Conjugated imines and iminium salts as versatile acceptors of nucleophiles

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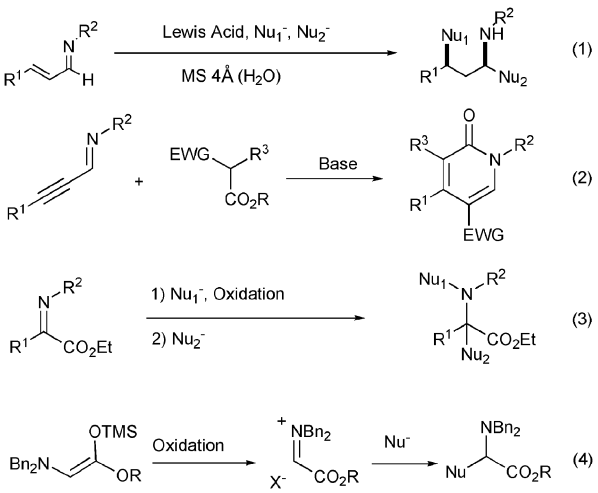
Growing interests in nitrogen-containing molecules involving bioactive and functional materials have stimulated the recent development of synthetic methodologies where nucleophilic addition reactions to imino carbons are utilized in crucial steps. This article summarizes double nucleophilic addition reactions with α,β-unsaturated aldimines, addition reactions using alkynyl imines, "umpoled" reactions of α-imino esters, and the use of iminium salts as reactive electrophiles.

Introduction

The widespread existence of nitrogen-containing compounds such as amino acids, alkaloids, and functional materials coupled with their use as useful synthons has prompted exploration of new activation methods for imino compounds and subsequent intriguing reactions. For the synthesis of nitrogen-containing compounds, addition reactions to α,β-unsaturated imines constitute one of the most straightforward approaches. However, since there are two electrophilic carbons in α,β-unsaturated imines, difficulties are always encountered regarding the regioselectivity. On the other hand, imino compounds do not always have enough electrophilicity as compared with their parent carbonyl counterparts. For the activation of imino carbons, use as iminium salts offers one solution. The following new reactions are discussed: (1) 1,4- and 1,2- double nucleophilic addition reactions with α,β-unsaturated aldimines (eqn (1)), (2) addition reactions using alkynyl imines (eqn (2)), and (3) reactions of α-imino esters and iminium salts (eqn (3) and (4)).



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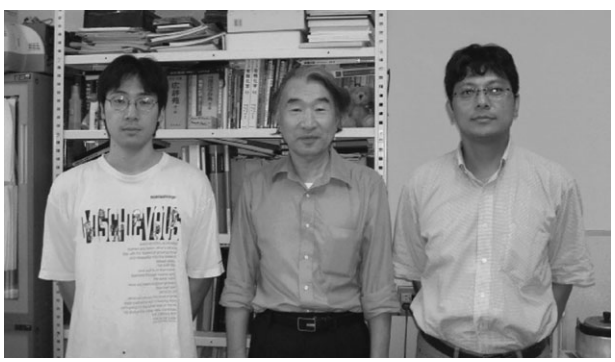

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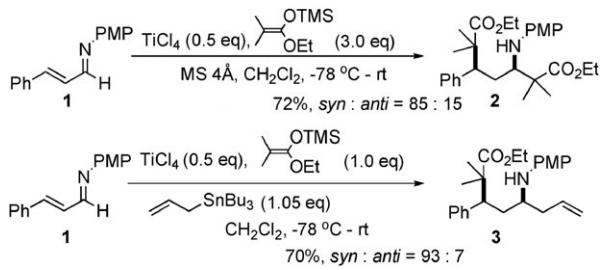
Their research interests focus on the exploration into new C–C bond forming and/or asymmetric reactions using organometallics and application to the synthesis of new functional materials and bioactive natural or unnatural products, where imino and iminium species are utilized in crucial steps.

1,4- and 1,2-double nucleophilic addition reactions to α,β-unsaturated aldimines

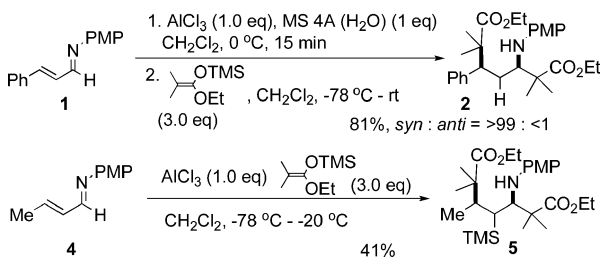
1. Ketene silyl acetals and allylstannanes as nucleophiles[1,2]

α,β-Unsaturated aldimines are readily accessible from the parent aldehydes *via* simple condensation with amines. Although α,β-unsaturated imines potentially possess two electrophilic centers, use of both the carbons for carbon to carbon bond forming reactions in a stereocontrolled fashion has been a difficult task.[3] Tandem alkylation reaction to α,β-unsaturated imines appears to eliminate several drawbacks, and therefore, it is highly desirable to develop an operationally simple procedure for the addition reaction of two nucleophiles to α,β-unsaturated imines in a single-step. The first example of double nucleophilic addition to α,β-unsaturated aldimines induced by TiX_4 was reported in 1999.[1] In the presence of $TiCl_4$, ketene silyl acetals underwent 1,4- and subsequently 1,2-addition to α,β-unsaturated aldimines **1** to give doubly alkylated products **2** in good yields. The best result was obtained when the reaction was carried out in the presence of 4 Å molecular sieves (4 Å MS) using the *N*-anisyl derivative, and the desired double alkylation product **2** was formed in 72% yield. Moreover, the reaction of a mixture of a ketene silyl acetal and an allyltributylstannane with α,β-unsaturated aldimine **1** gave regio- and chemoselectively 1,4- and 1,2-doubly alkylated products **3**, in which the ketene silyl acetal underwent a 1,4-addition, while the allyltributylstannane did a 1,2-addition. In these cases, the formation of the *syn*-adduct predominated (Scheme 1).

In the presence of 1.0 equiv. of $AlCl_3$ and 4 Å MS containing 1.0 equiv. of H_2O, reaction of ketene silyl acetals with α,β-unsaturated aldimines also gave 1,4- and 1,2-alkylated products in good yields with excellent diastereoselectivities.[2] Under these reaction conditions, a variety of ketene silyl acetals and/or thioacetals gave 1,4- and 1,2-addition products in good yields.[2] The use of 4 Å MS (H_2O) promoted the isomerization after 1,4-addition. The intermediary metalloenamine and/or α-metalloimine were successfully trapped by a TMS group when the reaction was carried out in the absence of 4 Å MS (H_2O) (Scheme 2).



Scheme 1 Double nucleophilic addition to α,β-unsaturated aldimine **1** induced by titanium tetrachloride.



Scheme 2 Double nucleophilic addition to α,β-unsaturated aldimines **1** in the presence or absence of 4 Å MS containing H_2O.

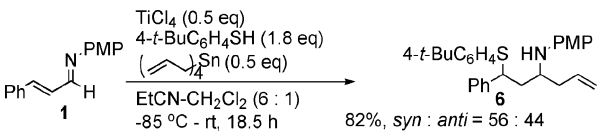
2. Thiols and allylstannanes as nucleophiles[4]

Conjugate addition of thiols to α,β-unsaturated carbonyl compounds constitutes one of the most popular modes of reactions in organic synthesis.[5] However, its imino versions have received little attention, since the addition products to α,β-unsaturated imines, β-sulfenyl imines and/or their enamine counterparts, are readily hydrolyzed to the parent carbonyl compounds.[6] A double nucleophilic addition reaction of thiols and tetraallyltin to α,β-unsaturated aldimines was also reported, where the presence of added water was not necessary due to the acidic hydrogen of the thiol (Scheme 3).

3. TMSCN as the nucleophile[7,8]

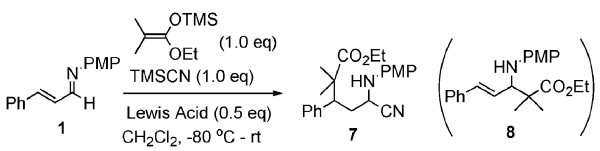
The Strecker reaction is one of the most efficient methods for the synthesis of α-amino acids.[9] A variety of asymmetric Strecker reactions have been reported to date. The double nucleophilic addition of ketene silyl (thio)acetals and trimethylsilyl cyanide to α,β-unsaturated aldimines also proceeds.[7] Among the Lewis acids, $AlCl_3$ and TMSI were found to be the most efficient promoters (Table 1). Although there is much room for the improvement of diastereoselectivities, the imines having not only an aromatic group but also an aliphatic group work well (Table 2).

To clarify the reaction mechanism, the reaction of imine with ketene silyl acetal was carried out in the presence of 3 Å MS pretreated with D_2O (treated with D_2O and dried) to give the deuterated product **11** in 73% yield with 56% deuterium incorporation. The same reaction conducted in the absence of



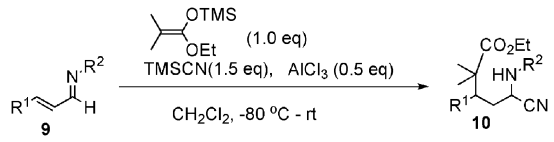
Scheme 3 Double nucleophilic addition with thiol and allyltin.

