Radical Synthesis of 1,2-Diamines

Introduction

Vicinal diamines represent indispensable structural motifs in many natural and bioactive compounds. Some pharmaceutically interesting substances are presented in Figure 4.1. Massadine is one of the few described inhibitors of geranylgeranyl--transferase type I (GGTase I), which was isolated from the marine sponge Stylissa aff.[118] (-)-Agelastatin A is a naturally occurring oroidin alkaloid with powerful antitumor activity. It inhibits cancer cell proliferation by causing cells to accumulate in the G2 phase of cell cycle.[119] Penicillins, a group of hugely important antibiotics, are still widely used today. Their discoveries date back to 1928 to the famous work of the Scottish scientist and Nobel laureate A. Fleming.[120] Biotin, also known as vitamin H, is essential in fatty acid biosynthesis, branched-chain amino acid catabolism, and gluconeogenesis.[121] Synthetic 1,2-diamines have also proved of some importance. Thus, Tamiflu is an antiviral widely utilized to prevent or slow down the spread of flu virus between cells in the body;[122] A-315675, [123] a novel trisubstituted pyrrolidine carboxylic acid, is a highly potent inhibitor of influenza neuraminidase and has been synthesized by several groups; Oxaliplatin[124] (Eloxatin; Sanofi-Synthelabo), the first platinum-based antineoplastic agent, used to treat cancer, was discovered in 1976 at Nagoya City University by professor Kidani; Diazepam, a benzodiazepine drug, is used to treat anxiety, panic attacks, insomnia.[125]

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[118] Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W.; Fusetani, N. *Org. Lett.*, **2003,** *5*, 2255.

[119] (a) Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012,** *134*. 7516. (b) Mason, C. K.; McFarlane, S.; Johnston, P. G.; Crowe, P.; Erwin, P. J.; Domostoj, M. M.; Campbell, F. C.; Manaviazar, S.; Hale, K. J.; El-Tanani, M. *Mol. Canc. Therapeu.* **2008,** *7*, 548.

[120] Nicolaou, K.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993.

[121] Jestin, E.; Moreau, F.; Florentin, D.; Marquet, A. *Bioorg. Med. Chem.* **1996,** *4*, 1065.

[122] Burch, J.; Corbett, M.; Stock, C.; Nicholson,K.; Elliot, A. J.; Duffy, S.; Westwood, M.; Stephen, P.; Lesley, S. *Lancet Infect Dis* 2009, 9, 537.

[123] Hanessian, S.; Bayrakdarian, M.; Luo, X. *J. Am. Chem. Soc.* **2002**, *124*, 4716.

[124] Wheate, N. J.; Walker, S.; Craig, G. E.; Oun, R. *Dalton Trans.*, **2010**, *39*, 8113.

[125] Ravenell, R.; Neugebauer, N. M.; Niedzielak, T.; Donaldson, S. T. *Behav Brain Res.*, **2004**, *270*, 68.

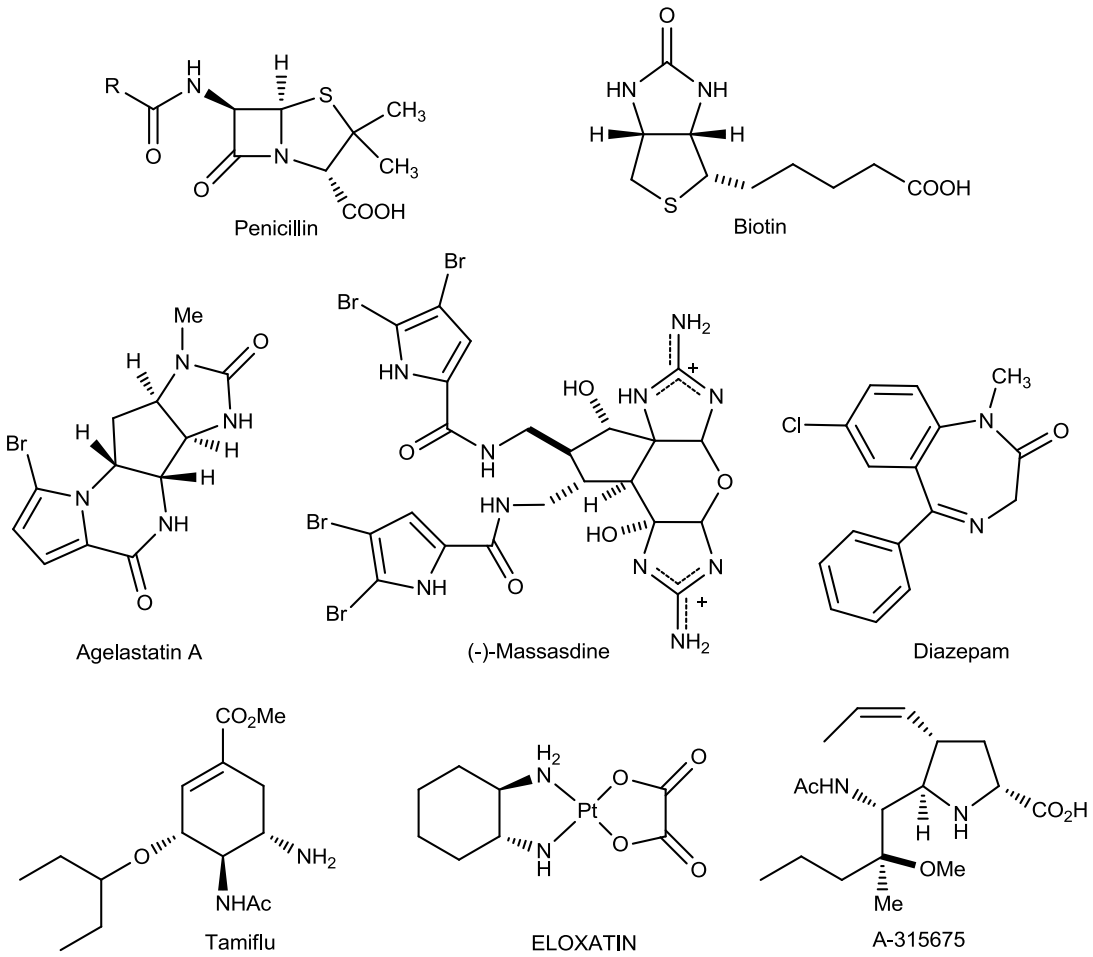

Figure 4.1 Structures of some pharmaceutical interesting compounds

Due to the highly valuable medicinal applications of diamines, there has been a great interest in their preparation. We therefore directed our studies on the degenerative transfer of xanthates towards the construction of highly functionalized diamines. Our results will be described in this chapter.

I. Preparation of 1,2-diamines and their applications in organic synthesis

1. Preparation of 1,2-diamines

A plethora of methods to access diverse 1,2-diamines have been developed in the past decades.[126] In the following paragraphs, a few of the more well-known strategies for the synthesis of 1,2-diamines, such as diamination of alkenes, ring-opening reactions of aziridines, reductive coupling of imines and classical named reactions such as the Mannich reaction and the aza-Cope rearrangement will be briefly introduced.

1.1. Diamination of alkenes

Diamination of olefins is an effective and concise strategy to synthesize vicinal diamine. It has been intensively studied and reported; however, especially for internal alkenes, accomplishing this difunctionalization with high chemo-, regio- and diastereoselectivity remains a significant challenge. Among various metal-catalyzed diamination protocols, one powerful Cu (I)-catalyzed regioselective diamination of conjugated dienes was developed by Shi and co-workers.[127] As shown in Scheme 4.1, various dienes could be regioselectively diaminated by using di-*tert*-butyldiaziridinone as the nitrogen source. This Cu (I)-catalyzed diamination can be accomplished in good yield even on a large scale.

