Pure Appl. Chem., Vol. 82, No. 3, pp. 541–554, 2010.
doi:10.1351/PAC-CON-09-08-04

Thioamide dianions derived from *N*-arylmethyl thioamides: Generation and application as carbon nucleophiles adjacent to the nitrogen atom*

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Abstract: This review illustrates the ready availability of thioamide dianions and their versatility as carbon nucleophiles adjacent to the nitrogen atom. The products derived from the addition of thioamide dianions to a range of electrophiles can participate in a cyclization reaction to form nitrogen-containing heterocycles. The electronic properties of thioamide dianions are also considered.

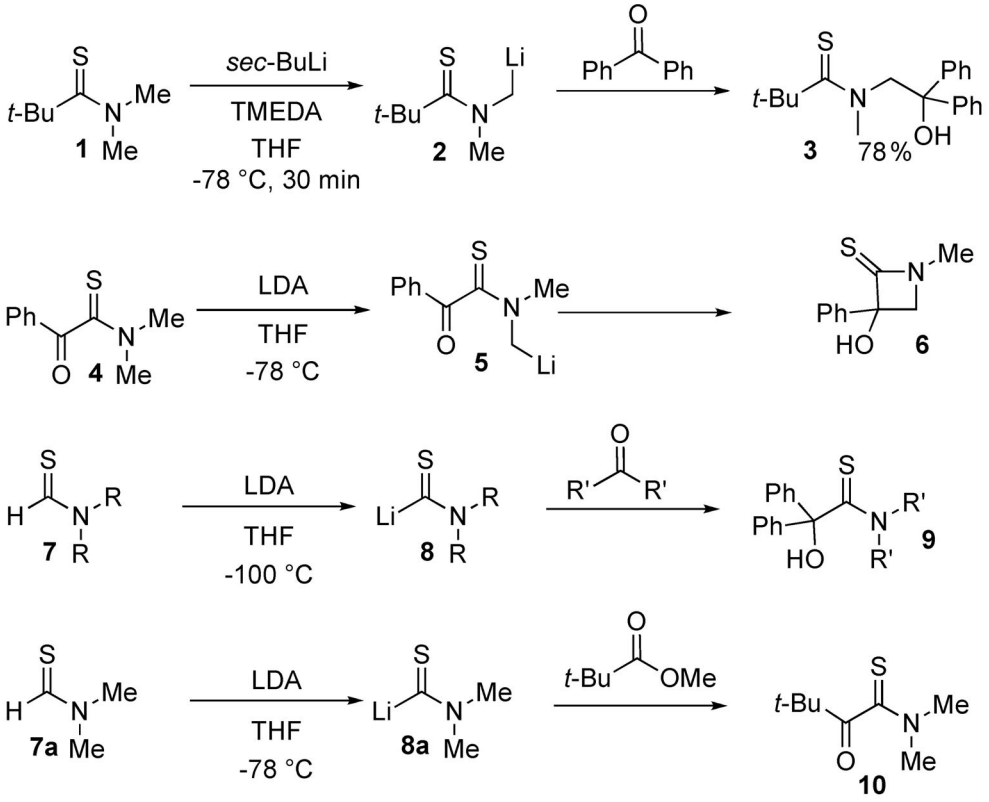
Keywords: dianions; intramolecular cyclization; iodocyclization; ring opening; thioamides.

INTRODUCTION

Carbanions are amongst the most fundamental and important reactive species. Deprotonation of carbonyl compounds constitutes one familiar method for their generation. Thiocarbonyl compounds have also been used as precursors of carbanions [1]. The generation and use of sulfur isologues of enolates, i.e., enethiolates, as carbon nucleophiles have been studied in great detail. In these cases, sulfur isologues of esters and amides, i.e., dithioic acid esters and thioamides, are used more often than thioaldehydes and thioketones.

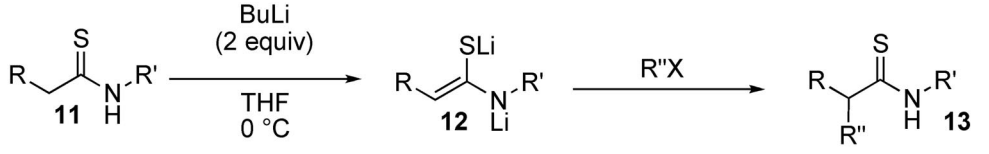
Thioamides show specific and unique reactivity and reaction patterns. Generally, α-protons of thiocarbonyl compounds are more acidic than those of the corresponding carbonyl compounds. Moreover, selective deprotonation depending on the substitution patterns is observed for thioamides. The deprotonation of *N*,*N*-dimethyl thiopivalamide (**1**) with *sec*-BuLi takes place efficiently at the methyl group attached to a nitrogen atom at –78 °C to form the carbanion **2** (eq. 1) [2]. The trapping of **2** with benzophenone gives thioamide **3**. In this case, the deprotonation at the α-position of the nitrogen atom is specific with an *N*,*N*-dimethylamino group. Attempts to perform similar reactions with *N*,*N*-diethyl, and *N*,*N*-benzyl,methyl thioamides have not been successful. Application of this deprotonation to α-oxo thioamide **4** leads to intramolecular cyclization of the in situ-generated carbanion **5** to give thiolactam **6** (eq. 2) [3]. Unlike thioamide **1**, *N*,*N*-dialkyl thioformamides **7** undergo deprotonation at thioformyl carbon atoms by reacting with lithium diisopropylamide (LDA) at –100 °C to generate thiocarbamoyl anions **8** (eq. 3) [4]. The trapping of **8** with ketones produces α-hydroxy thioamides **9**. The use of methyl pivalate as a trapping agent in the reaction of *N*,*N*-dimethyl thioformamide (**7a**) leads to α-oxo thioamide **10** (eq. 4) [3].

*Paper based on a presentation at the 9th International Conference on Heteroatom Chemistry (ICHAC-9), 30 June–4 July 2009, Oviedo, Spain. Other presentations are published in this issue, pp. 505–677.



(1) (2) (3) (4)

Secondary thioamides are also subjected to deprotonation to selectively form a variety of carbanions, depending on the substituents. The reaction of secondary alkylthioamides **11** with excess BuLi generates Y-shaped dianions **12** (eq. 5) [5]. The dianions behave like enethiolates, and the alkylation of **12** with alkyl halides takes place at the carbon atom α to the thiocarbonyl group to yield α,α-disubstituted secondary thioamides **13**. For the reaction of secondary aromatic thioamides **14**, the second lithiation takes place on the aromatic ring to generate dianions **15** (eq. 6) [6]. Selective trapping at the aromatic rings of **15** proceeds with disulfides, aldehydes, silyl chlorides, and dimethylformamide (DMF) to form adducts **16**. In contrast, secondary *o*-toluyl thioamide **17a** is deprotonated at the nitrogen atom and benzylic carbon atom to form benzyl anion **18a** (eq. 7). Addition of **18a** to adamantanone occurs to give **19a**. The trapping of **18a** with acid chlorides selectively takes place at the nitrogen atom to form *N*-acyl thioamides **19b** (eq. 8) [7]. *N*-(Benzotriazol-1-ylmethyl) thiobenzamides **20** are also used as secondary thioamides (eq. 9). Deprotonation of **20** with LDA or BuLi generates dianions **21**, followed by the reaction with electrophiles to give thioamides **22** [8]. In this case, the second deprotonation selectively takes place at the carbon atom bearing two nitrogen atoms.



