Pure Appl. Chem., Vol. 84, No. 12, pp. 2609–2617, 2012.
http://dx.doi.org/10.1351/PAC-CON-12-01-03

Integrated reactions using addition to conjugated imines and iminium salts*

Takafumi Nishi, Isao Mizota, and Makoto Shimizu‡

Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507, Japan

Abstract: Recently, nucleophilic addition reactions to imino functions have been utilized in many crucial steps for the synthesis of bioactive and functional materials. This article summarizes the integrated "umpolung" reactions of α-imino esters and the use of iminium salts as reactive electrophiles. Regarding the umpolung reactions, the following five reactions are discussed: (1) *N*-alkylation/homocoupling; (2) tandem *N*-ethylation/*C*-allylation; (3) tandem *N*-ethylation/*C*-cyanation; (4) reduction of imines with tris(trimethylsilyl)aluminum; and (5) *N*-alkylation and Claisen rearrangement. Moreover, the generation and reactions of alkoxycarbonyl iminium species are also discussed. These are prepared easily from trisubstituted amino ketene silyl acetals by oxidation, and the subsequent nucleophilic addition of various nucleophiles readily affords the addition products.

Keywords: alkoxycarbonyl iminium salt; electrophilic amination; α-imino ester; integrated reactions; *N*-alkylation; umpolung.

INTRODUCTION

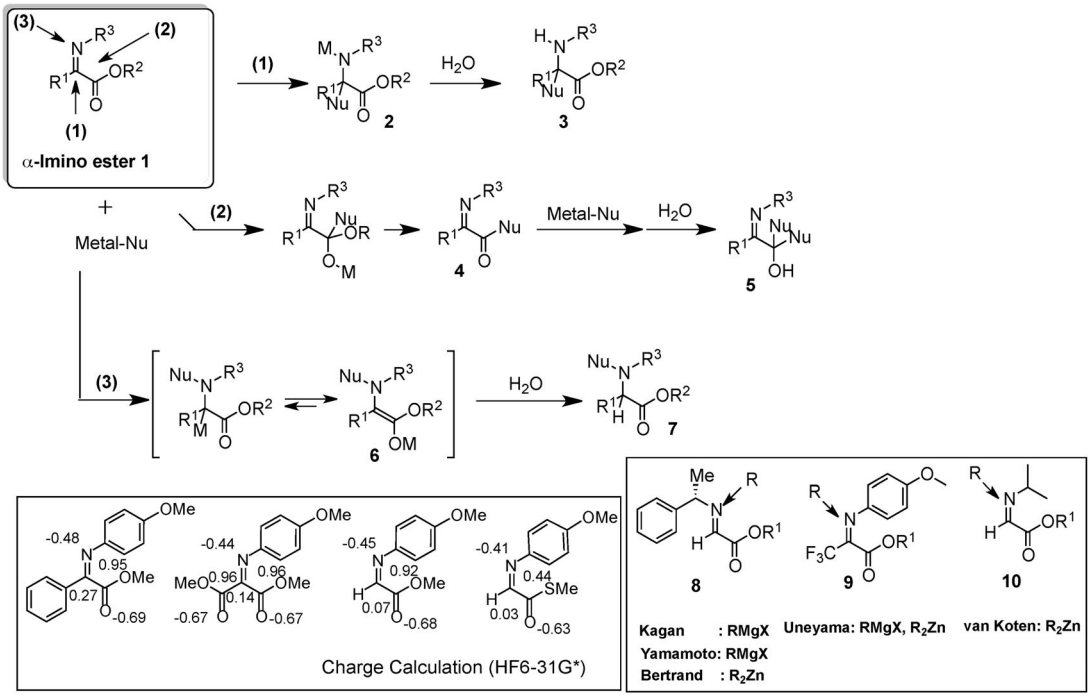
Nitrogen-containing organic molecules, as represented by amino acids, alkaloids, β-lactam antibiotics, and so on, have received considerable attention as useful bioactive compounds as well as functional materials. For example, diamines have widespread utilities as synthetic intermediates for medicines and functional materials such as ligands for transition-metal catalysts and electronic industry materials. Since the search for new synthetic reactions for nitrogen-containing molecules leads to the development of many functional substances, it is one of the most important and attractive areas in synthetic organic chemistry. The most straightforward approach providing nitrogen-containing organic molecules is nucleophilic addition to an imine, and many examples have been reported in which various nucleophiles undergo 1,2-addition to imines.