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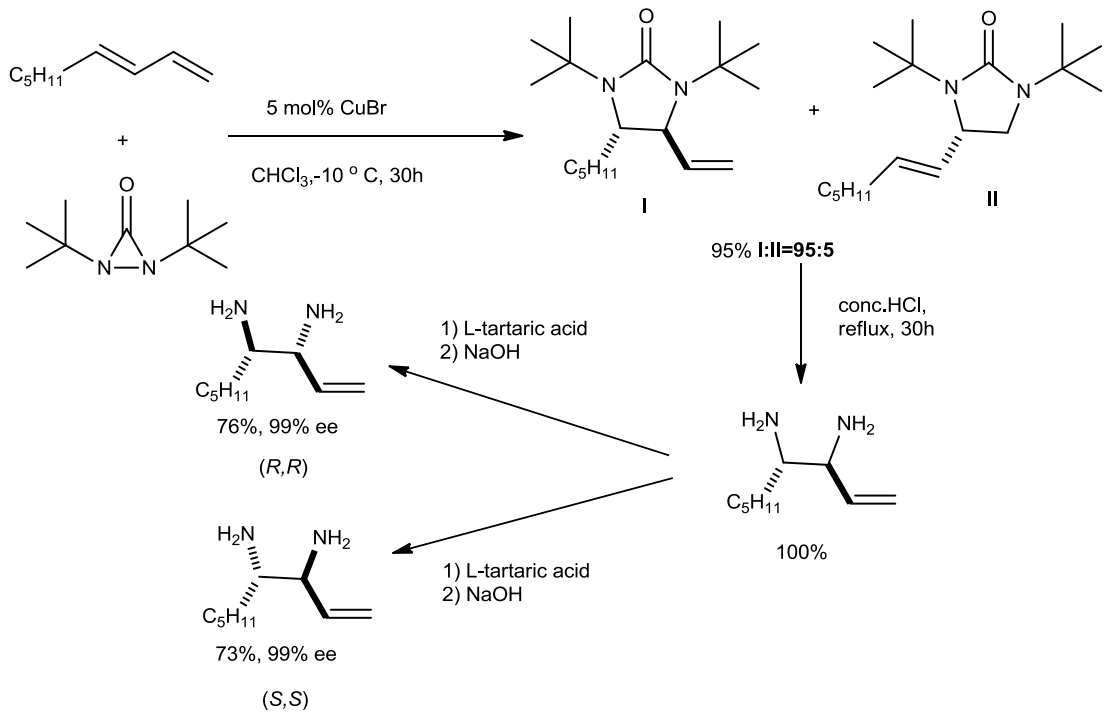
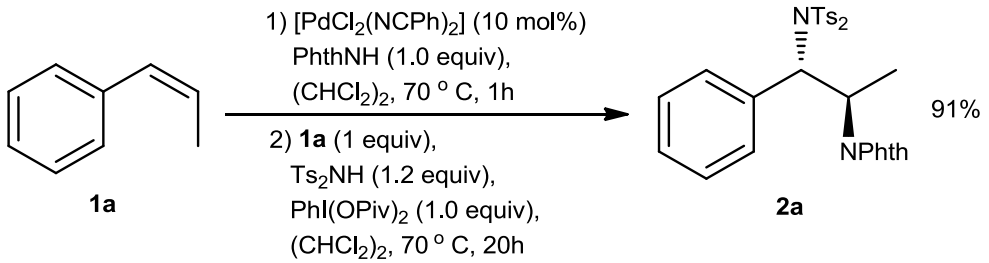
[126] (a) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887. (b) Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 7516. (c) Ooi, T.; Kameda, M.; Fujii, J.-i.; Maruoka, K. *Org. Lett.*, **2004**, *6*, 2397. (d) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763. (e) Muñiz, K.; Iesato, A.; Nieger, M. *Chem. Eur. J.* **2003**, 9, 5581. (f) Li, G.; Wei, H.-X.; Kim, S. H.; Carducci, M. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277. (g) Kim, H.; Nguyen, Y.; Yen, C. P.-H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 12184. (h) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.*, **2004**, *6*, 4747. (i) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.*, **2004**, 6, 3953. (j) Mercer, G. J.; Sigman, M. S. *Org. Lett.*, **2003**, *5*, 1591.

[127] (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Zhao, B.; Peng, X.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2012**, *132*, 11009.



Scheme 4.1 Copper-catalyzed diamination of alkenes

Recently, another study on the diamination of (Z)-*β*-methylstyrene based on a palladium (II/IV) catalyzed process was reported by Muniz and co-workers (Scheme 4.2). Phthalimide and bistosylimide as the nitrogen source were incorporated into (Z)-*β*-methylstyrene.[128] This highly chemo-, regio- and diastereoselective reaction can afford the corresponding diamine products on a 17 mmol scale, which is difficult to accomplish by traditional methods.



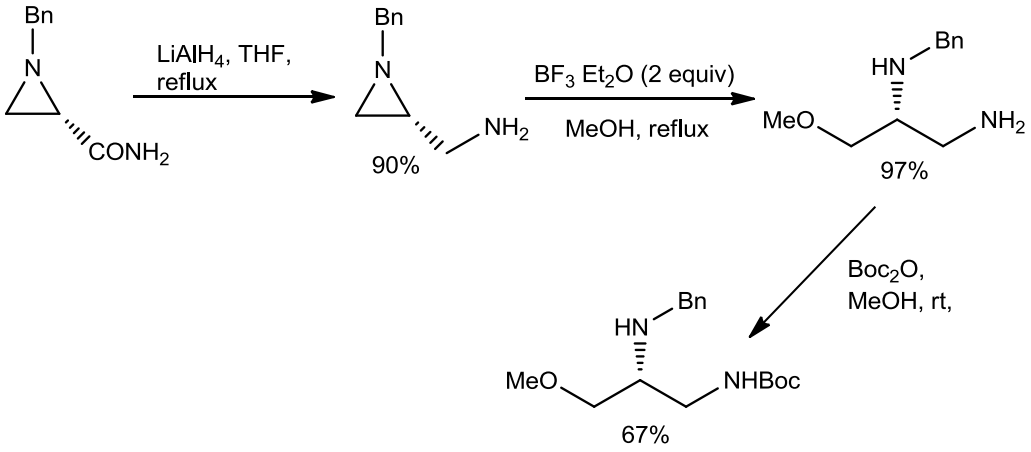
Scheme 4.2 Palladium catalyzed diamination of (Z)-*β*-methylstyrene

[128] Mart ńez, C.; Muniz, K. *Angew. Chem. Int. Ed.* **2012,** *51*, 7031.

1.2. Ring-opening of aziridines

Aziridines have been widely implicated in organic synthesis. Due to their strong ring strain, ring-opening reactions of aziridines with many nucleophiles have been reported by numerous groups. In 1976, an access to either syn- or anti- vicinal diamines was developed by Swift and Swern,[129] who disclosed another possibility to synthesize vicinal diamines from aziridines.[130]

A recent study illustrates how this strategy is applied in vicinal diamine synthesis. Gotor and co-workers initially prepared enantiopure aziridines by exploiting the amidase-containing, commercially available bacterium *Rhodococcus rhodochrous* IFO 15564 for the enantioselective hydrolysis of several unactivated 1-benzyl- or 1-arylaziridine-2-carboxamides (Scheme 4.3). [131] The enantiopure aziridines underwent nucleophilic attack by methanol or by sodium azide to afford the enantiopure 1,2-diamines in good yield.