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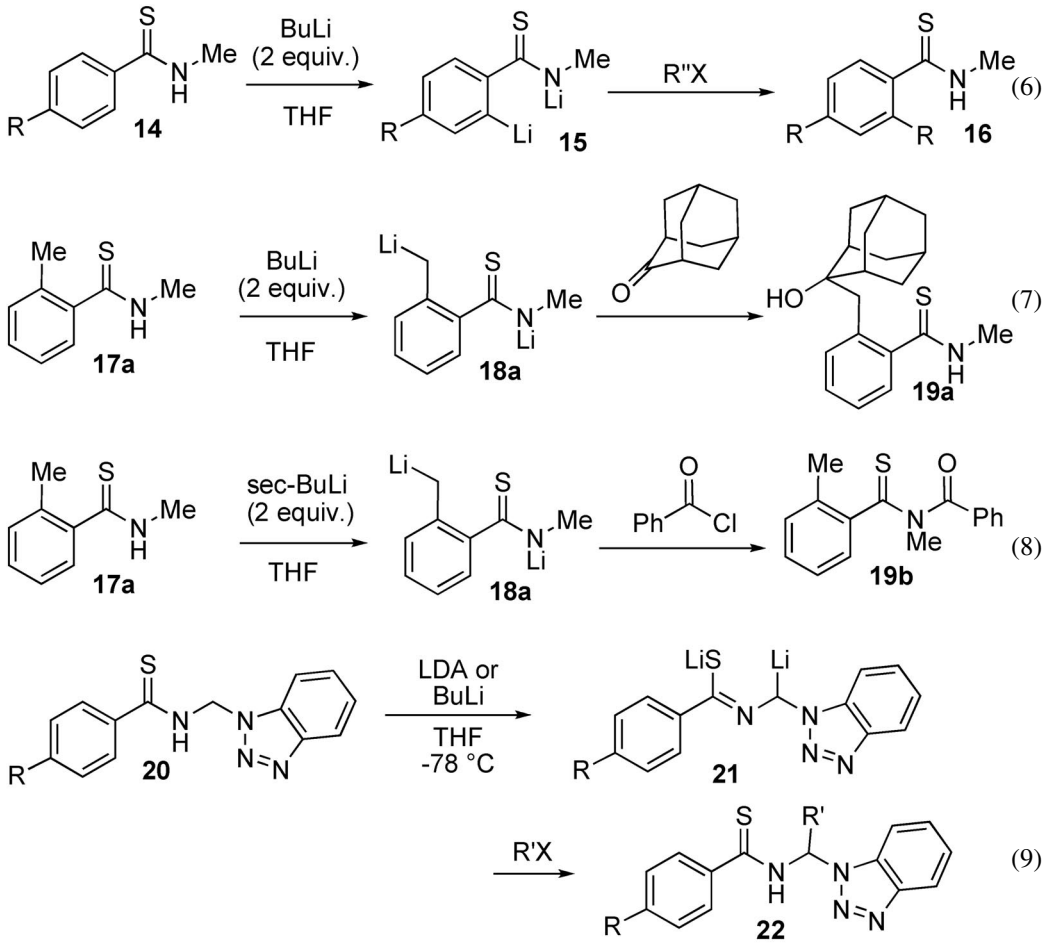

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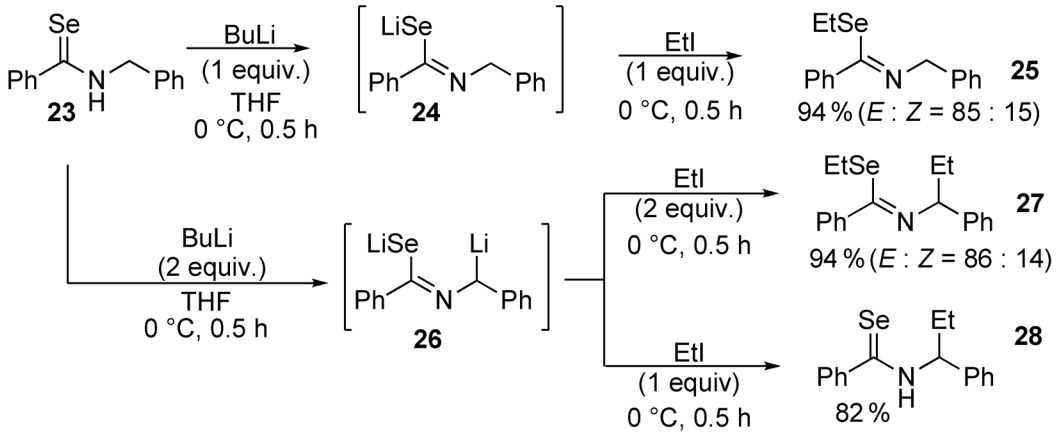
RESULTS AND DISCUSSION

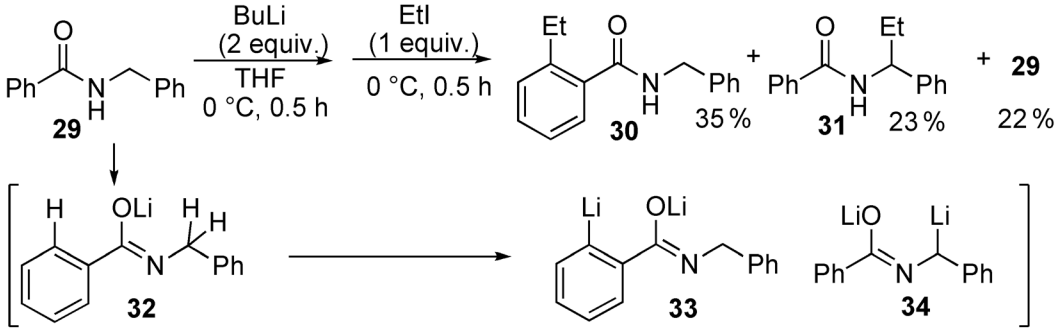
Amide and selenoamide dianions

Against this background, we have extensively studied the syntheses and properties of heavier isologues of amides [9–11]. In particular, the electronic structures of selenium-containing charged species [12] have been elucidated since ^{77}Se NMR spectra are informative on subtle change of electronic structures of selenium-containing compounds.

