme 2.12).[53] Various primary amines can be easily obtained from the corresponding alkyl halides by a simple two steps sequence.



Scheme 2.12 Gabriel synthesis

Chen and co-workers proposed a modification of the Gabriel synthesis (Scheme 2.13). The alkylation of the phthalimide is done in ionic liquids such as [bmim] BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate) by using potassium hydroxide as the base.[54] Lower reaction temperatures, higher yields and reaction rates were achieved by using ionic liquids as the solvent.



Scheme 2.13 Gabriel synthesis in ionic liquids

The use of azide as the nucleophile is also a convenient route to amines, especially in small scale work. The azide group is then easily converted into an amine by various reducing agents.

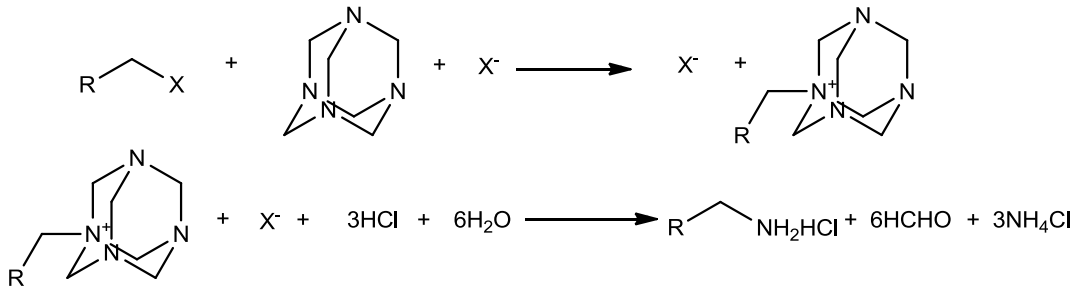
1.7. Delépine reaction

In 1895, the French chemist Delépine initially reported this practical way to

[53] Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2224.

[54] Le, Z.; Chen, Z.; Hu, Y.; Zheng, Q. *Synthesis*, **2004**, 208.

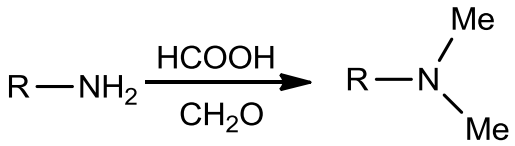
access primary amines (Scheme 2.14). Compared with the Gabriel synthesis, the Delépine reaction introduces an amino unit by using urotropine, which also behaves like an amine nucleophile. The hydrolysis of the quaternary ammonium salt was assisted by acid.[55]



Scheme 2.14 Delépine reaction

1.8. The Eschweiler-Clarke reaction

Since Leuckart reported the first reductive alkylation of an amine in 1885, Eschweiler and Clarke found that formaldehyde could introduce a methyl group to a primary or a secondary amine to furnish the corresponding tertiary amine in one-pot, which is essentially an amine methylation process (Scheme 2.15).[56]



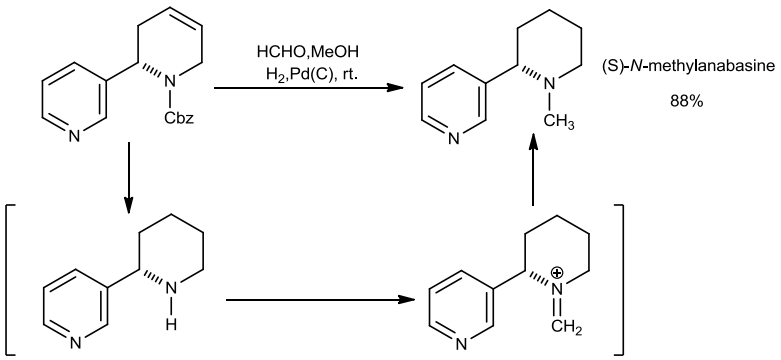
Scheme 2.15 Eschweiler-Clarke reaction

During the enantioselective total syntheses of several piperidine and pyrrolidine alkaloids involving an Eschweiler-Clarke reaction, Lebreton and co-workers completed the total synthesis of (S)-*N*-methylanabasine at room temperature in high

[55] Brandänge, S.; Rodriquez, B. *Synthesis*, **1988**, 347-348.

[56] (a) Eschweiler, W. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 880. (b) Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571. (c) Moore, M. L. *Org. React.* **1949**, *5*, 301. (d) Pine, S. H.; Sanchez, B. L. *J. Org. Chem.* **1971**, *36*, 829.

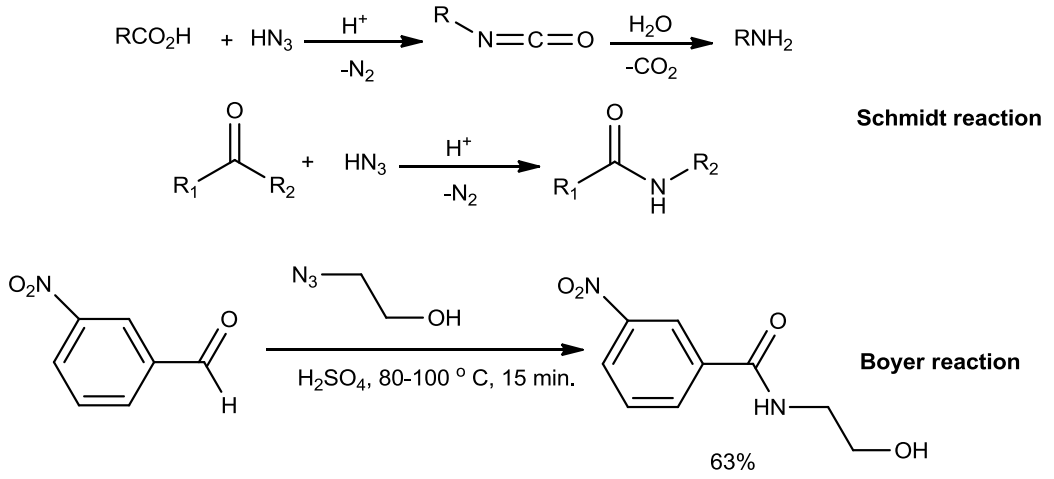
yield (Scheme 2.16).[57]



Scheme 2.16 Synthesis of (S)-*N*-methylanabasine

1.9. The Schmidt reaction

In 1923, Schmidt found a C-to N alkyl migration in an acyl azide with the loss of nitrogen (Scheme 2.17). Unlike the related Curtius and Hoffmann rearrangements, this reaction is completed in one single step from carboxylic acids.[58] Later in 1955, Boyer extended the scope of this reaction by using alkyl azides.[59]



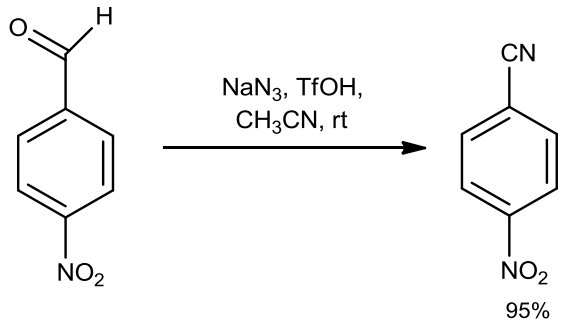
Scheme 2.17 Schmidt reaction

[57] Felpin, F. X.; Girard, S.; Vo-Thanh, G.; Robins, R.J.; Villieras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305.

[58] (a) Schmidt, K. F. Z. *Angew. Chem.* **1923**, *36*, 511. (b) Schmidt, K. F. *Ber. dtsch. Chem. Ges.* **1924**, *57*, 704.

[59] Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951.

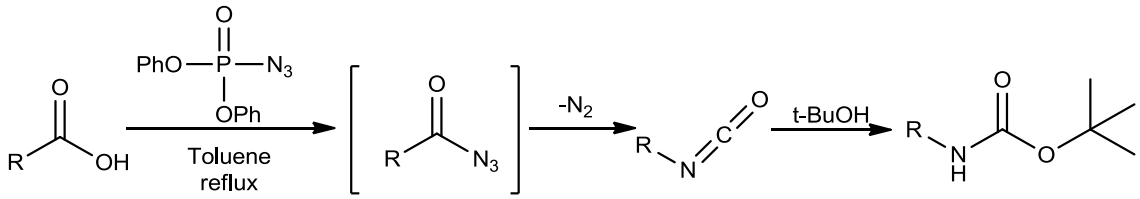
The Schmidt reaction of aldehydes results in the formation of mixtures of the corresponding formanilides and nitriles, and this remains a problem. Recently, a chemoselective Schmidt reaction mediated by trifluoromethanesulfonic acid converts aldehydes into nitriles as the sole products and is described by Prabhu and co-workers (Scheme 2.18).[60]



Scheme 2.18 Schmidt reaction mediated by trifluoromethanesulfonic acid

1.10. The Curtius rearrangement

The rearrangement of an acyl azide to an isocyanate was first discovered by Curtius in 1890 and is now known as the Curtius rearrangement (Scheme 2.19).[61] Following loss of nitrogen, the isocyanate intermediate can be trapped by different nucleophiles such as water, amines or alcohols. In the case of water as the nucleophile, a primary amine can be obtained. The Curtius rearrangement has found wide application in organic synthesis, especially in the total synthesis of natural products.



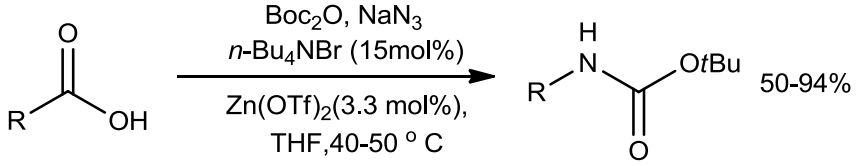
Scheme 2.19 Curtius rearrangement

A mild and efficient one pot Curtius rearrangement was reported by Leogane and

[60] Rokade, B. V., Prabhu, J. R., *J. Org. Chem.*, **2012**, *77*, 5364-5370.

[61] (a) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023. (b) Curtius, T. *J. Prakt. Chem.* **1894**, *50*, 275.

