Contribution

Development of New Iodocyclization and Radical Cycloaddition Reaction

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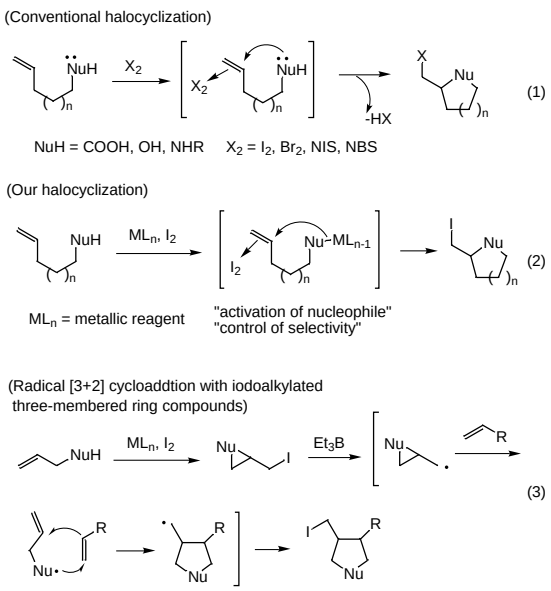
1. Introduction

Alicyclic and *N*-heterocyclic compounds are basic structures that are often found in natural products, medical and agricultural drugs as well as other functional materials. Given their importance, there are already many reports regarding the synthetic methods of these cyclic compounds, such as the cyclization reactions. The importance of new cyclization reactions lies in the novelty and exhibition of high-selectivity, as well as the possibility of easy procurement and synthesis of cyclization precursors. It is difficult to say if any of these reports about cyclization reaction meet all of these criteria.

As new cyclization reactions, we have recently succeeded in developing an iodocyclization (halocyclization) reaction mediated by metallic reagents and a radical [3+2] cycloaddition reaction using the iodoalkylated three-membered ring compounds obtained by our iodocyclization reaction (Scheme 1, Formulas 2 and 3). These reactions can be conducted using precursors which can be readily synthesized in short steps to give carbocyclic and *N*-heterocyclic compounds with high regio- and stereo-selectivity. In this article we describe these reactions which we have been working on for the last 10 years or so.

Halocyclization is a reaction whereby the intramolecular nucleophilic species (or group) attacks the carbon-carbon double bond activated by electrophilic halogenating reagents to give cyclic compounds. This is widely used for synthesizing heterocyclic compounds and functionalization of alkenes.[1)] The first report on halocyclization reactions dates back to about 100 years ago;[2)] however, there is almost no difference regarding the reagents and the reaction conditions used in modern times from those reported 100 years ago. The old and new methods simply involve adding the halogenating reagents to the substrate or simultaneously adding a base such as $NaHCO_3$ in order to trap the generated hydrogen halide (Scheme 1, Formula 1).

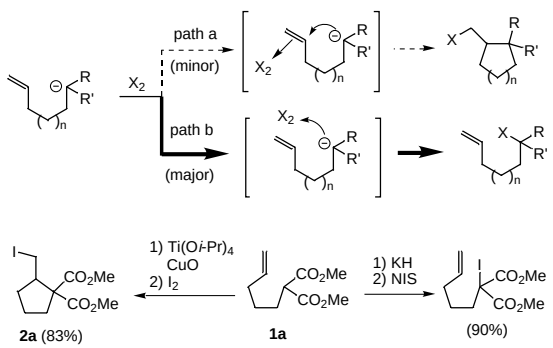


Scheme 1. Halocyclization and radical [3+2] cycloaddition.

On the other hand, metallic reagents are now indispensable reagents for developing new synthetic reactions and manifesting selectivity. However, there have been few report in which metallic reagents were effectively used for halocyclization. This is caused by the fact that halogenating reagents react readily with most metallic reagents. We have focused our attention on the fact that iodine can stably coexist with some metallic reagents, which resulted in the successful development of an iodocyclization reaction possessing excellent selectivity, hitherto unknown. This is achieved by performing an iodocyclization reaction in the presence of a certain type of metallic reagent (Scheme 1, Formula 2).[3] We also found that iodomethyl cyclopropane and iodoaziridine derivatives, obtained by these reactions, can act as excellent precursors for homoallyl radicals and azahomoallyl radicals respectively. Thus we have succeeded in developing iodine atom transfer type [3+2] cycloaddition reactions with various alkenes (Scheme 1, Formula 3). The details of these reactions are discussed below.