On the other hand, because of the electronegativity of the carbon and nitrogen atoms of imines, it is not easy for the nucleophile to add to the nitrogen in an umpoled manner. Although it is limited to certain examples, nucleophilic attack at the nitrogen atom can sometimes takes place when an electron-deficient imine such as an α-imino ester is subjected to nucleophilic addition. We were interested in the reactivity of α-imino esters, and found several intriguing and useful features leading to new integrated synthetic reactions [1]. These are also discussed.

Pure Appl. Chem.* **84, 2499–2675 (2012). A collection of invited papers based on presentations at the 7th International Conference on Novel Materials and their Synthesis (NMS-VII) and the 21st International Symposium on Fine Chemistry and Functional Polymers (FCFP-XXI), Shanghai, China, 16–21 October 2011.
‡Corresponding author

UMPOLUNG OF α-IMINO ESTERS

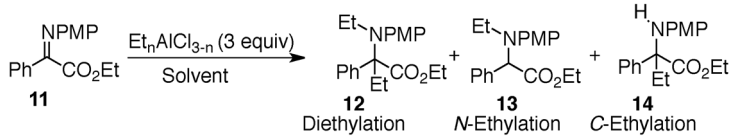
There are three possible electrophilic sites (imino carbon, ester carbonyl, and imino nitrogen) in the α-imino ester **1**, as shown in Scheme 1. The nucleophilic attack usually takes place at the imino carbon to give the amino ester **3**. In some cases, the ester part is attacked by the nucleophile to give either the α-imino ketone **4** or the β-imino alcohol **5**. The third pattern, in which the imino nitrogen is attacked by a certain nucleophile to give the umpoled addition product **7**, is very rare. In fact, simple charge calculation (HF6-31G*) of imines indicates that all the imino nitrogens examined by the present calculation are more negatively charged than the imino carbons, suggesting that nucleophilic attack at the nitrogen is not trivial. However, umpolung of α-imino esters has some precedents. A few research groups discovered the *N*-alkylation reaction of α-imino esters. For example, Grignard reagents undergo addition to the imino nitrogen in good yields, and dialkyl zinc reagents also effect the *N*-addition reactions [2].



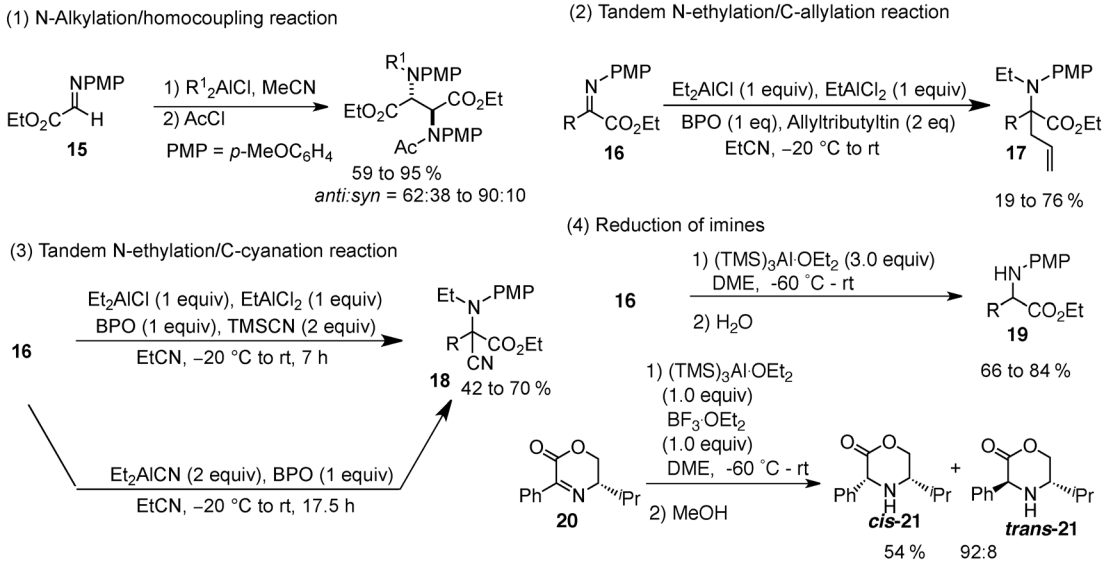
Scheme 1 Characteristics of α-imino ester.