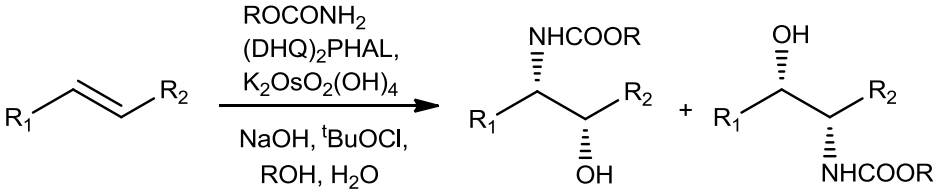
co-workers (Scheme 2.20).[62] Instead of diphenylphosphorazidate, they used sodium azide to work with di-*tert*-butyl dicarbonate and carboxylic acid to form the acyl azide intermediate followed by the assistance of tetrabutylammonium bromide and zinc (II) triflate to provide the *N*-Boc-protected amines.



Scheme 2.20 Curtius rearrangement by using sodium azide

1.11. The Sharpless asymmetric aminohydroxylation

The transformation of simple alkenes into protected amino alcohols in an enantioselective manner was reported by Sharpless et al. in 1996. It is now known as the Sharpless asymmetric aminohydroxylation (Scheme 2.21).[63] Since *β*-amino alcohols are important fragments in many biologically interesting compounds, this method has found application in the development of pharmaceutical libraries and in the stereocontrolled total synthesis of natural products.



Scheme 2.21 Sharpless asymmetric aminohydroxylation

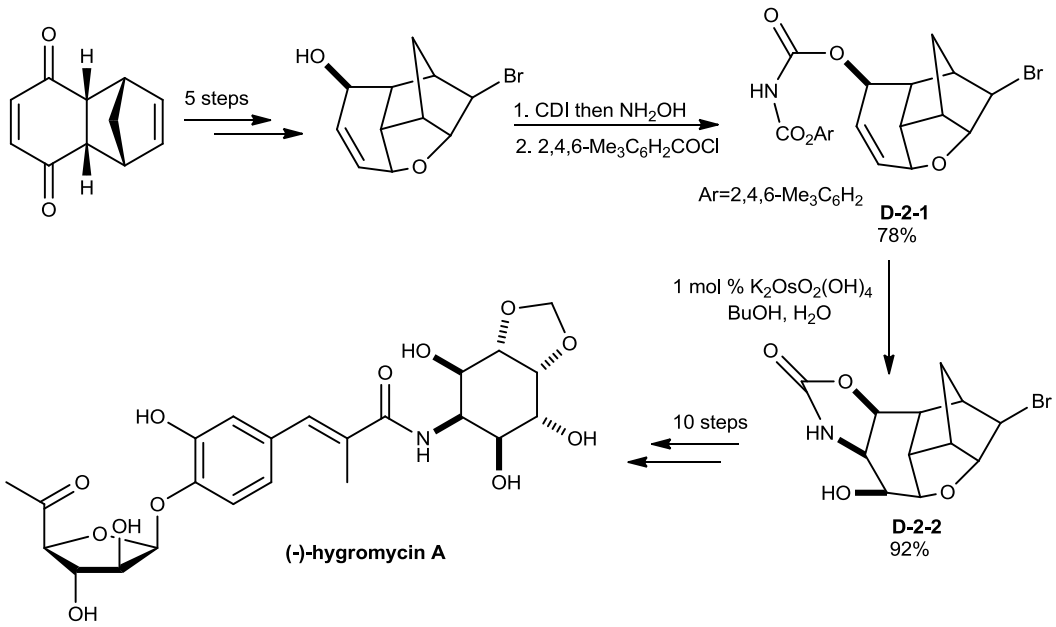
Thus, during the total synthesis of (-)-hygromycin A, Donohoe and co-workers accomplished the transformation of **D-2-1** into **D-2-2** via a Sharpless asymmetric aminohydroxylation (Scheme 2.22).[64] In the presence of catalytic amount of

[62] Lebel, H.; Leogane, O. *Org. Lett.*, **2005**, *7*, 4107.

[63] (a) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1997**, *36*, 1483. (b) Mcleod, M. D.; Bodkin, J. A. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 2733.

[64] Donohoe, T. J.; Flores, A.; Bataille, C. J. R.; Churruca, F. *Angew. Chem. Int. Ed.* **2009**, *121*,

potassium osmate (1 mol %), **D-2-1** was converted into **D-2-2** in aqueous butanol at room temperature in high yield.



Scheme 2.22 Total synthesis of (-)-hygromycin A

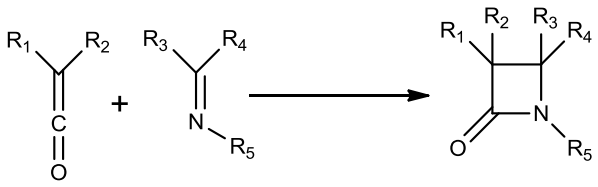
1.12. The Staudinger ketene cycloaddition

β-Lactams can be formed by a formal [2+2]-cycloaddition of imines to ketenes, and this transformation was initially reported by Staudinger in 1907. Either the ketene or the imine can act as the nucleophile or the electrophile in this reaction (Scheme 2.23). [65] Besides imines, compounds such as alkenes, ketones, acetylenes, thiocarbonyls, isocyanates, carbodiimides, *N*-sulfinylamines, nitroso- and azo-derivatives can also react with ketenes to form four-membered ring derivatives.[66]

6629.

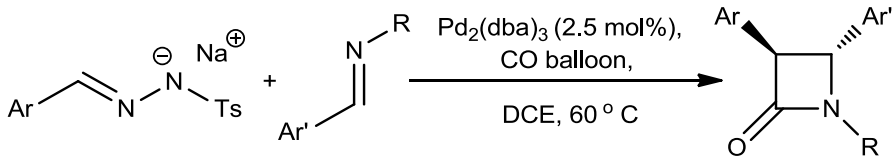
[65] Staudinger, H. *Ber*. **1907**, *40*, 1145.

[66] (a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.*, **2002**, *124*, 1578. (b) Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060.



Scheme 2.23 Staudinger ketene cycloaddition

Recently, a new Pd-catalyzed tandem carbonylation-Staudinger cycloaddtion method was established by Wang and co-workers (Scheme 2.24).[67] The ketene intermediate was formed by heating *α*-diazo-carbonyl compounds or *N*-tosylhydrazone salts in the presence of a palladium catalyst and CO. Then various nucleophiles underwent the cycloaddition with the ketene intermediates to give *β*-lactam derivatives with excellent *trans* diastereoselectivity.



Scheme 2.24 Pd-Catalyzed tandem carbonylation-Staudinger cycloaddtion

2. The hydroaminomethylation of alkenes

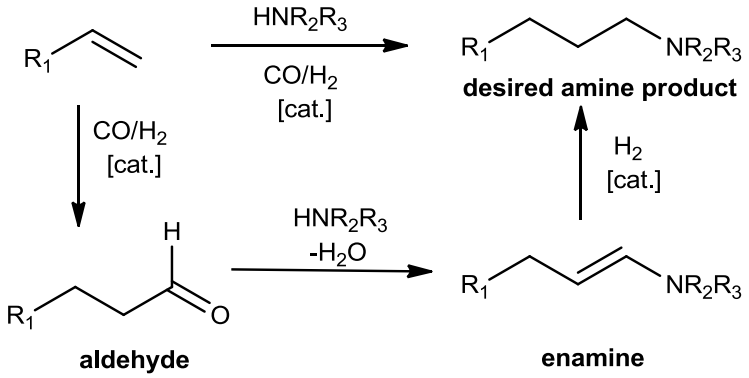
Although both the hydroamination and the hydrocyanation of alkenes have atom efficiencies of 100%, their application in industrial processes for the production of amines usually results in large amounts of waste, together with other problems. In contrast, the hydroaminomethylation of alkenes as an alternative method, initially reported by Reppe in 1949 at BASF, has a greater potential for commercial application.[68]

As described in Scheme 2.25, the hydroaminomethylation of alkenes is usually a one-pot cascade reaction consisting in a hydroformylation and a reductive amination

[67] Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330.

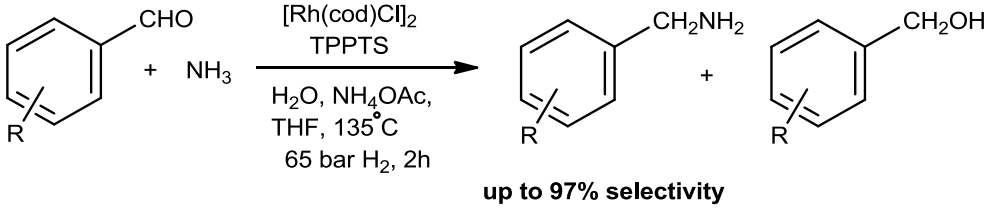
[68] (a) Reppe, W.; Vetter, H. *Liebigs Ann. Chem.* **1953**, *582*, 133. (b) Reppe, W. *Experientia* **1949**, *5*, 93. (c) Crozet, D.; Urrutigoity, M.; Kalck, P. *ChemCatChem* **2011**, *3*, 1102.

to produce the desired amine. In this reaction, primary and secondary amines can be used as the nitrogen sources; however, due to the higher nucleophilicity of primary amines compared to ammonia, the direct use of ammonia in hydroaminomethylation to produce primary amines is still a quite challenging task.



Scheme 2.25 Hydroaminomethylation of alkenes

The first examples of a reductive amination with ammonia were reported by Beller and co-workers in the early 2000s (Scheme 2.26).[69] In a biphasic system the transformation of benzaldehydes to benzylamines was achieved by using an Rh-catalyst together with water-soluble phosphine and ammonium acetate. The high yield and up to 97% selectivity of this reaction made it extremely powerful to produce benzylamines.