2. Iodocarbocyclization Reaction

As typified by halolactonization and halo-aminocyclization, in the halocyclozation reactions the intramolecular nucleophiles generally consist of hetero atoms such as oxygen and nitrogen atoms (Scheme 1, Formula 1). In contrast, the so-called 'halocarbocyclization reaction' which involves carbon nucleophile, especially carbanion, were not known. When carbanions are involved, as indicated in Scheme 2, the direct halogenation of the carbanion (Path **b**) precedes the halocarbocyclization (Path **a**); therefore, halocarbocyclizations are difficult to realize. In fact, even when a soft carbanion, such as 4-pentenyl-malonate anion (prepared from 4-pentenylmalonate **1a** and potassium hydride) was used, no iodocarbocyclization product was obtained at all from the reaction with NIS and only α-iodomalonate was formed (Scheme 2).[4]

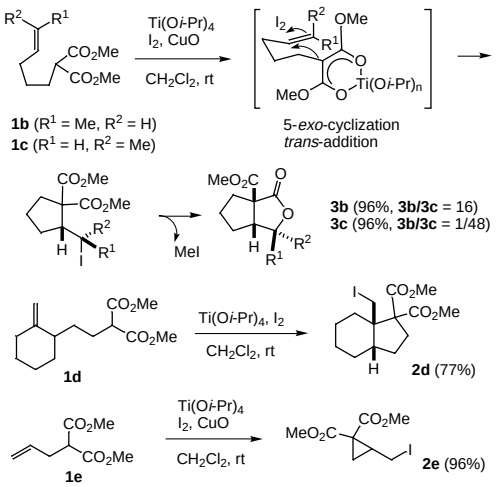


Scheme 2. Halocarbocyclization and direct halogenation.

2.1. Iodocarbocyclization Reaction of Alkenylated Malonates

We have found that, when a reaction between 4-pentenylmalonate **1a** and iodine is conducted in the presence of titanium alkoxide and copper oxide (II), α-iodomalonate is not generated while iodocarbocyclization product **2a** is obtained in a high yield (83%) (Scheme 2).[5] This reaction proceeds *via* the titanium enolate, as shown in Scheme 3. In the absence of titanium alkoxide no cyclized product **2a** was formed. When copper oxide (II) was not added, the yield of **2a** slightly decreased to 74%. These results indicate that the key to success in this reaction is the use of a weak base such as titanium alkoxide, while using a strong base would lead an α-iodination reaction.

This reaction proceeds with complete regioselectivity (5-*exo*-cyclization) and high stereospecificity (*trans*-addition). Thus, when (*E*)- and (*Z*)-4-hexenylmalonate **1b** and **1c** were used, the bicyclic lactones **3b** and **3c** having three consecutive chiral centers were fomed in a highly stereospecific manner through substitution reaction of the primarily formed secondary iodide with ester carbonyl group (Scheme 3). Furthermore, malonate (**1d**) also reacted with complete selectivity to produce the bicylic compound **2d** having mode to give adjacent two quaternary carbons (Scheme 3). In addition, the cyclization reaction of allylmalonate **1e** also proceeded with complete 3-*exo*-iodomethylcyclopropane **2e** in high yield (Scheme 3).[6]



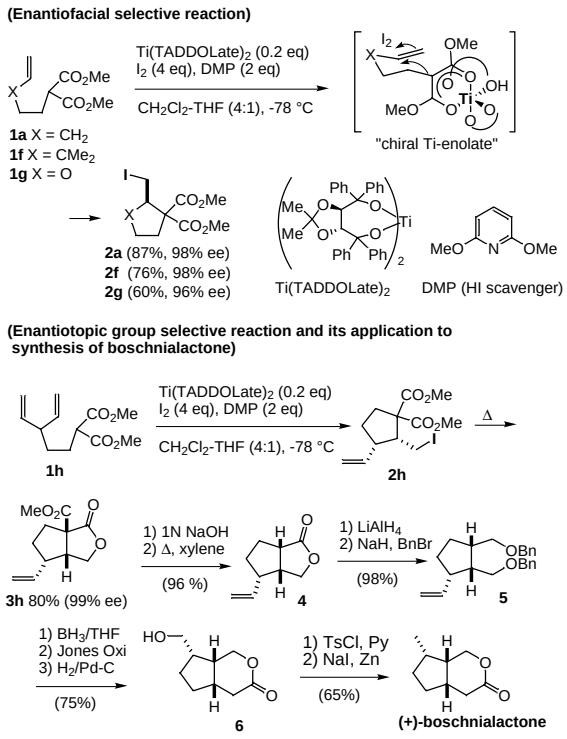
Scheme 3. $Ti(OR)_4$-mediated iodocarbocyclization of various alkenylated malonates.

