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Highlight Review

Thioamides and Thioformamides for Sequential Reactions with Organolithium and Grignard Reagents

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Abstract

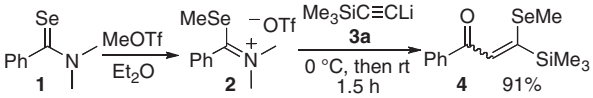
Sequential reactions of thioamides and thioformamides with organolithium and Grignard reagents are described. Thioiminium salts derived from these sulfur isologues of amides readily react with lithium acetylides to lead to several types of products, including α,β-unsaturated ketones, whereas sequential additions of lithium acetylides and Grignard reagents afford propargylamines. The direct addition of organolithium and Grignard reagents to thioformamides proceeds with high efficiency to give a range of tertiary amines.

♦ Introduction

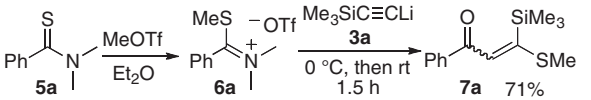
Amides have been considered to be one of the least-reactive classes of compounds among carboxylic acid derivatives. In contrast, the replacement of the oxygen atom of amides with a sulfur atom can enhance the reactivity of the resulting thioamides.[1] In addition, they are less polar than the corresponding amides and can be easily handled during their purification via chromatography and recrystallization. Therefore, synthetic reactions that use thioamides similar to carbonyl compounds such as aldol-type reactions and Michael-type additions have been extensively studied,[2] and their asymmetric versions with high efficiency and selectivity[3] are important topics in current synthetic chemistry. The sulfur atom on thioamides is highly nucleophilic, and alkylation of thioamides has been known to take place at the sulfur atom to give thioiminium salts.[4] These studies started more than 60 years ago.[5] The resulting thioiminium salts are susceptible to nucleophilic attack at their carbon atoms, and a range of nucleophiles have been used. As carbon nucleophiles, Grignard reagents,[6] metal cyanides,[7] and intramolecularly generated enolates[8] have successfully been used in carbon–carbon bond-forming reactions. Alternatively, the formation of alkenes from thioiminium salts via extrusion of the sulfur atom is well known as the Eschenmoser coupling.[9,10] However, the potential utility of thioamides, thioformamides, and thioiminium salts for carbon–carbon bond-forming reactions has yet to be fully disclosed. Furthermore, heavier isologues of these species, i.e., seleno-[11] and telluroamides[12] and their alkylated iminium salts,[13] have been studied to a much lesser extent.

♦ Addition Reaction of Lithium Acetylides with Thioiminium Salts

In light of the background described above, we first studied the syntheses and properties of selenoiminium salts as very rare species.[14] During the course of these studies, the addition reaction of lithium acetylides to selenoiminium salt **2** generated from selenobenzamide **1** and MeOTf within 30 s was found to proceed smoothly to give β-methylselanyl α,β-unsaturated ketone **4** with high *Z*-selectivity as a product (eq 1).[15]



(1)



(2)

We then focused on a similar reaction with a thioiminium salt. In fact, the reaction of thioiminium salt **6a** derived from thioamide **5a** proceeded in an identical manner to produce β-methylsulfanyl α,β-unsaturated ketone **7a** as a product (eq 2). Several types of thioamides **5** participated in the reaction to lead to the corresponding α,β-unsaturated ketones **7** in low to moderate yields (Table 1).[16] In contrast to the reaction of selenoiminium salts **2**, where the *Z*-selective formation of β-methylselanyl α,β-unsaturated ketones **4** was observed, the ratio of *E*- and *Z*-isomers of **7** depended on the substituents, and in some cases, they gradually isomerized even at low temperatures. The reaction of **6a** with lithium (triphenylsilyl)acetylide (**3b**) gave *Z*-**7b** (Entry 1), whereas the combination of **6c** and **3a** led to *E*-**7c** (Entry 2). Lithium acetylides **3c**–**3e** derived from aliphatic and aromatic acetylenes could also be used for the addition reaction to give the corresponding β-methylsulfanyl α,β-unsaturated ketones **7d**–**7f** (Entries 3–5). The reaction with lithium acetylide **3f** derived from 2-methylbut-1-en-3-yne proceeded smoothly, but the corresponding product **7i** was isolated in low yield (Entry 8).

