Organometal additions to α-iminoesters: *N*-alkylation *via* umpolung

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α-Iminoesters are useful precursors to substituted α-amino acid derivatives and are utilized in a number of organic transformations. As a consequence of the adjacent ester functionality, these imines are more reactive relative to other types of imines. While a significant body of work has focused on nucleophilic additions to the imine carbon (*C*-alkylation), a second pathway that involves nucleophilic reaction at the nitrogen (*N*-alkylation) is much less explored. This *tutorial review* highlights work that has exploited this unusual α-iminoester reactivity mode.

Introduction

α-Iminoesters have enjoyed a prominent place in the synthesis of α-amino acid derivatives. This role is a consequence of the enhanced electrophilicity of the imine carbon due to the adjacent electron withdrawing ester (Fig. 1). The synthesis of *N*-substituted α-amino acids and α-amino acid derivatives[1–4] is a vital field of research in both chemistry and biology. These compounds have wide utility in natural product synthesis, pharmaceutical research, and the study of biological systems. As a result, the rapid and efficient synthesis of these versatile building blocks is a widely pursued area.

Reactivity modes of α-iminoesters

Facile imine *C*-alkylation (Scheme 1, path *a*) has been documented on numerous occasions (Scheme 2). However, α-iminoesters have the potential to react *via* three distinct modes (Scheme 1).

Based upon simple charge calculations (HF6-31G*) performed on α-iminoester **5** (Fig. 1, PMP = *para*-methoxyphenyl), the imine carbon has a partial positive charge value of +0.21 while the imine nitrogen has a partial negative charge value of −0.56.

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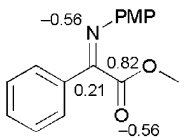

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Fig. 1 Model α-iminoester for charge calculations.

As a result of this normal polarization of the C=N bond, nucleophilic addition to the carbon center (path *a*, above) is expected and is well precedented in the literature (Scheme 2).[5–11] Examples are known of both electron rich and electron poor imines reacting in this way with hard and soft nucleophiles. Nucleophilic addition to the polarized carbonyl of the ester functionality (path *b*) is also viable but has not been reported frequently.[12,13] This result is in line with the lower electrophilicity of esters compared to imines.

However, addition to the imine double bond in which the nitrogen acts as the electrophilic center (path *c*) has not been studied to the same degree. Such an addition mode requires a reversal of polarity of the imine group, which is referred to as *umpolung*. Umpolung has been defined by Seebach as "any *process* by which donor and acceptor reactivity of an atom are interchanged."[14] This review will focus on instances where α-iminoesters undergo this type of umpolung reactivity in the presence of hard nucleophiles, in particular Grignard and alkylaluminium reagents, resulting in *N*-alkylation (Scheme 3).