TPPTS= tri sodium salt of meta trisulfonated triphenylphosphine

Scheme 2.26 Reductive amination of benzaldehyde using a Rh-catalyzed process

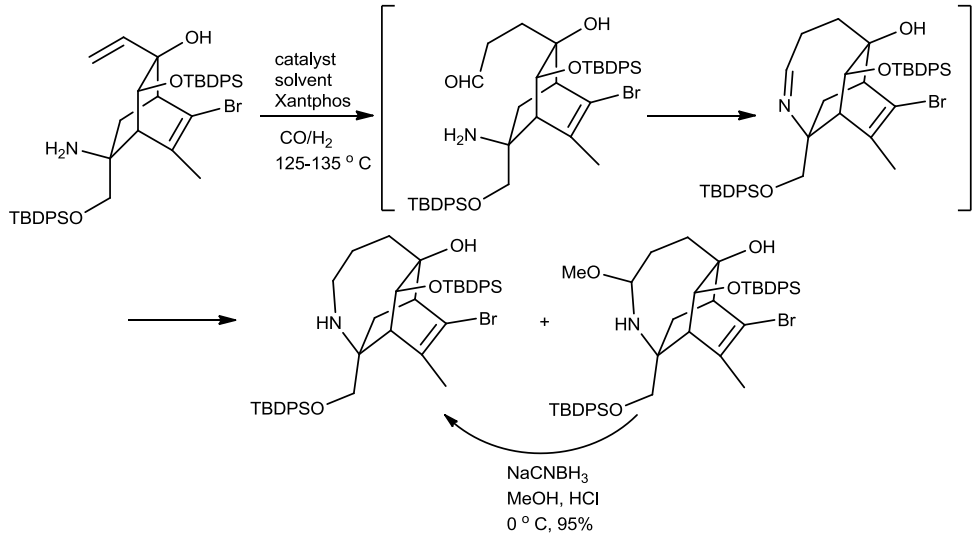
Recent improvements of the hydroaminomethylation of alkenes by the design of efficient metal catalysts open numerous opportunities for the synthesis of amines,

[69] Gross, T.; Seayad, A.M.; Ahmed, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055.

which will emerge in the future.

2.1. Intramolecular hydroaminomethylation of alkenes

The intramolecular hydroaminomethylation has gained importance for the building of nitrogen-containing heterocycles, such as pyrrolidines, piperidines and azepines.[70] As illustrated in Scheme 2.27, during the synthesis of the lycopladine H, Weinreb and co-workers constructed an eight membered azocane ring via an intramolecular hydroaminomethylation.[71]



Scheme 2.27 Synthesis of the lycopladine H

2.2. Hydroaminomethylation of alkenes based on rhodium-catalyzed process

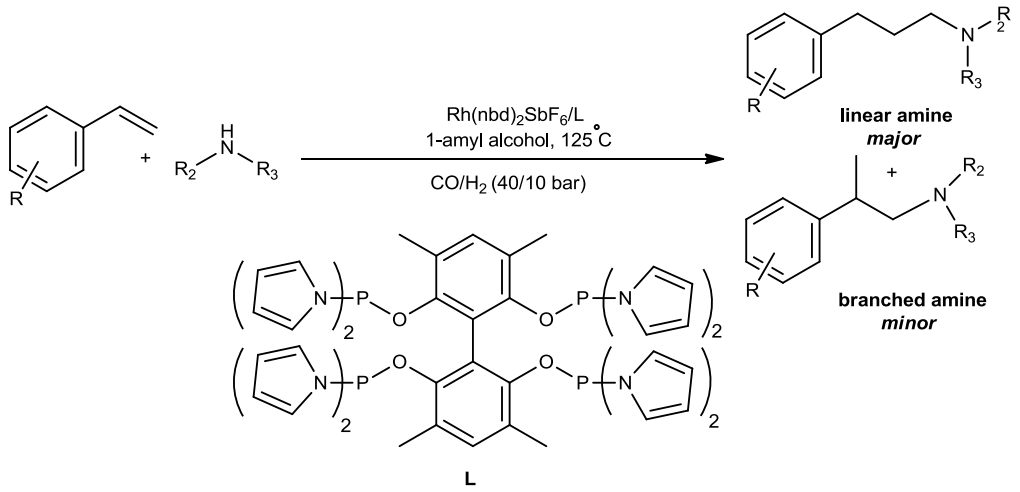
Due to the intrinsic tendency to form the branched amines, the selectivity between the linear and branched amines in hydroaminomethylations, especially for hydroaminomethylation of styrenes, remains challenging.[72] Recently, an efficient,

[70] (a) Eilbracht, P.; Barfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. (b)Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

[71] Sacher, J. R.; Weinreb, S. M. *Org. Lett.* **2012**, *14*, 2172.

[72] (a) Lin, Y.-S.; Ali, B. E.; Alper, H. *Tetrahedron Lett.* 2001, *42*, 2423. (b) Kostas, I. D. *J. Chem. Res. (S)* **1999**, 630. (c) Kostas, I. D.; Screttas, C. G. *J. Organomet. Chem.* **1999**, *585*, 1. (d) Seayad, A. M.; Selvakumar, K.; Ahmed, M.; Beller, M. *Tetrahedron Lett.* **2003**, *44*, 1679. (e) Routaboul, L.; Buch, C.; Klein, H.; Jackstell, R.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 7401. (f) Sun, Y.; Ahmed,

highly linear-selective hydroaminomethylation (*l/b* up to >99:1) of styrenes involving in $Rh(nbd)_2SbF_6$ together with a pyrrole-based 3,3',5,5'-substituted tetraphosphorus ligand as the catalyst was reported by Zhang and co-workers. This is so far the highest liner selectivity observed (Scheme 2.28).[73]



Scheme 2.28 Linear selective hydroaminomethylation of styrenes

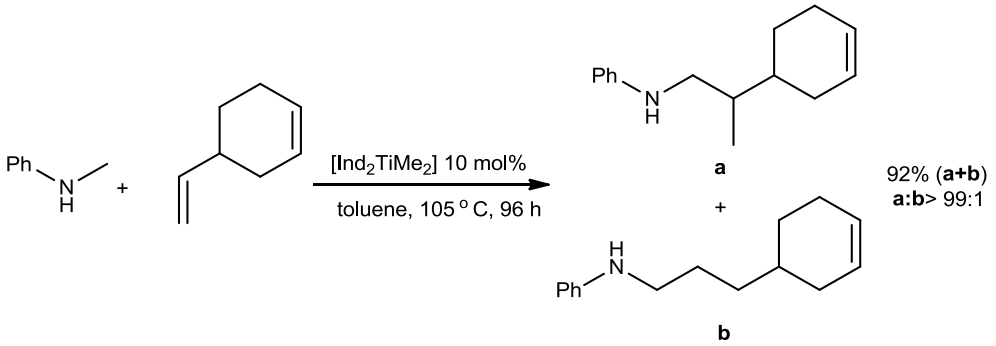
2.3. Hydroaminomethylation of alkenes based on titanium-catalyzed process

Traditionally, the hydroaminomethylation of alkenes was mainly based on Rhodium catalyzed processes. Recently, Doye and co-workers reported an efficient hydroaminomethylation of alkenes based on titanium catalysts to achieve a high branched amine selectivity at low temperature (Scheme 2.29).[74] For example, the reaction of 4-vinylcyclohex-1-ene with *N*-methylaniline can be mediated by a catalytic amount of Ind_2TiMe_2 and provides a regioselectivity > 99:1 at 80 ℃ within 24h.

M.; Jackstell, R.; Beller, M.; Thiel, W. R. *Organometallics* **2004**, *23*, 5260.

[73] Li, S., Huang, K., Zhang, J., Wu, W., Zhang, X. *Org. Lett*. **2013**, *15*, 3078.

[74] Kubiak, R., Prochnow, I., Doye, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 2626.

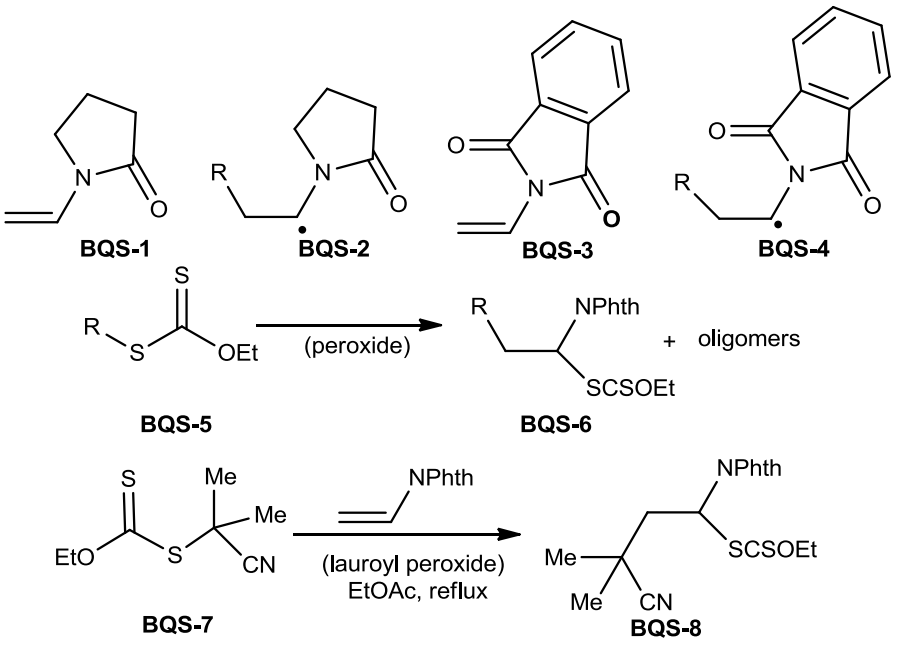


Scheme 2.29 Titanium catalyzed hydroaminomethylation of alkenes

II Applications of xanthate chemistry in amine synthesis

1. *S*-phthalimidomethyl xanthate

An interesting observation was disclosed by our group: the radical addition of *N*-vinyl phthalimide **BQS-3** with many xanthates formed mostly oligomers other than the desired adducts **BQS-6**, in contrast to *N*-vinyl pyrrolidone **BQS-1** which underwent generally an efficient addition (Scheme 2.30). Only the addition of *N*-vinyl phthalimide with **BQS-7** could secure a good yield of **BQS-8** under usual conditions. From these results, it appears that adduct radical **BQS-4** was more stable than adduct radical **BQS-2**. At first glance comparing **BQS-4** and **BQS-2,** one might consider the electron density on the nitrogen of **BQS-2** to be higher than that of **BQS-4**. Therefore, an investigation was undertaken by our group to further explore this unanticipated observation.[75]