A plausible reaction pathway to **7** is shown in Scheme 1. Lithium acetylide **3** initially attacks the carbon atom of the salts **6** to form alkynyl *S*,*N*-acetals **8**, which may then undergo 1,3-rearrangement to form aminoallenes **9**. The acidic hydrolysis of **9** may lead to ketones **7**. To prove that **8** and **9** act as intermediates, the reaction mixture of thioiminium salts **6** derived from aromatic thioamides **5** with different alkyl substituents on their nitrogen atoms and lithium acetylide **3a** was carefully monitored before chromatographic purification (Table 2). Interestingly, in all cases, before purification by column chromatography on silica gel, the formation of β-methylsulfanyl α,β-unsaturated ketones **7** was not observed.

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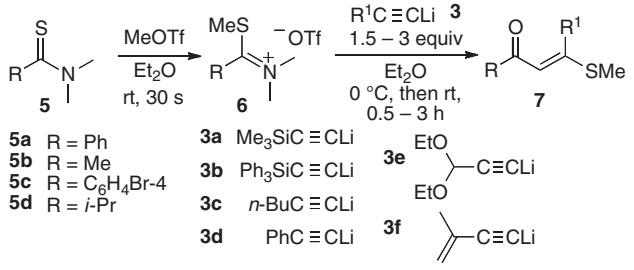
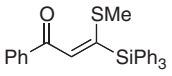
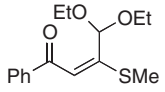
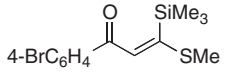
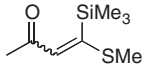
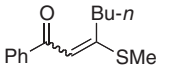
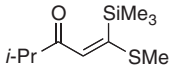
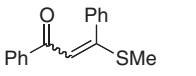
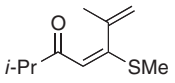
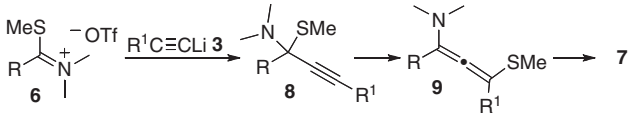
Table 1. Reaction of thioiminium salts **6** with lithium acetylides **3**[a]



Entry	Substrate **5** and **3**	Product **7** Yield[b] (*E*/*Z*)[c]	Entry	Substrate **5** and **3**	Product **7** Yield[b] (*E*/*Z*)[c]
1	**5a** **3b**	 **7b** 40%	5	**5a** **3e**	 **7f** 68%
2	**5c** **3a**	 **7c** 60%	6	**5b** **3a**	 **7g** 41% (45/55)
3	**5a** **3c**	 **7d** 29% (77/28)	7	**5d** **3c**	 **7h** 62%
4	**5a** **3d**	 **7e** 80% (67/37)	8	**5d** **3f**	 **7i** 34%[d]

[a]The reaction was carried out as follows, unless otherwise noted: To an Et_2O solution of the lithium acetylide **3** (3 mmol) was added thioiminium salts **6** (1 mmol), and the mixture was stirred. [b]Isolated yields. [c]The stereochemistry of the ketones **7c**, **7g**, **7h**, and **7i** was determined by phase-sensitive NOESY spectroscopy, and that of others was estimated on the basis of ^{1}H NMR spectra. [d]Purified through GPC.

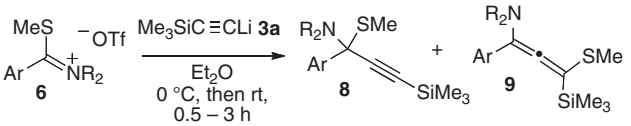


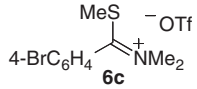
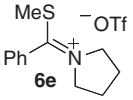
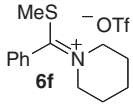
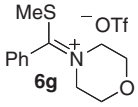
Scheme 1. Plausible reaction pathway to α,β-unsaturated ketones.