Table 1 Examination of Lewis acids



Entry	Lewis acid	**7** (%)	*syn* : *anti*	**8** (%)
1	$SnCl_4$	35	47 : 53	—
2	$TiCl_4$	56	48 : 52	5
3	TMSI	74	56 : 44	2
4	$EtAlCl_2$	62	45 : 55	7
5	Et_2AlCl	47	35 : 65	20
6	$AlCl_3$	73	45 : 55	7
7	$AlBr_3$	67	50 : 50	5
8	AlI_3	61	48 : 52	7

Table 2 Examination of α,β-unsaturated aldimines

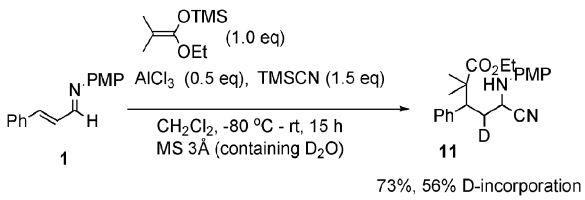


R^1	R^2	Yield (%)	*syn* : *anti*
Ph	PMP	84	47 : 53
Me	PMP	81	49 : 51
^{n}Pr	PMP	55	52 : 48
Ph	$CHPh_2$	78	49 : 51

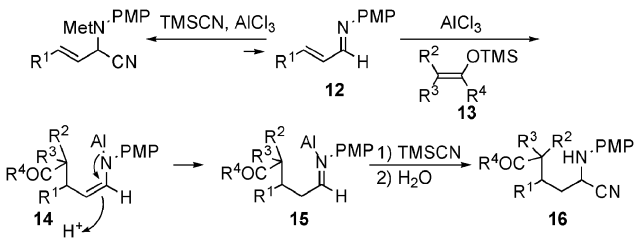
3 Å MS followed by quenching with CD_3COOD gave the adduct in 53% yield with only trace of deuterium incorporation. (Scheme 4).

Moreover, close examination of the reaction of imine with ketene silyl acetal and TMSCN in the presence of $AlCl_3$ as monitored by TLC revealed that the initial 1,2-addition of TMSCN occurred at −20 °C. A new spot which was assigned to be a 1,4- and 1,2-adduct gradually appeared at −10 to 0 °C. From these results, a plausible reaction mechanism was proposed as shown in Scheme 5. The initial 1,2-addition of TMSCN occurs, which, however, is a reversible process to regenerate the parent imine **12**. Metalloenamine **14** would be generated *via* an $AlCl_3$-promoted 1,4-addition reaction of ketene silyl (thio)acetal **13** and reacts with a certain proton source to give imine **15**, which in turn is attacked by TMSCN to afford 1,4- and 1,2-adduct **16**.

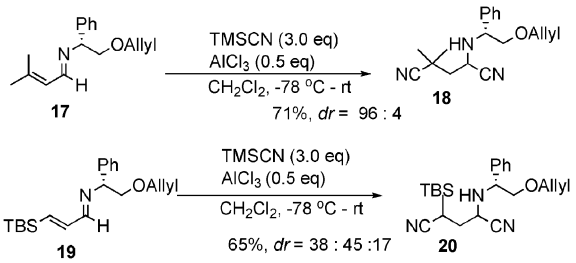
TMSCN[9d] is also an excellent nucleophile for both the 1,4- and 1,2-additions to α,β-unsaturated aldimines to give 2-aminopentanedinitriles. The imines possessing chiral auxiliaries derived from (*R*)-phenylglycinol underwent diastereoselective addition.[8] Regarding the derivatives, methyl, allyl, and methallyl ethers induced good diastereoselectivities. In order to check the diastereoselectivity in the first conjugate addition reaction, the *tert*-butyldimethylsilylated derivative **19** was subjected to these double addition conditions. In this case, however, three peaks for the adducts **20** were detected by



Scheme 4 Examination into D-incorporation.



Scheme 5 Proposed mechanism of double nucleophilic addition.



Scheme 6 Double nucleophilic addition of the imines possessing chiral auxiliaries derived from (*R*)-phenylglycinol.

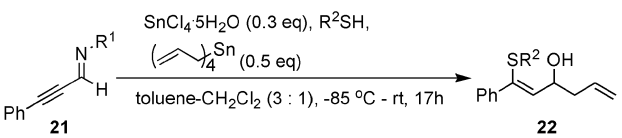
HPLC, indicating that the first conjugate addition was not diastereoselective (Scheme 6).

4. Use as latent α,β-unsaturated aldehydes[10,11]

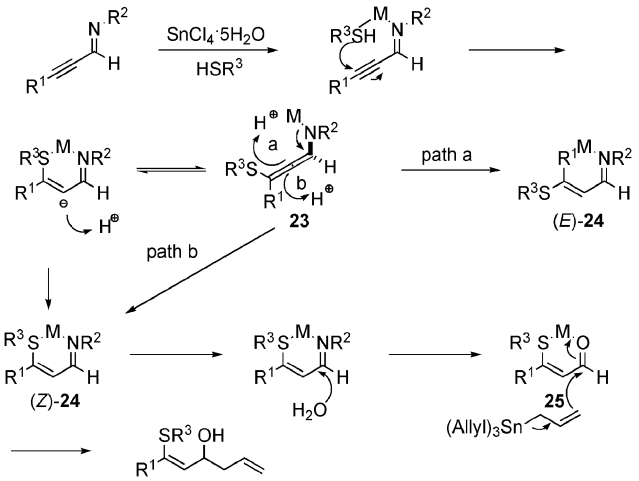
One of the most important functional groups in organic transformations involves vinyl sulfides, since C–C bond forming reactions,[12] hydrolysis to carbonyl compounds,[13] and desulfenylation to olefins[14] are readily carried out using the characteristics of such functionalities. For the preparation of a useful vinylsufenyl functionality, the most direct way appears to be the addition of thiols to triple bonds. However, control of the resulting olefin geometry is not trivial under the radical addition conditions. On the other hand, conjugate addition of thiols to the electron-deficient alkynes also enables direct access to vinyl sulfides.[15] Stereoselective access to (*Z*)-1-sulfenyl-1,5-alkadien-3-ols is possible using a double nucleophilic addition of thiols and allylstannane to the imines derived from 2-alkynals with $SnCl_4{\cdot}5H_2O$, where *in situ* hydrolysis of an intermediary imine to an aldehyde is crucial for the success of this approach. Switching the anisyl imine to a sterically more hindered diphenylmethyl derivative increased the product yields. The *tert*-butyl, cyclohexyl, and 1-phenylethyl imines can also be used with equal efficiency in terms of stereoselectivity. Regarding thiols, *n*-hexanethiol also serves as a stereoselective 1,4-addition nucleophile (Table 3).

This reaction most probably proceeds *via* the following mechanisms. First, the initial addition of thiol is promoted by $SnCl_4{\cdot}5H_2O$. The subsequent protonation is effected by the liberated HCl from $SnCl_4{\cdot}5H_2O$ and the thiol to generate the vinyl sulfide possessing an aldehyde moiety **25**, which in turn is attacked by the allyltin to give the double nucleophilic addition product (Scheme 7). The diastereoselectivity is explained by

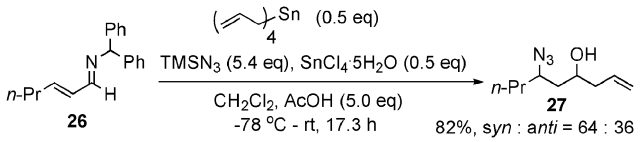
Table 3 Examination of thiols and substituents at the nitrogen



R^1	R^2/equiv.	Yield (%)	*Z* : *E*
$CHPh_2$	4-*t*-BuC_6H_4/2.5	79	71 : 29
t-Bu	MeO_2CCH_2/1.5	70	100 : 0
c-Hex	MeO_2CCH_2/1.5	68	100 : 0
4-ClC_6H_4	MeO_2CCH_2/1.5	51	65 : 35
CH(Me)Ph	MeO_2CCH_2/1.5	76	100 : 0
CH(Me)Ph	*n*-Hex/1.5	96	100 : 0



Scheme 7 Proposed mechanism of vinyl sulfide formation.



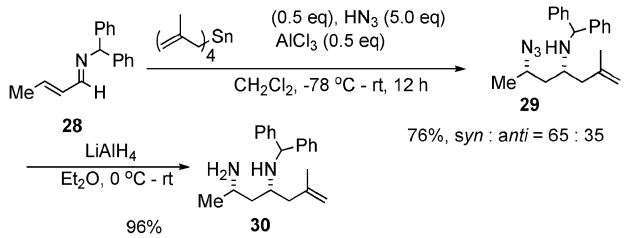
Scheme 8 Synthesis of 1,3-hydroxy azide **27**.

the direct protonation of the adduct derived from a relatively reactive alkylmercaptan as a nucleophile to give (*Z*)-isomer **24**, whereas in the cases with aromatic thiols, the involvement of non-selective protonation of the allenyl species **23** may account for the formation of a mixture of (*E*)- and (*Z*)-isomers.

Based on these results, it is possible to use α,β-unsaturated aldimines as latent α,β-unsaturated aldehydes for the double nucleophilic addition. 1,3-Amino alcohols have received considerable attention as useful units for the synthesis of a variety of biologically important materials. For the synthesis of such units, Mannich-type reactions offer convenient precursors, and several important methodologies have been developed. Addition of a nitrogen atom to α,β-unsaturated carbonyl compounds also enables a rapid access to precursors to 1,3-amino alcohols. However, α,β-unsaturated aldehydes are not always good acceptors of nitrogen nucleophiles due to the concomitant side reactions involving polymerization. $SnCl_4{\cdot}5H_2O$ also promoted a double nucleophilic addition of azide and allylstannane to α,β-unsaturated aldimines to give 1,3-hydroxy azides (Scheme 8).[11]

5. HN_3 as the nucleophile[16]

Although there are several reports on 1,3-amino alcohols and 1,3-diols, limited examples are available for their 1,3-diamine analogues.[17] This is due in part to lack of general synthetic methodologies for 1,3-diamines. However, recent interests in 1,3-diamine derivatives for use as catalysts in the asymmetric synthesis and medicinal chemistry involving HIV protease inhibitors have prompted exploration of simple approaches to them. In contrast to the above reaction using $SnCl_4{\cdot}5H_2O$, in the presence of $AlCl_3$ a mixture of hydrogen azide and



Scheme 9 Synthesis of a 1,3-diamine.

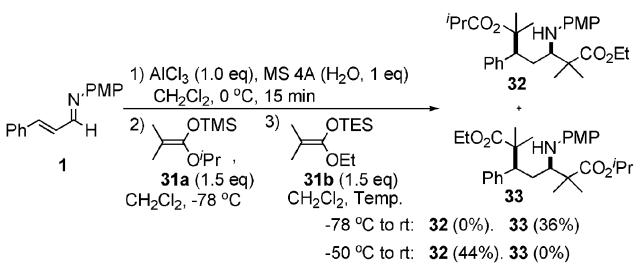
tetramethallyltin underwent a double nucleophilic addition with α,β-unsaturated aldimines to give 1,3-amino azides in good yields. Reduction to 1,3-diamines **30** was readily carried out using $LiAlH_4$ as a reducing agent (Scheme 9).