Scheme 4.3 Diamines derived from aziridines

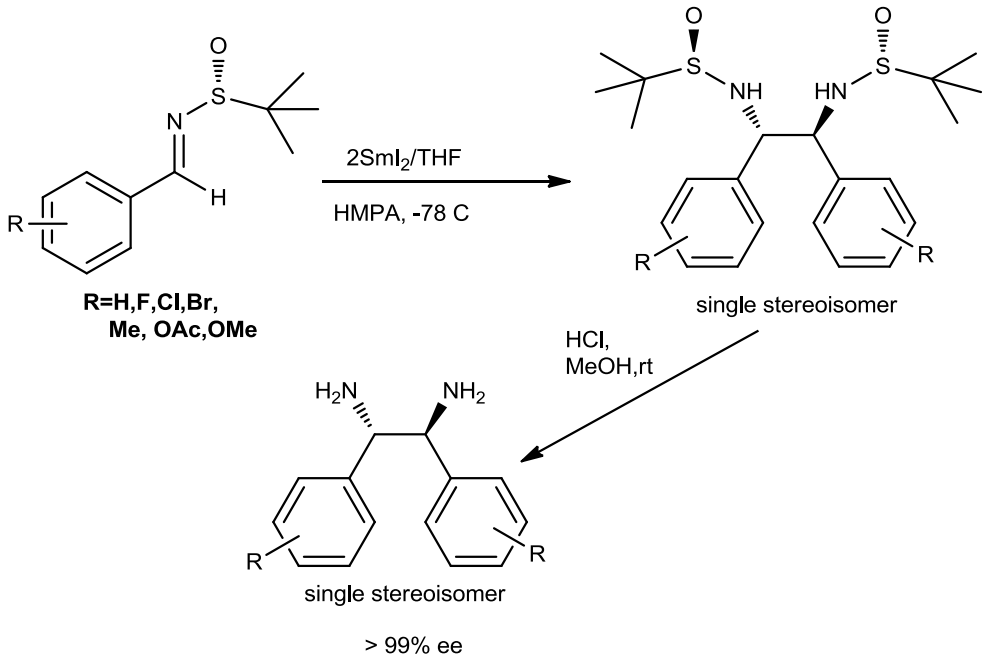
[129] Swift, G.; Swern, D. *J. Org. Chem.* **1967**, *32*, 511.

[130] (a) Leung, W.-H.; Yu, M.-T.; Wu, M.-C.; Yeung, L.-L. *Tetrahedron Lett.* **1996**, *37*, 891. (b) Kuroki, T.; Katsuki, T. *Chem. Lett.* **1995**, 337. (c) Dureault, A.; Tranchepain, I.; Greck, C.; Depezay, J.-C. *Tetrahedron Lett.* **1987**, *28*, 3341. (d) Dureault, A. Tranchepain, I. Depezay, J.-C. *J. Org. Chem.* **1989**, *54*, 5324. (e) Kelley, B. T.; Joulli é, M. M., *Org Lett.*, **2010,** *12*, 4244.

[131] Moran-Ramallal, R.; Liz, R.; Gotor, V. *Org. Lett.*, **2007**, *9*, 521.

1.3. Reductive coupling of imines

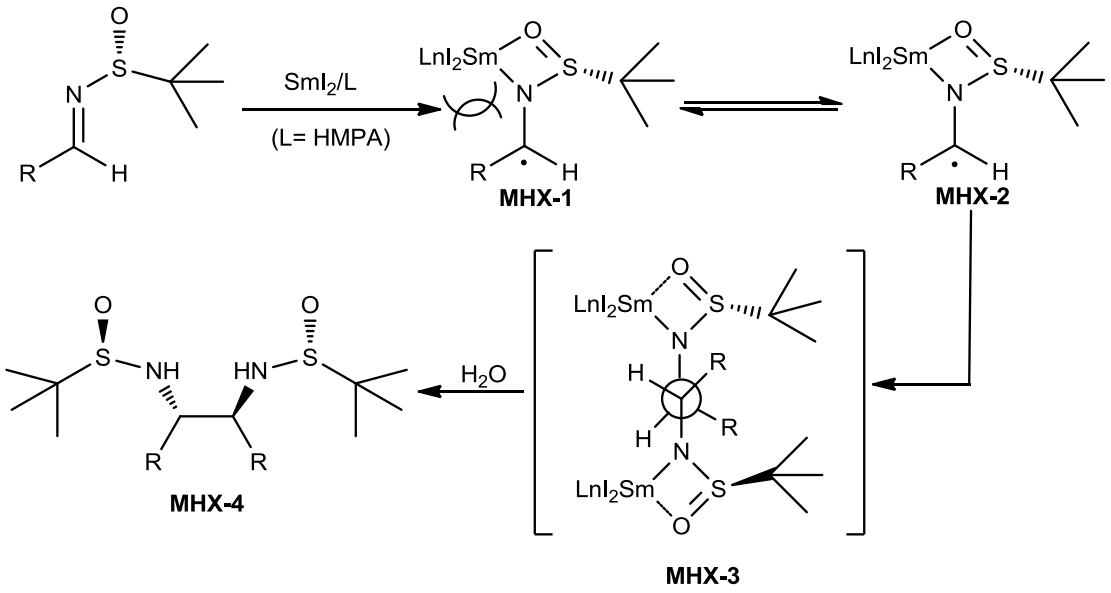
The reductive coupling of imines is one of the most efficient approaches to diamine and has been studied intensively. Recently, Xu and co-workers investigated the reductive coupling of chiral *N*-*tert*-butanesulfinyl imines by exposure to 2 equiv of SmI_2 in the presence of HMPA(Scheme 4.4).[132] The formation of chiral diamines is observed, and this appears to be the first radical dimerization of *N*-*tert*-butanesulfinyl imines that has been reported.



Scheme 4.4 Reductive coupling of imines

A plausible mechanism is shown in Scheme 4.5. The bulkiness of the samarium complex with HMPA results in the rapid formation of the more favorable and stable radical intermediate *trans* **MHX-2** instead of *cis* **MHX-1**. The dimerization of **MHX-2** gives the stable intermediate**MHX-3** which will be converted into the corresponding diamine **MHX-4** by hydrolysis.

[132] (a) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956. (b) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.*, **2004**, *6*, 4747.



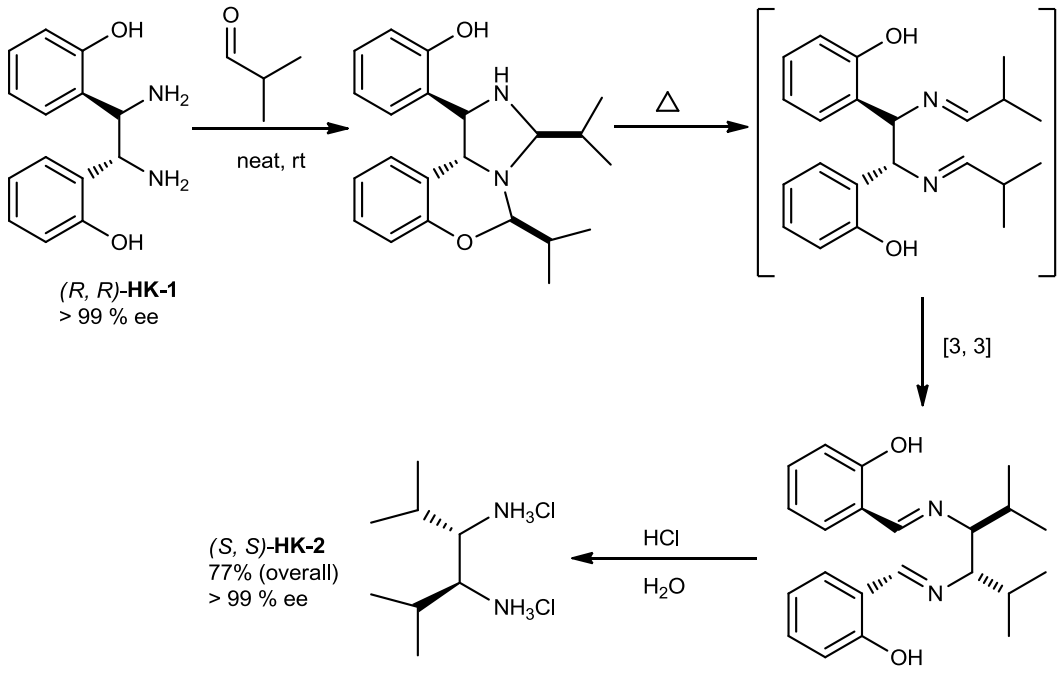
Scheme 4.5 Plausible mechanism

1.4. The Aza-Cope rearrangement

Other powerful methods involving classical named reactions, such as the aza-Cope rearrangement, have been developed by some groups for the construction of diamines. The first synthesis of aryl-substituted meso vicinal diamines via the diaza-cope rearrangement reaction was accomplished by Vogtle and Goldschmitt in 1973.[133] Recently, another strategy was developed by Chin and co-workers. [134] It opens access to the more synthetically challenging alkyl-substituted vicinal diamines via an aza-cope rearrangement. As shown in Scheme 4.6, the "mother diamine" **HK-1** underwent a directed diaza-Cope rearrangement reaction to make enantiopure "daughter" diamines **HK-2**. This is an extremely concise approach to build a chiral diamine library.