Instead, alkyl *S*,*N*-acetals **8** and/or aminoallenes **9** were obtained as products.[16] Their ratio depended on the substituents on the nitrogen atom of **6**. Salts bearing dimethylamino and pyrrolidyl groups **6c** and **6e** were selectively converted to **9** (Entries 1 and 2), whereas those with piperidyl and morpholyl groups **6f** and **6g** gave a mixture of **8** and **9** (Entries 3 and 4). Furthermore, alkynyl *S*,*N*-acetal **8** derived from **6g** slowly underwent 1,3-rearrangement, and after 24 h, the ratio between **8** and **9** changed from 97:3 to 17:83.[17]

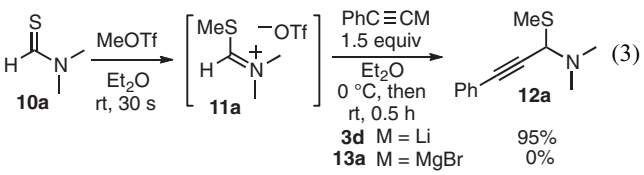
The reaction in eq 1 was then extended to thioiminium salts derived from thioformamides (eq 3). Methylation of thioformamide **10a** with MeOTf was complete within 30 s to afford thioiminium salt **11a**, and to the salt **11a** was then added lithium acetylide **3d**. Alkynyl *S*,*N*-acetal **12a** was obtained with high efficiency as a crude product, but chromatographic purification of the crude product did not give an α,β-unsaturated aldehyde at all. Since alkynyl *S*,*N*-acetals like **12a** are rare[18] and possess several electrophilic and nucleophilic centers,[19] reactions of **12a** with organometallic reagents were further elucidated. Among these compounds, phenylethynyl Grignard reagent **13a** was found to undergo a substitution reaction at the carbon atom having nitrogen and sulfur atoms of **12a** with concomitant elimination of a methylsulfanyl group to give *N*,*N*-dimethyl-2-propynylamine (tertiary propargylamine) **14a** as a product in high yield (eq 4). Furthermore, alkynylation of **12a** was specific to **13a**, and **12a** was inert to lithium acetylide **3d**, whereas no reaction took place between **11a** and **13a** below room temperature (eqs 3 and 4). This difference in the reactivity of these reagents is in marked contrast to the general understanding that organolithium and -magnesium reagents competitively react with carbonyl compounds. Furthermore, the reaction of a cyclic *O*,*N*-acetal with organolithium reagents takes place.[20]

Table 2. Reaction of thioiminium salts **6** with lithium acetylides **3a**[a]

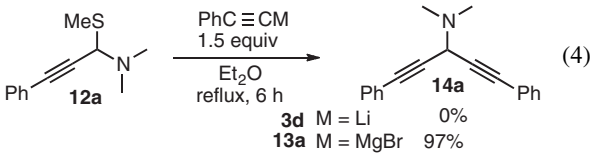


Entry	**6**	Yield/% **8** and **9**	Ratio[b] **8** and **9**
1	 **6c**	97	0:100
2	 **6e**	89	0:100
3	 **6f**	quant	45:55
4	 **6g**	99	97:3 (17:83)[c]

[a]The reaction was carried out as follows: To an Et_2O solution of lithium acetylide **3a** (1.5 equiv) was added thioiminium salts **6** (1 equiv) at 0 °C, and the mixture was stirred at room temperature. [b]The ratio of **8** and **9** was determined based on the ^{1}H NMR spectra of the reaction mixtures. [c]After 24 h.



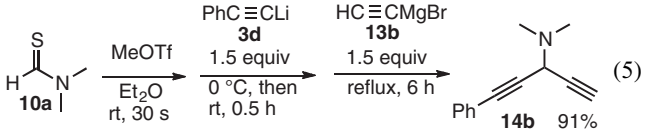
(3)



(4)

♦ One-pot Sequential Reactions of Lithium Acetylides and Grignard Reagents to Thioiminium Salts

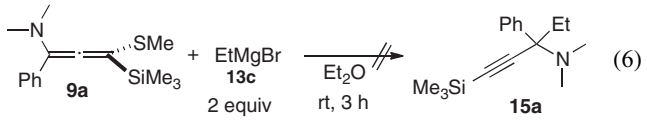
Based on the results in eqs 3 and 4, we expected that we could realize one-pot sequential reactions of thioiminium salts **11a** with organolithium and Grignard reagents. To thioformamide **10a** were successively added MeOTf, lithium acetylide **3d**, and ethynylmagnesium bromide (**13b**) to give 2-propynylamine **14b** in high yields (eq 5).[21] No products to which two identical organometallic reagents were introduced were observed despite the use of excess **3d** and **13b**.