The addition of BuLi (1 equiv) to *N*-benzyl selenoamide **23** followed by the addition of ethyl iodide gave selenoimidate **25** as a stereoisomeric mixture (Scheme 1) [13]. Selective deprotonation from the nitrogen atom of **23** takes place to generate lithium selenoimidate **24**. During the addition of BuLi, the reaction mixture once changed to deep purple, but the color instantly disappeared. BuLi (2 equiv) was then added to a tetrahydrofuran (THF) solution of **23** to give a deep purple solution. To this, ethyl iodide (2 equiv) was added to form the product **27**, in which two ethyl groups were introduced to the selenium and benzylic carbon atoms. The use of ethyl iodide (1 equiv) and aqueous work-up of the reaction mixture gave selenoamide **28**, in which an ethyl group was selectively introduced to the benzylic carbon atom. These results suggested the formation of selenoamide dianion **26**. This is in marked contrast to the reaction of *N*-benzyl benzamide (**29**) with BuLi (Scheme 2) [14]. Ethylation at the benzylic carbon atom as well as at the aromatic carbon atom led to the formation of **30** and **31** along with the recovery of **29**. This implied the formation of two types of dianions, **33** and **34**, via monoanion



Scheme 1 Generation and reaction of selenoamide mono- and dianions.

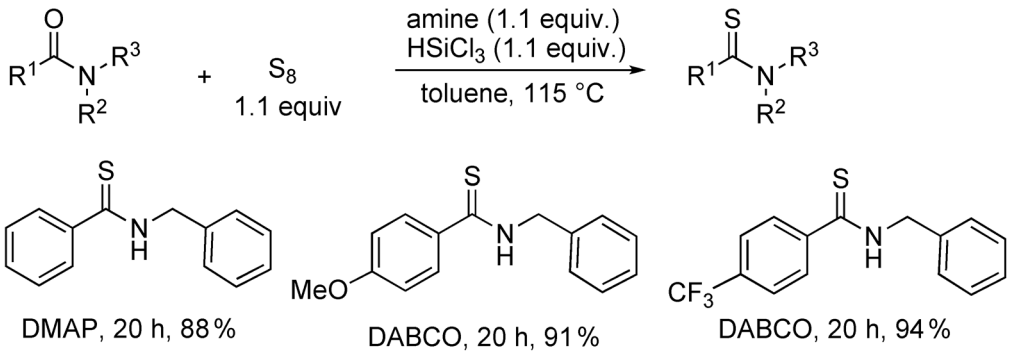


Scheme 2 Generation and reaction of amide dianion.

32. The selenoamide dianion **26** can be used as a carbanion adjacent to a secondary nitrogen atom, but to enhance the synthetic availability, the use of selenoamides should be avoided because of the belief that selenium-containing compounds are toxic. We then shifted our attention to thioamides, since thio- and selenoamides often show similar reaction patterns.

Thionation of ordinary amides

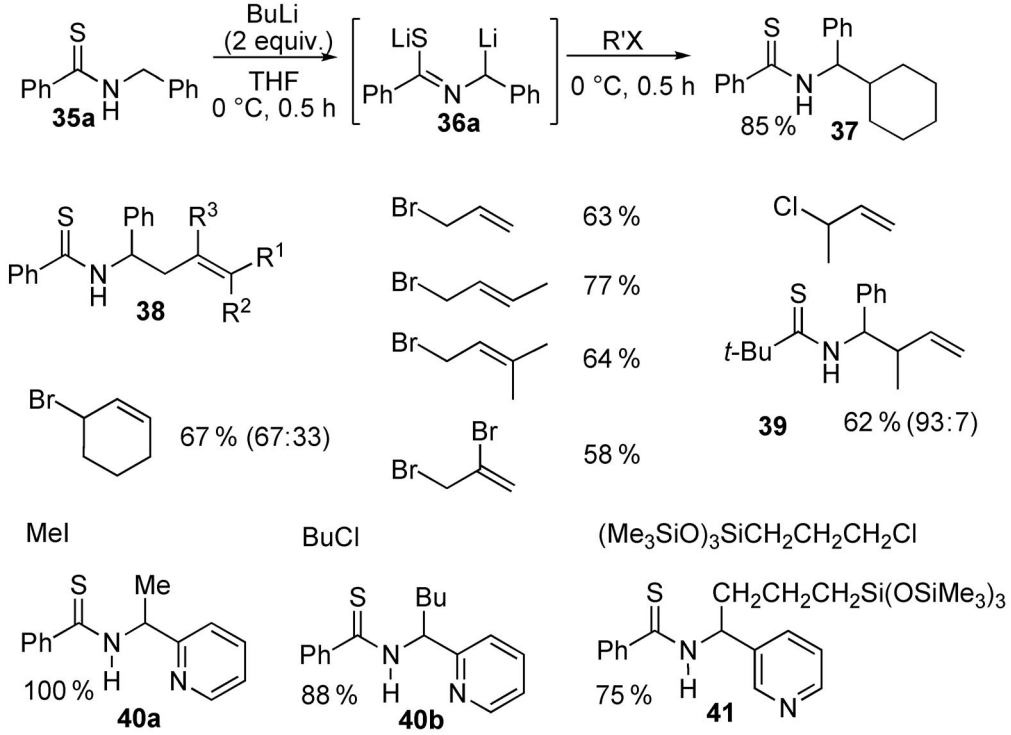
A variety of methods for the synthesis of secondary thioamides have been reported [15]. The condensation reaction of aromatic aldehydes, elemental sulfur, and primary amines, which has been called the Willgerodt–Kindler reaction, is known [16]. The thionation of ordinary amides with commercially available Lawesson reagent is also effective [17]. In the former reaction, the yields of thioamides highly depend on the substituents on aldehdyes and amines. In the latter case, phosphorus-containing byproducts sometimes hamper the isolation of thioamides with high purities. Therefore, we developed a more direct, widely accessible thionation. S^{2-} species was generated in situ by reacting elemental sulfur with $HSiCl_3$ in the presence of tertiary amines and directly used as a thionating agent (Scheme 3) [18]. *N*-Benzyl aromatic amides were stirred with elemental sulfur, tricholorosilane, and amines under reflux in toluene to give the desired thioamides. The appropriate choice of amines enhanced the yields of the thioamides.



Scheme 3 Thionation of *N*-benzyl aromatic amides with S_8, amine, $HSiCl_3$.