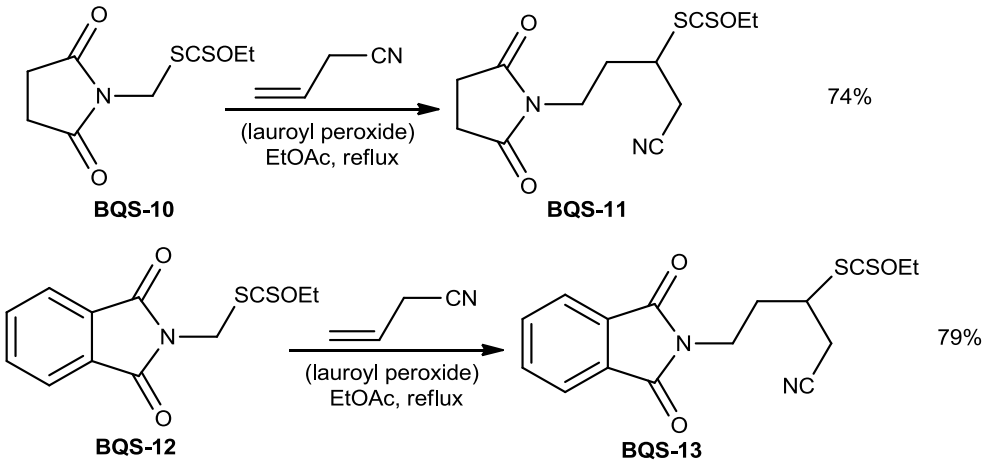


Scheme 2.30 Addition of xanthate to *N*-vinyl phthalimide

The results shown in Scheme 2.31 demonstrated that the aromatic ring had only a

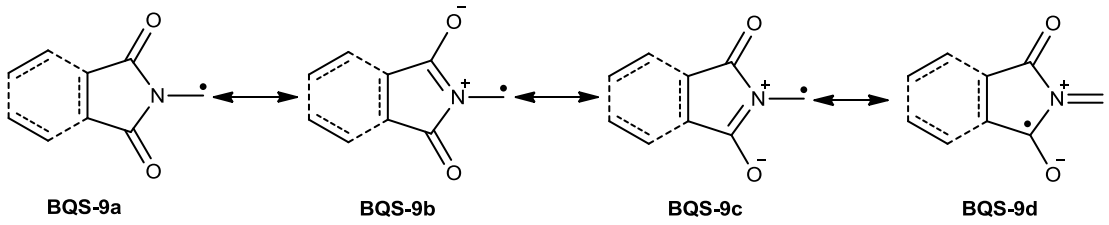
[75] Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279.

limited effect on the efficiency of the process, which turned our attention to the effect of the second carbonyl group.



Scheme 2.31 Addition of xanthate **BQS-10** and **BQS-12** to allyl cyanide

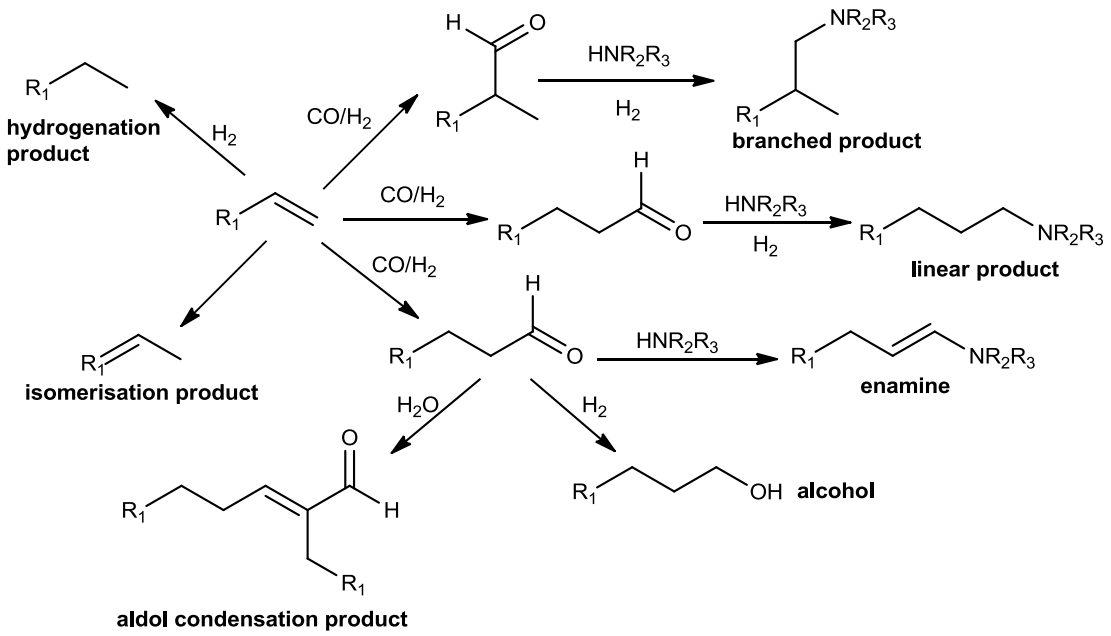
By closely studying the resonance structures of radical intermediate **BQS-9** (Scheme 2.32), the structures of contributors **9b**, **9c** and **9d** where the radical appears to benefit some allylic character, can give us a plausible explanation: the more extended delocalization has small but sufficient stabilizing effect on radical **BQS-9** to allow the formation of the desired products instead of unwanted oligomers.



Scheme 2.32 Resonance structures of radical intermediate **BQS-9**

Hydroaminomethylation, as a powerful tool for the synthesis of amines, was introduced in the previous paragraph. However, because the higher nucleophilic property of the primary amine product towards the aldehyde generated in the hydroformylation step, undesired amine products are observed in hydroaminomethylation with ammonia. Furthermore the lack of selectivity between

linear and branched products as shown in Scheme 2.33 along with all other possible side reactions may lead to unsurmountable complexity.[76] These drawbacks make the chemical amino methylation of alkenes a less useful method for the synthesis of amines.

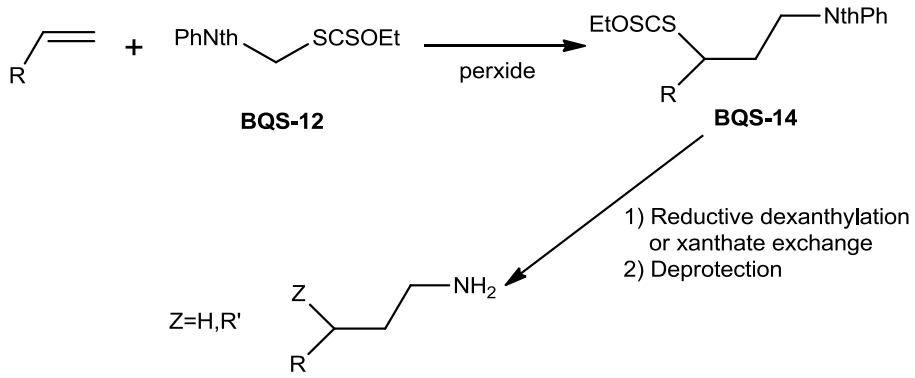


Scheme 2.33 Side reactions in hydroaminomethylation process

In contrast to the hydroaminomethylation based on metal catalyst and related methods, the approach based on xanthate chemistry outlined in Scheme 2.34 leads to the desired primary amines in a very straightforward manner and overcomes the problems mentioned above. The addition of xanthate **BQS-12** to various even unactivated olefins gives adducts **BQS-14**, and the xanthate group can be removed easily or made to undergo another radical reaction to produce more complex protected primary amines. Furthermore, the deprotection of the phthalimido by hydrazine or other suitable reagents makes the whole process strictly equal to a hydroaminomethylation of an alkene (Scheme 2.34). Therefore, the successful addition of xanthate **BQS-12** to various olefins opens up numerous possibilities to

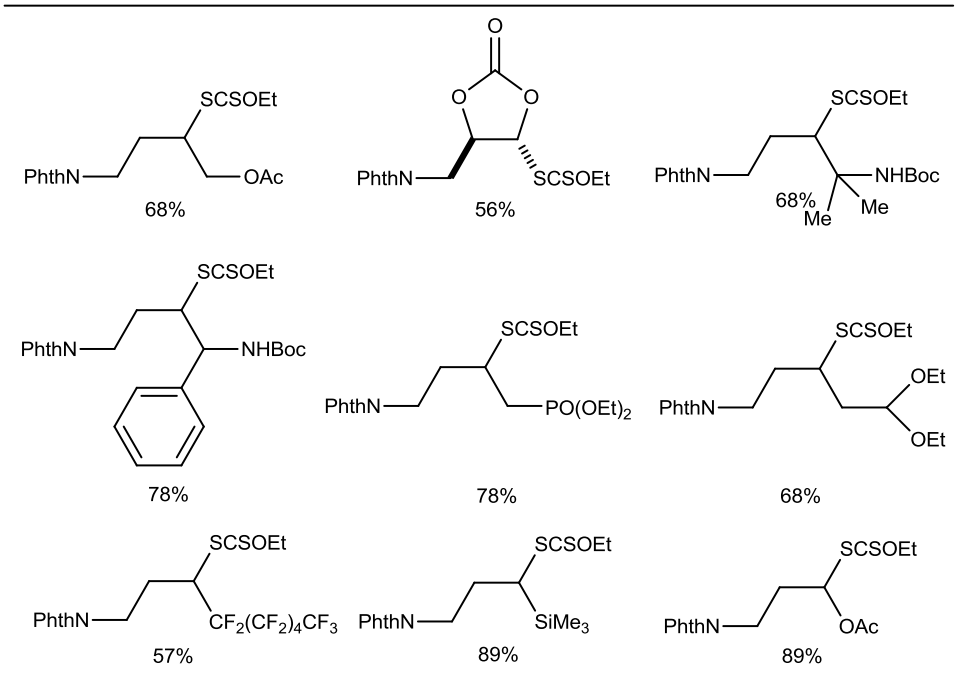
[76] (a) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem. Int. Ed.* **1990**, *29*, 558. (b) Chan, Y. N. C.; Meyer, D.; Osborn, J. A. *J. Chem. Soc. Chem. Commun.* **1990**, 869.

access highly functionalized primary amines which would be tedious to synthesize by traditional methods.