(5)

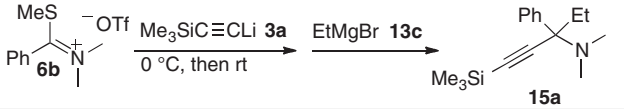
The importance of one-pot sequential reactions has been well-documented,[22] and these have been categorized as time integration.[23] The protocol in eq 5 is the first example of time integration using thioiminium salts to our best knowledge, and is widely applicable,[24] due to the ready availability of a range of thioiminium salts. Therefore, we applied one-pot sequential reactions to thioiminium salts **6** derived from aliphatic and aromatic thioamides **5** for the synthesis of *N*,*N*-dialkyl-2-propynylamines with a tertiary carbon atom adjacent to a nitrogen atom. Thus, thioiminium salt **6b** was sequentially reacted with lithium acetylide **3a** and ethylmagnesium bromide (**13c**) under various conditions (Table 3). The reaction with **13c** at room temperature gave the desired 2-propynylamine **15a** in only 41% yield (Entry 1). The use of excess **13c** and a longer reaction time slightly improved the yield of **15a** (Entries 3 and 4). The yield of **15a** was further improved by carrying out the reaction with 10 equiv of **13c** under reflux in THF (Entry 6).

As shown in Table 2, aqueous workup of the reaction mixture of **6b** and **3a** gave aminoallene **9a**. To prove that **9a** served as an intermediate for the sequential reaction in Table 3, **9a** was treated with **13c** (eq 6). However, amine **15a** was not obtained at all, and the starting compound **9a** was recovered quantitatively. Based on these results, the details of the reactivity of alkynyl *S*,*N*-acetals **8** derived from **3** and **6** are summarized in Scheme 2. The result in eq 6 shows that aminoallene **9** is not an intermediate for the reaction with **13** leading to **15**, but the hydrolysis of **9** leads to the formation of **7**. In the reaction mixture of **6** and **3**, alkynyl *S*,*N*-acetals **8** are exclusively present, and do not undergo 1,3-rearrangement to form **9** unless the mixture is subjected to aqueous workup. Alkynyl *S*,*N*-acetals **8** formed in situ then react with Grignard reagents **13** to lead to 2-propynylamines **15**.



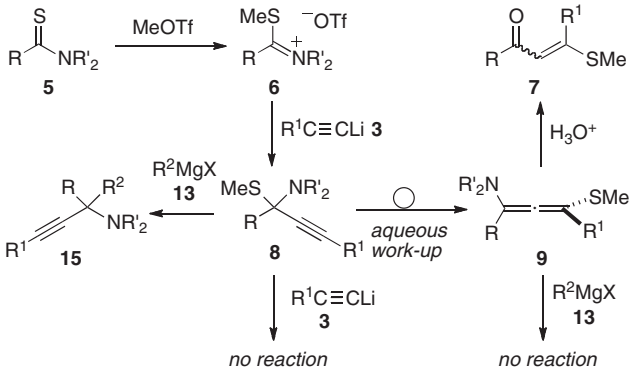
(6)

Table 3. Sequential reactions of thioiminium salt **6b** with **3a** and **13c**[a]



Entry	$Me_3SiC{\equiv}CLi$ **3a**		EtMgBr **13c**		Yield[b]/%
	Equiv	Time/h	Equiv	Temp, Time/h	
1	1.2	0.5	2	rt, 3	41
2	1.5	0.5	2	reflux, 2	46
3	1.5	0.5	4	reflux, 4	59
4	1.5	0.5	4	reflux, 12	58
5	1.5	0.5	10	rt, 3	66
6	1.5	0.5	10	reflux, 6	73

[a]The reaction was carried out as follows, unless otherwise noted: Thioiminium salt **6b** was stirred with lithium acetylide **3a**, and then with ethylmagnesium bromide (**13c**). [b]Isolated yield.

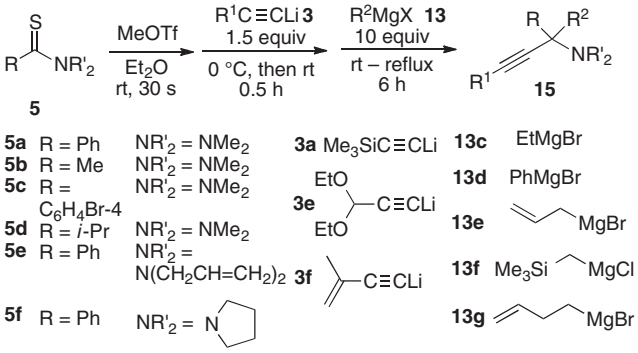


Scheme 2. Reaction sequence from **6** to **7** and **15**.