Thioamide dianions

Initially, *N*-benzyl benzthioamide (**35a**) was treated with BuLi (2 equiv) (Scheme 4) [14]. Cyclohexyl bromide was then added to the reaction mixture to produce thioamide **37** in high yield. Therefore, thioamide dianion **36a** was formed, and the alkylation of **36a** proceeded selectively at the benzylic carbon atom, as expected. Allylic halides were also used to trap thioamide dianion **36a**. In all cases, the substitution reaction of allylic halides took place at the carbon atom with halogen atoms, to lead to *N*-thioacyl homoallylic amines **38**, although the diastereoselectivity of the reaction was not high.

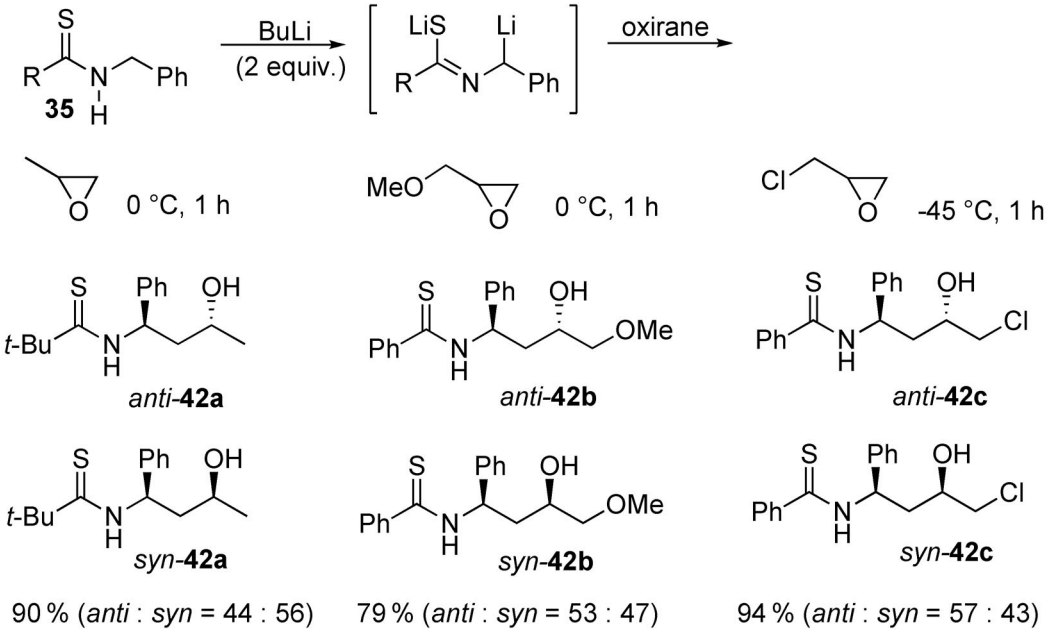


Scheme 4 Reaction of thioamide dianions with alkyl and allylic halides.

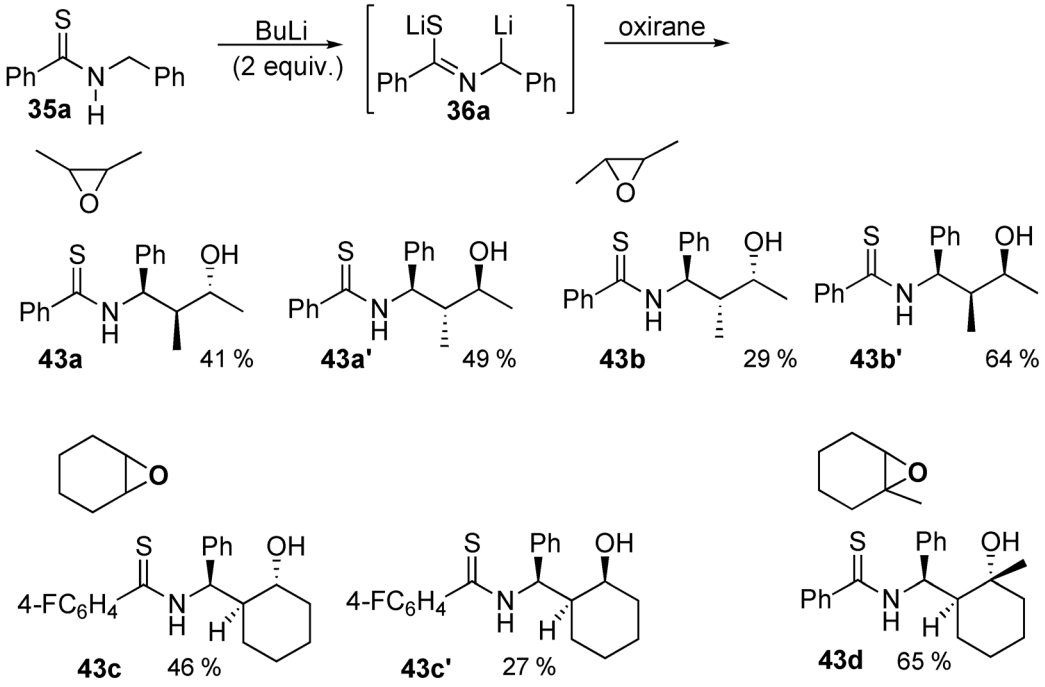
As thioamides, aliphatic thioamide, and *N*-benzylic *N*-2- and 3-pyridylmethyl aromatic thioamides participated in the generation of thioamide dianions, and their trapping with allylic chloride, methyl iodide, and alkyl chlorides led to thioamides **39–41** [19]. For the reaction with 3-chloro-1-butene, stereoisomers **39** were obtained in a ratio of 93:7, and no regioisomer was formed.

Ring opening of oxiranes

A variety of electrophiles were then used for the addition to thioamide dianions. The results of the reaction with monosubstituted oxiranes are shown in Scheme 5 [20]. The ring opening of propylene oxide took place selectively at the primary carbon atom to give *N*-thioacyl 1,3-aminoalcohol **42a** as a diastereomeric mixture. The methoxy group and chlorine atom did not affect the efficiency or diastereoselectivity of the reaction and led to **42b** and **42c**, although the reaction at lower temperature was preferable in the latter case. The diastereomers shown in Scheme 5 were readily separated during purification by column chromatography on silica gel, and the yellow color of the products was indicative of fractions containing the desired products. The stereochemical outcome of the ring opening of oxiranes is shown in Scheme 6. The ring-opening of *cis*-2-butene oxide with thioamide dianion **36a** proceeded smoothly to give two diastereomers **43a** and **43a'** out of four possible isomers. The use of *trans*-2-butene oxide also gave two other diastereomers **43b** and **43b'**. These diastereomers were readily separated during purification, and four diastereomers, where the stereochemistry of three successive carbon atoms was controlled, were obtained in pure form by the combination of two stereoisomeric 2-butene oxides with thioamide dianions. Cyclohexene oxide participated in ring opening with thioamide dianion derived from *N*-benzyl 4-fluorobenzthioamide to form two diastereomers **43c** and **43c'**. These results indicated that the ring-opening of oxiranes proceeds with an inversion of the configuration at the carbon atom attached to the oxygen atom of oxiranes. Formation of the single stereoisomer **43d** was observed for the reaction of 1-methylcyclohexene oxide.