Initially, we examined the reactivity of α-imino esters using the imine **11** derived from phenylglyoxylate, and obtained the following results (Table 1). In toluene solution, the use of diethylaluminum chloride as a nucleophile effected only *C*-ethylation, whereas the *N*-ethylation product was obtained in CH_2Cl_2, Et_2O, and 1,2-dimethoxyethane (DME). In particular, the diethylation product was obtained together with the *N*-ethylation product in Et_2O and DME. The formation of the double addition product may be due to the concomitant oxidation of the intermediary aluminum enolate by oxygen or other peroxides followed by the second ethylation. The use of triethylaluminum gave the *C*-ethylation product in CH_2Cl_2 and the *N*-ethylation product in DME. These results indicate that the aggregation state of the aluminum reagent alters the reaction pathway dramatically. On the basis of these solvent effects, we searched for the reaction conditions suitable for the *N*-alkylation of α-imino esters, and the following new reactions were discovered (Scheme 2).

Table 1 Solvent effect on umpolung.



Entry	Et_nAlCl_{3-n}	Solvent	Temp (°C)	Diethylation	*N*-Ethylation	*C*-Ethylation
1	Et_2AlCl	Toluene	–78 to rt	–	–	97
2	Et_2AlCl	CH_2Cl_2	–78 to rt	–	74	–
3	Et_2AlCl	Et_2O	–78 to rt	21	39	–
4	Et_2AlCl	DME	–50 to rt	35	38	–
5	Et_3Al	CH_2Cl_2	–78 to rt	–	–	79
6	Et_3Al	DME	–50 to rt	7	70	–



Scheme 2 Umpolung of α-imino ester.

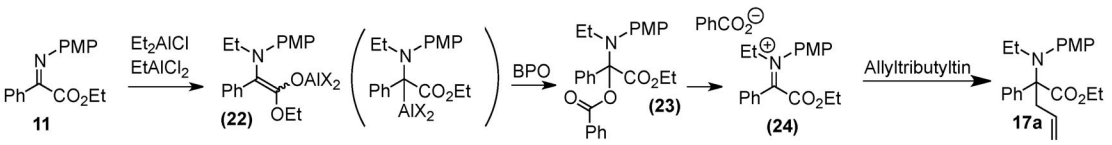
(1) *N*-Alkylation/homocoupling reaction: a coupling reaction of the imines derived from ethyl glyoxylate **15** proceeded with alkylaluminum reagents to give 1,2-diamines in good yields [3a].

(2) Tandem *N*-ethylation/*C*-allylation reaction: on treatment of the imino ester **16** with Et_2AlCl, $EtAlCl_2$, and allyltributyltin in the presence of benzoyl peroxide (BPO), the *N*-alkylation-*C*-allylation product **17** was obtained. A possible mechanism of the present tandem reaction is shown in Scheme 3. First, 1,4-addition of the ethyl group proceeds at the nitrogen atom of the imino ester to give an enolate species. The enolate (**22**) is subsequently oxidized with BPO to form an iminium salt (**24**), which is attacked by allyltributyltin to afford the *C*-allylation product [3b].