Scheme 2.34

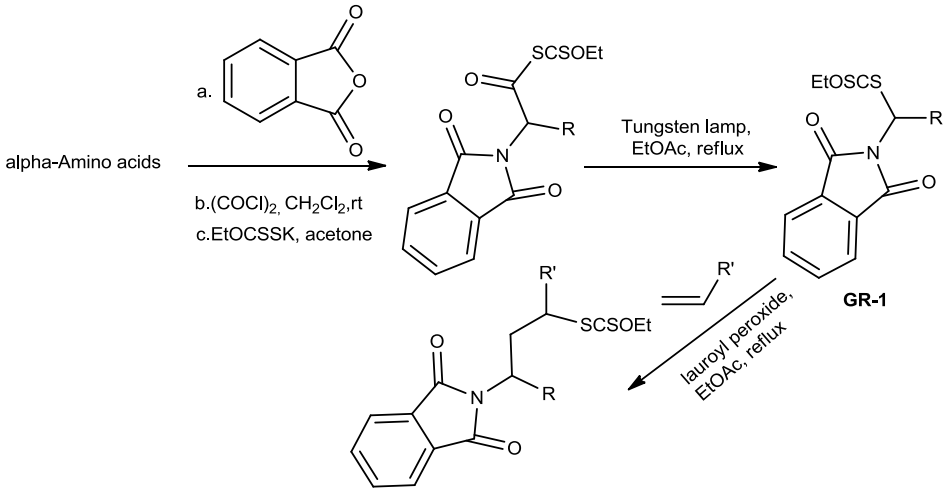
The scope of this method is illustrated by the examples in Scheme 2.35. A wide range of different functional groups such as an ester, an acetyl, a protected amino, a phosphonate, a trimethylsilyl, or a fluoroalkyl can indeed be incorporated into the adducts via this radical hydroaminomethylation of alkenes.



Scheme 2.35 Examples of phthalimidomethyl adducts

2. Xanthates from *α*-aminoacids

Although *S*-phthalimidomethyl xanthate, a nice crystalline solid, can be prepared from cheap and commercially available *N*-chloromethylphthalimide in one single step in high yield, the lack of generality of this method to introduce the xanthyl group at the *α*-position of more substituted amines encouraged us to develop other routes to this family of xanthates. Thus, Revol described the synthesis of *S*-acyl xanthates **GR-1** in three steps from the corresponding *α*-amino acids based on radical decarbonylation. Radical addition of xanthate **GR-1** to a broad range of alkenes proceeds efficiently to give a variety of highly functionalized, protected amines (Scheme 2.36).[77]



Scheme 2.36 Xanthates derived from α-aminoacids

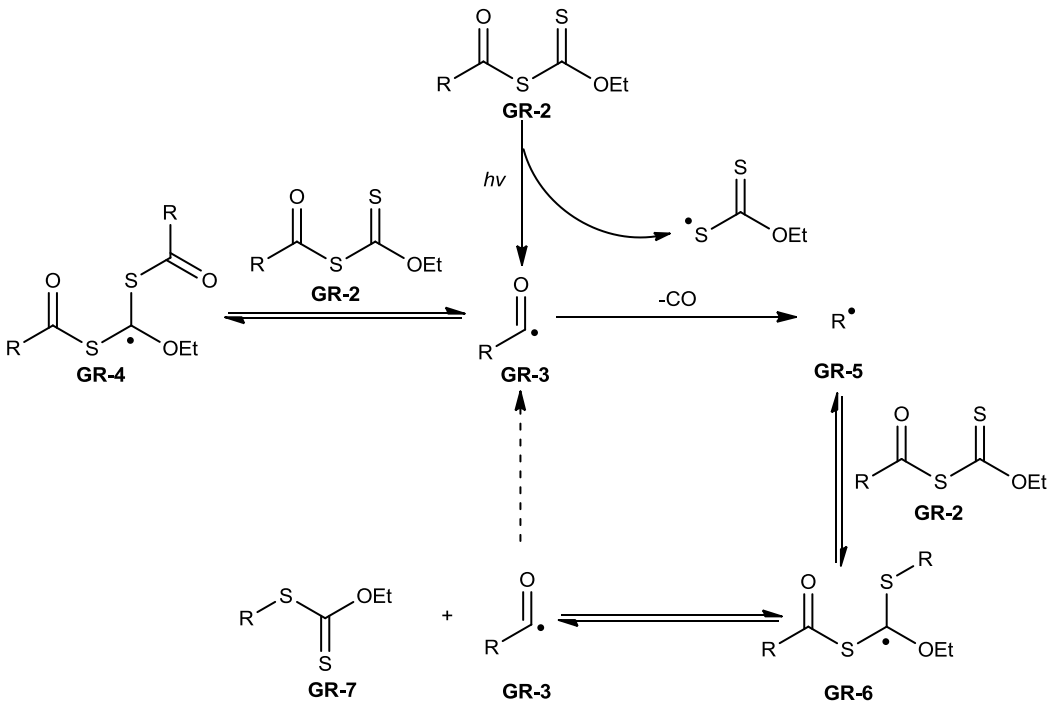
The radical decarbonylation as the key step was employed for the preparation of the xanthates and its mechanism is shown in Scheme 2.37.[78] The starting material **GR-2** undergoes homolytic cleavage upon irradiation with a tungsten lamp to give acyl radical **GR-3** which then expels carbon monoxide to generate **GR-5**.[79] The

[77] Quiclet-Sire, B.; Revol G.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 3554.

[78] Darji, R. R.; Shah, A. *Indian Journal of Chemistry* **1981**, *24*, 1077.

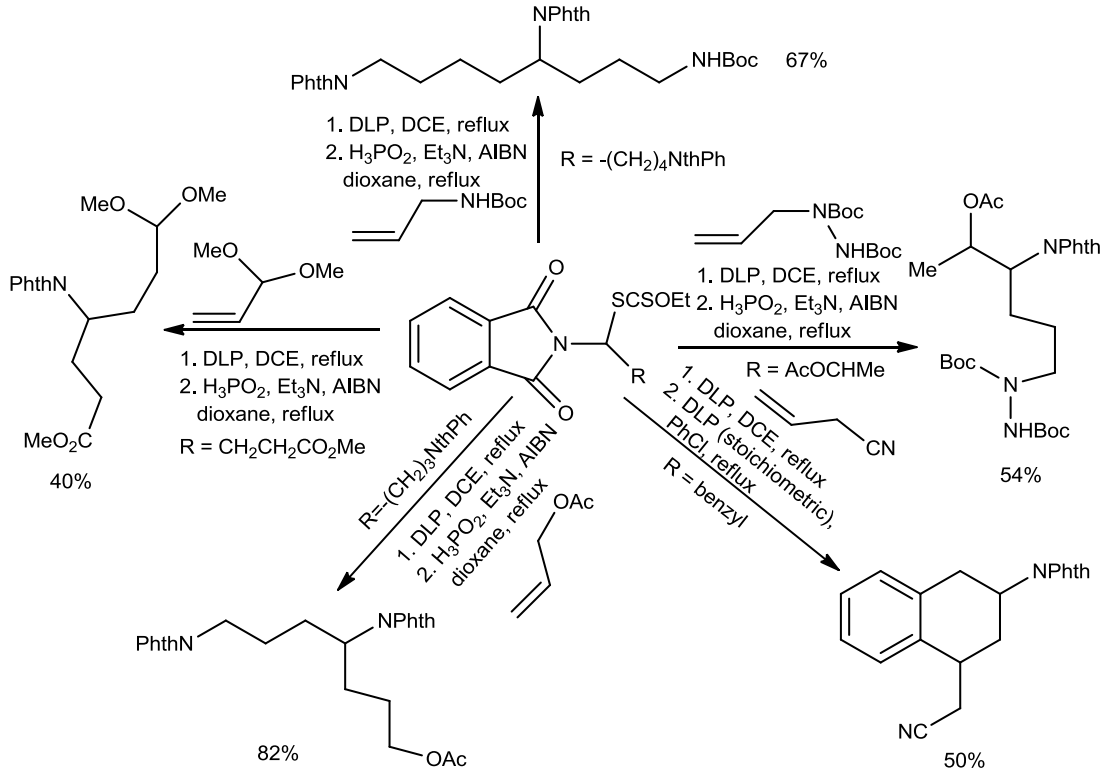
[79] (a) Barton, D. H. R.; George, M. V.; Tomoeda, M. *J. Chem. Soc.* **1962**, 1967. (b) Delduc, P.; Tailhan, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 308. (c) Heinrich, M.; Zard, S. Z. *Org. Lett.* **2004**, 6, 4969.

radical addition of **GR-5** to **GR-2** giving adduct **GR-6** is a reversible and degenerate process. Finally, the collapse of **GR-6** gives xanthate product **GR-7** and another acyl radical **GR-3** to sustain the free radical chain process.



Scheme 2.37 Decarbonylation pathway of xanthate

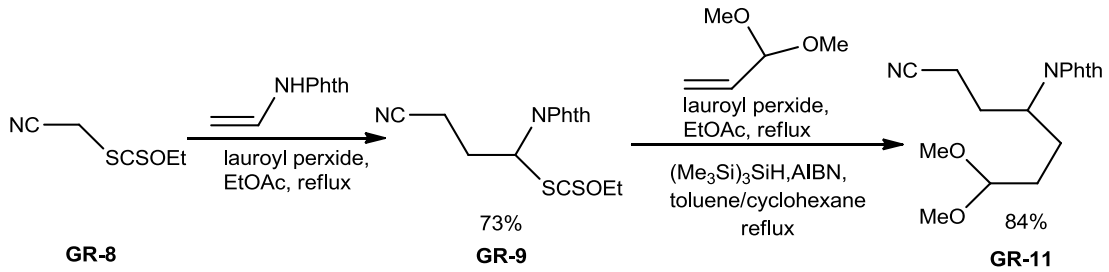
The numerous commercially available natural and unnatural α-amino acids that can be used as starting materials allow entry into a broad variety of phthalimido-substituted xanthates and following addition to alkenes, provide access to many complex amines. The scope is illustrated in Scheme 2.38 by the convergent syntheses of protected 1,4 and 1,5-diamines, γ-amino acids, β-aminoalcohols, 2-aminotetralines or triamines. It is worth noting that the stability of these *N*-phthalimido xanthates and their easy preparation on a multigram scale are further advantages of this approach.