6. Regioselectivity[18]

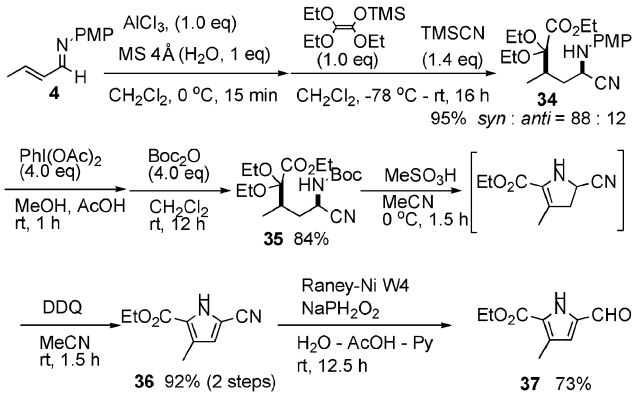
The regioselectivity of the double nucleophilic addition was highly dependent on the substituents of the ketene silyl acetals **31a,b**, and the factors mainly derived from the ability of the ketene silyl acetals to undergo the silicon–aluminium exchange reaction, where the aluminium enolate preferentially underwent 1,4-addition (Scheme 10). The formation of the aluminium enolate was confirmed by spectroscopic methods.

7. Pyrrole synthesis[19]

There are a variety of biologically important pyrrole derivatives. A potentially effective approach to construct a pyrrole ring involves cyclization of γ-amino carbonyl compounds followed by dehydrogenation. For the synthesis of γ-amino carbonyl compounds, crucial intermediates in this strategy, nucleophilic addition to γ-oxoimines constitutes a straightforward pathway. However, difficulty has often been encountered for the synthesis of γ-oxoimines due to susceptibility to hydrolysis and/or isomerization. For circumvention of such a drawback of isolating relatively unstable imine intermediates as well as use of an operationally simple experimental procedure, a straightforward approach to γ-amino carbonyl compounds was reported, and the subsequent transformation led to 2,3,5-trisubstituted pyrroles. This approach enables a six-step synthesis of imidazole glycerol phosphate dehydratase inhibitors (IGPDIs) of herbicidal activity.[20] A synthesis of the IGPDI **37** possessing herbicidal activity was carried out as follows (Scheme 11). The ketene silyl acetal and trimethylsilyl cyanide were treated with *N*-4-methoxyphenylcrotylidenamine **4** in the presence of $AlCl_3$ to give the doubly alkylated product **34** in 95% yield. Switching of the PMP group into a Boc analogue was carried out before cyclization into the pyrrole. The



Scheme 10 Double addition using two kinds of ketene silyl acetals.



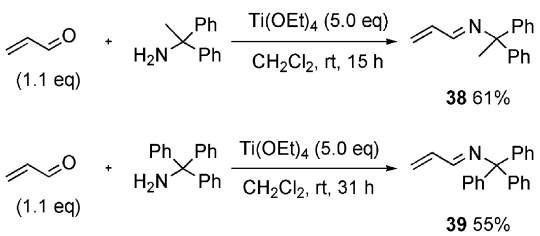
Scheme 11 Synthesis of monopyrrole aldehyde **37**.

Boc-protected double-addition product **35** was treated with $MeSO_3H$ and DDQ to afford the pyrrole **36** in 92% yield (2 steps), where the NH-free dihydropyrrole intermediate was not isolated. Finally reduction of the cyano group with Raney-Ni W4 in the presence of $NaPH_2O_2$ gave the desired monopyrrole aldehyde **37** in 73% yield.

8. Synthesis and reaction of *N*-allylideneamines[21]

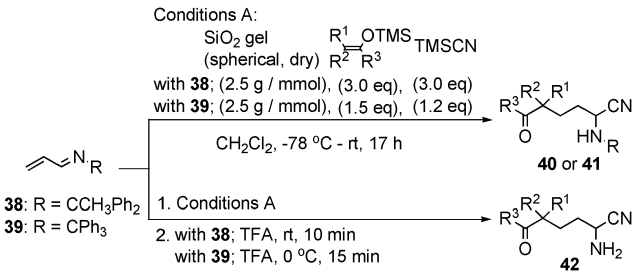
N-Allylideneamines derived from acrolein are expected to be important intermediates for the preparation of amino acid derivatives, when these imines are used as acceptors of nucleophiles in a 1,4- and 1,2-double nucleophilic addition. However, difficulties have been always reported for their syntheses, and therefore, there are only a few reports available for the synthesis of this type of imine.[3a,22] The preparation of *N*-allylideneamines derived from acrolein has been reported. The condensation of acrolein with amines was carried out in the presence $Ti(OEt)_4$, the reaction proceeded smoothly to afford **38**, **39** having a diphenylethyl or a trityl group (Scheme 12).

Regarding the 1,4- and 1,2-double nucleophilic additions of ketene silyl acetals and trimethylsilyl cyanide with *N*-allylideneamines **38**, **39**, among the promoters examined, silica gel, a weak acid, was found to be the most effective. The use of ketene silyl acetals derived from ethyl isobutyrate and methyl isobutyrate gave the desired 1,4- and 1,2-adducts **40** in high yields (Table 4, entries 1 and 2). Use of ketene silyl thioacetal (KSTA) also gave the desired 1,4- and 1,2-addition adduct **40** in 56% yield (entry 7). Upon quenching with TFA after double nucleophilic addition, the reaction gave the amino nitrile **42** in 78% yield (entry 1). Using the *in situ* hydrolysis, the reaction gave amino nitriles **42** in moderate to high yields



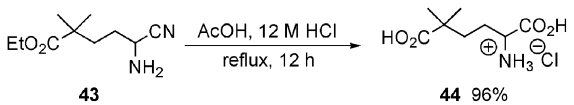
Scheme 12 Synthesis of *N*-allylideneamines.

Table 4 Double nucleophilic addition of *N*-allylideneamine



Entry	R^1	R^2	R^3	With **38** **40**[a] (**42**)[b] (%)	With **39** **41**[a] (**42**)[b] (%)
1	Me	Me	OEt	83 (78)	80 (56)
2	Me	Me	OMe	87 (57)[c]	64 (67)
3	Me	Me	O^{n}Pr	— (47)	58 (54)
4	Me	Me	O^{i}Pr	— (27)	68 (59)
5	–$(CH_2)_5$–		OMe	87 (76)	59 (61)
6	OEt	OEt	OEt	— (40)	51 (12)
7	H	H	S^{t}Bu	56	22 (—)[d]

[a] Under the conditions A. [b] Under the conditions A followed by TFA treatment. [c] Formation of the cyclized valerolactam (17%) was observed. [d] Although formation of valerolactam was confirmed by ^{1}H NMR, isolation was not successful.



Scheme 13 Synthesis of amino acid **44**.

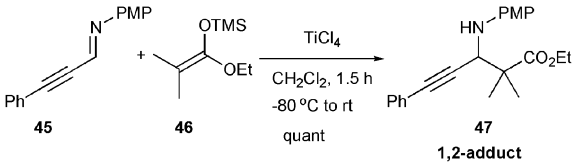
(entries 2–6). Hydrolysis of the nitrile moiety of amino nitrile **43** gave amino acid **44** in high yield (Scheme 13).

Alkynyl imines

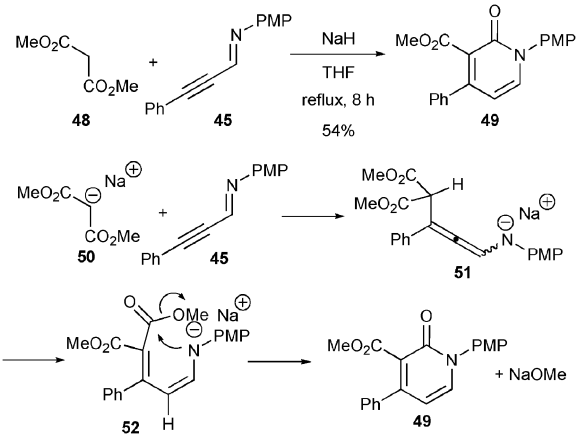
1. Synthesis of 3,4,5-trisubstituted-2-pyridones[23,24]

Alkynyl imines are one of the most important nitrogen-containing starting materials due to their extensive use for the synthesis of heterocycles such as pyrazoles,[25] pyrimidines,[25] pyrrolinones,[26] pyrroles,[3j] indolizines,[3j] quinolines,[27] fused pyrrolines,[27] and pyridines.[28] Alkynyl imines are used in [2 + 2]-cycloaddition reactions with ketenes or the reaction with several enolates to give β-lactams.[6] The reactivity at the β-position of alkynyl imines is of interest. The reaction of alkynyl imine **45** with ketene silyl acetal **46** in the presence of $TiCl_4$ as a Lewis acid proceeded to give only the 1,2-addition product **47** in quantitative yield (Scheme 14). A Mannich-type reaction proceeded under these reaction conditions.[29]

To facilitate the conjugate addition, dimethyl malonate **48**, a "soft" carbon nucleophile frequently employed in conjugate addition reactions, was used as a nucleophile. The reaction of sodio dimethyl malonate **50** gave 2-pyridone **49**, formed by the mechanism shown in Scheme 15. Metalloallenamine **51** is generated by the 1,4-addition reaction of the sodio dimethyl malonate **50** to alkynyl imine **45**. The metalloallenamine **51** in



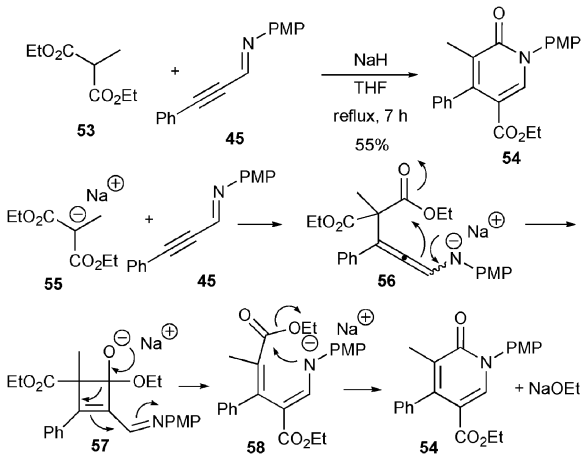
Scheme 14 Mannich-type reaction of alkynyl imine **45** with ketene silyl acetal **46**.