(3) Tandem *N*-ethylation/*C*-cyanation reaction: the tandem reaction was also carried out using trimethylsilyl cyanide instead of allyltributyltin to give the amino nitrile **18**. In the presence of BPO, diethylaluminum cyanide acted as both the ethylation and subsequent cyanation reagents, also affording the amino nitrile [3b].

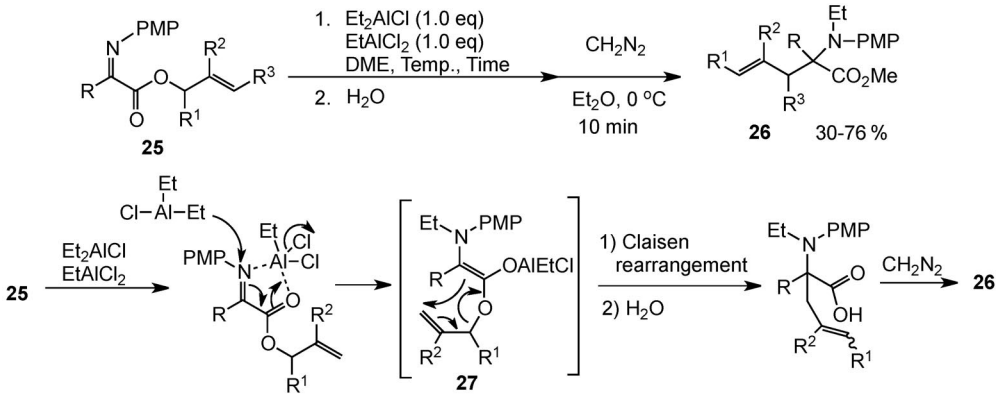
(4) Reduction of imines: tris(trimethylsilyl)aluminum was found to be a good chemoselective reducing reagent, giving α-amino esters in good yields. Application to the reduction of 3,5-disubsti-

tuted 5,6-dihydro-2*H*-1,4-oxazine-2-one **20** offers stereoselective conversion into *cis*-3,5-disubstituted morpholine-2-one **21** [3c].



Scheme 3 *N*-Ethylation/*C*-allylation mechanism.

Recently, a new synthesis of γ,δ-unsaturated quaternary α-amino acid derivatives was developed, utilizing *N*-alkylation and the Claisen rearrangement of allyl α-iminocarboxylates. First, ethyl aluminum dichloride, which is a stronger Lewis acid than diethyl aluminum chloride, coordinates to the nitrogen atom of the imino group and the carbonyl oxygen atom. This is followed by *N*-ethylation of diethyl aluminum chloride to give the intermediary aluminum enolate **27**. The Claisen rearrangement in turn takes place to give the amino acid derivative, which is methylated with diazomethane [3d] (Scheme 4).

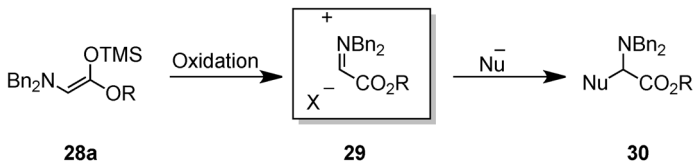


Scheme 4 *N*-Alkylation/Claisen rearrangement.

USE OF ALKOXYCARBONYL IMINIUM SALTS AS REACTIVE ELECTROPHILES

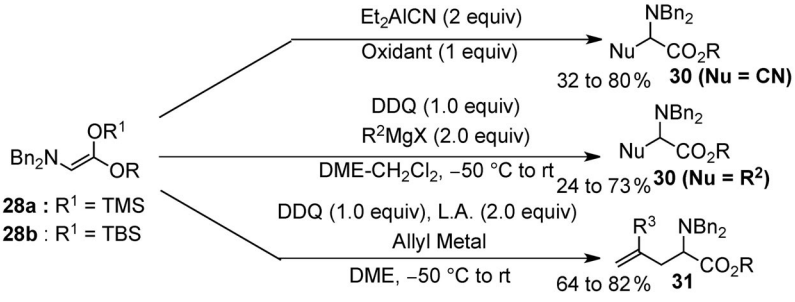
Iminium salts are very reactive and attractive species in organic synthesis, and therefore, the search for an easy preparation method for these species has received considerable attention [4].