Scheme 2.38 Synthesis of 1,4 and 1,5-diamines, *γ*-amino acids, *β*-aminoalcohols, 2-aminotetralines or triamines

3. Xanthates from the radical addition of various xanthates to *N*-vinylphthalimide

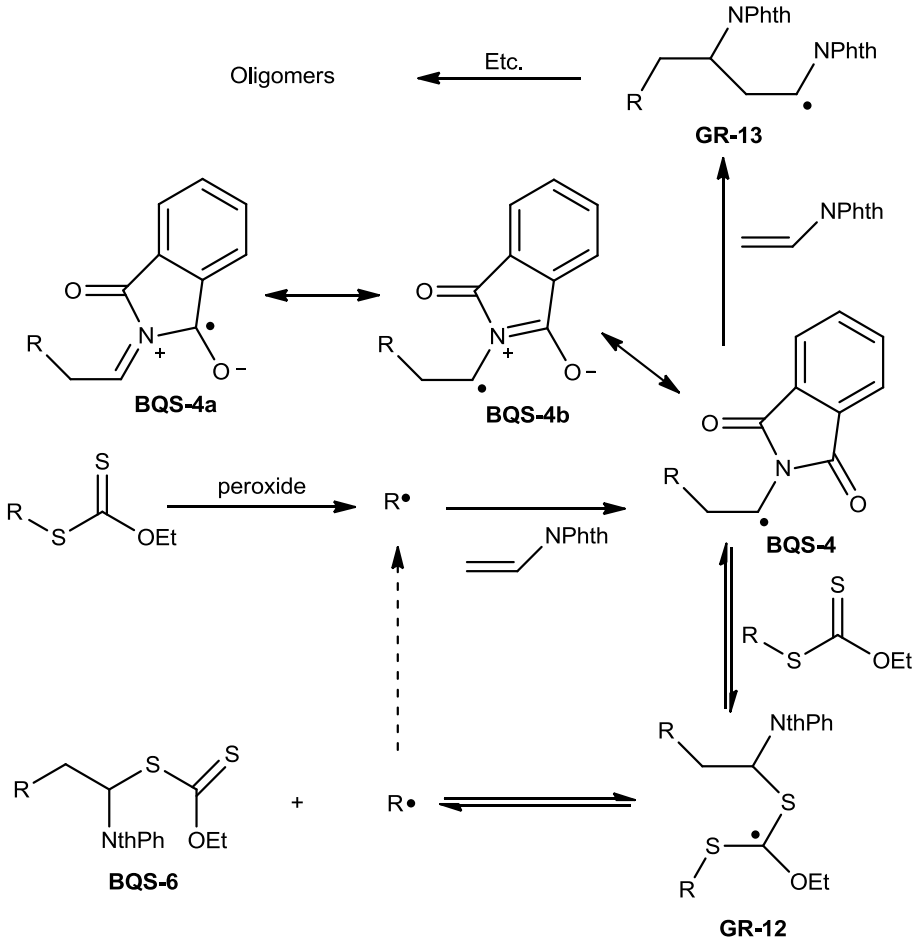
Although the addition of *N*-vinylphthalimide with many xanthates provided mostly oligomers, the successful addition of AIBN derived xanthate **GR-8** under the usual conditions encouraged us to reinvestigate the addition of other xanthates to *N*-vinylphthalimide (Scheme 2.39).[80]



Scheme 2.39 Addition of xanthate GR-8 to *N*-vinylphthalimide

[80] Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Tetrahedron* **2010**, *66*, 6656.

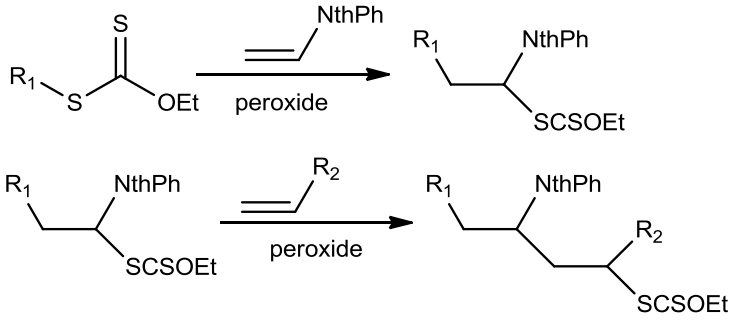
As shown in Scheme 2.40, the resonance structures of **BQS-4a** and **BQS-4b** as significant contributors increases the allylic character of radical intermediate **BQS-4** and therefore an increase of its stability is observed. Due to the fact that radical **BQS-4** is more stable than the R radical from the starting xanthate, radical **BQS-4** will undergo another radical addition with *N*-vinylphthalimido to generate radical **GR-13**, and finally furnish mostly oligomers.



Scheme 2.40 Mechanism of addition of xanthate to *N*-vinylphthalimide

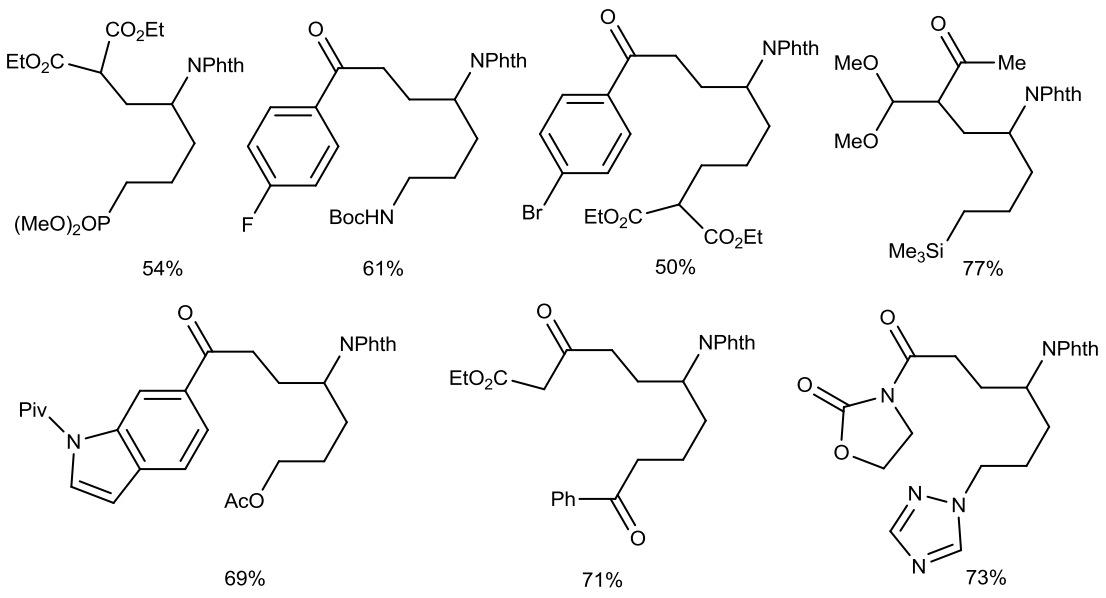
Considering that the difference between the stability of R radical and **BQS-4** must be quite small and since the olefin is often used in 1.5 to 3-fold and in some cases up to 5-fold excess, we reexamined this process by reversing the molar ratio of the xanthates to *N*-vinylphthalimide. This increases the chance of capture of radical BQS-4 to give GR-12 and therefore less oligomerization. Furthermore, by diminishing the concentration of *N*-vinylphthalimide, the possibility of a second

addition becomes even less likely. The results indeed proved that successful and efficient additions could be achieved in most cases. As summarized in Scheme 2.41, rapid combination of *N*-vinylphthalimide with different xanthates can provide various *N*-phthalimidoxanthates bearing new functional groups from the xanthate partner which can undergo further radical additions to produce even more complex protected primary amines.



Scheme 2.41 General synthetic route

As illustrated in Scheme 2.42, based on this procedure, highly functionalized amines which contain at least two different functional groups from the different reaction partners are obtained in generally good yield.

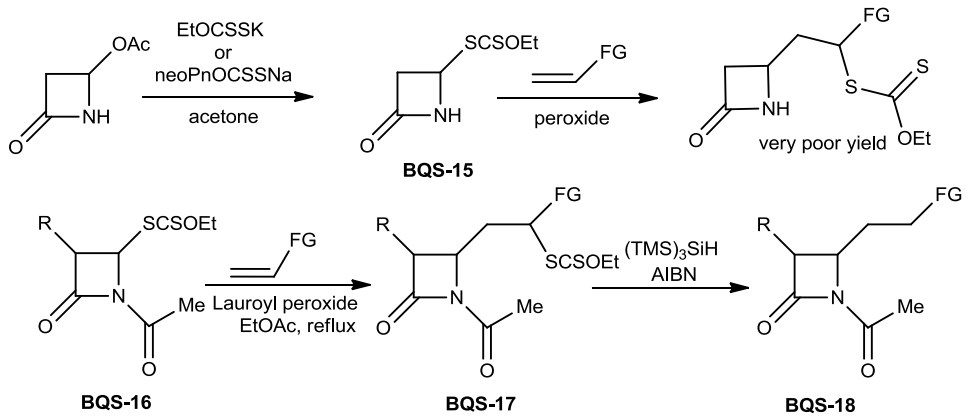


Scheme 2.42 Examples of *N*-phthalimide protected amines

4. Xanthates from other amine sources

4.1. Xanthates from *β*-lactams

β-Lactam often can be found as the core of some biologically and pharmaceutically active compounds such as penicillins, cephalosporins, carbapenems, and monobactams.[81] As a consequence, much ongoing effort has been devoted to the development of their synthesis.[82] Several years ago, a *β*-lactam derived xanthate **BQS-15** was prepared in our lab, but the addition of this xanthate furnished mostly oligomers (Scheme 2.43). The successful radical addition of *N*-phthalimidoxanthates to various unactivated olefins inspired us to introduce another carbonyl group by acylation to obtain the corresponding imide **BQS-16**. Indeed, the clean radical addition of **BQS-16** to olefins was observed, which opened up numerous opportunities to modify the initial of *β*-lactam.[83]



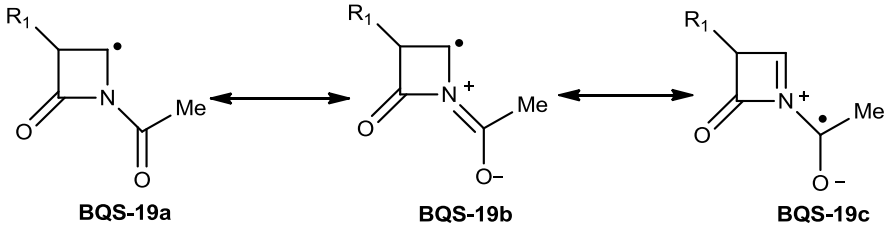
Scheme 2.43 Addition of xanthate derived from *β*-lactam to olefins

[81] (a) *Chemistry and Biology of β-Lactam Antibiotics;* Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1-3. (b) Burnett, D. A. *Curr. Med. Chem.* **2004**, *11*, 1873. (c) Buynak, J. D. *Curr. Med. Chem.* **2004**, *11*, 1951. (d) Niccolai, D.; Tarsi, L.; Thomas, R. *J. Chem. Commun.* **1997**, 2333.