Scheme 15 Possible mechanism for the synthesis of 2-pyridone **49**.

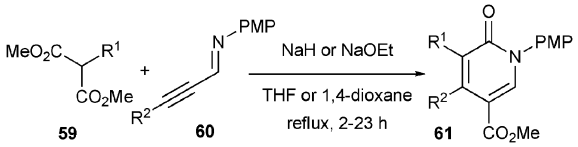
turn isomerizes into metalloenamine **52**, and the cyclization gives 2-pyridone **49**.

The reaction of diethyl methylmalonate **53** possessing a single acidic proton was examined to prevent isomerization of the double bond. The reaction of sodio diethyl methylmalonate **55** with alkynyl imine **45** afforded 2-pyridone **54** in 55% yield. A possible reaction mechanism is shown in Scheme 16. The metalloallenamine **56** would be generated *via* a 1,4-addition reaction of sodio diethyl methylmalonate **55** to alkynyl imine **45** and undergoes an intramolecular cyclization to give cyclobutenoxide **57**. Cyclobutenoxide **57** would collapse into metalloenamine **58** *via* a ring-opening reaction to release ring strain in the cyclobutene, and the subsequent cyclization gives 2-pyridone **54**.



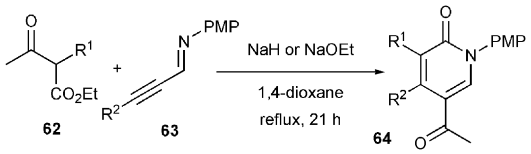
Scheme 16 Possible mechanism for the synthesis of 2-pyridone **54**.

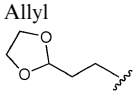
Table 5 Synthesis of 3,4,5-trisubstituted-2-pyridones **61** using nucleophilic addition of malonic esters **59** to alkynyl imines **60**



Entry	R^1	R^2	Yield (%)
1	Me	Ph	91
2	Me	$TBSO(CH_2)_3$	57
3	Me	1-Cyclohexenyl	82
4	Me	*n*-Bu	71
5	Allyl	Ph	59
6	Allyl	$TBSO(CH_2)_3$	46
7	Allyl	1-Cyclohexenyl	63

Table 6 Synthesis of 5-acetyl-2-pyridones **64** using nucleophilic addition of β-keto esters **62** to alkynyl imines **63**



Entry	R^1	R^2	Yield (%)
1	Me	Ph	66
2	Me	$TBSO(CH_2)_3$	69
3	Me	1-Cyclohexenyl	31
4	Me	*n*-Bu	58
5	Allyl	Ph	49
6	Allyl	$TBSO(CH_2)_3$	33
7		Ph	43

The development of synthetic methods for functionalized 2-pyridone is of importance as a result of the large number of biologically active compounds containing a 2-pyridone structure.[30] Representative examples of this 2-pyridone synthesis are summarized in Table 5.

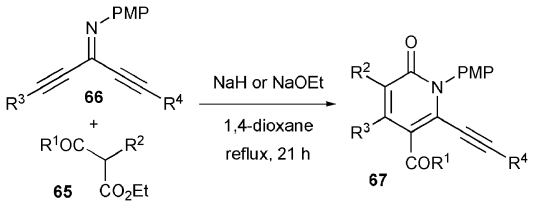
Not only aromatic but also aliphatic groups as a substituent in the alkynyl imines are used to give 2-pyridones **61** in moderate to good yields. Numerous methods for the synthesis of 2-pyridones have been reported.[31] However, this 2-pyridone synthesis is an attractive alternative method because alkynyl imines and substituted malonic esters are readily available.

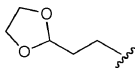
Based on the results, the use of other active methine compounds was examined instead of 2-substituted malonic esters. When β-keto esters **62** were used as active methine compounds, the reactions with imines **63** gave 5-acetyl-2-pyridones **64**. Several 5-acetyl-2-pyridones **64** were obtained in moderate yields (Table 6).

2. Synthesis of 3,4,5,6-tetrasubstituted-2-pyridones[32]

3,4,5,6-Tetrasubstituted-2-pyridone synthesis was carried out by the nucleophilic addition of active methine compounds to

Table 7 Synthesis of 3,4,5,6-tetrasubstituted-2-pyridones **67** using addition of active methine compounds **65** to alkynyl imines **66**



Entry	R^1	R^2	R^3	R^4	Yield (%)
1	OEt	Me	Ph	Ph	66
2	OEt	Me	*n*-Bu	*n*-Bu	44
3	Me	Me	Ph	Ph	52
4	Me	Me	*n*-Bu	*n*-Bu	56
5	OEt	Me	Ph	TBS	71
6	OEt	Allyl	*n*-Bu	TBS	55[a]
7	Me	Me	Ph	TBS	40
8	Me	Me	*n*-Bu	TBS	51
9	Me	Allyl	*n*-Bu	TBS	42
10	OEt		H	TBS	51

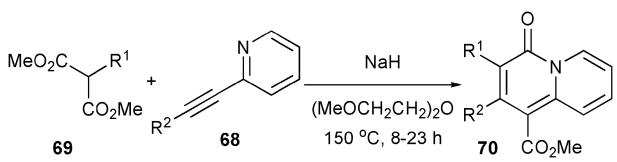
[a] 2-Pyridone (R^2 = (*E*)-1-propenyl) possessing a double bond that isomerized internally was obtained.

dialkynyl imines, directed to the synthesis of (−)-A58365A, which was obtained from a fermentation broth of the bacterium *Streptomyces chromofuscus* in the Eli Lilly laboratories and found to be an angiotensin-converting enzyme inhibitor at nanomolar concentrations.[33,34] The reaction of active methine compounds such as malonic esters or β-keto esters with dialkynyl imines proceeded to give 3,4,5,6-tetrasubstituted-2-pyridones in moderate to good yields (Table 7). The reaction of unsymmetrical dialkynyl imine **66** proceeded regioselectively to give only 2-pyridone **67** where the less hindered sp carbon reacted preferentially (entries 5–10).

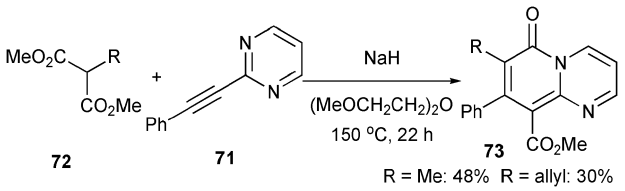
3. Synthesis of bicyclo-2-pyridones[35]

Bicyclic compounds containing a 2-pyridone structure are key intermediates for the total synthesis of anagyrine,[36] lupinine,[36a] and ipalbidine.[37] There are also biologically active compounds having 2-pyridone structures such as (−)-A58365A. 2-Alkynylpyridine, 2-alkynylpyrimidine, and 2-alkynylthiazole were used as a cyclic alkynyl imine equivalent. The reaction of

Table 8 Synthesis of 4*H*-quinolizin-4-ones **70**

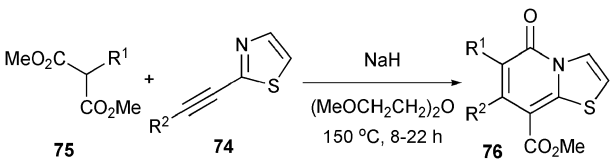


Entry	R^1	R^2	Yield (%)
1	Me	Ph	38
2	Me	*n*-Bu	36
3	4-$MeOC_6H_4$	H	77
4	2-Pyridyl	H	43



Scheme 17 Synthesis of 6*H*-pyrido[1,2-*a*]pyrimidin-6-ones **73**.

Table 9 Synthesis of 5*H*-thiazolo[3,2-*a*]pyridin-5-ones **76**



Entry	R^1	R^2	Yield (%)
1	Me	Ph	83
2	Allyl	Ph	61
3	Me	*n*-Bu	75
4	Allyl	*n*-Bu	53

2-alkynylpyridines **68** with several malonic esters **69** proceeded to give 4*H*-quinolizin-4-ones **70**, in moderate to good yields (Table 8).

The reaction of 2-phenylethynylpyrimidine **71** with dimethyl methylmalonate (R = Me) or dimethyl allylmalonate (R = allyl) **72** gave the desired 6*H*-pyrido[1,2-*a*]pyrimidin-6-ones **73** in 48% and 30% yields, respectively (Scheme 17).

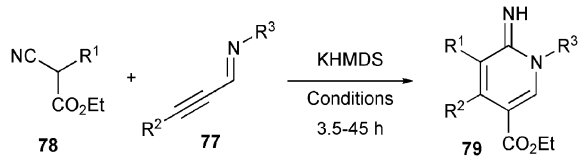
The reaction of 2-alkynylthiazole **74** with malonic esters **75** proceeded to give 5*H*-thiazolo[3,2-*a*]pyridin-5-ones **76** in good to high yields (Table 9).

4. Synthesis of multi-substituted 2-iminopyridines and 2-aminopyridines[38]

Biologically active compounds containing a 2-iminopyridine structure are less known than those containing the 2-pyridone counterpart.[39] However, 2-iminopyridines are highly attractive compounds compared with members of the large group of biologically active 2-pyridones.[30,40] Several methods for the synthesis of 2-iminopyridines by condensation reactions of cyano derivatives[41] and other reactions[42] using transition metals have already been reported. However, the former methods are not yet satisfactory from the viewpoint of synthesizing 2-iminopyridines possessing the desired substituents. Therefore, it is strongly desired to develop alternative synthetic methods for multi-substituted 2-iminopyridines from easily available starting materials. On the basis of the 2-pyridone synthesis, the reaction of alkynyl imines **77** was carried out with ethyl cyanoacetate derivatives **78** (Table 10).