2.2. Catalytic Asymmetric Iodocarbocyclization Reaction

Based on the consideration of titanium enolate intermediate in the present reaction, we examined the enantioselective iodocarbocyclization reaction mediated by a variety of chiral titanium reagents. We considered that if chiral titanium enolate intermediate is generated, the

enantiofacial differentiation of the alkene moiety would be realized at the cyclization step. Consequently, in the presence of Ti(TADDOLate)$_2$ complex the iodocarbocyclization of various alkenylated malonates **1a**, **1f** and **1g** proceeded highly enantioselectively to give the products **2a**, **2f** and **2g**, respectively.[7] If 2,6-dimethoxypyridine (DMP) is added as the hydrogen iodide scavenger, a high enantioselectivity (>96% ee) was demonstrated even when a catalytic amount (20 mol%) of Ti(TADDOLate)$_2$ complex was used (Scheme 4).[8] Without DMP, Ti(TADDOLate)$_2$ complex is decomposed by hydrogen iodide generated as the reaction proceeds, resulting in a drastic decrease in both chemical yield and optical purity of the product. These are the first examples of catalytic asymmetric reaction in the field of halocyclization reaction.

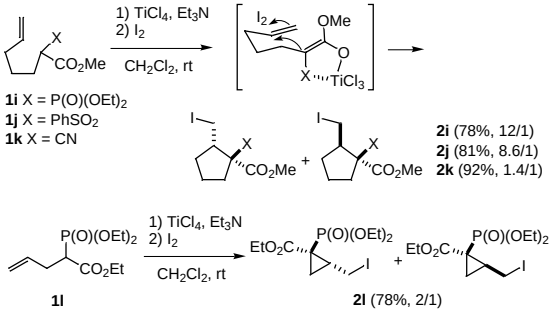
This catalytic asymmetric iodocarbocyclization reaction is also applicable to the enantiotopic group selective reaction. For instance, when the iodocarbocyclization of bisalkenylmalonate **1h** is performed under the above conditions, only one of the prochiral alkenes in malonate **1h** reacted giving rise to the trisubstituted cyclopentane derivative **2h** with an extremely high enantio excess (99% ee) (Scheme 4). The cyclized product **2h** can be converted to boschnialactone, an iridoid natural product, in high yield, *via* the path indicated in Scheme 4.



Scheme 4. Catalytic asymmetric iodocarbocyclization with chiral titanium alkoxide.

2.3. Iodocarbocyclization Reaction of Various Alkenylated Active Methines

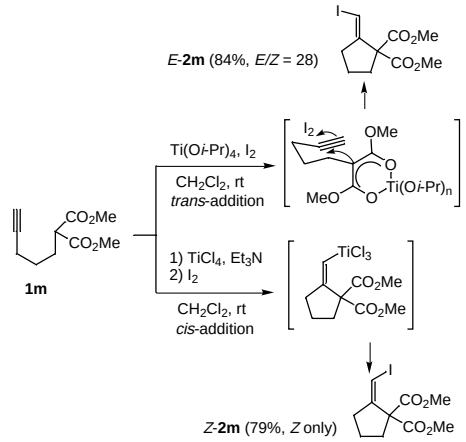
The above-mentioned iodocarbocyclization reaction is applicable only to alkenylated malonate. No products were generated in the case of iodocarbocyclization of 4-pentenyl-2-phosphonoacetate **1i** and sulfonyl acetate **1j** in the presence of titanium alkoxide and iodine. It seems that this is because the titanium enolates of **1i** and **1j** were not generated under the above-mentioned conditions. We have found that when titanium tetrachloride and triethylamine are used, the titanium enolate is effectively generated from a variety of alkenylated active methine compounds **1i**-**1l**, and that by subsequently adding iodine, iodocarbocyclization products **2i**-**2l** are obtained in good yield (Scheme 5).[9]



Scheme 5. $TiCl_4$-mediated iodocarbocyclization of various alkenylated active methine compounds.