[82] (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. (b) Dhawan, R.; Dghaym, R. D.; Syr, D. J.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 3927. (c) Zhao, L.; Li, C.-J. *Chem. Asian J.* **2006**, *1*, 203. (d) Ye, M.-C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, *71*, 3576. (e) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4082. (f) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572.

[83] Quiclet-Sire, B.; Zard, S. Z. *Heterocycles* **2010**, *82*, 263.

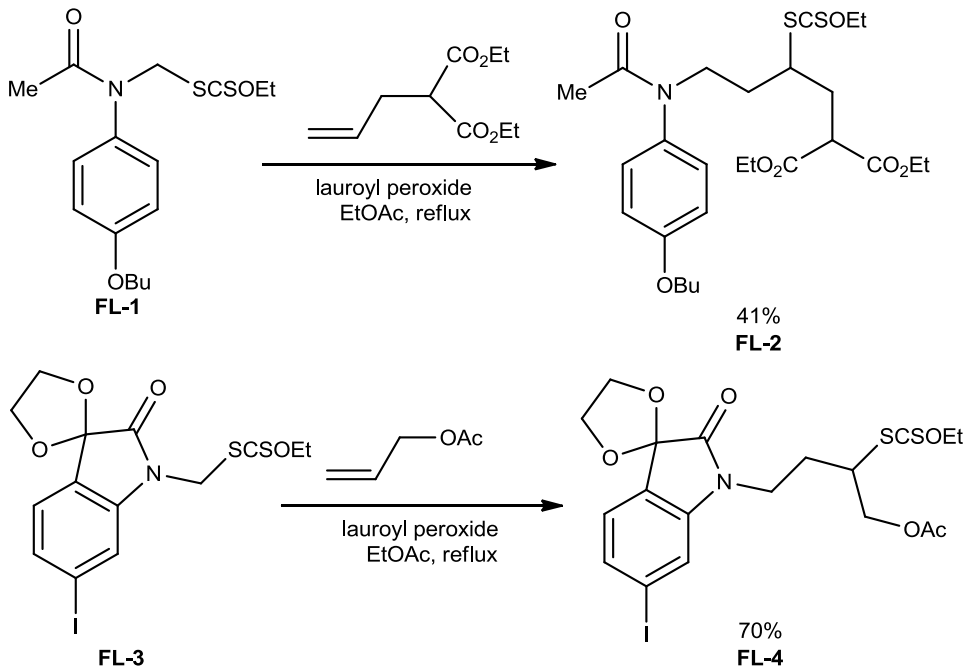
Through the resonance structures of radical intermediate **BQS-19**, we can find it possesses the same increasing allylic character similar to the carbon radical geminal to phthalimido group (Scheme 2.44).



Scheme 2.44 Resonance structures of radical intermediate **BQS-19**

4.2. Xanthate from methylanilines

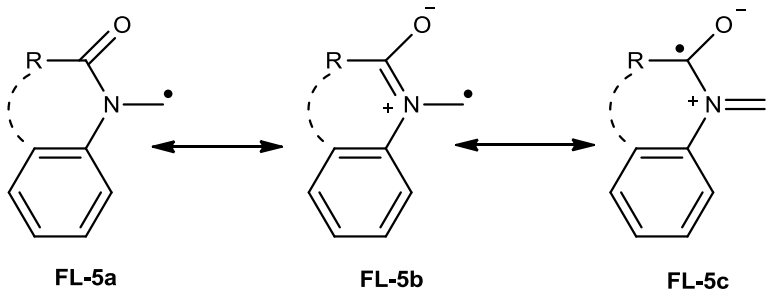
It is possible to obtain a comparable stabilisation by replacing one of the carbonyl group in the imide by an aromatic heteroamomatic ring. For example, xanthates **FL-1** and **FL-3** add clearly to various unactivated alkenes give adducts **FL-2** and **FL-4** in good yield (Scheme 2.45).



Scheme 2.45 Radical addition of xanthates FL-1 and FL-3 to olefins

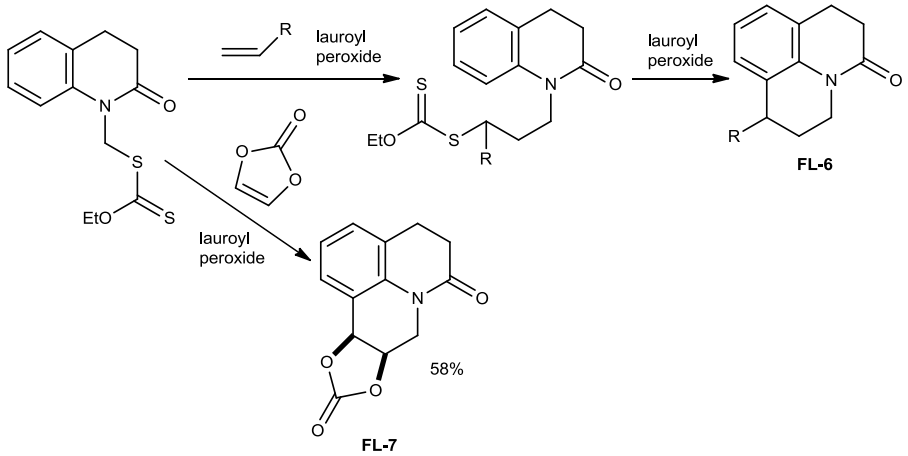
The aromatic ring provides a "vinylogous" type stabilization for radical

intermediate **FL-5** which is sufficient to allow control of the radical addition process (Scheme 2.46).



Scheme 2.46 "Vinylogous" type stabilization of **FL-5**

Interestingly, the adducts can undergo ring closure to form various polycyclic aniline derivatives. This is illustrated by the concise synthesis of compounds **FL-6** and **FL-7** depicted in Scheme 2.47.



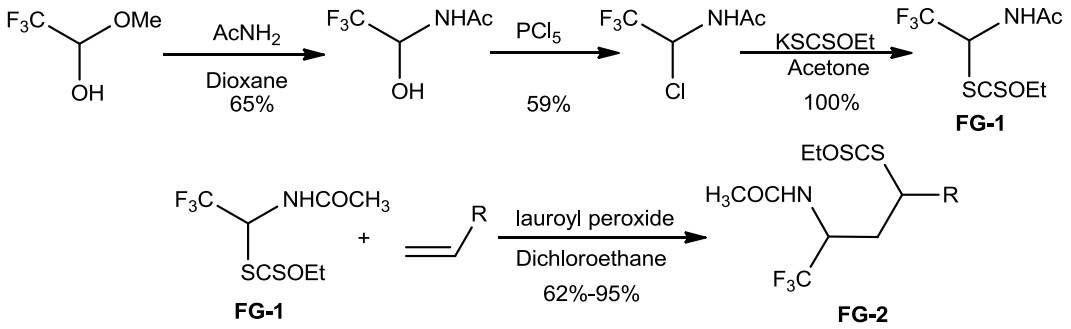
Scheme 2.47

4.3. Xanthate from α-trifluoromethylamine

As part of the continuing work for the applications of xanthate for the construction of organofluorine compounds,[84] a direct, highly flexible, and efficient

[84] (a) Boivin, J.; Elkaim, L.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2573. (b) Boivin, J.; Elkaim, L.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2585. (c) Denieul, M. P.; Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1996**, 2511. (d) Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 9057. (e) Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 1069.

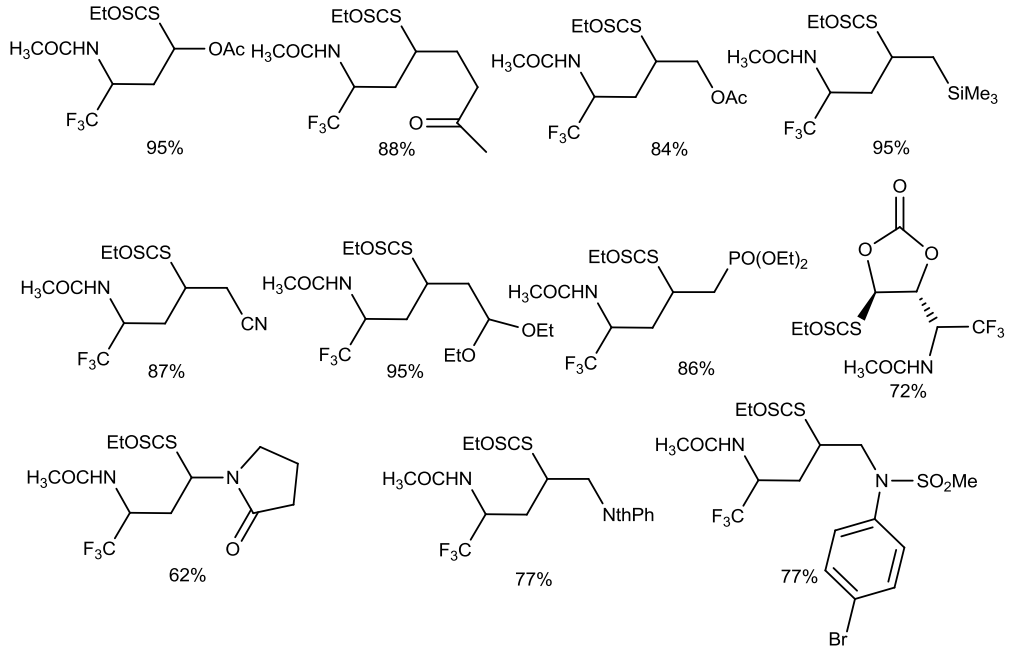
method to access α-trifluoromethylamines was developed in 2003.[85] As shown in Scheme 2.48, the trifluoromethylamine xanthate **FG-1** can be prepared in three simple steps. In this case, a second carbonyl group is not necessary since the carton-sulfur bond is sufficiently weakened by the more readily available lone pair on the nitrogen (anomeric effect). Furthermore, the electron-withdrawing trifluoromethyl group gives the radical increased electrophilic character and improves the rate of addition to the alkene partner.