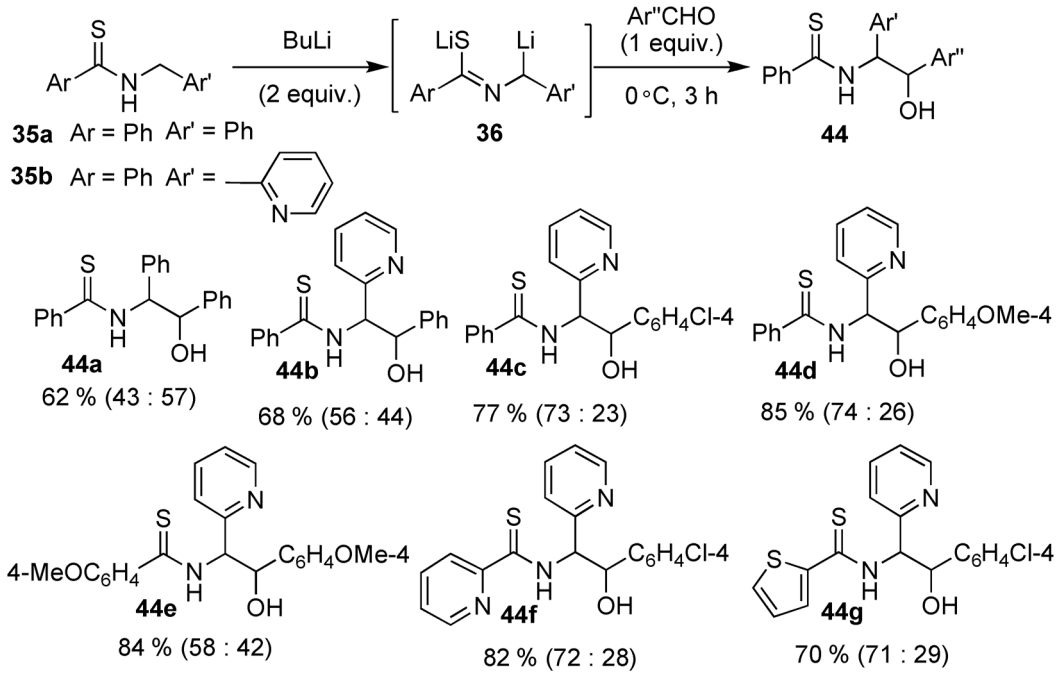
Scheme 5 Ring opening of monosubstituted oxiranes with thioamide dianions.



Scheme 6 Ring opening of di- and trisubstituted oxiranes with thioamide dianions.

Addition to aldehdyes

The carbonyl compounds were used as electrophiles in the reaction of thioamide dianions **36**. Acetone can be used as a reaction partner leading to adduct, and no products derived from the deprotonation of acetone with thioamide dianions were observed. This result suggested that thioamide dianions are highly nucleophilic and less basic. The results of the reaction with aromatic aldehydes are shown in Scheme 7. The reaction of **36a** with benzaldehyde went to completion within 3 h to give *N*-thioacyl 1,2-aminoalcohol **44a** as a stereoisomeric mixture. *N*-2-Pyridyl thiobenzamide **35b** was used as a precursor of a thioamide dianion. Deprotonation of **35b** with BuLi proceeded in a similar manner to form **36b**. The addition of aromatic aldehydes to **36b** took place efficiently to form adducts **44b–d**, but the diastereoselectivity of the reaction was only slightly improved. As thioamides, those with 4-methoxyphenyl, 2-pyridyl, and thienyl groups could be used to generate the corresponding dianions, and their additions to aromatic aldehydes gave products **44e–g**.



Scheme 7 Addition reaction of thioamide dianions to aromatic aldehdyes.

Electronic properties

To elucidate the electronic properties of thioamide dianions, their NMR spectra was measured [14]. ^{13}C NMR spectra of thioamide dianion **36a** were measured, and it showed the formation of stereoisomeric mixtures probably due to isomerism of the carbon–nitrogen bonds. After several disappointing results, ^{13}C NMR spectra of thioamide monoanion **45c** and dianion **36c** derived from thioamide **35c** were observed as single stereoisomers with sharp signals. The differences in the chemical shifts of all the carbon atoms are listed, and some are shown in Fig. 1. For **45c** and **36c**, the signals at ipso and ortho carbon atoms are shifted downfield, whereas those at meta and para carbon atoms shifted upfield. This is in marked contrast to the tendency of the known carbanion adjacent to the nitrogen atom **46**, which showed large upfield shifts at ortho and para carbon atoms [21].

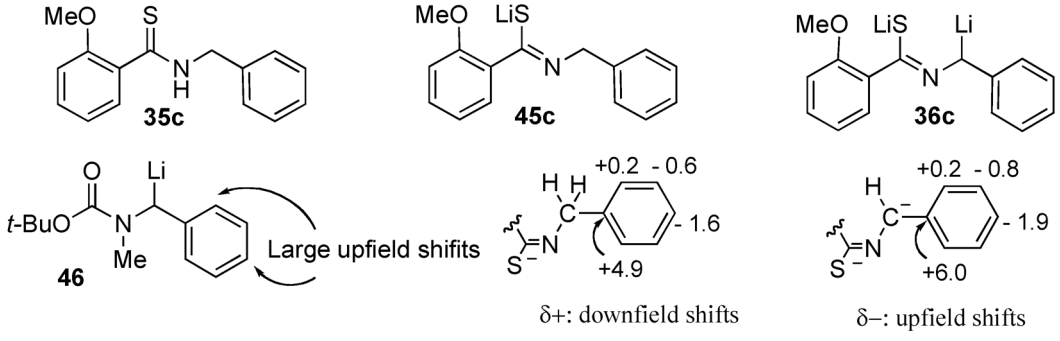


Fig. 1 Relative chemical shifts of thioamide mono- and dianions.

All of the chemical shifts of **45c** and **36c** are plotted in Fig. 2. A very strong linear correlation was observed between these signals. Therefore, these two anions appear to adopt similar aggregation states, which may be monomeric based on the sharpness of the signals.