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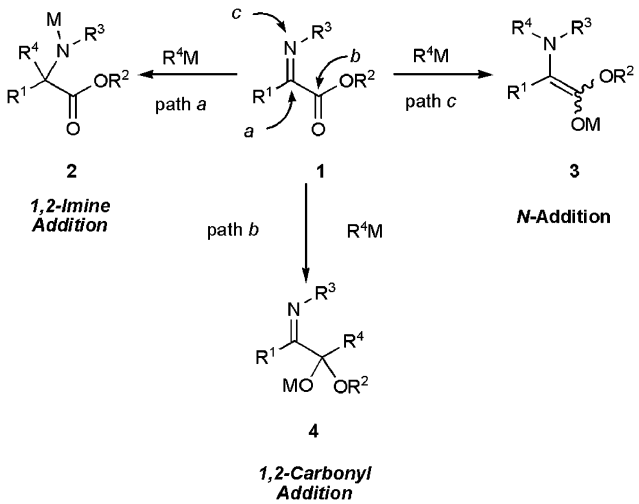
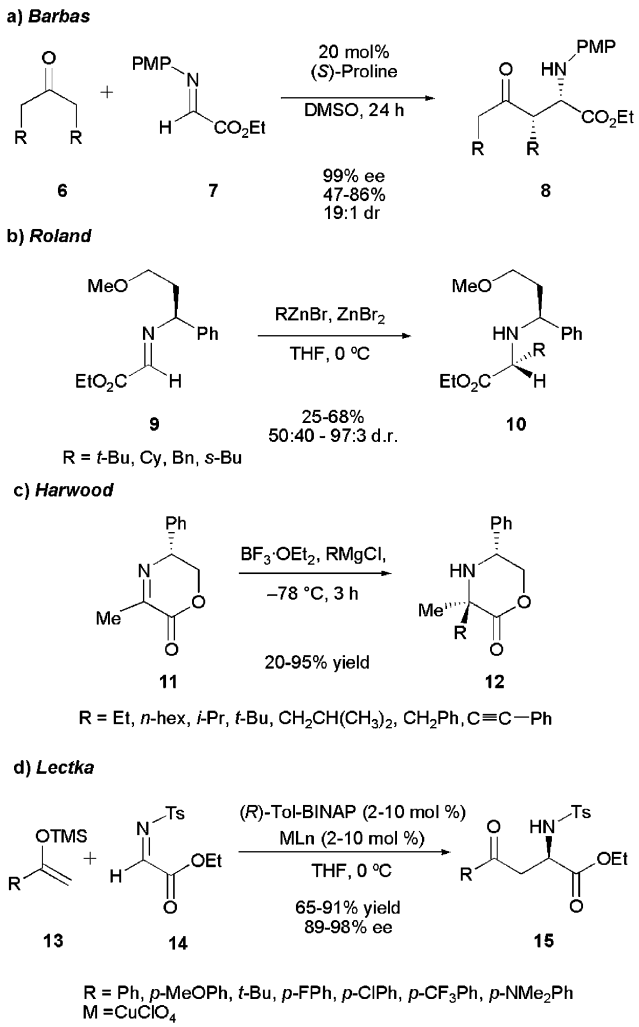
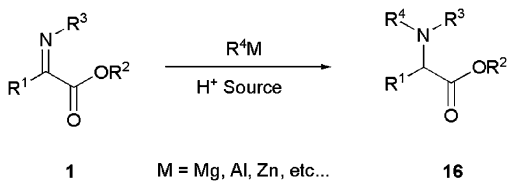


Scheme 1 Addition modes to α-iminoesters.

Nitrogen acting as an electrophilic center is not without precedent as seen in the reactions of diazoesters and nitroso compounds (Scheme 4).[15–19] In these examples, the reacting double bonds are comprised of two heteroatoms and there is



Scheme 2 *C*-Alkylation of α-iminoesters.



Scheme 3 General α-iminoester *N*-alkylation reaction.

no clear umpolung. In contrast, nucleophilic additions to the *N*-terminus of the imine double bond in α-iminoesters definitely requires an interchange of the donor/acceptor properties of the imine.

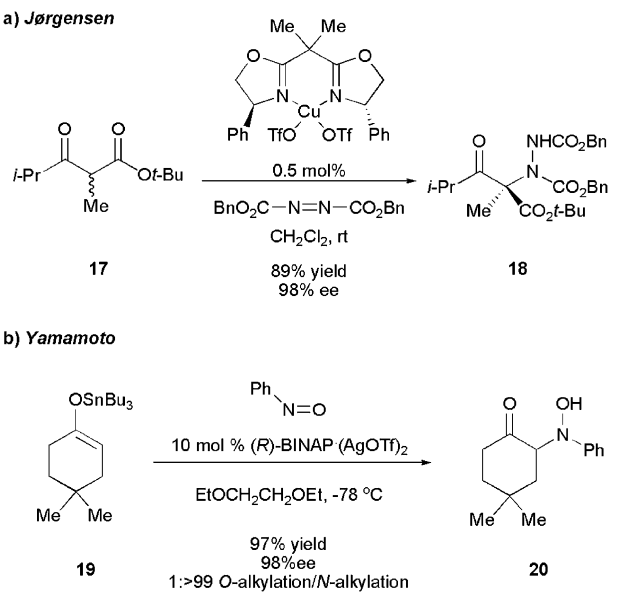
Mechanism of *N*-alkylation

The proposed mechanism (Scheme 5) of these reactions involves bidentate coordination of the metal species between the nitrogen of the imine and the oxygen of the ester (**21**). This locks the conformationally flexible α-iminoester into a geometry in which the imine carbon is hypothesized to be more hindered. As a consequence, addition occurs onto the nitrogen as illustrated and an enolate species (**3**) results.