The sequential reaction using some aromatic and aliphatic thioamides **5** was then conducted with 10 equiv of Grignard reagents under reflux in Et_2O/THF (Table 4). *N*,*N*-Dimethylthioamides **5a**–**5d** worked well as starting thioamides to give the expected tertiary 2-propynylamines **15b**–**15d**, **15h**, and **15i** with a tertiary carbon atom adjacent to a nitrogen atom (Entries 1, 2, 3, 7, and 8), although the use of **5d** gave the product **15i** in lower yield (Entry 8). In the reaction with allylmagnesium bromide (**13e**), the sequential reactions were performed at room temperature to form 1,5-enynes **15b**, **15d**, **15f**, and **15i** in moderate yields (Entries 1, 3, 5, and 8). The use of homoallylmagnesium bromide (**13g**) with thioamide **5f**, MeOTf, and lithium acetylide **3a** gave 1,6-enyne with a pyrrolidine ring **15g** in high yield (Entry 6).

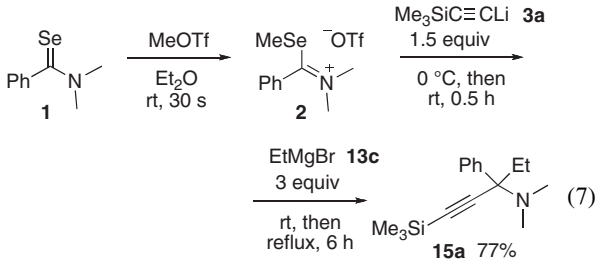
The use of selenoamides was effective for reducing the amounts of aliphatic Grignard reagents.[25] As shown in eq 7, the transformation of selenoamide **1** with MeOTf, lithium acetylide **3a**, and ethylmagnesium bromide (**13c**) proceeded smoothly with smaller amounts of **13c** to give 2-propynylamine **15a**, which was also obtained from thioamide **5a** with 10 equiv of **13c**.

Table 4. Sequential reactions of thioamides **5** with MeOTf, organolithium **3** and -magnesium reagents **13**[a]



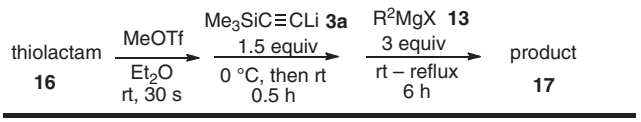
Entry	Substrate 5, 3, 13	Product 15 Yield[b]	Entry	Substrate 5, 3, 13	Product 15 Yield[b]
1	**5a** **3a** **13e**	**15b** 56%	5	**5e** **3a** **13e**	**15f** 61%
2	**5a** **3e** **13f**	**15c** 67%	6	**5f** **3a** **13g**	**15g** 82%
3	**5c** **3f** **13e**	**15d** 70%	7	**5b** **3a** **13d**	**15h** 68%
4	**5e** **3a** **13c**	**15e** 63%	8	**5d** **3a** **13e**	**15i** 44%

[a]The reaction was carried out as follows, unless otherwise noted: A mixture of thioamides **5** and MeOTf was stirred with organolithium reagents **3**, and then with Grignard reagents **13**. [b]Isolated yields.



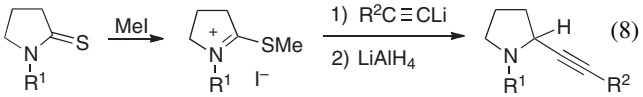
The sequential reactions of thioamides with lithium acetylides and Grignard reagents were applied to thiolactams.[26] Methylation of γ-thiolactams with methyl iodide followed by alkynylation and reduction has been known to give 2-alkynylpyrrolidines (eq 8).[27]

Table 5. Sequential reactions of thiolactams **16** with MeOTf, lithium acetylide **3a**, and Grignard reagents **13**[a]