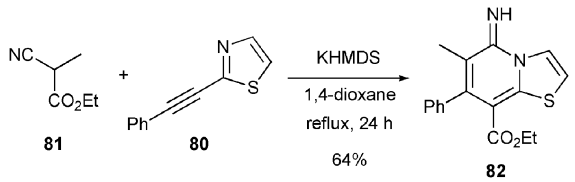
The reaction of the alkynyl imines **77** (R^3 = MPM) bearing a *p*-methoxyphenylmethyl group at the nitrogen with ethyl cyanoacetate derivatives **78** proceeded to give the corresponding 2-iminopyridines **79** (R^3 = MPM) in moderate yields (entries 1–4). Those bearing a *p*-methoxyphenyl group **77** (R^3 = PMP) also gave 2-iminopyridines **79** (R^3 = PMP) in moderate to good yields (entries 5–12).

Table 10 Synthesis of 2-iminopyridines **79** by the conjugate addition reaction of ethyl cyanoacetate derivatives **78** to alkynyl imine **77**



Entry	R^1	R^2	R^3	Conditions[a]	Yield (%)
1	Me	Ph	MPM	A	70
2	Me	1-Cyclohexenyl	MPM	A	57
3	Me	*n*-Bu	MPM	A	47
4	Ph	Ph	MPM	B	51
5	Allyl	Ph	PMP	C	81
6	Allyl	1-Cyclohexenyl	PMP	C	84
7	Me	*n*-Bu	PMP	C	48
8	Ph	Ph	PMP	B	84
9	Ph	1-Cyclohexenyl	PMP	B	45
10	Ph	*n*-Bu	PMP	B	50
11	Allyl	Ph	PMP	B	66
12	Allyl	1-Cyclohexenyl	PMP	B	66

[a] Conditions A: in $(CH_3OCH_2CH_2)_2O$–toluene (3 : 1 : 1) at 160 °C. Conditions B: in 1,4-dioxane under reflux. Conditions C: in 1,4-dioxane–toluene (2.4–3 : 1 : 1) under reflux.

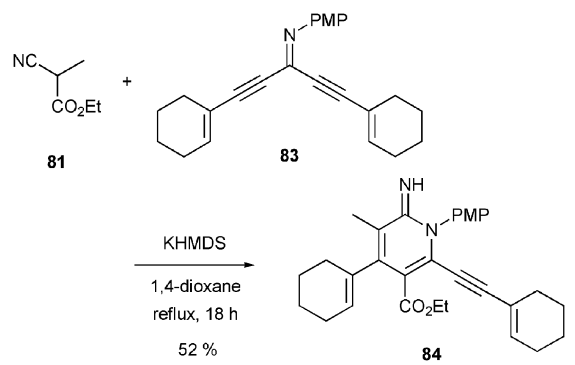


Scheme 18 Synthesis of bicyclo-2-iminopyridine **82**.

Alkynylthiazole **80** was used instead of alkynyl imines **77** to synthesize a bicyclic compound containing a 2-iminopyridine structure. The reaction of **80** with ethyl 2-cyanopropanoate **81** gave the cyclized product **82** in 64% yield (Scheme 18).

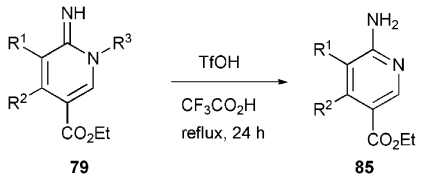
The synthesis of a 3,4,5,6-tetrasubstituted-2-iminopyridine was carried out. The reaction of dialkynyl imine **83** with **81** gave 2-iminopyridine **84** in 52% yield (Scheme 19).

The transformation of 2-iminopyridine into 2-aminopyridine was also conducted by deprotection of the substituent at the nitrogen.[43] 2-Aminopyridines are one of the most important heterocycles due to their biological activity.[44] Deprotection of the *p*-methoxyphenyl group of 2-iminopyridine



Scheme 19 Synthesis of 3,4,5,6-tetrasubstituted-2-iminopyridine **84**.

Table 11 Synthesis of 2-aminopyridines **85** by deprotection of 2-iminopyridines **79** (R^3 = MPM)



Entry	R^1	R^2	Yield (%)
1	Me	Ph	70
2	Me	*n*-Bu	59
3	Ph	Ph	62

79 (R^3 = PMP) under several reaction conditions was attempted. However, the desired 2-aminopyridine was not obtained. Trifluoromethanesulfonic acid (TfOH) was found to promote the deprotection of **79** (R^3 = MPM) in trifluoroacetic acid (TFA) under reflux to give the desired 2-aminopyridine **85** in moderate to good yields (Table 11).

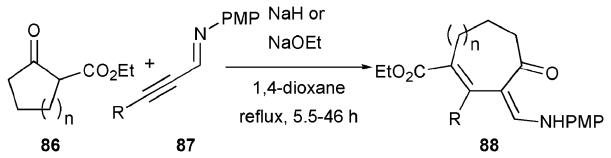
5. Synthesis of functionalized medium-sized carbocycles[45]

Although the development of synthetic methods for medium-sized carbocycles (8, 9, and 10) is important as a result of many biologically active compounds in naturally occurring products, the formation of medium-sized carbocycles is relatively difficult as compared with those of other small or large-sized carbocycles because of well-known entropic and enthalpic factors.[46] Many synthetic methods have been reported to overcome these drawbacks for medium-sized carbocycles,[47] *e.g.*, cycloadditions,[48] cyclizations,[49] cross-coupling reactions,[50] a ring-closing metathesis,[51] and so on.[52] Ring expansion reactions of small-sized carbocycles (4, 5, 6, and 7) are the most useful methods because many small-sized carbocycles are easily available.[53] Especially, ring expansion reactions including Grob-type fragmentation have an attractive characteristic, the fragmentation proceeds under moderately mild conditions in excellent yields.[54]

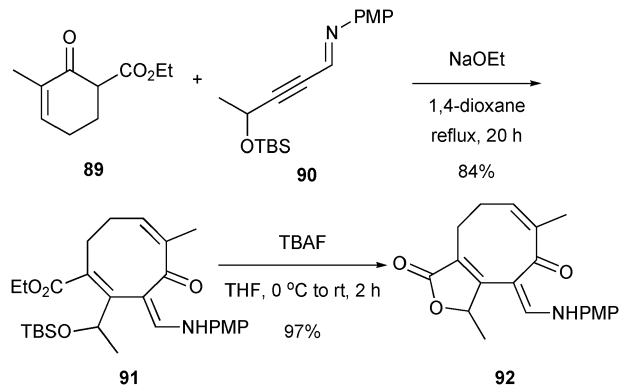
The initial examination of the ring expansion reaction of cyclic β-keto esters **86** (*n* = 1 or 2) with phenylpropynal gave the two-atom enlarged carbocyclic products in low yields, because of the high reactivity of the formyl group. On the other hand, when alkynyl imines, which have different reactivity from the parent alkynyl aldehydes, were used as electrophiles in conjugate additions, the ring expansion reactions proceeded *via* a cyclobutenoxide as a Grob-type fragmentation intermediate to give two-atom enlarged carbocyclic products **88** possessing a masked formyl group (Table 12).[55] Not only aromatic but also aliphatic groups as substituent R in imines **87** worked well. Even with the use of cyclic β-keto ester **89** which has a double bond, the reaction of alkynyl imine **90** proceeded to give the desired ring expansion product **91** in 84% yield. Since bicyclic lactones have been found in many natural products,[56] desilylation–lactonization of the ring expansion product **91** with TBAF was successfully conducted to give bicyclic lactone **92** in high yield (Scheme 20).

Cyclic α-cyano ketones **93** were used as nucleophiles (Table 13). The reactions proceeded in 1,4-dioxane under

Table 12 Synthesis of medium-sized carbocycles **88** by ring-expansion reaction of cyclic β-keto esters **86** with alkynyl imines **87**

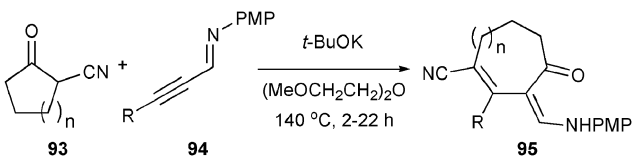


Entry	*n*	R	Yield (%)
1	1	Ph	68
2	1	*n*-Bu	58
3	2	Ph	70
4	3	Ph	87
5	3	*n*-Bu	56
6	3	$TBSO(CH_2)_3$	71
7	4	Ph	86
8	4	*n*-Bu	52
9	4	$TBSO(CH_2)_3$	63



Scheme 20 Synthesis of bicyclic lactone **92** *via* a ring-expansion reaction.