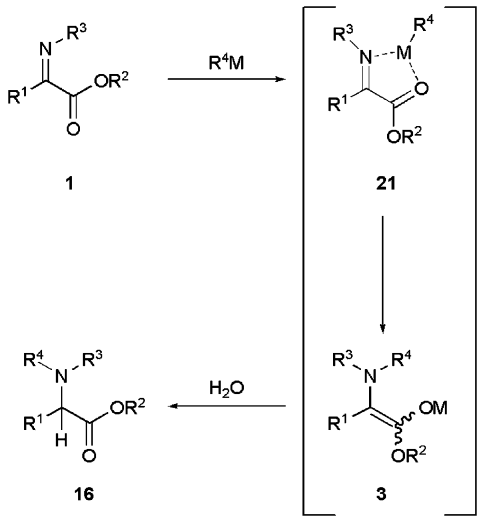
The electron flow in addition of the organometal is reasonable if the N=C–C=O system behaves in an analogous fashion to the C=C–C=O system. In particular, the carbonyl acts as an electron-withdrawing group and polarizes the N=C bond to facilitate the illustrated addition. Upon quenching with water, the enolate generates the indicated *N*-alkylation product (**16**).

Magnesium reagents

Fiaud and Kagan first observed this unusual addition mode in 1971[12,20] when α-aldiminoester (**22**) underwent *N*-alkylation in the presence of Grignard reagents (Scheme 6). While the overall yields in these additions were fairly low (45–55%), large differences in regioselectivity were seen with various



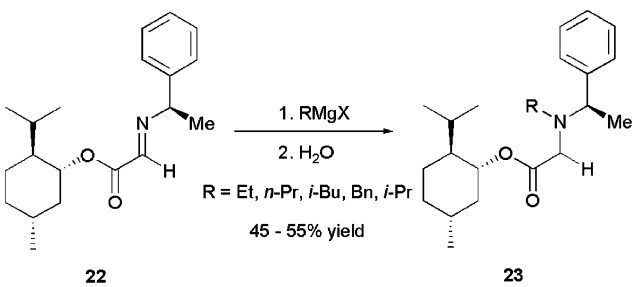
Scheme 4 Additions to N=N and N=O bonds.



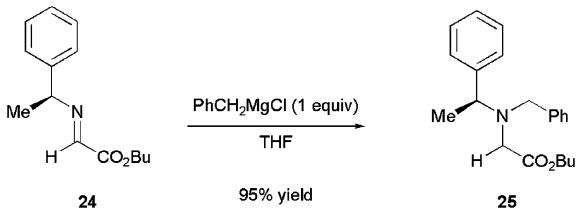
Scheme 5 Proposed mechanism of *N*-alkylation.

Grignard reagents. The use of primary Grignard reagents such as ethyl, *n*-propyl, and isobutyl gave at least 95 : 5 regioselection in favor of the *N*-alkylation product (**23**). When the secondary Grignard reagent isopropyl was utilized the regioselection dropped to only 60 : 40 in favor of *N*-alkylation. The use of *tert*-butyl Grignard led to only the *C*-alkylation product. However, Roland and co-workers[8] later showed that when the reaction of **22** with *tert*-butyl Grignard was conducted from −78 to 20 °C, a 55 : 45 ratio of products, in favor of *N*-alkylation, could be obtained. Addition of the Grignard at 20 °C led to a ratio of 91 : 9 in favor of *C*-alkylation. Peculiar results were seen when methyl, allyl, and benzyl Grignard reagents were employed. The methyl Grignard, although primary, provided only the *C*-alkylation product. Benzyl Grignard gave the expected *N*-alkylation product, but oddly no *C*-alkylation was observed. However, the allyl Grignard, which is also primary, yielded completely regioselective *C*-alkylation.

Later work by Yamamoto *et al*.[21,22] also detected *C*-alkylation products in the reaction of allyl Grignards with imino esters, as well as reaction at the ester carbon. A further example of allyl Grignards reacting by all three pathways from Scheme 1 can be seen in work by Miginiac.[13] Yamamato and Ito also studied the reaction of a benzyl Grignard reagent with a similar α-aldiminoester (**24**).[23] In this case, addition to the nitrogen (**25**) was obtained in 95% yield with no observed *C*-alkylation (Scheme 7).