Entry	16	13	Product 17	Yield[b]/%
1	**16a**	PhMgBr **13d**	**17a**	87
2	**16a**	EtMgBr **13c**	**17b**	58
3	**16a**	**13h**	**17c**	70
4	**16a**	**13e**	**17d**	96
5	**16a**	**13g**	**17e**	88
6	**16b**	EtMgBr **13c**	**17f**	77

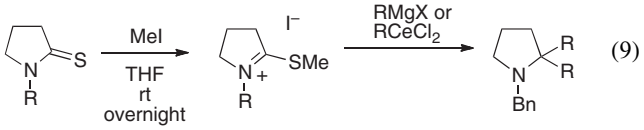
[a]The reaction was carried out as follows, unless otherwise noted: A mixture of thiolactams **16** and MeOTf was stirred with lithium acetylide **3a** and Grignard reagents **13**. [b]Isolated yields.

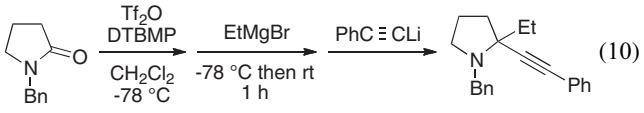


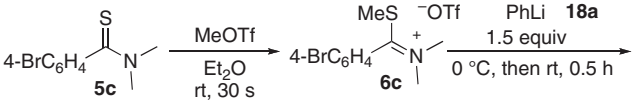
For rapid methylation, MeOTf was used in the reaction with thiolactams, and the results of sequential reactions are shown in Table 5. While a range of lithium acetylides **3** can be used, lithium acetylide **3a** showed the best yield. Compared to the reaction of thioamides, the yields of the products **17** were not improved for the reaction with a large excess of Grignard reagents. Nevertheless, a range of Grignard reagents **13** participated in the sequential reactions of γ-thiolactam **16a** to give 2-alkyl-2-alkynylpyrrolidines[28] **17a**–**17e** (Entries 1–5). The reaction of δ-thiolactam **16b** was also successful with high efficiency for the combination of lithium acetylide **3a** and aliphatic Grignard reagents such **13c**. The use of aromatic Grignard reagents gave the corresponding products in lower yields.

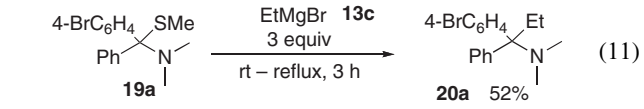
The development of new synthetic reactions that lead to 2-propynylamines, in particular those with a tetrasubstituted carbon atom adjacent to the nitrogen atom, is an important topic.[29] Our methods, which can be used complementarily in this field, involve geminal disubsitution[30] seen with the use of thiocarbonyl compounds.

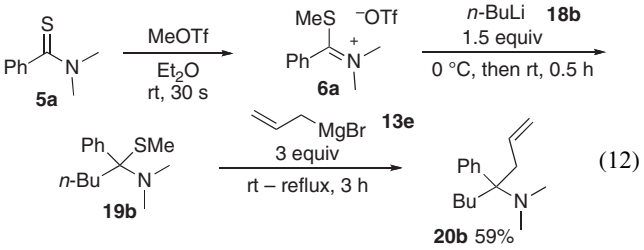
A similar reaction in which two identical aliphatic carbon nucleophiles are introduced to carbon atoms next to the nitrogen atoms in thiolactams has been reported with Grignard and organocerium reagents (eq 9).[31] Very recently, lactams have been used as starting materials for sequential geminal disubstitution with two different organometallic reagents (eq 10).[32] In the initial step, triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine are necessary to preactivate the lactams.