[133] Vogtle, F.; Goldschmitt, E. *Angew. Chem., Int. Ed.* **1973**, *12*, 767.

[134] (a) Kim, H.; Nguyen, Y.; Yen, C. P.-H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J., *J. Am. Chem. Soc.* **2008**, *130*, 12184. (b) Kim, H.; Staikova, M.; Lough, A. J.; Chin, J. *Org. Lett.*, **2009**, 11, 157.

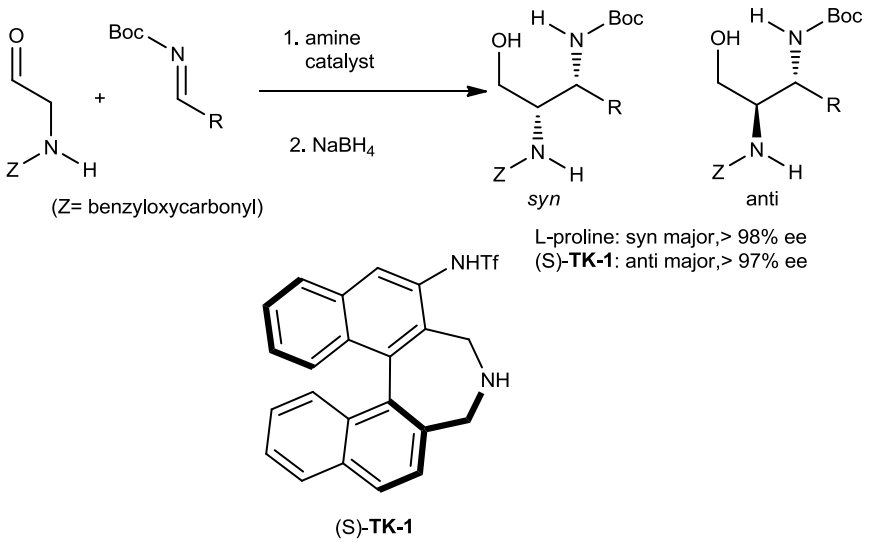


Scheme 4.6 Diaza-Cope rearrangement in diamine synthesis

1.5. The Mannich reaction

The Mannich-Reaction is employed in the organic synthesis of complex compounds bearing amino groups such as peptides, nucleotides, antibiotics, and alkaloids. Therefore, it is not surprising to find that the Mannich reaction has been applied to the synthesis of chiral diamines. Generally, carbonyl compounds having an α-nitrogen functional group can be involved in such kinds of reactions. Recently, a highly stereocontrolled synthesis of vicinal diamines by organocatalytic asymmetric Mannich reaction of *N*-protected aminoacetaldehydes was described by Maruoka and co-workers.[135] As shown in Scheme 4.7, by adding L-proline or the axially chiral amino sulfonamide (S)-**TK-1** as the catalyst, the corresponding *syn* or *anti*- diamines could be readily obtained in high enantiopurity

[135] Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K., *J. Am. Chem. Soc.* **2012,** *134*, 7516.

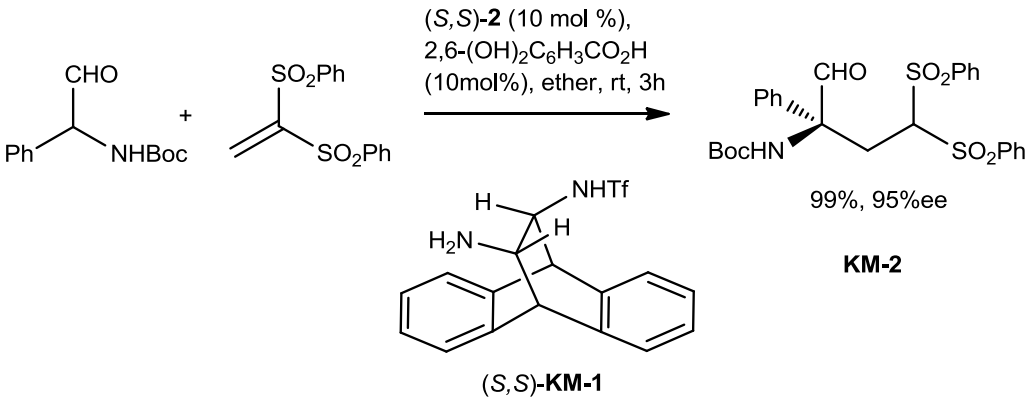


Scheme 4.7 Mannich reaction in diamine synthesis

2. 1,2-Diamines in organic synthesis

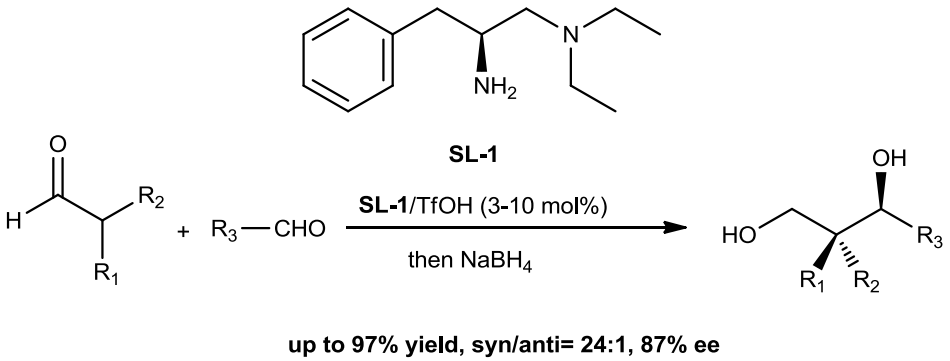
In organic synthesis, vicinal diamines as various chiral ligands play a crucial role especially in the field of catalytic asymmetric synthesis.[136] Therefore, intense efforts have been devoted to their synthesis and applications in organic synthesis. Among recent results, (S,S)-**KM-1** as an asymmetric catalyst used in asymmetric conjugate addition of heterosubstituted aldehydes to vinyl sulfone, was developed by Maruoka and co-workers (Scheme 4.8). It is a highly stereoselective reaction that produces **KM-2** in high yield.[137]

[136] (a) Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed.* **1994**, *33*, 497. (b) Tomioka, K. *Synthesis* **1990**, 541.
[137] Moteki, S. A.; Xu, S.; Arimitsu, S.; Maruoka, K. *J. Am. Chem. Soc.*, **2010**, *132*, 17074.