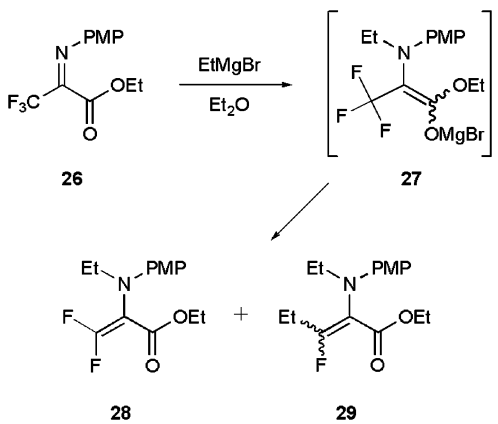


Scheme 6 Kagan's *N*-alkylation.



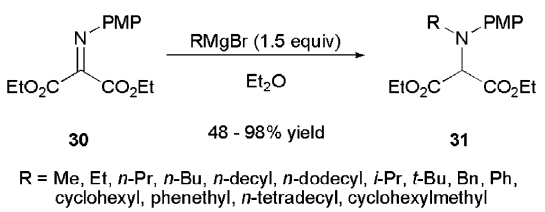
Scheme 7 Study of benzyl organometals in *N*-alkylation.

In 1996, Uneyama *et al*. examined the reaction between magnesium reagents and α-ketiminoester **26**.[24] In this case, an electron-withdrawing trifluoromethyl group was used to further activate the N=C bond toward nucleophilic attack at nitrogen (Scheme 8). In this example, the intermediate magnesium enolate (**27**) can collapse back to the ester by eliminating fluoride to provide the unusual difluoroenamine (**28**). Addition of 1.1 equivalents of ethylmagnesium bromide provided the *N*-alkylated product (**28**) in 50% yield along with 15% of the monofluoroolefin side product (**29**) and recovery of the starting material (30%). Increasing the Grignard reagent to 2.5 equivalents yielded just the monofluoroolefin side product (**29**) in 61% yield with no *N*-alkylation product or recovered starting material. No reaction was seen in the presence of diethylmagnesium and **26**.

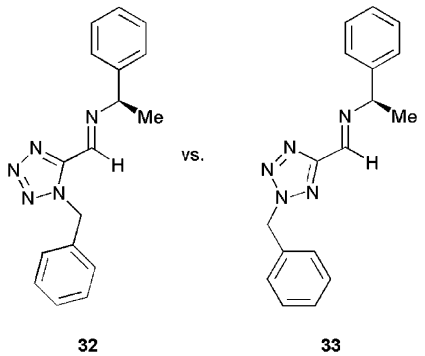


Scheme 8 Grignard additions to α-ketiminoesters.

Iminomalonate (**30**) was also shown to undergo facile *N*-alkylation in the presence of Grignard reagents.[25,26] A wide variety of Grignard reagents were shown to be useful in this *N*-alkylation reaction (Scheme 9). Primary Grignard reagents provided high yields of product **31** (79–98%). The addition of the more sterically hindered secondary Grignards, isopropyl and cyclohexyl, generated the *N*-alkylated products in 86 and 48% yield, respectively. The bulky *tert*-butyl and the phenyl



Scheme 9 Grignard additions to iminomalonates.



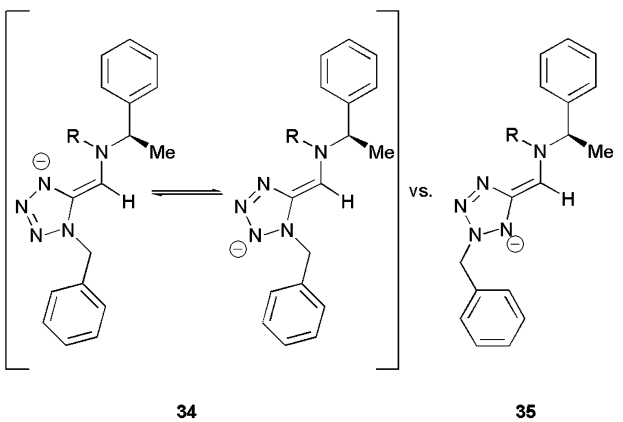
32 33

Scheme 10 *N*-Alkylation of tetrazolylimines.

Grignard performed modestly in the reaction resulting in 56 and 59% yield, respectively. All attempts to use CuI, $BF_3{\cdot}OEt_2$, $CeCl_3$ and $MgBr_2$ as additives proved ineffective.