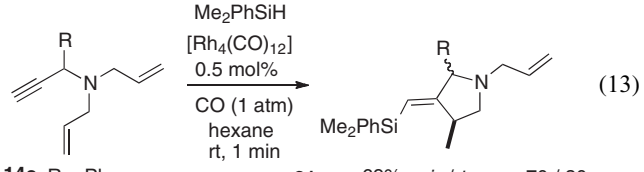


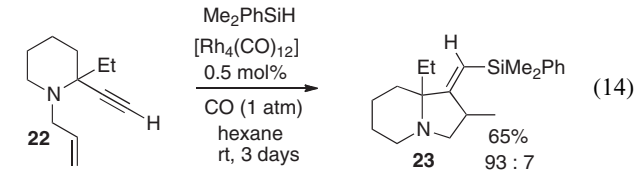


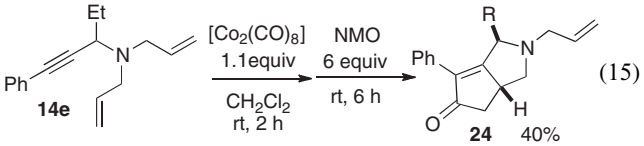


In our sequential reactions, the applicability of aromatic and aliphatic organolithium reagents was then tested (eqs 11 and 12). MeOTf, phenyllithium (**18a**), and ethylmagnesium bromide (**13c**) were successively added to an Et_2O solution of 4-bromobenzothioamide **5c** to give amine **20a** (eq 11). The addition of **18a** to the iminium carbon atom of **6c** predominates the lithium–bromine exchange reaction, and the substitution reaction takes place at the tetrasubstituted carbon atom of *S*,*N*-acetal **19a** with the elimination of a methylsulfanyl group. The combination of butyllithium (**18b**) and allylmagnesium bromide (**13e**) could also be applied to the sequential reaction to the salt **6a** to give amine **20b** via **19b** in good yield (eq 12).

2-Propynylamines obtained in this section were subjected to silylcarbocyclization.[33] *N*,*N*-Diallyl-2-propynylamines **14c** and **14d** were reacted with $PhMe_2SiH$ in the presence of a catalytic amount of $[Rh_4(CO)_{12}]$ to give 2,3,4-trisubstituted pyrrolidines **21** with high regio- and stereoselectivity (eq 13). Similarly, cyclization was applied to substituted piperidine **22** (eq 14).





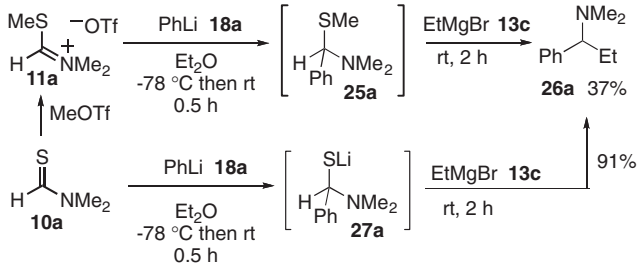


Although the reaction required about 3 days for completion, it gave indolizine derivative **23** as a mixture of two diastereomers out of four possible isomers in good yields. *N*,*N*-Diallyl-2-propynylamine **14e** was subjected to the Pauson–Khand reaction[34] to give cyclopenta[*c*]pyrroline derivative **24** in moderate yield (eq 15).

♦ *One-pot Sequential Reaction of Organolithium and Grignard Reagents to Thioformamides*

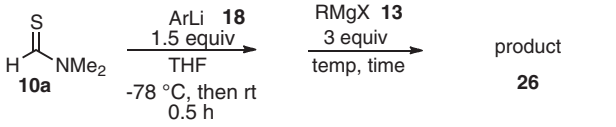
In our investigation of the sequential addition reactions of thioiminium salt **11a** derived from thioformamide **10a** with phenyllithium (**18a**), the reproducibility of the reactions was not consistent. By examining several reaction conditions, we found that preactivation with MeOTf was not necessary for the reaction of thioformamides with aliphatic and aromatic organolithium reagents (Scheme 3).[35] The sequential reaction of thioformamide **10a** with **18** and Grignard reagent **13c** proceeded smoothly to give amine **26a** in high yield. In contrast, the reaction via the salt **11a** gave **26a** in only 37% yield. As shown in Scheme 3, interestingly, these results suggest that the lithiumsulfanyl group (LiS) in **27a** is a better leaving group than the methylsulfanyl group in **25a**.

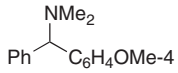
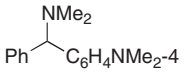
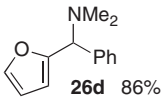
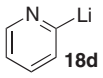
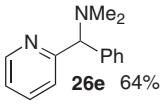
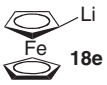
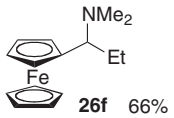
The one-pot sequential reaction of several organolithium **18** and Grignard reagents **13** to thioformamide **10a** was carried out (Table 6). The combination of phenyllithium (**18a**) and arylmagnesium bromides **13i** and **13j** successfully gave the corresponding diarylmethylamines[36] **26b** and **26c** in high yields (Entries 1 and 2). Heteroaryllithiums **18c** and **18d** and ferrocenyllithium (**18e**) participated in the reaction to give the products **26d**–**26f**, where a geminal disubstitution reaction of **11a** with organolithium and –magnesium reagents took place in good to high yields (Entries 3–5). Diarylmethylpiperazines are a biologically important class of compounds.[37] The thioform-



Scheme 3. Sequential reaction of thioforamide **10a** with **18a** and **13c**.