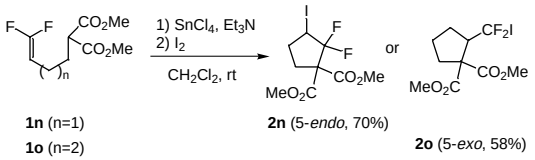
Interestingly, when the iodocarbocyclization reaction was applied to alkynyled malonate **1m**, inversed stereoselectivity was observed depending on the titanium reagent used.[9] When **1m** was reacted with titanium alkoxide and iodine, (*E*)-**2m** was obtained with high selectivity (*E*/*Z* = 28) through the iodocarbocyclization reaction (*trans*-addition). When **1m** was reacted with titanium tetrachloride, triethylamine, and iodine, the reaction proceeded through an intramolecular carbotitanation of the the titanium enolate to the alkyne (*cis*-addition) to generate the (*Z*)-vinyl titanium intermediates which on subsequently iodination gives (*Z*)-**2m** with complete stereoselectivity (Scheme 6).

Therefore, when titanium tetrachloride is used, the alkyne bond would be activated by the strong Lewis acidity of the titanium atom of trichlorotitanium enolate intermediates to promote carbotitanation prior to the iodocarbocyclization.



Scheme 6. Iodocarbocyclization and intermolecular carbotitanation of alkynylated malonates.

Furthermore, we examined iodocarbocyclization of difluoroalkenylated malonates and obtained satisfactory results by using tin tetrachloride and triethylamine.[10] Which a 5-*endo* cyclization product **2n** was obtained from reaction of 4,4-difluoro-3-butenylmalonate **1n**, and a 5-*exo* cyclization product **2o** was obtained as the principal component from reaction of 5,5-difluoro-4-pentenyl malonate **1o** (Scheme 7), which was similar to the reaction of the non-fluorinated substrate **1a**. The iodocarbocyclization reaction of 3-butenylmalonate, a non-fluorinated counter part of **1n**, was examined under various conditions; however, no cyclized product could be isolated. Therefore, it is evident that the *endo*-cyclization selectivity of **1n** is caused by the effect of the fluorine substituent.



Scheme 7. Iodocarbocyclization of difluoroalkenylated malonates.

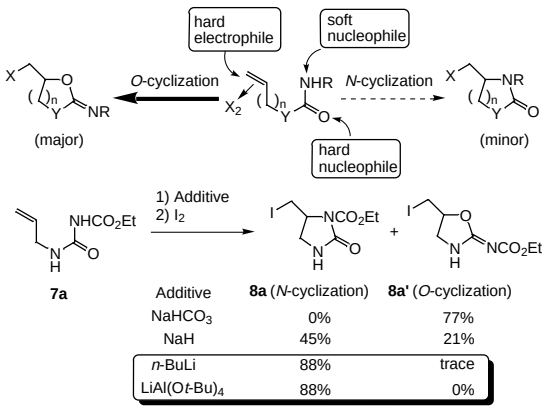
As shown above, the iodocarbocyclization reaction developed by us is applicable to various alkenylated and alkynylated active methine compounds. The reaction proceeds with complete regioselectivity and with high stereoselectivity. Furthermore, the cyclization precursor (**1**) can be synthesized in a short steps in a satisfactory yield, by means of an alkylation reaction of active methylene compounds.

3. Iodoaminocyclization Reaction

The iodoaminocyclization reaction has already been reported[11] and thus it is not necessarily a novel reaction, though some issues still remain to be solved. For instance, *N*- or *O*-cyclization is possible with the substrates having an ambident nucleophilic centers such as amide, carbamate, and urea. In these cases, *N*-cyclization has not been prevalent. Furthermore, haloaminocyclization to form the three-membered aziridine ring, i.e., haloaziridination reaction, has never been reported. We have succeeded in developing a method for *N*-selective cyclization of ambident nucleophiles including the haloaziridination reaction.

3.1. *N*-Selective Iodoaminocyclization Reaction of Alkenylted Amide, Carbamate, and Urea Derivatives

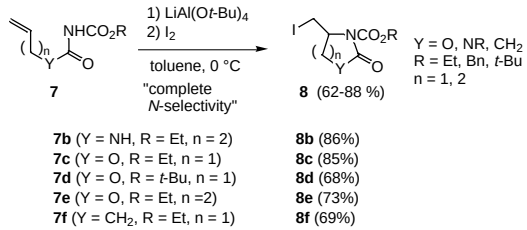
It is well known, that in the halocyclization reactions of alkenylated amide, carbamate, and urea derivatives, *O*-cyclization is preferred to *N*-cyclization. This is readily understood in terms of the HSAB theory as shown in Scheme 8. We have found that the iodocyclization reaction of an ambident nucleophile proceeds with a complete *N*-cyclization selectivity when mediated by a lithium reagent.[12] For instance, the iodocyclization reaction of *N*-allylurea **7a** gave only *O*-cyclized product **8a′** under normal conditions using sodium bicarbonate (I_2-$NaHCO_3$), while a reaction using *n*-BuLi or LiAl(O*t*-Bu)$_4$ gave *N*-cyclization product **8a** with almost complete selectivity (Scheme 8). Although the effect of lithium reagents on the *N*-cyclization selectivity have not been clear, we have shown that this selectivity was greatly influenced by the metallic reagent used. When sodium hydride was used, a mixture of *N*-cyclization product **8a** and *O*-cyclization product **8a′** was obtained.