Scheme 4.8 Conjugate addition of heterosubstituted aldehydes to vinyl sulfone

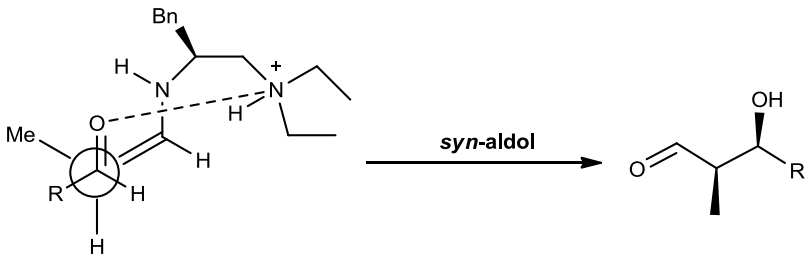
The search for a highly syn-selective cross-aldol reaction of aldehydes has remained a big challenge for chemists.[138] Various vicinal chiral diamines have been screened by Luo and co-workers to mediate syn-selective cross-aldol reactions of aldehydes (Scheme 4.9).[139] L-phenylalanine derived **SL-1**/TfOH was found to be the best catalyst in this cross-aldol reaction of aldehydes. As shown in Scheme 4.10, the corresponding transition state of *syn*-aldol reaction is proposed.



Scheme 4.9 Cross-aldol reaction of aldehydes

[138] (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (b) List, B. *Chem. Commun.* **2006**, 819. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (d) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (e) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2007**, *20*, 131. (f) List, B.; Lerner, R. A.; Barbas, C. F., *J. Am. Chem. Soc.* **2000**, *122*, 2395. (g) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (h) Torri, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (i) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285.

[139] Li, J.; Fu, N.; Li, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010,** *75*, 4501.

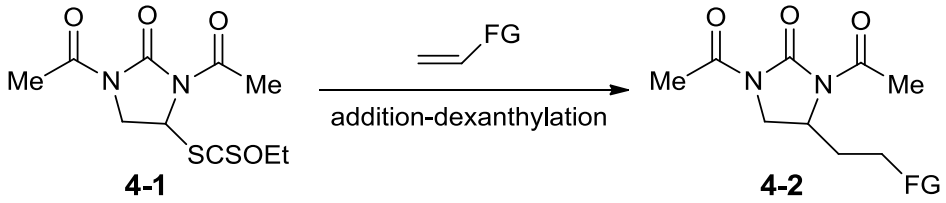


Scheme 4.10

II. Synthesis of 1,2-diamine via degenerative transfer of xanthates onto alkenes

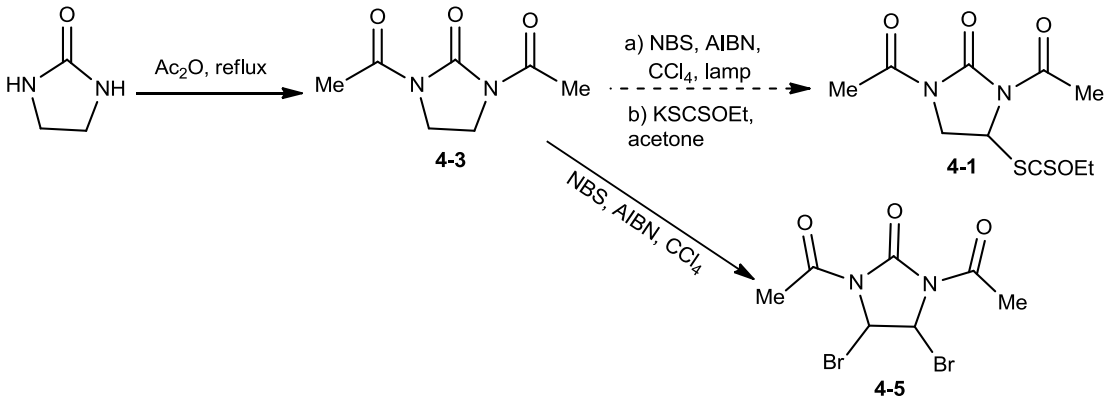
1. Radical addition of xanthates to 1,2-diaminoalkenes

The radical addition of xanthates to alkenes allows a modular, convergent access to complex structures. For the synthesis of 1,2-diamines, we considered the utilisation of xanthate **4-1** and as a flexible reagent for the preparation of 1,2-diamines as pictured in Scheme 4.11.



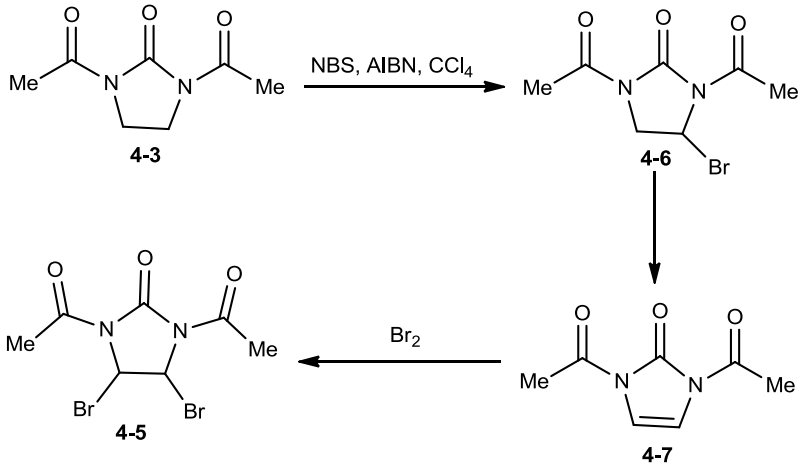
Scheme 4.11

First we tried the bromination of **4-3** using the Wohl-Ziegler reaction as a potentially rapid route to xanthate **4-1**. Since imidazolidin-2-one is quite cheap and readily available, its acylation could furnish **4-3** as the starting material for the bromination reaction. However, as illustrated in Scheme 4.12, using the same bromination procedure, a mixture of dibrominated and unsaturated products **4-5** and **4-7** were observed instead of the desired mono brominated product.



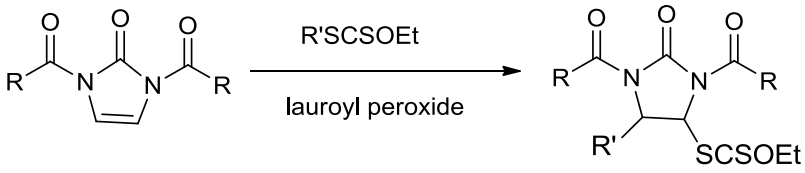
Scheme 4.12 Synthesis of xanthate **4-1**

The dibrominated product could arise from the bromination of **4-7** generated from the elimination of **4-6** (Scheme 4.13). A possible remedy was to lower the concentration of the bromine by diluting the solution and adding the NBS portion-wise over a longer period. Unfortunately, even under quite dilute conditions, none of the desired mono brominated product **4-6** was observed in the crude NMR spectrum.



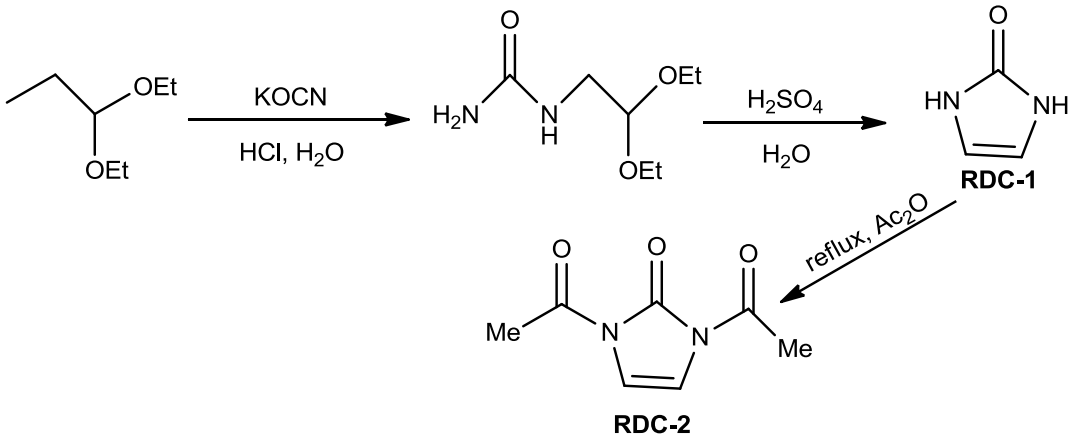
Scheme 4.13 Bromiantion of **4-3**

The unsuccessful bromination of **4-3** persuaded us to find an alternative method for the synthesis of xanthate **4-1**. In 2010, Guillaume Revol reported a powerful strategy for the preparation of complex primary amines based on the radical addition of various xanthates to *N*-vinyl phthalimide. Therefore, we next tested the applicability of this method for the synthesis of 1,2-diamines as shown in Scheme 4.14.