We recently reported that the alkoxycarbonyl iminium species **29** is generated easily from trisubstituted amino ketene silyl acetal **28** by oxidation, and that the subsequent nucleophilic addition of various nucleophiles readily affords the addition products (Scheme 5) [5].



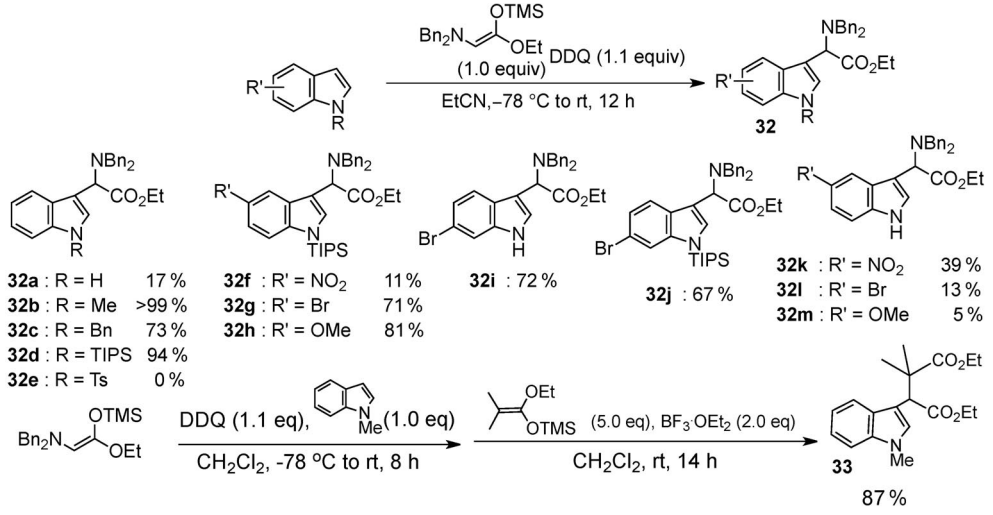
Scheme 5 Formation and reaction of alkoxycarbonyl iminium salt.

The examination of the generation of the iminium salt was carried out using the reaction of amino ketene silyl acetal **28** with oxidizing reagents followed by the reaction with diethylaluminum cyanide. Among the oxidants used, good to excellent results were recorded with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Alkylation, arylation, and allylation were also carried out successfully. Grignard reagents underwent addition reactions to the iminium salt generated by the oxidation of the amino ketene silyl acetal **28** with DDQ, to give the addition products **30** in moderate to good yields. The reaction was influenced by the steric bulk of the Grignard reagents: secondary Grignard reagents depressed the yields, and *tert*-BuMgBr did not give the addition product. Regarding the allylation reaction, tetraallyltin and tetramethallyltin reagents effected allylation reactions to give the adducts in moderate yields, while allyltributyltin could also be used with a comparable efficiency under the influence of diethylaluminum chloride as a Lewis acid. A better result was obtained using allyltrimethylsilane; in this case, the reaction of the *tert*-butyldimethylsilyl (TBS) derivative **28b** in propionitrile in the presence of tin(IV) chloride was proved to be superior (Scheme 6).



Scheme 6 Reaction of alkoxycarbonyl iminium salt.

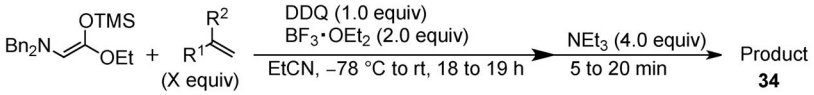
The Friedel–Crafts reactions of various indole derivatives proceeded with the iminium salt generated by the oxidation of amino ketene silyl acetal to give the addition products in good yields. Further reaction of the introduced glycine moiety of the adduct with the second nucleophile provided the double nucleophilic addition product **33** (Scheme 7) [6]. The ene reaction of various olefins also proceeded