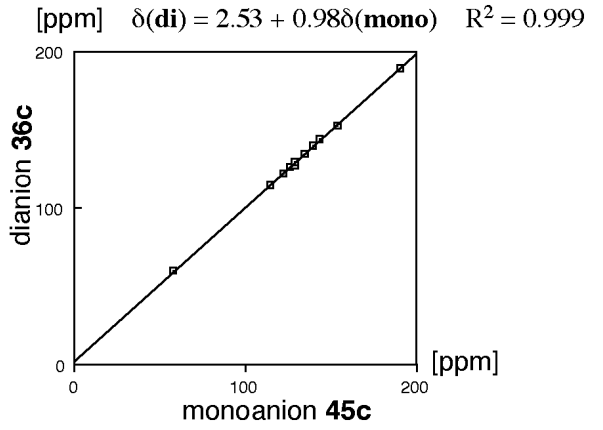
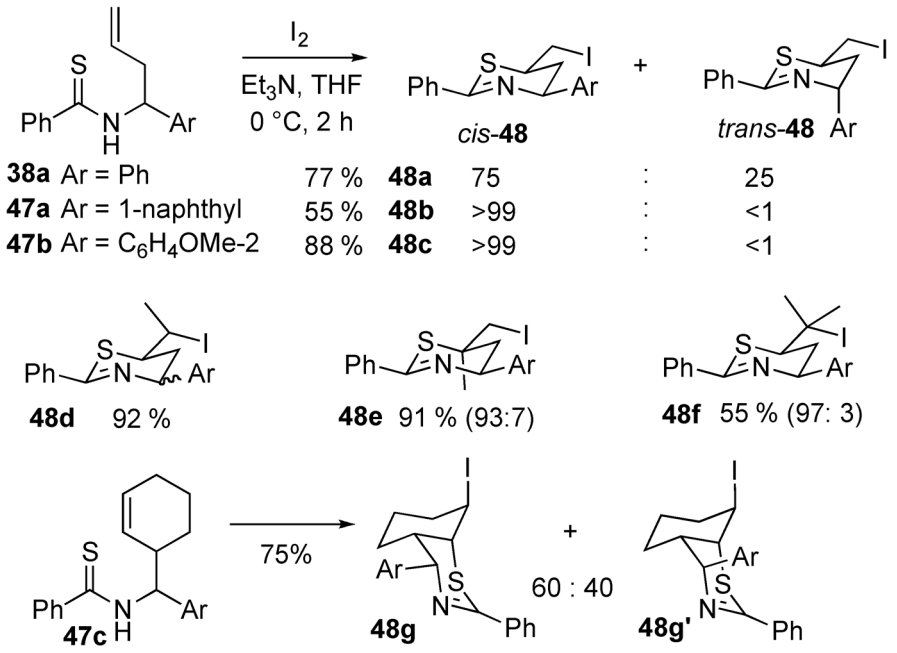


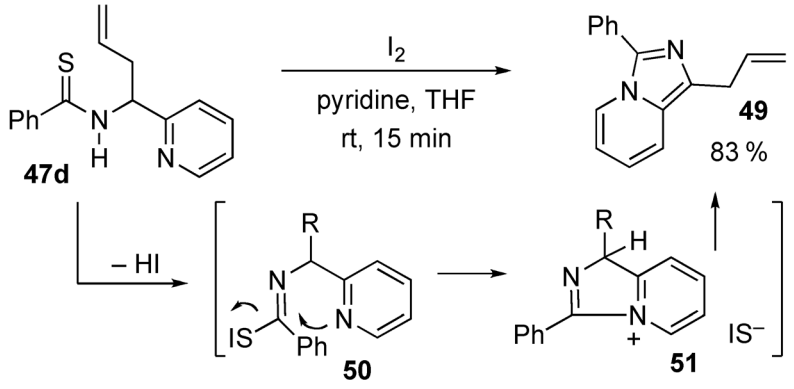
Fig. 2 Correlation in ^{13}C NMR spectra between thioamide mono- and dianions.

Iodocyclization

We then examined the cyclization of the products obtained from the reaction of thioamide dianions and electrophiles, since thioamides are already known to be useful precursors that lead to heterocycles [22,23]. Initially, the iodocyclization of *N*-homoallylic thioamides was carried out (Scheme 8). Previous examples of the iodocyclization of compounds with thiocarbonyl groups have shown that the reaction proceeds in both *exo* and *endo* modes [24]. In contrast, the selective *exo* cyclization proceeded smoothly when *N*-homoallylic thioamide **38a** was treated with iodine and Et_3N to give thiazine **48a** as a mixture of *cis* and *trans* isomers in a ratio of 75:25 [25]. The use of thioamides with 1-naphthyl and 2-methoxy groups **47** enhanced the stereoselectivity to give *cis*-**48** as single stereoisomers. Thioamides with crotyl, metallyl, and prenyl groups were also used. In all cases, *exo* cyclization took place to lead to thiazines **48d–f**. Iodocyclization was also applied to *N*-cyclohexenylmethyl thioamide **47c**. The *exo* cyclization proceeded under identical reaction conditions to give bicyclic product **48g** as two diastereomeric mixtures out of 8 possible isomers. *N*-Homoallylic thioamide bearing a 2-pyridyl group **47d** was then subjected to iodocyclization (Scheme 9). However, a similar cyclization did not take place. Instead, imidazo[1,5-a]pyridine **49** was obtained as a product [26]. In this case, the initial iodination may take place selectively at the sulfur atom of **47d**, and this is followed by the elimination of HI to form thioimidate **50**, which then undergoes intramolecular cyclization induced by the attack of a pyridyl group to the imino carbon atom to form **51**. The aromatization of **51** may lead to **49**.



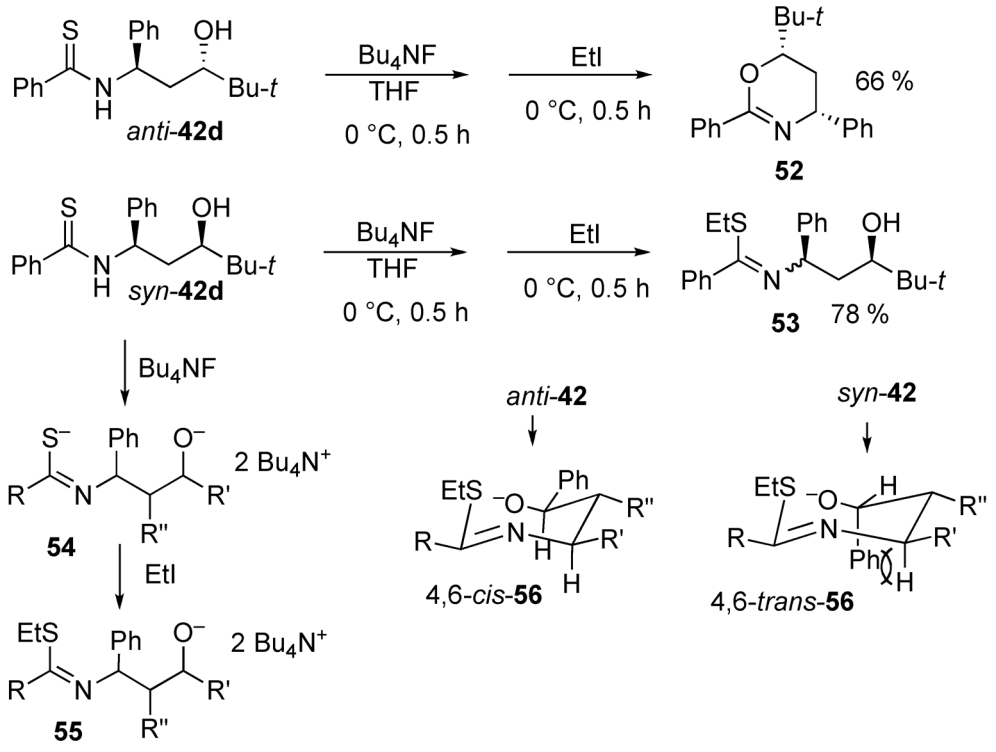
Scheme 8 Iodocyclization of *N*-thioacyl homoallylic amines.