Scheme 4.14

Following the literature procedure, alkene **RDC-1** was quickly available via two steps on multigram scale.[140] The formation of ureidoacetaldehyde diethyl acetal was accomplished by treatment of aminoacetaldehyde diethyl acetal with potassium cyanate in aqueous HCl. In the presence of sulfuric acid, this white crystalline solid undergoes a dehydrative intramolecular cyclization to form 2-imidazolinone **RDC-1** in good yield. With quantities of 2-imidazolinone **RDC-1** in hand, we prepared 1,3-diacetyl-1,3-dihydro-2*H*-imidazol-2-one **RDC-2** by the same acetylation procedure as for imidazolidin-2-one **4-3**.

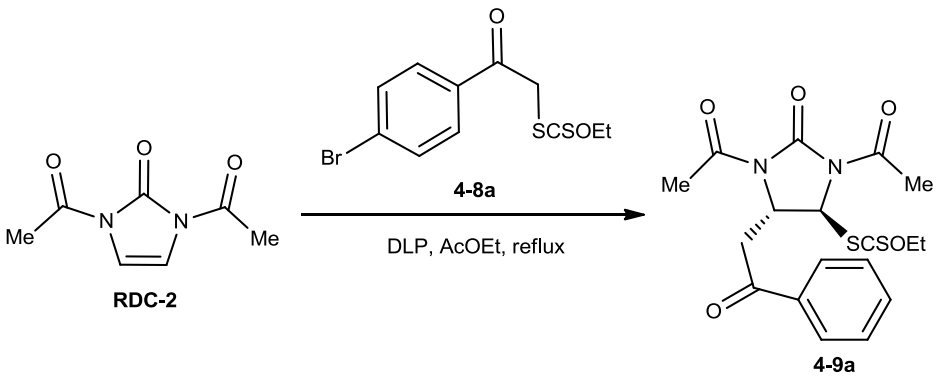


Scheme 4.15 Synthesis of **RDC-2**

We first tried the radical addition of xanthate **4-8a** to olefin **RDC-2** according to the general procedure and added excess olefin **RDC-2**. However, a large amount of oligomer was then observed. Probably, as for *N*-vinyl phthalimide, olefin **RDC-2** is an active alkene which generates a stable radical to form the oligomer during this radical

[140] Fischer, W.; Hollins, R. A.; Lowe-Ma, C. K.; Nissan, R. A.; Chapman, R. D. *J. Org. Chem.* **1996**, *61*, 9340.

process. Therefore, applying the same approach as for the radical addition of xanthates to *N*-vinyl phthalimide, we lowered the concentration of the solution and increased the ratio of xanthate **4-8a** to olefin **RDC-2**, in order to reduce the chances to form oligomer. After a simple optimization, the yield of adduct **4-9a** increased to 62% (Scheme 4.16).



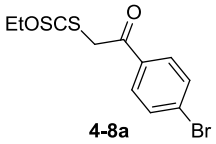
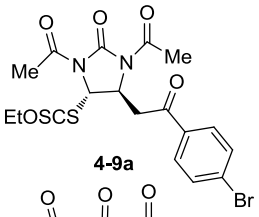
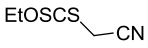
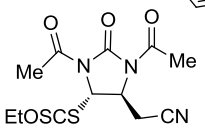
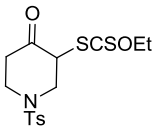
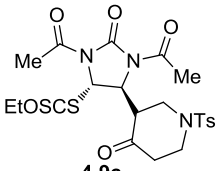
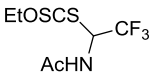
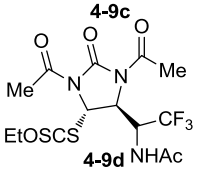
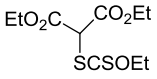
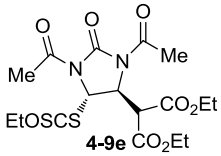
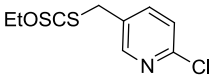
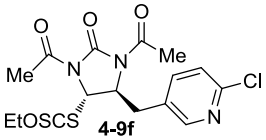
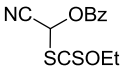
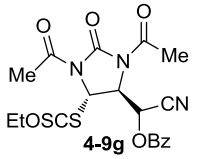
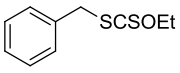
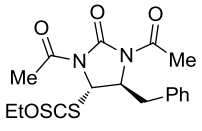
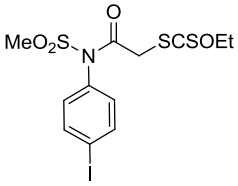
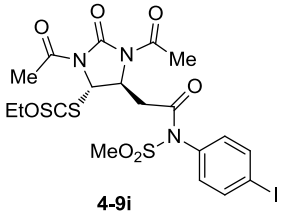
Concentration	Xanthate **4-8a**	Yield %
1 M	1.5 equiv.	trace
0.5 M	2 equiv.	33%
0.25 M	3 equiv.	62%

Scheme 4.16 Synthesis of **4-9a**

As shown by the results in Table 1, the radical addition of various xanthates **4-8** to **RDC-2** gave generally good yields of the *trans* adduct **4-9**. It is worthwhile to note that the radical addition of xanthates **4-8** to alkene **RDC-2** gives only *trans* adducts **4-9** in a highly stereoselective process. Addition of the carbon radical from the xanthate onto one face of alkene **RDC-2** leads an intermediate radical where this face is now sterically blocked, forcing the transfer of the xanthate from the opposite side.

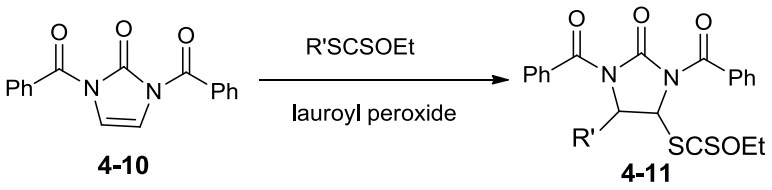
Furthermore, it is clear from the transformations in Table 4.1 that numerous functional groups may be introduced through the xanthate partner **4-8**. Therefore, functionality in the xanthate allows the incorporation of an aryl, a cyano, a protected cyclic or open-chain amino, a trifluoromethylamino, or a heterocyclic groups. The presence of the xanthate group in the adducts should allow for a second radical addition.

Table 4.1 Diamine **4-9**

Xanthate **4-8**	Radical adduct **4-9**	Yield %	DLP %	
 **4-8a**	 **4-9a**	62%	45%	
 **4-8b**	 **4-9b**	76%	10%	
 **4-8c**	 **4-9c**	61%	55%	dr:3:2[a]
 **4-8d**	 **4-9d**	68%	45%	dr:2:1[a]
 **4-8e**	 **4-9e**	88%	15%	
 **4-8f**	 **4-9f**	54%	60%	
 **4-8g**	 **4-9g**	68%	45%	dr:1:1[a]
 **4-8h**	 **4-9h**	56%	45%	
 **4-8i**	 **4-9i**	52%	30%	

[a] The dr was measured by NMR spectroscopy after purifiction by column chromatography.