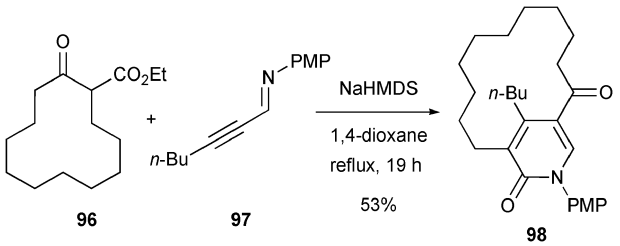
Table 13 Synthesis of medium-sized carbocycles **95** by ring-expansion reaction of cyclic α-cyano ketones **93** with alkynyl imines **94**



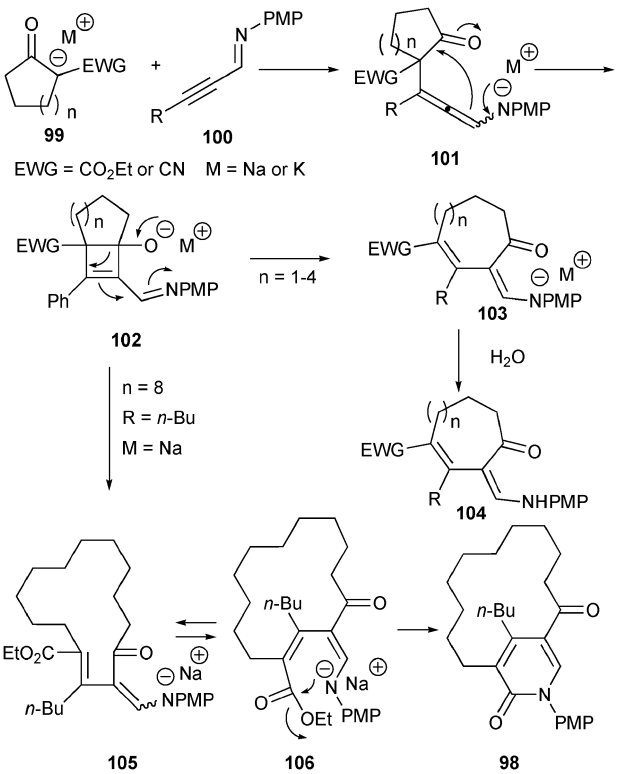
Entry	*n*	R	Yield (%)
1	1	Ph	76
2	1	*n*-Bu	33
3	1	TMS	43[a]
4	2	Ph	54
5	3	*n*-Bu	37
6	3	TMS	44[a]

[a] Desilylated ring-expansion products (R = H) were obtained.

reflux or in diethylene glycol dimethyl ether at 140 °C to give the desired ring expansion products **95** in moderate to good yields. Reaction of the alkynyl imine **94** bearing a TMS group (R = TMS) gave the desilylated ring expansion product **95** (R = H) in moderate yield (entries 3 and 6).



Scheme 21 Synthesis of bicyclo-2-pyridone **98** by a ring-expansion reaction.



Scheme 22 Possible reaction mechanism of the ring-expansion reaction.

When ethyl 2-oxocyclododecanecarboxylate **96**, a more flexible molecule, was used as the nucleophile, the reaction with alkynyl imine **97** gave the bicyclo-2-pyridone **98** in 53% yield (Scheme 21).

A plausible reaction mechanism is shown in Scheme 22. Metalloallenamine **101** would be generated *via* conjugate addition of the sodium or potassium salt of active methine compound **99** to alkynyl imine **100** and would undergo a chemoselective intramolecular cyclization at the keto carbonyl group to give cyclobutenoxide intermediate **102**. The cyclobutenoxide **102** would collapse into metalloenamine **103** *via* a ring-opening reaction to release the ring strain in the cyclobutene, and the subsequent protonation with water to quench the reaction would give the ring expansion product **104**. On the other hand, in the reaction of ethyl 2-oxocyclododecanecarboxylate **96**, (*E*)-metalloenamine **105** generated *via* the ring-opening reaction would isomerize into (*Z*)-metalloenamine **106** due to the

flexibility of the large carbocycle, and the subsequent cyclization would give bicyclo-2-pyridone **98**.

Reactions of α-imino esters and iminium salts

Nucleophilic addition to the nitrogen atom of simple imines is, in principal, difficult due to the electronegativity of the imino functionality. Only limited examples are available for nucleophilic addition to the nitrogen atom of α-imino esters.[57] The reactivity of α-imino esters is of interest and several intriguing features have been discovered. *N*-alkylation of the imines derived from glyoxylate esters was conducted with dialkylaluminium chloride in acetonitrile to give an *N*-monoalkylated intermediate, which in turn underwent a subsequent addition reaction with another imine. When the *N*-monoalkylated intermediate was oxidized with BPO (benzoyl peroxide) in the presence of allyltributyltin, *N*-alkylation–*C*-allylation products were obtained in good yields. When an imine had two electron-withdrawing groups, *i.e.*, 2-[*N*-(*p*-methoxyphenyl)imino]malonate, this derivative served as an excellent *N*-alkylation reagent for Grignard reagents. Subsequent oxidative removal of the malonate and *p*-methoxyphenyl (PMP) moieties offered a new amination methodology for carbanions.

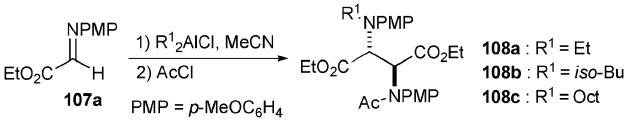
As mentioned above, aluminium enolates were readily oxidized with BPO to give iminium species, which were very reactive and attractive electrophiles in organic synthesis. An easy and convenient method was found for the generation of such species using the oxidation of amino ketene silyl acetals with certain oxidants. The iminium salts thus generated showed excellent reactivities as electrophiles to give, after addition reaction with nucleophiles, α-amino esters in good to excellent yields.

1. *N*-Alkylation-coupling reaction of α-imino esters

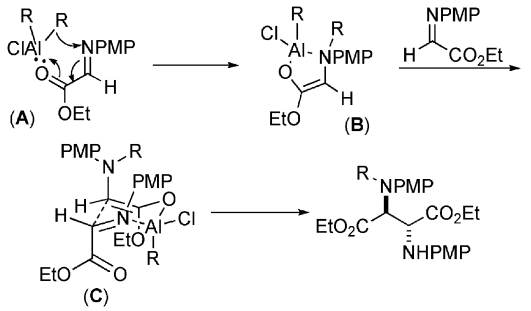
1,2-Diamines are useful units for the synthesis of biologically active compounds[58] and are widely used as ligands in many transition metal-mediated reactions,[59] and therefore, new synthetic methods for 1,2-diamines have been studied extensively.[60] A coupling reaction of the imines derived from ethyl glyoxylate proceeded with alkylaluminium reagents to give 1,2-diamines in good yields (Table 14).[61a]

Diethylaluminium chloride effected the *N*-alkylation-coupling reaction, and the product **108a** was obtained, whereas the use of diisobutylaluminium chloride gave the coupling product **108b** along with the reduction product. In the case of dioctylaluminium chloride, the desired product **108c** was obtained in high yield. In each case, *anti*-selectivity was observed, in which a bulky ester group caused a good diastereoselectivity. When triethylaluminium or ethylaluminium dichloride was used, the coupling product was not formed but the *C*-ethylation product or a mixture of *C*- and *N*-ethylation products was obtained, respectively. The amount of diethylaluminium chloride was also important. For example, the use of 3 equivalents of diethylaluminium chloride decreased the formation of the desired coupling product to 33% yield along with the ethylation products. This may be due to the competing *C*-alkylation reaction caused by the low aggregated alkylaluminium species, whereas the use of a large excess of the aluminium reagent suppressed *C*-alkylation.

Table 14 Coupling reaction using $R^1{}_2AlCl$



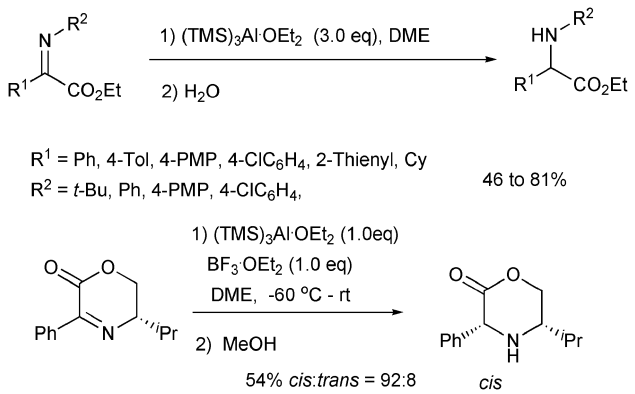
$R^1{}_2AlCl$ (eq)	Yield (%)	*anti* : *syn*
Et_2AlCl (5 eq)	79	70 : 30
i-Bu_2AlCl (5 eq)	59	90 : 10
i-Bu_2AlCl (7 eq)	61	88 : 12
n-Oct_2AlCl (5 eq)	81	62 : 38
n-Oct_2AlCl (7 eq)	95	72 : 28



Scheme 23 1,2-Diamine synthesis using homo-coupling.

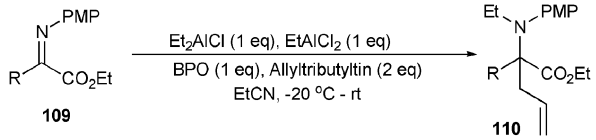
A possible mechanism of the present coupling reaction is shown in Scheme 23. Dialkylaluminium chloride which has a strong oxophilicity initially coordinates with the ester carbonyl group (**A**), making the electron density of the nitrogen atom decrease. Then, 1,4-addition of an alkyl group of the aluminium reagent proceeds on the nitrogen atom to form the ester enolate (**B**) which has a five-membered (*Z*)-conformation because of coordination of the aluminium with the nitrogen atom. This ester enolate attacks another imine *via* a chair-like six-membered cyclic transition state (**C**) to give the *anti*-coupling product.

As a related "umpoled" reaction, tris(trimethylsilyl)aluminium is used as a chemoselective reducing reagent for α-imino esters to give α-amino esters in good yields. Application to the reduction of 3,5-disubstituted 5,6-dihydro-2*H*-1,4-oxazine-2-ones offers a stereoselective conversion into *cis*-3,5-disubstituted morpholine-2-one (Scheme 24).[61b]



Scheme 24 Stereoselective reduction with $(TMS)_3Al{\cdot}OEt_2$.