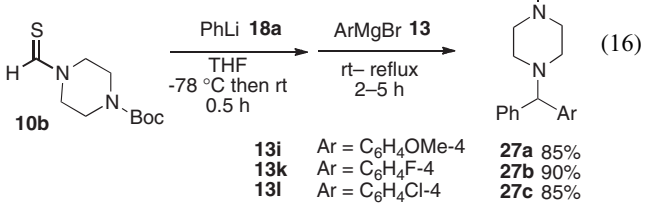
Table 6. Sequential reactions of thioformamide **10a** with aryllithiums **18** and Grignard reagents **13**[a]



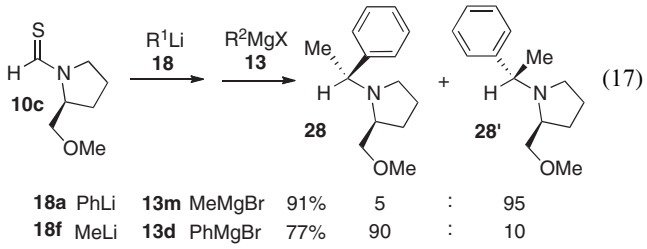
Entry	18	13	Temp, Time/h	Product 26 Yield[b]
1	PhLi **18a**	4-MeOC$_6$H$_4$MgBr **13i**	rt, 2	 **26b** 95%
2	PhLi **18a**	4-Me$_2$NC$_6$H$_4$MgBr **13j**	rt, 2	 **26c** 91%
3	 **18c**	PhMgBr **13d**	rt, 2	 **26d** 86%
4[c]	 **18d**	PhMgBr **13d**	rt, 2	 **26e** 64%
5	 **18e**	EtMgBr **13c**	reflux, 5	 **26f** 66%

[a]The reaction was carried out as follows, unless otherwise noted: To thioformamide **10a** were added organolithium reagents **18** and Grignard reagents **13**, and the mixture was stirred. [b]Isolated yields. [c]The reaction with **18d** was carried out at −20 °C.

amide bearing a piperazyl group was subjected to sequential reactions (eq 16). The reaction of thioformamide **10b** with **18a** and aryl Grignard reagents **13i**, **13k**, and **13l** was carried out to give the corresponding diarylmethylamines **27a**–**27c**. Notably, a methoxy group, and fluorine and chlorine atoms on **13i**, **13k**, and **13l** did not affect the efficiency of the reaction. Finally, the diastereoselectivity of the sequential reaction with thioformamide was noted (eq 17).[38] The reaction of thioformamide **10c**, which was prepared from (*S*)-2-methoxylmethylpyrrolidine, was sequentially reacted with phenyllithium (**18a**) and methyl Grignard **13m**. The reaction proceeded smoothly to give two diastereomers **28** and **28′**[39] with high diastereoselectivity. The reverse combination of the substituents on the lithium and magnesium reagents was further found to give the identical products with high reverse selectivity.



(16)



(17)

18a	PhLi	**13m**	MeMgBr	91%	5	: 95
18f	MeLi	**13d**	PhMgBr	77%	90	: 10

♦ Summary

In summary, our recent efforts to prove that thioamides, thioformamides, and the iminium salts derived from them are powerful synthetic tools for one-pot sequential reactions have been demonstrated in this Highlight Review. We started our studies with their selenium and tellurium isologues, which have been relatively less explored, but found that a series of organosulfur compounds could be fruitful for carbon–carbon bond-forming reactions. New reactions with these compounds are still unexplored and undiscovered.

The reaction described in this review involves geminal disubstitution reactions. In particular, two different carbon nucleophiles are introduced to the carbon atom of thiocarbonyl groups in a single operation. The development of analogous reactions using ordinary carbonyl[40] and thiocarbonyl compounds[41] is currently an important topic. In the near future, the use of an asymmetric version of a geminal disubstitution reaction may become mainstream in synthetic reactions.

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