Scheme 9 Iodine-mediated cyclization of thioamide with a 2-pyridyl group.

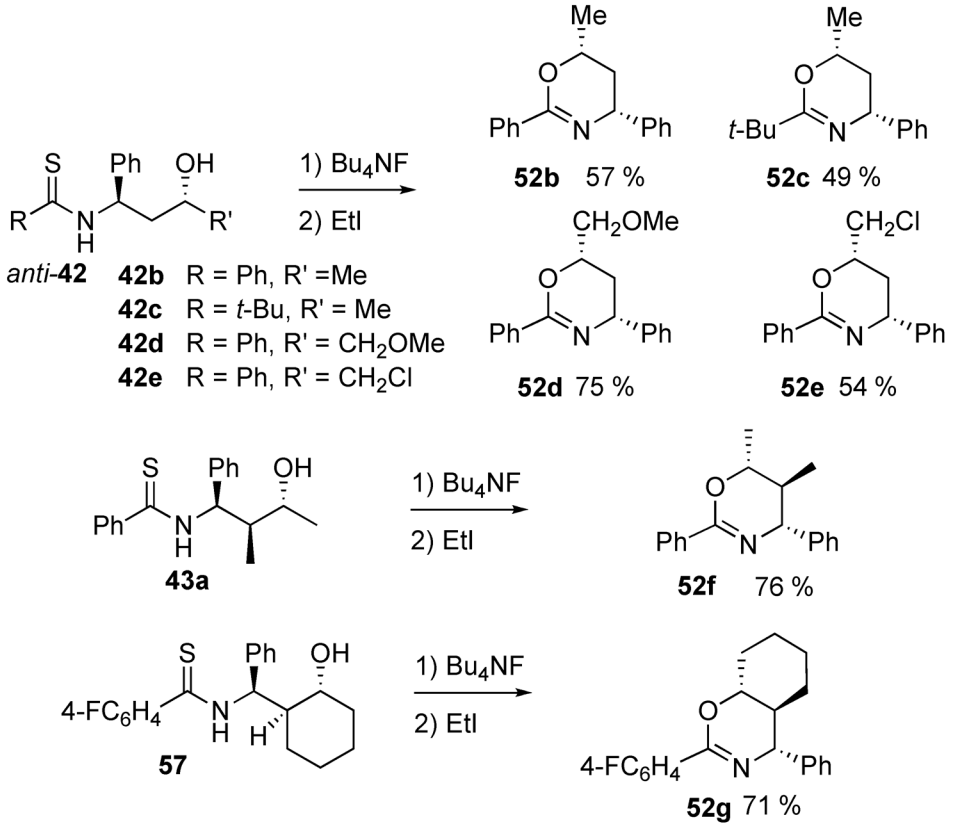
Intramolecular cyclization

Finally, the cyclization reaction of *N*-thioacyl 1,3-aminoalcohols, in which hydrogen sulfide is formally eliminated, is considered [20]. The treatment of *anti*-**42d** with Bu_4NF (2 equiv) and ethyl iodide gave *cis*-oxazine **52** in good yield, whereas the reaction of *syn*-**42d** gave thioimidate **53** (Scheme 10). In the initial stage, deprotonation of thioamides with fluoride ion takes place at both the nitrogen and oxygen atoms to generate dianions **54**. Ethylation may then take place at the more nucleophilic sulfur atom of **54** to give thioimidates **55**. The intramolecular attack of alkoxide ion to the iminium carbon atom proceeds with the elimination of an ethylthio group to give an oxazine as product **52**. The selective cyclization of *anti*-**42** may be due to the steric hindrance in the transition states of the cyclization of the *syn* isomer (4,6-*cis*-**56** vs. 4,6-*trans*-**56**).



Scheme 10 Reaction of *N*-thioacyl 1,3-aminoalcohols with Bu_4NF and EtI.

A variety of *anti*-**42** were used as starting materials to produce *cis*-oxazines **52b–e** (Scheme 11). Thioamides derived from *cis*-2-butene oxide and cyclohexene oxide **43a** and **57** also participated in the cyclization reaction to give the products **52f** and **52g**, where the stereochemistry of three successive carbon atoms is regulated.



Scheme 11 Cyclization of *N*-thioacyl 1,3-aminoalcohols.

SUMMARY

In summary, the generation of thioamide dianions and their application as carbanions adjacent to the nitrogen atom have been demonstrated. The treatment of *N*-benzylic thioamides with 2 equiv of BuLi selectively generates thioamide dianions, which is in marked contrast to the deprotonation of ordinary amides. In the latter case, deprotonation on the aromatic ring also occurs. Thioamide dianions are highly nucleophilic and less basic, and can add to a wide range of electrophiles. For alkylation and allylation, alkyl and allylic chlorides are also used. The addition to oxiranes shows high regioselectivity. The ring-opening of oxiranes proceeds with an inversion of configuration at the carbon atom. The addition of aldehydes gives a mixture of two diastereomers. The electronic properties of thioamide dianions as investigated by ^{13}C NMR spectra suggested that they are present as monomeric forms. The products obtained from the addition of thioamide dianions to electrophiles can be used as starting materials in several cyclization reactions. The iodocyclization of *N*-homoallylic thioamides proceeds in an *exo* mode. *Anti*-*N*-thioacyl 1,3-aminoalcohols are converted to *cis*-oxazines by reacting them with Bu_4NF and ethyl iodide. In these cyclization reactions, the stereochemistry of the products is highly regulated. The wide applicability of thioamides and the versatility of carbon electrophiles as well as heteroatom-containing electrophiles may provide further unprecedented transformations of thioamide dianions leading to nitrogen- and/or sulfur-containing compounds.

ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research on Priority Area (No. 20036020, ''Synergy of Elements'') from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

REFERENCES

1. For a review, see: P. Metzner. In *Topics in Current Chemistry*, Vol. 204, P. C. B. Page (Ed.), p. 127, Springer-Verlag, Berlin (1999).
2. W. Lubosch, D. Seebach. *Helv. Chim. Acta* **63**, 102 (1980).
3. X. Creary, C. Zhu. *J. Am. Chem. Soc.* **117**, 5859 (1995).
4. D. Seebach, W. Lubosch, D. Enders. *Chem. Ber.* **109**, 1309 (1976).
5. Y. Tamaru, M. Kagotani, Y. Furukawa, Y. Amino, Z. Yoshida. *Tetrahedron Lett.* **22**, 3413 (1981).
6. J. J. Fitt, H. W. Gschwend. *J. Org. Chem.* **41**, 4029 (1976).
7. (a) D. Ach, V. Reboul, P. Metzner. *Eur. J. Org. Chem.* 2573 (2002); (b) D. Ach, V. Reboul, P. Metzner. *Eur. J. Org. Chem.* 3398 (2003).
8. A. R. Katritzky, O. Denisko, H. Lang. *Tetrahedron* **51**, 8703 (1995).
9. For thioamides, see (a) T. Murai, Y. Mutoh, Y. Ohta, M. Murakami. *J. Am. Chem. Soc.* **126**, 5968 (2004); (b) T. Murai, Y. Ohta, Y. Mutoh. *Tetrahedron Lett.* **46**, 3637 (2005); (c) T. Murai, Y. Mutoh, K. Fukushima. *Lett. Org. Chem.* **3**, 409 (2006); (d) T. Murai, R. Toshio, Y. Mutoh. *Tetrahedron* **62**, 6312 (2006); (e) T. Murai, F. Asai. *J. Am. Chem. Soc.* **129**, 780 (2007); (f) F. Shibahara, A. Suenami, A. Yoshida. *Chem. Commun.* 2354 (2007); (g) T. Murai, K. Fukushima, Y. Mutoh. *Org. Lett.* **9**, 5295 (2007); (h) F. Shibahara, A. Yoshida, T. Murai. *Chem. Lett.* **37**, 646 (2008); (i) T. Murai, F. Asai. *J. Org. Chem.* **73**, 9518 (2008); (j) F. Shibahara, E. Yamaguchi, A. Kitagawa, T. Murai. *Tetrahedron* **65**, 5062 (2009); (k) F. Shibahara, R. Sugiura, E. Yamaguchi, A. Kitagawa. *J. Org. Chem.* **74**, 3566 (2009); (l) T. Murai, K. Ui, Narengerile. *J. Org. Chem.* **74**, 5703 (2009).
10. For selenoamides, see: (a) T. Murai, M. Ishizuka, A. Suzuki, S. Kato. *Tetrahedron Lett.* **44**, 1343 (2003); (b) Y. Mutoh, T. Murai. *Org. Lett*. **5**, 1361 (2003); (c) Y. Mutoh, T. Murai. *Organometallics* **23**, 3907 (2004); (d) T. Murai, S. Nogawa, Y. Mutoh. *Bull. Chem. Soc. Jpn.* **80**, 2220 (2007).
11. For telluroamides, see: (a) Y. Mutoh, T. Murai, S. Yamago. *J. Am. Chem. Soc.* **126**, 16696 (2004); (b) Y. Mutoh, T. Murai, S. Yamago. *J. Organomet. Chem.* **692**, 129 (2007).
12. (a) T. Murai, T. Kamoto, S. Kato. *J. Am. Chem. Soc.* **122**, 9850 (2000); (b) O. Niyomura, K. Sakai, T. Murai, S. Kato, S. Yamaguchi, K. Tamao. *Chem. Lett.* 968 (2001); (c) T. Murai, S. Hayakawa, S. Kato. *J. Org. Chem.* **66**, 8101 (2001); (d) K. Tani, T. Murai, S. Kato. *J. Am. Chem. Soc.* **124**, 5960 (2002).
13. T. Murai, H. Aso, S. Kato. *Org. Lett.* **4**, 1407 (2002).
14. T. Murai, H. Aso, Y. Tatematsu, Y. Itoh, H. Niwa, S. Kato. *J. Org. Chem.* **68**, 8514 (2003).
15. For recent reviews: (a) A. J. Moore. *Comprehensive Organic Functional Group Transformations II*, A. R. Katritzky, R. J. K. Taylor (Eds.), Elsevier, Oxford, **5**, 519 (2005); (b) C. Flynn, L. Haughton. *Comprehensive Organic Functional Group Transformations II*, A. R. Katritzky, R. J. K. Taylor, Elsevier, Oxford, **5**, 571 (2005); (c) T. Murai. *Topics in Current Chemistry*, S. Kato (Ed.), p. 247, Springer GmbH, Heidelberg (2005); (d) M. Koketsu, H. Ishihara. *Curr. Org. Synth.* **4**, 15 (2007); (e) M. Koketsu, H. Ishihara. *Handbook of Chalcogen Chemistry: New Perspectives in Sulfur, Selenium, Tellurium*, F. A. Devillanova (Ed.), pp. 145–194, Royal Society of Chemistry, Cambridge (2007).
16. (a) O. I. Zbruyev, N. Stiasni, C. O. Kappe. *J. Comb. Chem.* **5**, 145 (2003); (b) G. Purrello. *Heterocycles* **65**, 411 (2005).

17. M. Jesberger, T. P. Davis, L. Barner. *Synthesis* 1929 (2003).
18. F. Shibahara, R. Sugiura, T. Murai. *Org. Lett.* **11**, 3064 (2009).
19. T. Murai, T. Michigami, M. Yamaguchi, N. Mizuhata. *J. Sulfur Chem.* **30**, 225 (2009).
20. T. Murai, H. Sano, H. Kawai, H. Aso, F. Shibahara. *J. Org. Chem.* **70**, 8148 (2005).
21. P. Grana, M. R. Paleo, F. J. Sardina. *J. Am. Chem. Soc.* **124**, 12511 (2002).
22. T. S. Jagodzinski. *Chem. Rev.* **103**, 197 (2003).
23. (a) S. Lehnhoff, I. Ugi. *Heterocycles* **40**, 801 (1995); (b) S. D. Larsen, B. A. DiPaolo. *Org. Lett.* **3**, 3341 (2001).
24. P. I. Creeke, J. M. Mellor. *Tetrahedron Lett.* **30**, 4435 (1989).
25. T. Murai, H. Niwa, T. Kimura, F. Shibahara. *Chem. Lett.* **33**, 508 (2004).
26. (a) F. Shibahara, A. Kitagawa, E. Yamaguchi, T. Murai. *Org. Lett.* **8**, 5621 (2006); (b) S. Tahara, F. Shibahara, F. Maruyama, T. Murai. *Chem. Commun.* 7009 (2009).