Table 15 Tandem *N*-ethylation–*C*-allylation reaction with α-imino esters



Entry	R (**109**)	Time/h	Product	Yield (%)
1	Ph (**109a**)	7	**110a**	75
2	*o*-$MeOC_6H_4$ (**109b**)	8	**110b**	47
3	*p*-$MeOC_6H_4$ (**109c**)	7	**110c**	62
4	*p*-MeC_6H_4 (**109d**)	7	**110d**	63
5	*p*-ClC_6H_4 (**109e**)	7	**110e**	76
6	2-Thienyl (**109f**)	7	**110f**	34
7	Cyclopropyl (**109g**)	7	**110g**	50
8	Cyclohexyl (**109h**)	7	**110h**	39
9	H (**109i**)	8	**110i**	18

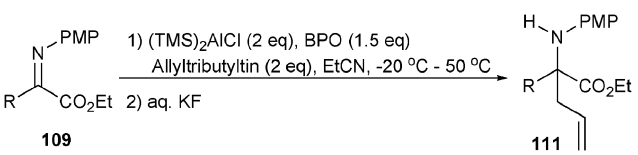
2. Tandem *N*-alkylation–*C*-allylation reaction of α-imino esters

On treatment of the imino ester **109a** with Et_2AlCl, $EtAlCl_2$, and allyltributyltin in the presence of BPO, *N*-alkylation–*C*-allylation product **110a** was obtained. The reaction was carried out as follows: to a solution of BPO and the imino ester in propionitrile were added Et_2AlCl, $EtAlCl_2$, and allyltributyltin successively at −20 °C. After the starting material disappeared on TLC, a usual work-up followed by purification gave the *N*-ethylation–*C*-allylation product **110a–i**. The aliphatic as well as aromatic imino esters underwent the tandem *N*-ethylation–allylation to give the addition products in moderate to good yields (Table 15).[62]

A tandem *N*-silylation–*C*-allylation reaction also proceeded with bis(trimethylsilyl)aluminium chloride on heating the mixture to 50 °C to afford the homoallylamine **111a**. The allylation did not proceed in the absence of BPO. Other α-imino esters could also be used for the present *N*-silylation–*C*-allylation reaction to give the products in good to excellent yields (Table 16).

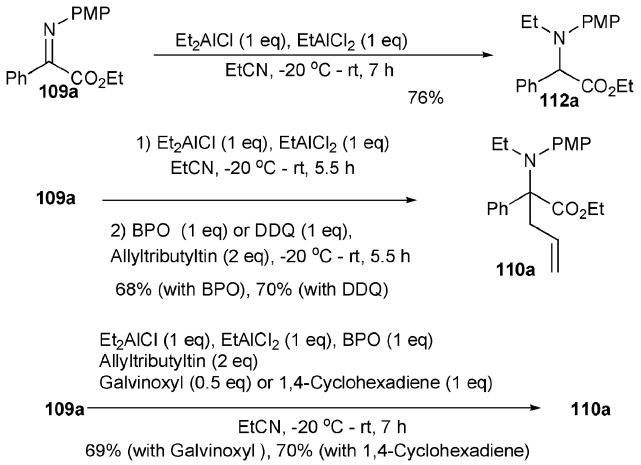
Several reaction conditions were examined to clarify the reaction mechanism (Scheme 25). When the imino ester **109a** was treated with a mixture of diethylaluminium chloride and ethylaluminium dichloride, *N*-ethylation product **112a** was

Table 16 Tandem *N*-silylation–*C*-allylation reaction

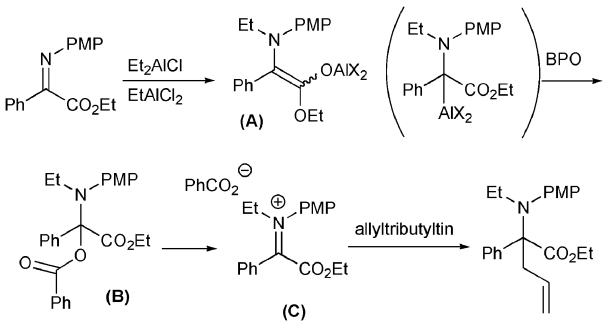


Entry	R	Time/h	Product	Yield (%)
1	Ph (**109a**)	23	**111a**	93
2	Ph (**109a**)	25	**111a**	0[a]
3	*p*-$MeOC_6H_4$ (**109c**)	25	**111c**	84
4	*p*-MeC_6H_4 (**109d**)	24	**111d**	83
5	*p*-ClC_6H_4 (**109e**)	24	**111e**	73
6	2-Thienyl (**109f**)	28	**111f**	61
7	Cyclopropyl (**109g**)	23	**111g**	58

[a] In the absence of BPO.



Scheme 25 Control experiments.

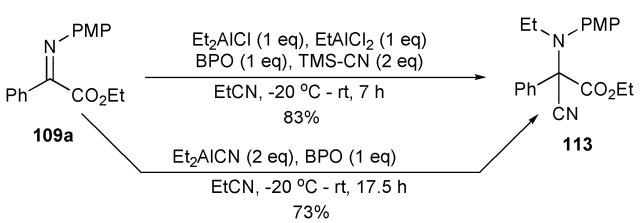


Scheme 26 Possible reaction mechanism.

obtained in 76%. After the *N*-ethylation, BPO or DDQ with allyltributyltin was added, which actually gave the desired allylation product **110a**. The tandem reaction was carried out in the presence of galvinoxyl or 1,4-cyclohexadiene as a radical scavenger. However, the yields did not decrease, indicating that an ionic mechanism might be involved.

Based on these results, a possible mechanism of this tandem reaction is shown in Scheme 26. Firstly, 1,4-addition of the ethyl group proceeds at the nitrogen atom of the imino ester to give an enolate species. The enolate (**A**) is subsequently oxidized with BPO (**B**) to form an iminium salt (**C**), which is attacked by allyltributyltin to afford the *C*-allylation product.

The tandem reaction was also carried out using trimethylsilyl cyanide instead of allyltributyltin to give the amino nitrile **113**. It is interesting to note that in the presence of BPO, diethylaluminium cyanide acted as both ethylation and subsequent cyanation reagent to afford the amino nitrile **113** (Scheme 27). Although diethylaluminium cyanide has been



Scheme 27 *N*-Alkylation–cyanation reaction.

used as the cyanide source in the Strecker reaction,[63] its intriguing behavior as an ethylating reagent is unknown.

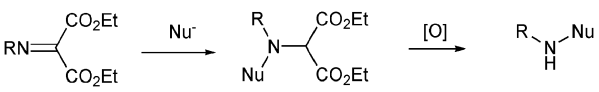
3. Iminomalonate as an electrophilic amination reagent

Electrophilic amination is a useful method for C–N bond formation, and several reagents including azodicarboxylates have been developed for this purpose.[64] New reagents, such as oxaziridines,[65] oximes,[66] and oxime *O*-sulfonates[67] have also been developed as electrophilic amination reagents. However, because amination reactions using these reagents were not always readily carried out, the development of a new electrophilic amination reagent has been highly desirable. On the other hand, some *N*-alkylation reactions to α-imino esters are known.[57] In particular, the Grignard reagent is one of the most convenient *N*-alkylation reagents for α-imino esters. Imines with two electron-withdrawing substituents possess a good ability to react with nucleophiles at the nitrogen atom in a regioselective manner. 2-[*N*-(*p*-Methoxyphenyl)imino]-malonate is an efficient reagent for the electrophilic amination of Grignard reagents to give *N*-alkylation products, and the subsequent oxidation of the malonate moiety affords *N*-alkyl-*p*-anisidines in good yields.

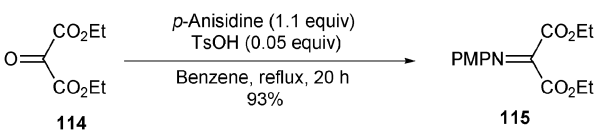
The following sequence shows the strategy. The new electrophilic amination methodology consists of two reactions: (1) a nucleophilic addition to the nitrogen atom, and (2) an oxidative removal of the malonate moiety (Scheme 28). Among various imine derivatives possessing electron-withdrawing groups, iminomalonate was chosen as an amination reagent. Several iminomalonates are already known and have been used for the synthesis of heterocycles. However, the nucleophilic addition of organometals to this imine has not received much attention. Due to a ready oxidative removal from the nitrogen atom after the addition of nucleophiles, the *p*-methoxyphenyl group was chosen as the substituent at the nitrogen.

The amination reagent, diethyl 2-[*N*-(*p*-methoxyphenyl)-imino]malonate **115**,[68] was easily prepared by the condensation of commercially available diethyl 2-oxomalonate **114** with *p*-anisidine in 93% yield (Scheme 29).

Electrophilic amination using primary alkyl Grignard reagents afforded the aminated products in good to excellent yields. Subsequent oxidative cleavage of the *N*-alkylated products also proceeded smoothly to give *N*-alkyl-*p*-anisidines (Table 17). Various alkylations including the use of secondary or tertiary alkyl and aryl Grignard reagents could be carried out (entries 6–10). Isopropylation gave *N*-isopropyl-*p*-anisidine in low yield. When the reaction was carried out at

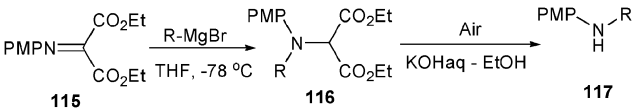


Scheme 28 Reaction strategy.



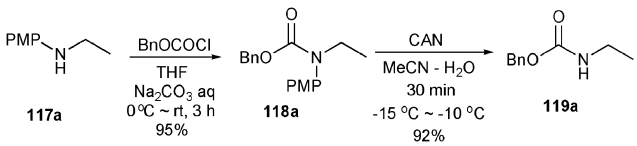
Scheme 29 Synthesis of iminomalonate.

Table 17 Synthesis of *N*-alkyl-*p*-anisidine by electrophilic amination



Entry	R	**116** (%)	**117** (%)
1	Methyl	98	63
2	Ethyl	91	93
3	*n*-Propyl	81	79
4	*n*-Phenethyl	86	89
5	Cyclohexylmethyl	93	91
6	Isopropyl	86[a]	57
7	Cyclohexyl	48	29
8	Benzyl	80	64
9	Phenyl	59	55
10	*tert*-Butyl	56	67

[a] Carried out at −95 °C.



Scheme 30 Removal of the PMP group.