Scheme 8. Halocyclization of ambident nucleophile.

An iodoaminocyclization reaction that uses a lithium reagent is applicable to various alkenylated urea, carbamate, and amide derivatives **7a**-**7f** and in all cases, *N*-cyclized products **8** were exclusively obtained in satisfactory yield and with complete selectivity (Scheme 9). Furthermore, this reaction is applicable not only to form five-membered ring cpmpounds, but also to form six-membered rings, as in the cases of **7b** and **7e** (n=2). Fukuyama *et al.* recently reported that this reaction is also useful for the construction of the nitrogen-containing quaternary center.[13)]

The cyclization substrates for this reaction, alkenylated urea, carbamate, and amide derivatives **7**, can be readily synthesized by reactions of commercially available *N*-alkoxycarbonylisocyanates with alkenyl alcohols, alkenylamines, and alkenylmagnesium reagents.

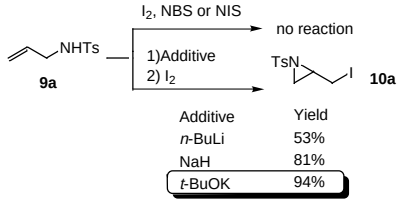


Scheme 9. Regio-controlled iodoaminocyclization of ambident nucleophile mediated by lithium reagent.

3.2. Iodoaziridination Reaction of *N*-Allyltosylamide Derivatives

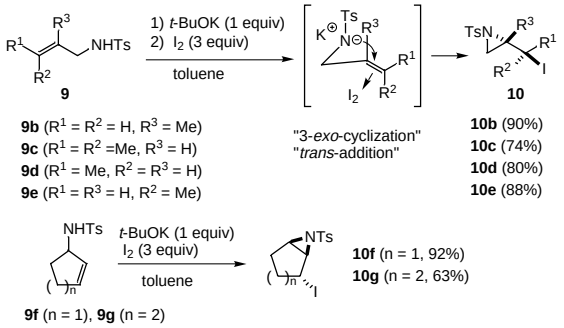
For the three-membered ring-forming reaction using halocyclization, there is one report on halo epoxidation reaction of allyl alcohol derivative.[14)] However, only limited substrates gave the products in satisfactory yield. As described above, we found that in the iodocarbocyclization reaction of allylated active methine compounds **1e** and **1l**, the iodomethylcyclopropane derivatives **2e** and **2l** were obtained in good yield (Schemes 3 and 5). This result indicates that a three-membered ring-forming reaction using halocyclization would be feasible. With this in mind, we examined the three-membered haloaminocyclization reactions (haloaziridination reactions), which had not been previously reported.

As shown in Scheme 10, with *N*-allyltosylamide **9a** occured no reaction when just treating with the halogenating reagent. On the other hand, we found that iodomethylaziridine **10a** was obtained in satisfactory yield when this reaction was run in the presence of an alkali metal reagent and iodine.[15)] For the metallic reagent, *t*-BuOK was the most effective, giving **10a** in 94% yield.



Scheme 10. Additive effect in iodoaziridination reaction.

Iodoaziridination reaction using *t*-BuOK and iodine was applied to various *N*-allyltosylamide derivatives **9a**-**9e**, to give the products **10a**-**10e** in satisfactory yield. The reactions proceeded with complete regioselectivity (3-*exo*-cyclization) and stereoselectivity (*trans*-addition). Moreover, reactions of *N*-cycloalkenyltosylamide such as **9f** and **9g** also proceeded in satisfactory yield to afford the bicyclic iodoaziridine **10f** and **10g**.