In order to fine tune the stability of the alkene and perhaps improve the efficiency, we replaced the acetyl by benzoyl as the *N*-protecting group and then alkene **4-10** was prepared by standard benzoylation. The radical addition of several xanthates to alkene **4-10** was then investigated.

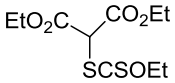
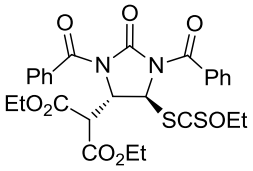
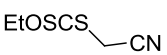
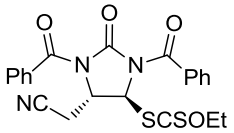
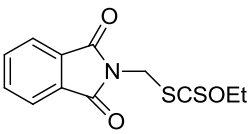
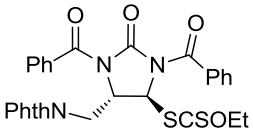


4-10 **4-11**

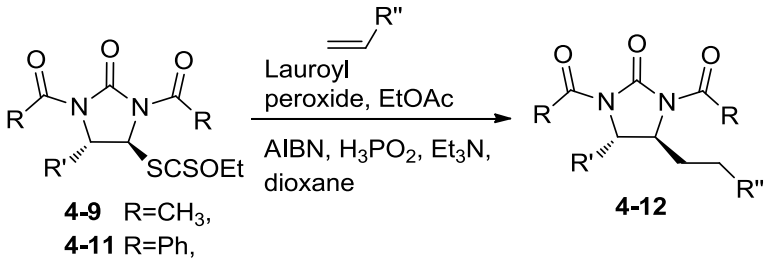
Scheme 4.17 Synthesis of **4-11**

The radical addition required in general a little bit more DLP as compared with alkene **RDC-2** (Scheme 4.17). The benzoyl group may stabilize the carbon radical somewhat better than acetyl group, but this does not make a significant difference in the efficiency. Not surprisingly, the *trans* adducts **4-11** were the only products as indicated in Table 4.2.

Table 4.2 Diamine **4-11**

Xanthate **4-8**	Radical adduct **4-11**	Yield %	DLP %
 **4-8e**	 **4-11a**	92%	15%
 **4-8b**	 **4-11b**	85%	20%
 **4-8h**	 **4-11c**	62%	45%

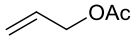
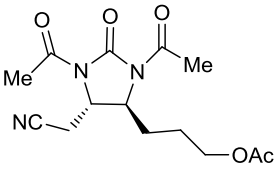
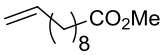
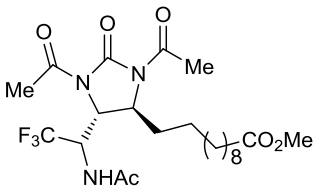
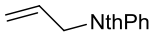
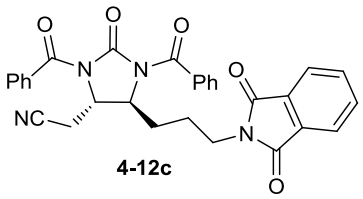
After we gained some experience in synthesis of these adducts, we examined the radical additions of those adducts **4-9** or **4-11** to various unactivated olefins (Scheme 4.18). We were quite delighted to observe the formation of the corresponding adduct **4-12** after a short reaction time. Reductive removal of the xanthate group simplified their NMR spectra and their characterization. Furthermore, the C-C bond formation, as expected, takes place from the opposite side to the R' side chain with net overall retention of configuration.



Scheme 4.18 Secondary radical addition

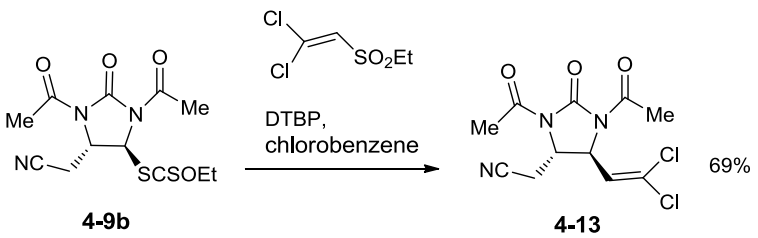
As shown in Table 4.3, the more complex *trans* diamines **4-12** can thereby be obtained in good yield for the combined two steps, which demonstrates the efficient radical additions of these newly synthesized diamine xanthates to various unactivated olefins. Furthermore, the radical addition of adduct **4-9d,** which is a triamine bearing a trifluoromethyl group, to various olefins can be considered as a concise and diverse synthetic route to access such kinds of triamines which would be extremely difficult to obtain by more conventional approaches. The addition of adduct **4-11b** to *N*-allyl phthalimide introduces another protected amino unit to the final diamine product, and this is another interesting triamine structure.

Table 4.3 Diamine **4-12**

Xanthate	Alkene	Radical adduct **4-12**	Yield % step1+step2	step1 DLP %
4-9b		 **4-12a**	54%	25%
4-9d		 **4-12b**	68%	10%
4-11b		 **4-12c**	64%	10%

2. Extension of 1,2-diamine synthesis

To extend the scope of this strategy, we carried out the transformation pictured in Scheme 4.19. As discussed in the introduction, the addition of xanthate **4-9b** to 1,1-dichloro-2-(ethylsulfonyl)ethylene gave diamine **4-13** in good yield. The dichlorovinyl motif may be converted into an alkyne by the powerful Corey-Fuchs reaction or used in organometallic coupling reactions.[141]

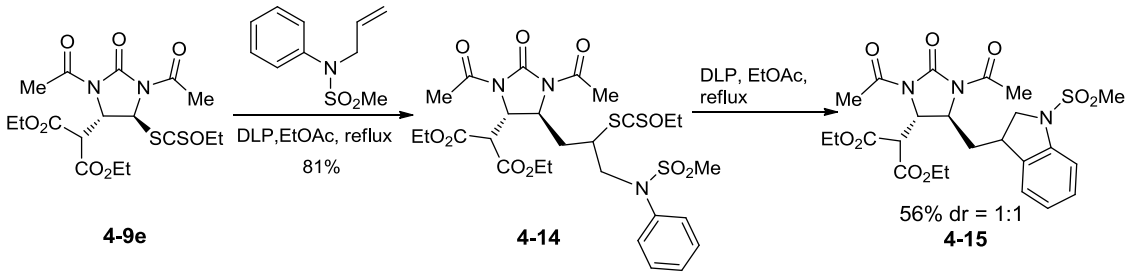


4-9b **4-13**

Scheme 4.19

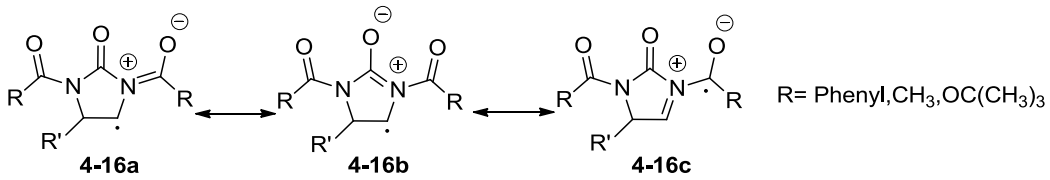
[141] Li, Z.; Zard, S. Z., *Org. Lett.* **2009**, *11*, 2868.

Another equally interesting extension is the combination of the diamine unit with an indoline. As illustrated in Scheme 4.20, we successfully incorporated the protected diamine unit to indoline **4-15** via a sequential radical addition and cyclization process. Based on this interesting structure **4-15**, the synthesis of more complex polycyclic compounds could be envisaged.