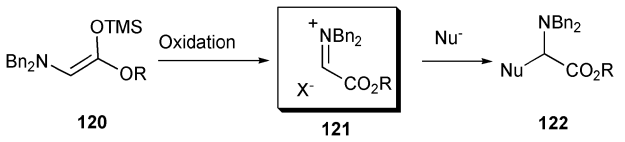
−95 °C, the yield was improved (entry 6). However, additives such as CuI, $BF_3{\cdot}OEt_2$, $CeCl_3$, and $MgBr_2$ were not effective. The *N*-methylation and *tert*-butylation of α-iminoacetate were reported to be highly difficult.[69] In strong contrast to the previous observations, due to the introduction of two ester groups onto the imino carbon, this amination tolerated a wide range of Grignard reagents, and showed high regioselectivity onto the nitrogen atom for the nucleophilic addition.[70]

The *p*-methoxyphenyl moiety of *N*-alkyl-*p*-anisidine was readily deprotected with ammonium cerium(IV) nitrate to give a primary amine (Scheme 30). *N*-Ethyl-*p*-anisidine **117a** was firstly converted into benzylcarbamate **118a** with benzyl chloroformate. This carbamate was exposed to CAN in the usual manner to give benzyl *N*-ethylcarbamate **119a**.

4. Formation of alkoxycarbonyl iminium salts

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.[71] Reported examples using iminium species involve addition of organometallic reagents to the iminium salt for the synthesis of β-amino acids,[72] β-amino ketones, and 1,3-amino alcohols,[73] and so on.[74] Use of acyl iminium and related species has been also reported.[75] Control of the reactivity of formaldehyde was successfully accomplished by the use of the Mannich reaction and Eschenmoser's salt, which have been used extensively for the introduction of an aminomethyl functionality into enolate equivalents.[76]

The generation of the iminium salt was carried out using the reaction of amino ketene silyl acetal **120** with oxidizing reagents followed by the reaction with diethylaluminium cyanide (Scheme 31, Table 18). BPO, *N*-chlorosuccinimide (NCS), and DDQ worked with comparable efficiency in the

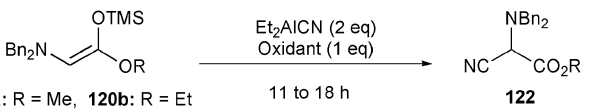


Scheme 31 Reaction strategy.

cases with the methyl derivative **120a**, whereas iodobenzene diacetate and its bistrifluoroacetate analogue gave slightly decreased amounts of the desired product (entries 1–6). Better yields of the adduct **122** were obtained using the ethyl ester **120b**, and among the oxidants DDQ recorded good to excellent results (entries 8, 9).[77]

Scheme 32 summarizes the addition of Grignard reagents to the iminium species. Aliphatic Grignard reagents underwent an addition reaction to the iminium salt to give the addition products **123** in moderate to good yields. The reaction was influenced by the steric bulk of the Grignard reagents, and secondary Grignard reagents depressed the yields. *t*-BuMgBr did not give the addition product, instead, the hydrolysis of the ketene silyl acetal occurred to give the parent ester. Functionalized Grignard reagents could also be used for the present reaction. Aromatic Grignard reagents bearing electron-donating and electron-withdrawing groups underwent the nucleophilic addition to give the addition products **123** in good yields. Cyclopropylmagnesium bromide and trimethylsilylmethylmagnesium chloride gave the addition products **123** in moderate to good yields. Grignard reagents bearing an olefin or an ether group were employable. Allylation was also carried out (Table 19).

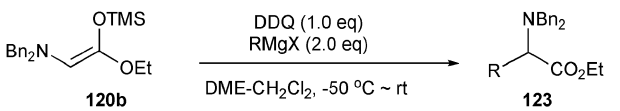
Table 18 Oxidation–cyanation of amino ketene silyl acetal **120** under various conditions



120a: R = Me, **120b**: R = Et — **122**

Entry	R	Solvent	Oxidant	Temp/°C	**122** (%)
1	Me	Et_2O	BPO	−78–rt	45
2	Me	DME	BPO	−78–rt	36
3	Me	DME	DDQ	−50–rt	44
4	Me	DME	NCS	−50–rt	44
5	Me	DME	$PhI(OAc)_2$	−78–rt	32
6	Me	DME	$PhI(OTFA)_2$	−78–rt	35
7	Et	Et_2O	BPO	−78–rt	53
8	Et	DME	DDQ	−50–rt	71
9	Et	DME	DDQ[a]	−78–rt	80

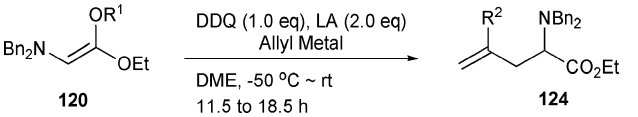
[a] DDQ (0.7 equiv.) was used.



MeMgBr 51%, EtMgBr 69%, *n*-PrMgBr 67%, $PhCH_2MgCl$ 51%
$PhCH_2CH_2MgCl$ 60%, *i*-PrMgBr 47%, CyMgBr 24%, *t*-BuMgBr 0%
PhMgBr 70%, *p*-MeC_6H_4MgBr 75%, *p*-ClC_6H_4MgBr 60%
p-$MeOC_6H_4MgBr$ 68%, CyclopropylMgBr 41%, $TMSCH_2MgCl$ 60%
CH_2=$CHCH_2CH_2MgBr$ 73%, *p*-$MeOC_6H_4O(CH_2)_6MgBr$ 55%

Scheme 32 Oxidation–alkylation of amino ketene silyl acetal **120b**.

Table 19 Oxidation–allylation of amino ketene silyl acetal **120**

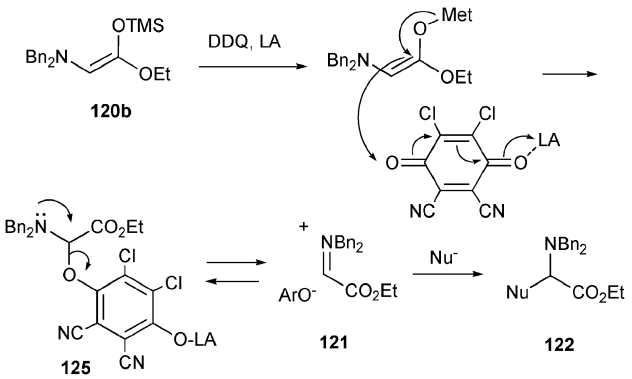


Entry	R^1	Allyl metal (equiv.)	Lewis acid	R^2	**124** (%)
1	TMS	$(Methallyl)_4Sn$ (0.5)	Et_2AlCl	Me	68
2	TBS	$(Methallyl)_4Sn$ (0.5)	Et_2AlCl	Me	72
3	TMS	$(Allyl)_4Sn$ (0.5)	Et_2AlCl	H	65
4	TMS	$AllylSn(^nBu)_3$ (1.0)	Et_2AlCl	H	69
5	TBS	$AllylSn(^nBu)_3$ (1.0)	Et_2AlCl	H	64
6	TBS	$AllylSiMe_3$ (2.0)[a]	$SnCl_4$	H	82

[a] In EtCN.

Tetraallyl- and tetramethallyltin reagents effected allylation reactions to give the adducts in moderate yields (entries 1–3), while allyltributyltin could also be used with comparable efficiency under the influence of diethylaluminium chloride as a Lewis acid (entries 4 and 5). Regarding the substituents at the silicon atom, TMS and TBS derivatives gave essentially the same range of product yields. A better result was obtained using allyltrimethylsilane, and in this case the reaction of the TBS derivative in propionitrile in the presence of tin(IV) chloride proved to be superior (entry 6).

Close examination of the ^1H and ^{13}C NMR spectra of the reaction mixture revealed a possible formation of the iminium species **121**. Upon treatment of the ketene silyl acetal **120b** with DDQ in CD_3CN at −40 °C and gradual warming of the mixture to room temperature over 12 h, new signals appeared at 9.27 and 193.6 ppm in the ^1H and ^{13}C NMR spectra, respectively, which actually indicated the formation of the iminium species **121**. The reaction was carried out in the presence of galvinoxyl or 1,4-cyclohexadiene as a radical scavenger. However, the yields did not considerably decrease, indicating that an ionic mechanism might be involved. On the basis of these results, a possible mechanism of the present iminium formation and nucleophilic addition reaction is shown in Scheme 33. First, DDQ reacts with the ketene silyl acetal **120b** to give the *N*,*O*-acetal **125**, which collapses to the iminium salt **121**. The subsequent nucleophilic attack gives the addition product **122**.



Scheme 33 Possible reaction mechanism.

Conclusions

The 1,4- and 1,2-double alkylation reaction studied here provides a new entry into reactions using α,β-unsaturated aldimines as a good acceptor of two kinds of nucleophiles in one-pot. Since discrimination between two kinds of nucleophiles upon addition to α,β-unsaturated aldimines is highly controlled, this approach offers a new method for a single-step double nucleophilic addition, an otherwise multi-step and rather tedious procedure.

An intriguing heterocycle synthesis was found in the nucleophilic addition of active methine compounds to alkynyl imines. Varying the active methine compounds leads to a specific approach to otherwise non-trivial heterocycles. When a transannular migration of the carbonyl group is involved, this methodology offers a Grob-type fragmentation reaction leading to ring-expansion products in a chemoselective manner.

α-Imino esters behave as acceptors of nucleophiles at their nitrogen atoms in an ''umpoled'' manner, when appropriate nucleophiles are used. The tandem *N*-alkylation–*C*-allylation and *N*-alkylation–*C*-cyanation reactions of several α-imino esters with organoaluminiums are carried out in good to excellent yields, where two nucleophiles attack across the C=N double bond. Iminomalonate is an efficient electrophilic amination reagent for Grignard reagents. In particular, diethyl 2-[*N*-(*p*-methoxyphenyl)imino]malonate is the most efficient amination reagent for primary alkyl Grignard reagents to give *N*-alkyl-*p*-anisidines in excellent yields, although electrophilic amination of secondary or tertiary alkyl, and aryl Grignard reagents gives slightly lower yields of the amination products. In view of preparing the iminomalonate and removing the *p*-methoxyphenyl moiety, this method is a useful addition to the existing methodologies for electrophilic amination.

The alkoxycarbonyl iminium salt is easily prepared using the oxidation of amino ketene silyl acetal with DDQ, and subsequent nucleophilic addition to this iminium species proceeds efficiently to afford the amino esters in good yields. This methodology provides us with a new and easy entry into reactive iminium salts, which are important synthetic intermediates for many nitrogen-containing bioactive compounds.

Acknowledgements

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