A similar umpolung reactivity pattern was seen by Yoo and Gong with tetrazolylimines in 1997.[27,28] Tetrazoles are often used as carboxylic acid isosteres due to their similar acidity and electron-withdrawing effects. In this work, 1-benzyltetrazole imine (**32**, Scheme 10) underwent regioselective reaction at the imine nitrogen with various Grignard reagents. The use of ethyl, isopropyl, and benzyl Grignard reagents led exclusively to the *N*-alkylation products in 85, 81, and 76% yield, respectively. However, when methylmagnesium bromide was attempted the reverse regioselectivity was seen with only the *C*-alkylation product forming in 51% yield. Use of allylmagnesium bromide led to a 45 : 55 regioisomeric mixture favoring the *C*-alkylation adduct.

Another surprising result was seen in the reaction of 2-benzyltetrazole imine (**33**). Again the use of methylmagnesium bromide provided only *C*-alkylation in 58% yield. In contrast to the congener **32**, reaction of ethyl and benzylmagnesium bromide with **33** now gave a mixture of regioisomers that was largely in favor of *C*-alkylation, 76 : 24 and 95 : 5, respectively. Isopropylmagnesium chloride still yielded a majority of the *N*-alkylation product (**35**) but only with a 64 : 36 ratio. Furthermore, allylmagnesium bromide now favored addition to the imine carbon with 99 : 1 regioselection. The relative stabilities of the anionic tetrazole adducts (Fig. 2) provide some insight into these results. In the case of 1-benzyl substitution (**32**) the resultant negative charge formed by *N*-alkylation can resonate over three nitrogens (**34**), but in the case of 2-benzyl substitution (**33**) the resultant negative charge is localized on just one nitrogen (**35**). Therefore, it appears that *N*-alkylation is favored when there is sufficient steric hindrance at the imine carbon, as well as added resonance stabilization of the resultant enolate anion.



34 35

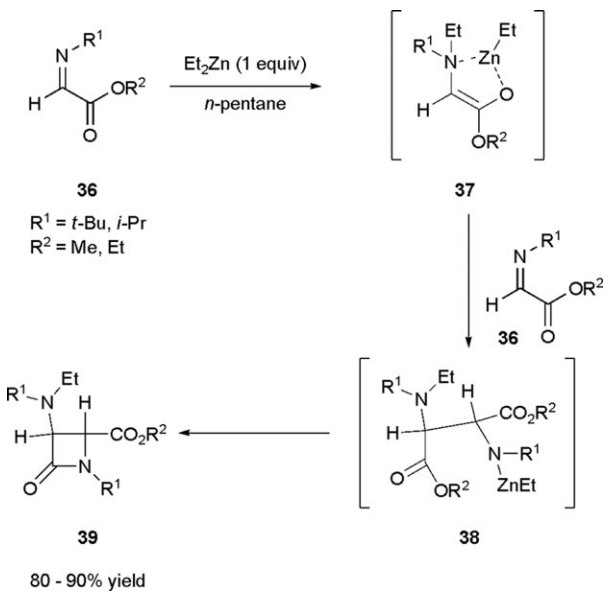
Fig. 2 Stability of tetrazole anions.

The nature of the nitrogen protecting group also plays a role in determining the regioselectivity of the reaction. In general, Grignard reagents add to the nitrogen of the imine when the nitrogen is protected with a *para*-methoxyphenyl[24–26] or α-methylbenzyl[12,20–23,27,28] group. However, when the protecting group is a tosyl,[21,22] α-methylcyclohexyl,[21,22] *tert*-butyl,[13] or *tert*-butoxycarbonyl,[29] addition to the imine carbon becomes the predominate reaction mode.

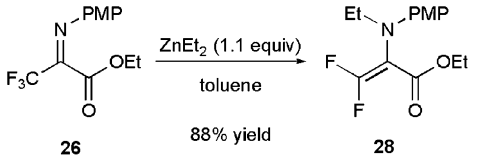
Zinc reagents

The potential of dialkyl zinc reagents to form reactive zinc enolates with α-aldiminoesters was observed by van Koten and co-workers (Scheme 11).[30,31] In this instance, the zinc enolate (**37**) formed by alkyl addition to the nitrogen of **36** adds to another molecule of substrate **36** in a Mannich type reaction. Subsequent intramolecular trapping of the amine anion (**38**) led to azetidinone **39** in 80–90% yield. The reaction forms the *trans*-β-lactam exclusively. A 1 : 1 molar ratio of diethylzinc and iminoester was needed for the reactions to proceed in high yields. Also, when a 1 : 1 mixture of different iminoesters was employed in the reaction all four possible *trans*-β-lactam products were formed in a 1 : 1 : 1 : 1 statistical mixture.[30]