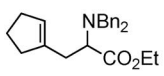
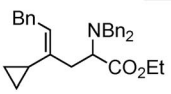
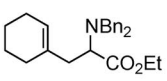
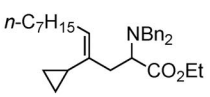
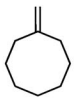
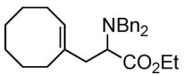
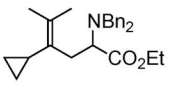


Scheme 7 Friedel–Crafts reaction of alkoxycarbonyl iminium salt.

with the iminium salt generated by the oxidation of amino ketene silyl acetal to give the addition products **34** in good yields (Table 2) [7].

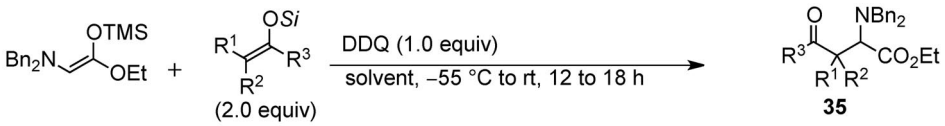
Table 2 Imino ene reaction of iminium salts.



Entry	Olefin	X equiv	Product **34**	Yield (%)	Entry	Olefin	X equiv	Product **34**	Yield (%)
1		1.2		55	4		3.0		94 (*Z*:*E* = >99:1)
2		4.0		62	5		3.0		43
3		1.2		82	6		3.0		49

Iminium salts generated by the oxidation of amino ketene silyl acetals underwent a facile Mannich reaction with another ketene silyl acetal to give the aspartic acid derivatives **35** in good yields. The diastereoselectivities were controlled to some extent by using an appropriate isomer of the ketene silyl (thio)acetal (Table 3) [8].

Table 3 Diastereoselective Mannich reaction.



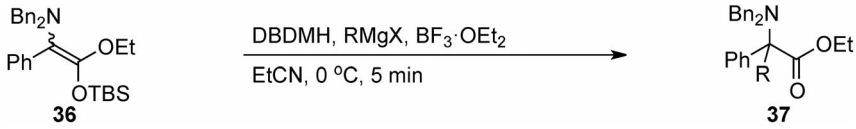
Conditions A: with $BF_3 \cdot OEt_2$ (2.0 equiv) in DME
Conditions B: without $BF_3 \cdot OEt_2$ in DMF
Conditions C: with Et_2AlCl (2.0 equiv) in DME
Conditions D: with $BF_3 \cdot OEt_2$ (2.0 equiv) in CH_2Cl_2

Entry	R^1	R^2	R^3	*Si*	Conditions	Yield (%)	*anti*:*syn*
1	H	Me	OEt	TBS	A	57	56:44
2	H	Me	SEt	TMS	D	74	30:70
3	Me	Me	OEt	TBS	A	50	81:19
4	Me	H	OEt	TBS	B	51	75:25
5	BnO	H	OMe	TMS	A	61	82:18
6	BnO	H	OMe	TBS	C	66	85:15
7	Me	H	OEt	TBS	C	52	83:17
8	Me	H	Ph	DMS	A	40	49:51
9	Me	H	Ph	TBS	A	58	42:58
10	Me	H	Ph	TIPS	A	60	14:86

As described above, an alkoxycarbonyl iminium species is generated easily from trisubstituted amino ketene silyl acetal by oxidation, and the subsequent nucleophilic addition of various nucleophiles readily affords the addition products. The applicability of the present iminium system is greatly enhanced with more convenient synthesis of α,α-disubstituted α-amino acids possessing sp or sp^2 hybridized carbons, e.g., α,α-diaryl α-amino acids. With this in mind, a convenient synthesis of α,α-disubstituted α-amino acids was discovered, which uses the nucleophilic addition of Grignard

reagents to iminium salts generated from tetrasubstituted amino ketene silyl acetals [9]. The results of the nucleophilic addition of several Grignard reagents are summarized in Table 4. The reaction of iminium salts derived from amino ketene silyl acetal **36** with Grignard reagents gave the desired product **37** with primary and secondary alkyl, aryl, and vinyl moieties at the α-position in moderate to good yields. However, bulky *tert*-butyl Grignard reagents did not give satisfactory results.