Scheme 4.20

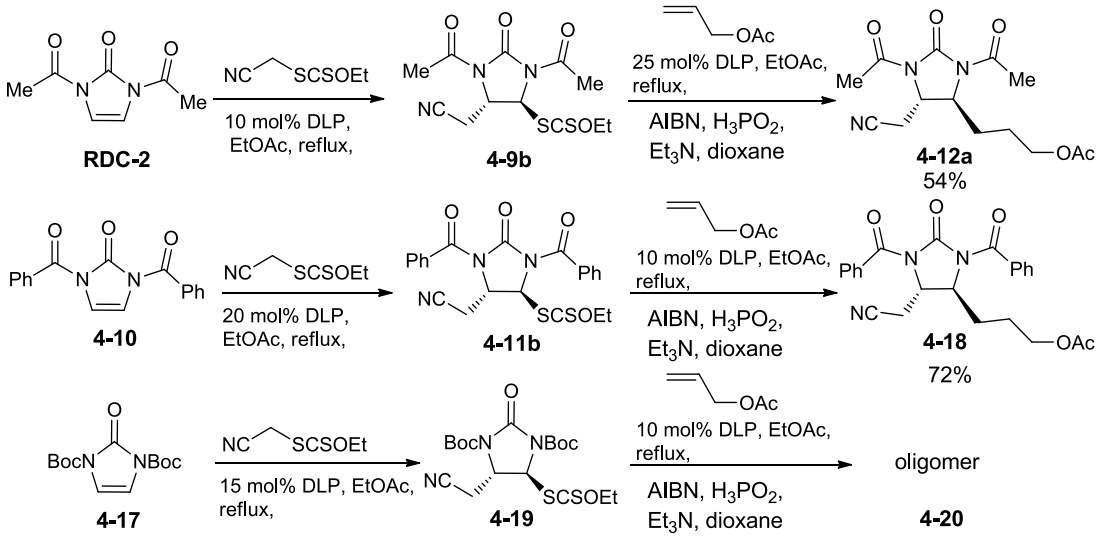
The success of the second addition can be explained by canonical forms **4-16 a-d** as shown in Scheme 4.21, which suggests how this imide structure could stabilize the radical intermediate. By replacing the acetyl with a benzoyl, we found, in general, that the first addition to the benzoyl protected olefin **4-10** with the same xanthate required more DLP to complete the reaction a compared with the acetyl analog. In the second radical additions to allyl acetate, a small amount of oligomer (double and triple addition to allyl acetate) could be observed in the case of the xanthate derived from olefin **RDC-2** and consequently, the second addition is more efficient in the benzoyl protected series.



Scheme 4.21 Canonical forms **4-16 a-c**

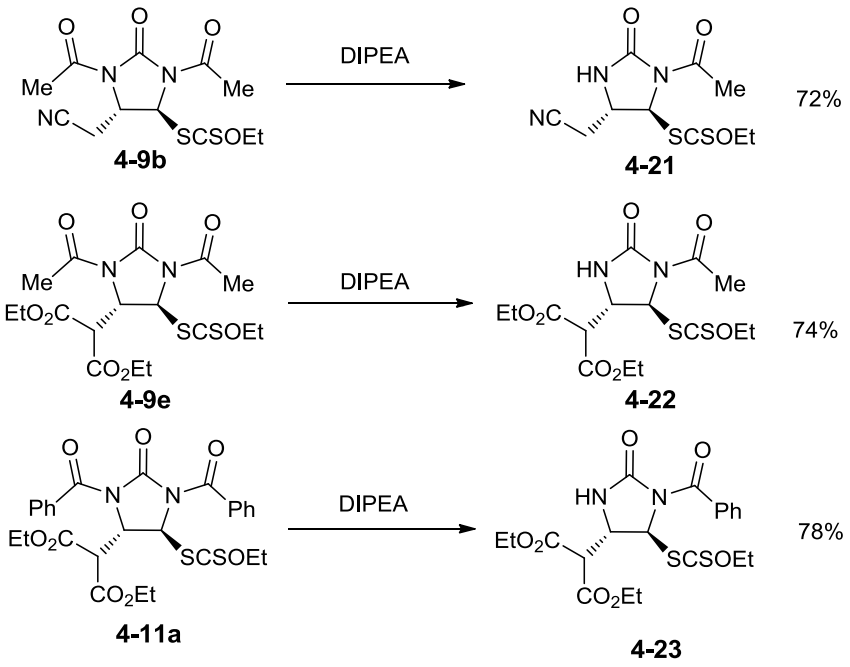
To better understand the stability of radical intermediates bearing different protecting groups, we started an investigation using acetyl, benzoyl or Boc as the

nitrogen protecting group. The sequential two radical additions involve the same xanthate and ally acetate as the second olefin. The results shown in Scheme 4.22 seem to suggest the notion that the greater resonance stabilization is provided by the benzoyl substituent in **4-11b** than by the acetyl substituent in **4-9a**.



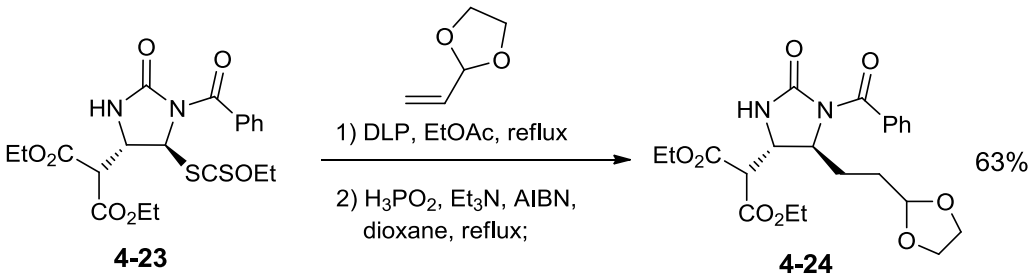
Scheme 4.22

An interesting observation concerning the protecting group is that the acyl group on the nitrogen distal from the xanthate can be selectively removed by *N*,*N*-diisopropylethylamine in high yield (Scheme 4.23). The causes underlying this regioselectivity are not clear. It is obviously not steric since both nitrogens appear to be comparably hindered



Scheme 4.23 Selective deprotection

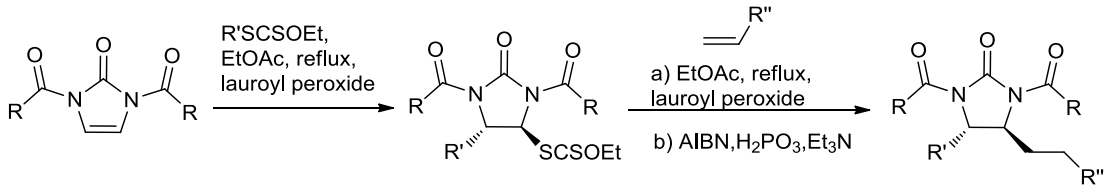
The mono protected diamine xanthate **4-23** was able to undergo a second radical addition. As shown in Scheme 4.24, the radical addition and reductive removal of the xanthate group furnished the corresponding protected diamine **4-24**. In the product the two nitrogens are clearly differentiated allowing subsequent regioselective modification.



Scheme 4.24

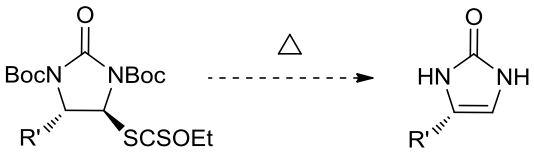
Conclusion

As summarized in Scheme 4.25, a modular and concise approach to access highly functionalized 1,2-diamines was investigated by us. The examples displayed in Table 4.1, Table 4.2 and Table 4.3 demonstrate that the radical addition of xanthates to 1,2-diamino substituted olefins followed by a second addition represents a highly efficient route to produce diversely complex 1,2-diamine structures. This approach complements the previous ones developed earlier. Taken together, these various transformations constitute a significant contribution to the synthesis of amines.



Scheme 4.25

Ongoing work to further explore the scope of this method is in progress. One reaction being tested is the possible elimination of the xanthate group by thermolysis of the addition products (Scheme. 4.26).



Scheme 4.26