Scheme 2.48 Synthesis of xanthate **FG-1** and its radical addition to olefins

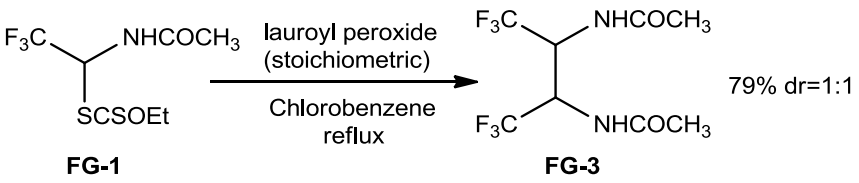
The examples outlined in Scheme 2.49 illustrate the radical addition of trifluoromethylamine xanthate **FG-1** to various olefins. A rapid and efficient introduction of trifluoromethylamine to form various complex fluorinated derivatives **FG-2** in generally high yield is now in hand.

[85] Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655.



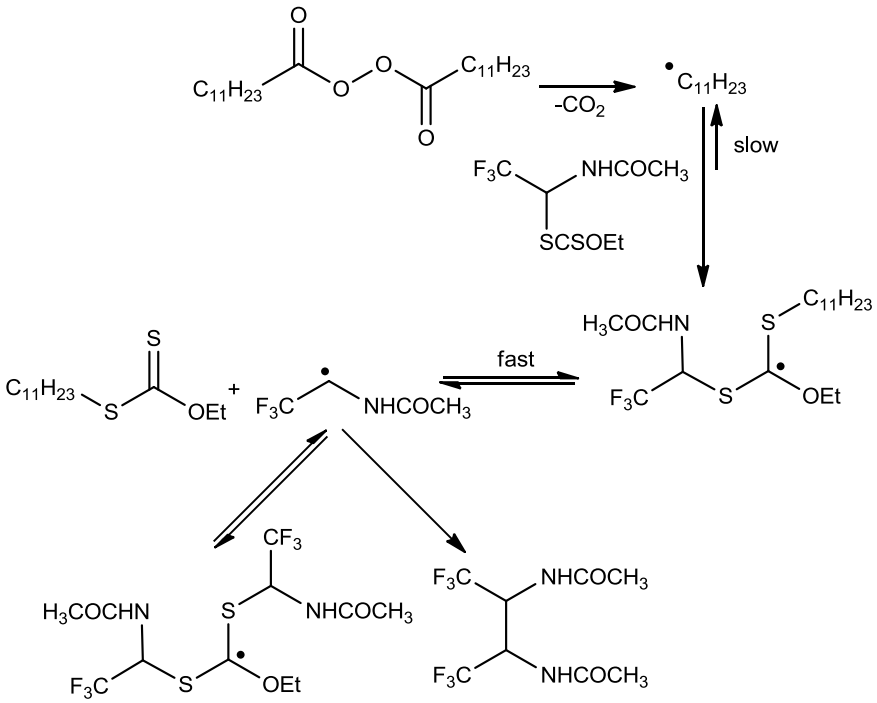
Scheme 2.49 Examples of adducts **FG-2**

Another interesting case in this study is the formation of dimer FG-3 from xanthate **FG-1**. The deprotection of **FG-3** should give a free diamine which would be a useful building block for novel ligands for transition metals (Scheme 2.50).



Scheme 2.50 Synthesis of dimer **FG-3**

A plausible mechanism for the formation of this dimer is outlined in Scheme 2.51. Since the trifluoromethylamine radical is more stable than the simple alkyl radical generated from dilauroyl peroxide, the reaction proceeds smoothly to furnish the desired dimer product.

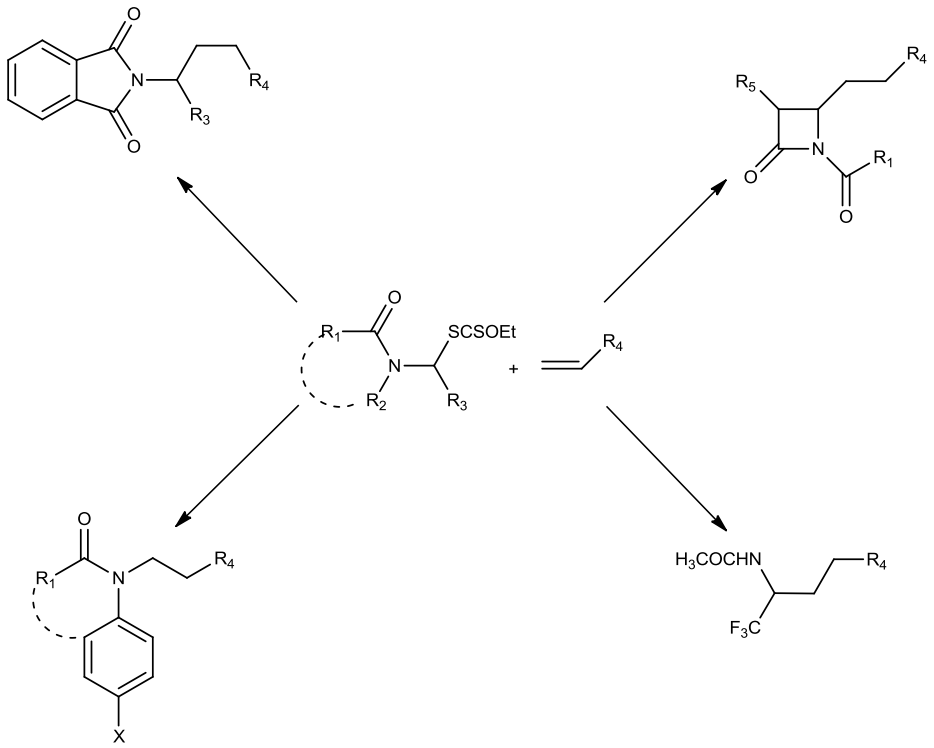


Scheme 2.51 Mechanism for the formation of dimer **FG-3**

Conclusion

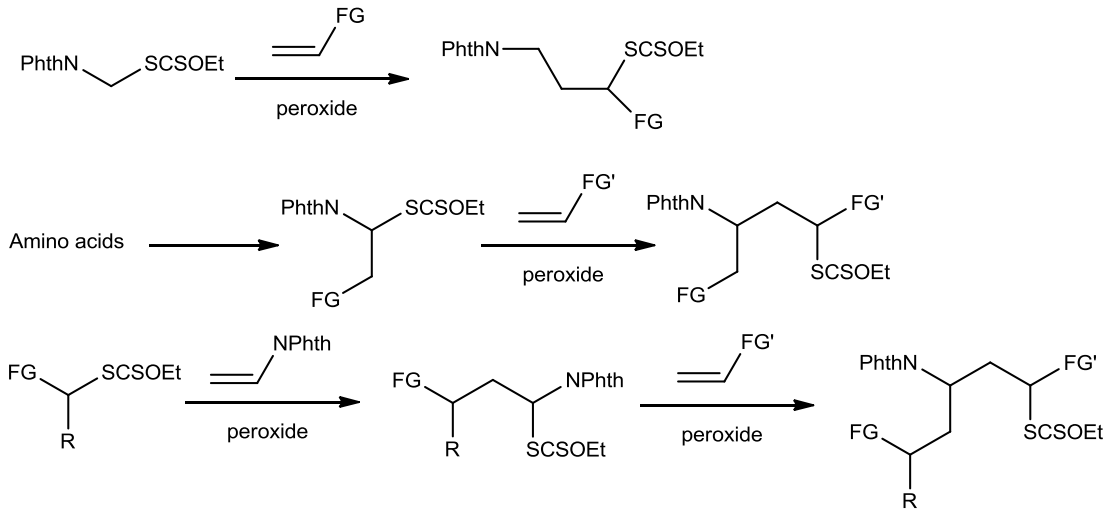
The synthesis of amines via classic named reactions and the non-radical and radical hydroaminomethylation of alkenes were briefly discussed. The radical hydroaminoalkylation of alkenes developed in our group resolves most of the problems met in most current hydroaminoalkylation methods.

The increased stability of carbon radicals geminal to an imide nitrogen atom is essential in designing radical hydroaminoalkylation processes. As illustrated in Scheme 2.52, these manners for stabilization of carbon radicals rely mainly on the introduction of a carbonyl, an aryl or a trifluoromethyl group. Many new opportunities arise for the construction of highly functionalized amines and aromatic amines.



Scheme 2.52

The three methods that have been developed are summarized in Scheme 2.53. The following chapter will detail the expansion of this approach to other substrates.


PhthN
SCSOEt
FG
peroxide
PhthN
SCSOEt
FG
Amino acids
PhthN
SCSOEt
FG
FG'
peroxide
PhthN
FG'
SCSOEt
FG
FG
SCSOEt
R
NPhth
peroxide
FG
NPhth
R
SCSOEt
FG'
peroxide
PhthN
FG'
FG
SCSOEt
R

Scheme 2.53