Table 4 Nucleophilic addition of Grignard reagent using **36**.

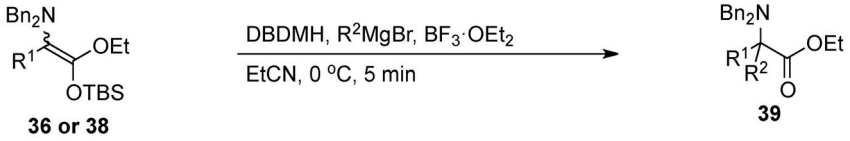


Entry	RMgX	Product	Yield (%)
1	MeMgBr	**37a**	83
2	EtMgBr	**37b**	78
3	*n*-PrMgBr	**37c**	80
4	*i*-PrMgBr	**37d**	74
5	*c*-PrMgBr	**37e**	84
6	*c*-HexMgBr	**37f**	66
7	*t*-BuMgCl	**37g**	18[a]
8	BnMgCl	**37h**	66
9	VinylMgBr	**37i**	80
10	PhMgBr	**37j**	65
11	4-MeC_6H_4MgBr	**37k**	52
12	4-MeOC_6H_4MgBr	**37l**	56
13	2-ThienylMgBr	**37m**	88
14	EthynylMgBr	**37n**	82

[a]Reaction was performed at −78 °C for 30 min.

The functionalized amino ketene silyl acetals **36** or **38** with aryl moieties bearing either electron-withdrawing or -donating groups were employed successfully to give the corresponding adducts in moderate to good yields. However, the alkynyl derivative **38e** was not a suitable substrate for the present oxidative generation of the iminium salt followed by nucleophilic addition, and the products were obtained in moderate yields (Table 5).

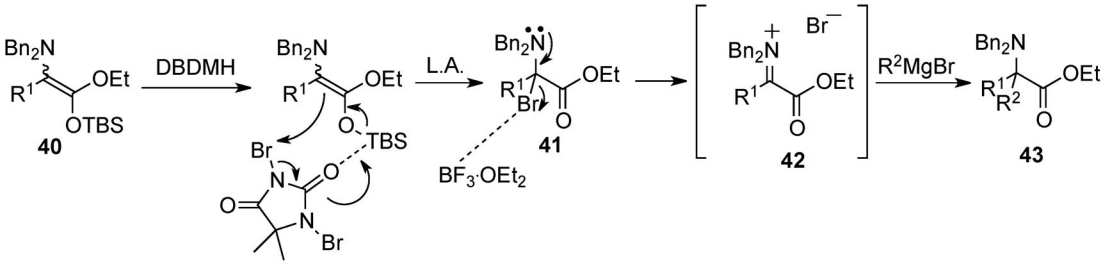
Table 5 Nucleophilic addition of Grignard reagent using **36** or **38**.



Entry	R^1	R^2	Yield (%)
1	Ph (**36**)	Et	78
2	4-MePh (**38a**)	Et	90
3	4-MeOPh (**38b**)	Et	81
4	4-ClPh (**38c**)	Et	95
5	1-Napht (**38d**)	Et	75
6[a]	Phenylethynyl (**38e**)	Et	57
7[a]	Phenylethynyl (**38e**)	Me	28
8[a]	Phenylethynyl (**38e**)	Vinyl	16
9[a]	Phenylethynyl (**38e**)	Ph	34

[a]Reaction was performed at –78 °C for 5 min and then at rt for 1 h.

A plausible mechanism is shown in Scheme 8. The oxidation of the amino ketene silyl acetal **40** gives the α-bromo ester **41**, and the subsequent elimination of the bromide ion leads to the formation of the iminium salt **42**. It seems that the presence of $BF_3{\cdot}OEt_2$ would promote the elimination of the bromide ion or activate the oxidation process as a Lewis acid. Finally, the nucleophilic addition reaction to the iminium salt gives the product **43**.