Uneyama *et al*.[24,32] also used zinc reagents in the reaction of α-ketiminoester **26** (Scheme 12). When diethylzinc was used in place of ethylmagnesium bromide, difluoroenamine **28** was formed in 88% yield with only a tiny amount (1%) of side product **29** (Scheme 8). Reaction of **26** with ethylzinc bromide led to exclusive formation of the *C*-alkylation product. Finally, the reaction of zinc metal in acetic acid with a similar α-aldiminoester led to reduction of the imine double bond.



Scheme 11 Synthesis of 3-amino-2-azetidinones.



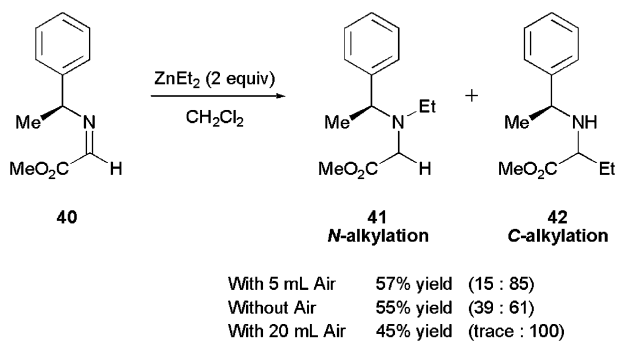
Scheme 12 Diethylzinc additions to α-ketiminoesters.

In the same paper, Uneyama *et al*. also screened the effect of the nitrogen protecting group in the *N*-alkylation reaction with zinc reagents. The results showed that while *para*-methoxyphenyl, *para*-chlorophenyl, and just phenyl substituted α-iminoesters gave high yields of the product corresponding to **28** from Scheme 12 (88, 84, and 80%, respectively), the more substituted 2,6-dimethylphenyl iminoester gave almost no reaction (1%) under the same conditions. The addition of just one *ortho*-ethyl substituent slowed down the reaction and yielded only 65% of the product corresponding to **28**, as well as recovered starting material and reduction of the imine moiety. However, it was found that the α-methylbenzyl substituted iminoester also provided the alkylated nitrogen product in high yield (85%). It seems quite reasonable that additional steric bulk in the vicinity of the nitrogen hinders *N*-addition.

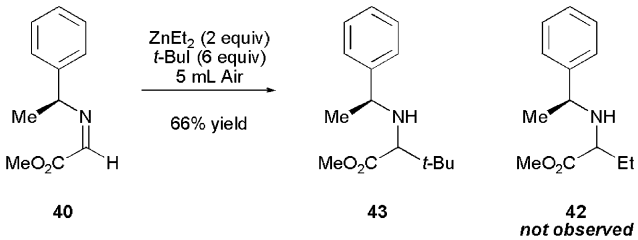
In 1999, Bertrand *et al*.[33] discovered that the composition of the reaction atmosphere contributed to the regioselectivity of reactions with diethylzinc. In the presence of air, addition to the imine carbon of α-aldiminoester (**40**) is highly favored (85 : 15), but under more stringent air-free conditions the proportion of *N*-alkylation (**41**) more than doubles to 39% (Scheme 13). Addition of excess air (20 mL) causes the reaction to become completely regioselective for *C*-alkylation (**42**).

When the reaction is run in the presence of air (5 mL), *tert*-butyl iodide, and diethylzinc the only product observed is *tert*-butyl addition to the imine carbon in 66% yield (**43**, Scheme 14). This is evidence of a radical pathway in air since the *tert*-butyl radical would be preferred if an ethyl radical is generated and no ethyl addition product should be obtained. Thus, it appears the diethylzinc addition to the imine proceeds *via* a radical pathway in the presence of oxygen whereas nucleophilic addition to the nitrogen occurs when oxygen is removed.

Bertrand's work also showed a significant chelate effect on the regioselectivity of the reaction. When an imine derived from norephedrine (**44**, Scheme 15) is treated under the standard conditions (diethylzinc and 5 mL air), the chelate



Scheme 13 Atmosphere effects on *N*-alkylation.