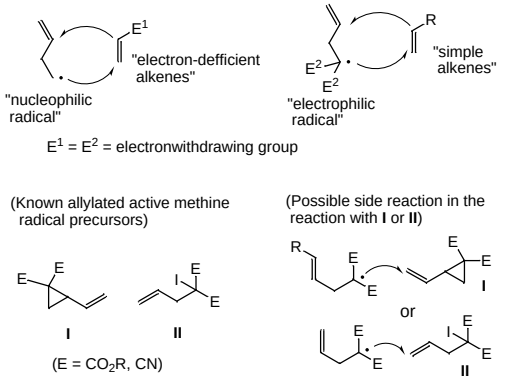
Scheme 11. Iodoaziridination of various *N*-allyltosylamides.

Next, we would like to report radical [3+2] cycloaddition reaction using iodoalkylated three-membered ring compounds **2e** and **10**, which were synthesized in the manner described above.

4. Radical [3+2] Cycloaddition Reaction Using Iodomethylcyclopropane Derivatives

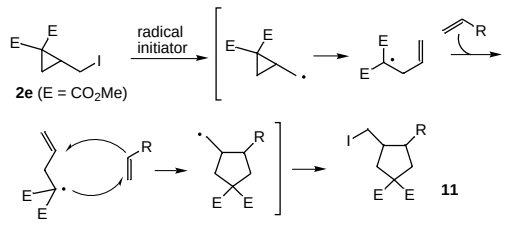
The radical [3+2] cycloaddition reaction of homoallyl radicals with alkenes, is useful for the one-step synthesis of cyclopentane compounds, and many reports dealing this reaction have been appeared (Scheme 12).[16)] The usual homoallyl radical is a nucleophilic radical, which reacts with electron-deficient alkenes such as α,β-unsaturated carbonyl compounds (Scheme 12). In contrast, allyl substituted

active methine radicals are known as electrophilic homoallyl radicals, and these are synthetically very useful because they can react with enol ether and simple alkyl substituted alkenes. Meanwhile, the vinylcyclopropane derivative I[17] and iodomalonate II[18], the precursors of the allylated active methine radicals so far reported, possess an alkene part and therefore, the generated allyl activated methine radical possibly attacks the alkene group of other radical precursor molecule, which is an undesired side reaction (Scheme 12). In order to avoid these side reactions, a large excess amount of alkene must be used or an alkene with high reactivity must be used. However, these are not always definite solutions.



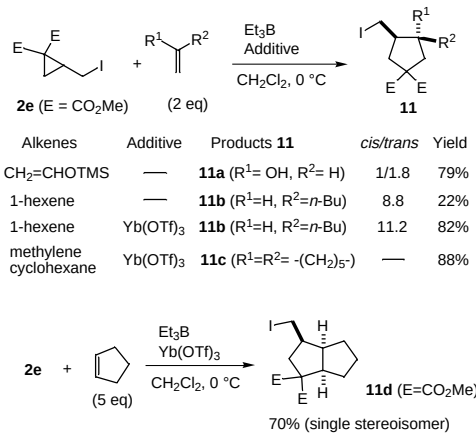
Scheme 12. [3+2] Cycloaddition with homoallyl radical species.

We considered that iodomethylcyclopropane-1,1-dicarboxylate **2e**, which can readily be synthesized by the above-mentioned iodocarbocyclization of allylmalonate **1e** (Scheme 3), could be an efficient allylated active methine radical precursor. We anticipated that when **2e** is treated with a radical initiator, the allylmalonate radical would be generated through regioselective cleavage of the cyclopropylmethyl radical. The resulting allyl radical is expected to undergo an iodine atom transfer [3+2] cycloaddition reaction with an alkene (Scheme 13). In this manner, **2e** was assumed to be an allylated active methine radical precursors with alkene moiety protected.



Scheme 13. Radical iodine atom transfer [3+2] cycloaddition with iodomethylcyclopropane.

The radical cycloaddition reactions of the iodomethylcyclopropane **2e** with a variety of alkenes provided satisfactory results (Scheme 14).[19] For instance, when the reaction between **2e** and silylenol ether was conducted using triethylborane as a radical initiator, we obtained the iodine atom transfer cycloaddition product **11a** in high yield (79%). On the other hand, the reaction with alkyl-substituted alkene such as 1-hexene required the presence of $Yb(OTf)_3$ in addition to triethylborane; without $Yb(OTf)_3$, the yield dropped significantly to 22%. It was considered that $Yb(OTf)_3$ enhances the electrophilicity of the allylmalonate radical and promotes the reaction by forming a chelated complex with the malonate carbonyl group. This reaction is applicable to a variety of alkenes. It is worth noting that even a 1,2-disubstituted alkene, which is generally unreactive by conventional methods because of the low reactivity can undergo the cycloaddition reaction in a satisfactory yield. For instance, bicyclo[3.3.0]octane derivative **11d** was obtained in a yield of 70% from the reaction with cyclopentene (Scheme 14). Furthermore, at a low temperature (0 °C and below), higher stereoselectivity was observed in the reactions with alkyl-substituted alkenes, when compared with that by conventional methods.