Scheme 8 Plausible reaction mechanism.

CONCLUSION

α-Imino esters behave as acceptors of nucleophiles at their nitrogen atoms under appropriate conditions. The tandem *N*-alkylation/*C*-allylation and *N*-alkylation/*C*-cyanation reactions of several α-imino esters with organoaluminums, where two nucleophiles attack across the C=N double bond, were carried out, giving good to excellent yields. A new one-pot synthesis of α-amino acid derivatives was also developed, in which an α-quaternary carbon utilizes the Claisen rearrangement of the aluminum enolate prepared by the umpolung reaction.

We also studied the generation and reactivity of alkoxycarbonyl iminium salts prepared by the oxidation of amino ketene silyl acetals followed by nucleophilic addition, and found several interesting features. We observed that the iminium salts from tetrasubstituted amino ketene silyl acetals (except for the alkylnyl-substituted case) were readily prepared through oxidation with *N*,*N*-dibromodimethylhydantoin, and that subsequent nucleophilic addition with several Grignard reagents proceeded in mod-

erate to good yields. These new reactions provide useful additions to existing methods for the synthesis of biologically active nitrogen-containing compounds and of many functional materials.

ACKNOWLEDGMENTS

We would like to thank our co-workers for their intellectual and experimental contributions to the present project. This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, of the Japanese Government. A grant from the Japan Science and Technology Agency is also gratefully acknowledged.

REFERENCES

1. (a) M. Shimizu. *Pure Appl*. *Chem*. **78**, 1867 (2006); (b) M. Shimizu, I. Hachiya, I. Mizota. *Chem. Commun*. 874 (2009).
2. (a) M. P. Bertrand, L. Feray, R. Nouguier, P. Perfetti. *Synlett* 1148 (1999); (b) K. Uneyama, F. Yan, S. Hirama, T. Katagiri. *Tetrahedron Lett*. **37**, 2045 (1996); (c) Y. Yamamoto, W. Ito. *Tetrahedron* **44**, 5415 (1988); (d) M. R. P. van Vliet, J. T. B. H. Jastrzebski, W. J. Klaver, K. Goubitz, G. van Koten. *Recl*. *Trav*. *Chim*. *Pays-Bas* **106**, 132 (1987); (e) J.-C. Fiaud, H. B. Kagan. *Tetrahedron Lett*. **12**, 1019 (1971).
3. (a) M. Shimizu, Y. Niwa. *Tetrahedron Lett*. **42**, 2829 (2001); (b) Y. Niwa, M. Shimizu. *J. Am. Chem. Soc.* **125**, 3720 (2003); (c) M. Shimizu, Y. Niwa, T. Nagai, I. Hachiya. *Heterocycles* **72**, 127 (2007); (d) I. Mizota, K. Tanaka, M. Shimizu. *Tetrahedron Lett*. **53**, 1847 (2012).
4. (a) U. Jahn, J. Andersch, W. Schroth. *Synthesis* 573 (1997); (b) E. C. Roos, H. H. Mooiweer, H. Hiemstra, W. N. Speckamp, B. Kaptein, W. H. J. Boesten, J. Kamphuis. *J. Org. Chem*. **57**, 6769 (1992).
5. M. Shimizu, H. Itou, M. Miura. *J. Am. Chem. Soc.* **127**, 3296 (2005).
6. T. Iwao, M. Shimizu. *Heterocycles* **77**, 767 (2009).
7. M. Shimizu, H. Itou, T. Iwao, Y. Umeda. *Chem*. *Lett*. **38**, 73 (2009).
8. M. Shimizu, T. Kusunoki, M. Yoshida, K. Kondo, I. Mizota*, Chem. Lett*. **40**, 351 (2011).
9. S. Hata, H. Koyama, M. Shimizu. *J*. *Org*. *Chem*. **76**, 9670 (2011).