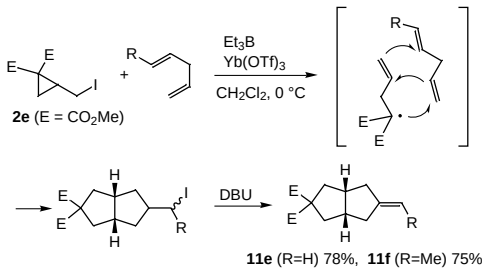


Alkenes	Additive	Products **11**	*cis/trans*	Yield
CH_2=CHOTMS	—	**11a** (R^1= OH, R^2= H)	1/1.8	79%
1-hexene	—	**11b** (R^1=H, R^2=*n*-Bu)	8.8	22%
1-hexene	$Yb(OTf)_3$	**11b** (R^1=H, R^2=*n*-Bu)	11.2	82%
methylene cyclohexane	$Yb(OTf)_3$	**11c** (R^1=R^2= -$(CH_2)_5$-)	—	88%

Scheme 14. Radical [3+2] cycloaddition of **2e** with various alkenes.

A cascade reactions could be performed when the cycloaddition reaction of **2e** is conducted with 1,4-diene derivative. This involves three separate carbon-carbon bond formation, that is, the initial [3+2] cycloaddition reaction is followed by a 5-*exo* cyclization, which produces the bicyclo [3.3.0]octane derivative **11** in one step (Scheme 15).[20] A complete regioselectivity was observed in the reaction of **2e** with an unsymmetrical 1,4-diene derivative (R≠H). For instance, in the reaction with 1,4-hexadiene (R=Me), the initial reaction by the allylmalonate radical occurred exclusively at the most reactive 1-alkene position.

Products derived from the initial attack of the active methine radical at the 1,2-disubstituted alkene moiety were not detected. Consequently, we established that radical cycloaddition using **2e** provides a useful one-step synthetic method not only for cyclopentane ring formation but also for bicyclo[3.3.0]octane ring formation.



2e (E = CO_2Me)

11e (R=H) 78%, **11f** (R=Me) 75%

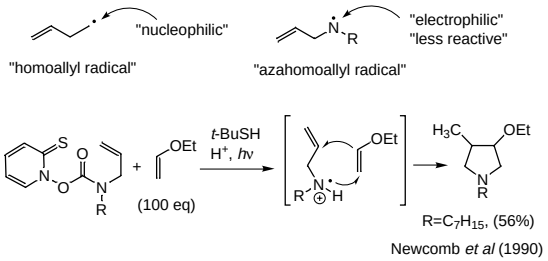
Scheme 15. Radical cascade cycloaddition of iodomethylcyclopropane with 1,4-dienes.

5. Radical [3+2] Cycloaddition Reaction Using Iodoaziridine Derivatives

Next, we would like to describe the radical [3+2] cycloaddition reaction using the iodoaziridine derivative **10** (Scheme 17). This reaction is similar to the reactions using iodoalkylcyclopropanes. The [3+2] cycloaddition reaction of azahomoallyl radicals (2-alkenylamine radical) with alkenes, provides a one-step synthetic route to pyrrolidine derivatives. In contrast to a number of examples with homoallyl radicals, only one report by Newcomb *et al.* has described such a reaction (Scheme 16),[21] in which there remained various issues, such as:

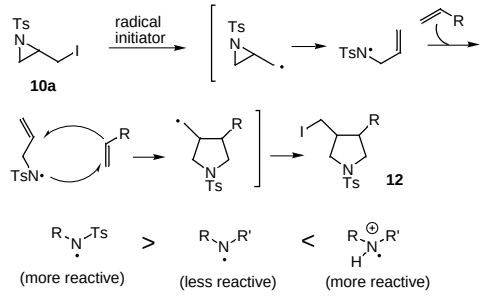
1) A large excess of alkene (100 equiv) was required, and the yield was only 50-59%.
2) Only three examples using enol ether derivatives, a sole structural variant, were shown and thus, the application and limitation of the reaction remain unclear.
3) A Brønsted acid was required in order to generate an allylamminium radical, which is more reactive species.

Most of the reactions between nitrogen radicals and alkenes, are limited to intramolecular 5-*exo* cyclization, which is due to entropy effects.[22] Only a few examples regarding intermolecular versions were reported because the reactivity of the nitrogen radical is known to be significantly lower than that of the carbon radical. Furthermore, efficient nitrogen radical precursors have not been developed.



Scheme 16. [3+2] Cycloaddition with azahomoallyl radical species.

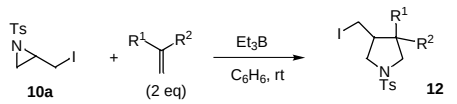
We anticipated that iodoaziridine derivatives would be efficient azahomoallyl radical precursors. Furthermore, these precursors could be readily synthesized by the above-mentioned iodocarbocyclization of *N*-allyltosylamide derivatives. When iodoaziridine **10a** is treated with triethylborane, the allylamidyl radical should be generated through regioselective cleavage of the initially generated aziridinylmethyl radical. The subsequent [3+2] cycloaddition reaction might proceed in the presence of alkenes to give the pyrrolidine derivatives. The nitrogen radical is an electrophilic radical (Scheme 16) whose reactivity is known to improve as the electron density is decreased (Scheme 17). Therefore, the tosylamidyl radical generated from **10a** was also expected to possess higher reactivity toward alkenes than the usual aminyl radical.



Scheme 17. Radical iodine atom transfer [3+2] cycloaddition with iodoaziridine.

First, we examined reactions between iodoaziridine **10a** and various alkenes (Scheme 18). Reactions with enol ether and ketene acetal were conducted in the presence of triethylborane, and both resulted in cycloaddition products **12a**-**12c** in high yield (62-71%).[23,24] As initially anticipated, the reactivity of *N*-allyl(tosyl)amidyl radical generated from this reaction was relatively high and the reactions proceeded effectively, even in the presence of only two-equivalent of alkenes. Next, we examined the reaction with

alkyl-substituted alkenes, which produced lower yields, compared to enol ether derivative (Scheme 18). As mentioned above, the nitrogen radical is an electrophilic radical, and therefore, its reactivity with an alkene is decreased as the electron density of the alkene declines. This was the case in the reaction of **10a** with 1-hexene where the yield was only 34% (**12e**). The stereoselectivity in reactions of allylamidyl radical and alkenes was generally low, and this issue remains to be solved.

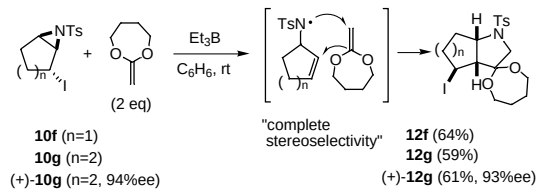


Alkenes	Products **12**	*cis/trans*	Yield
CH_2=CHOTMS	**12a** (R^1= OH, R^2= H)	1.3	66%
CH_2=C(Me)OMe	**12b** (R^1=Me, R^2=OMe)	1/1.7	71%
CH_2=C-O$(CH_2)_4$O-	**12c** (R^1=R^2= -O$(CH_2)_4$O-)	*a*	62%
methylene cyclohexane	**12d** (R^1=R^2= -$(CH_2)_5$-)	—	56%
1-hexene	**12e** (R^1=H, R^2=*n*-Bu)	2.1	34%

[a] single stereoisomer

Scheme 18. Radical [3+2] cycloaddition of **10a** with various alkenes.

On the other hand, a reaction between a bicyclic iodoaziridine **10f** (n=1), **10g** (n=2), and a ketene acetal proceeded with almost complete stereoselectivity and gave the bicyclic pyrrolidine derivatives **12f** and **12g** (Scheme 19). Since the octahydro-indole ring system is a basic structure that is often found in bioactive natural alkaloids, we examined asymmetric synthesis of **12g**. We conducted a reaction of the optically active iodoaziridine (+)-**10g** (94% ee) with the ketene acetal, which proceeded without racemization to yield (+)-**12g** with 93% ee. We are currently examining the synthesis of octahydro-indole natural products using optically active (+)-**12g**.



Scheme 19. Radical [3+2] cycloaddition with bicyclic iodoaziridines.

6. Conclusion

As described above, we have succeeded in developing new iodocyclization reactions mediated by metallic reagents. Furthermore, we have succeeded in developing a [3+2] cycloaddition reaction using the iodoaziridine as the radical precursor. The reactions proceed with high regioselectivity and stereoselectivity using readily synthesized precursors. Therefore, these are useful synthetic method of carbocyclic compounds and nitrogen heterocyclic compounds.

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