Scheme 14 Evidence of a radical pathway.

between the imine nitrogen and the ester oxygen (**45b**) is favored. Apparently, this adduct transfers the ethyl group selectively to the nitrogen leading to the *N*-alkylation product (**46**) in 35% yield and only trace amounts of the *C*-alkylation product. However, when imine **47** is employed the chelate equilibrium shifts toward **48a** and addition to the imine carbon leads to **49** as the only product (40% yield).

The use of diethylzinc in the reactions with iminomalonate (**30**)[25,26] resulted in mixtures of *N*-alkylation (**31**) and *C*-alkylation (**50**) products (Scheme 16). In tetrahydrofuran, the *N*-alkylation product was isolated in 40% yield along with 23% of the *C*-alkylation product. Switching to toluene provided the *N*-alkylation product in 80% yield. Unfortunately, the *C*-alkylation product was also obtained in 15% yield. For this substrate, the Grignard reagents are more regioselective (see last section).

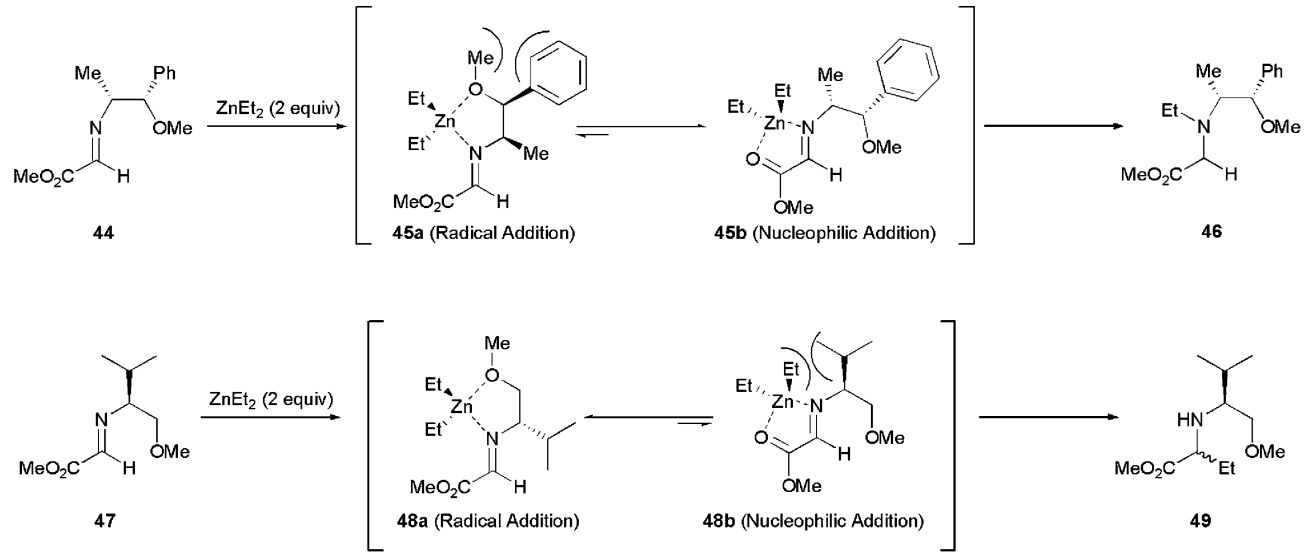
With all α-iminoesters studied,[13,21–24] the use of alkylzinc halides caused predominantly addition to the imine carbon, regardless of the nitrogen protecting group employed.

Aluminium reagents

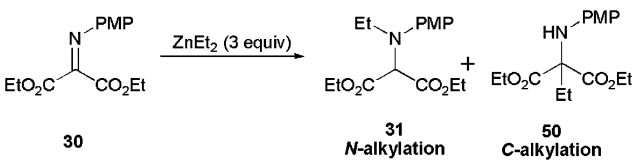
The first example of an aluminium reagent reacting at the imine nitrogen was seen by Yamamoto.[23] When iminoester **24** was treated with the benzyl organometal derived from triethylaluminium, the *N*-alkylation product (**25**) was obtained in 78% yield (Scheme 17). Conversely, the corresponding allylaluminium reagents cause *C*-alkylation.[13]

Aluminium reagents were also examined in the alkylations of iminomalonate **30**.[25,26] In this reaction, triethylaluminium provided 25% yield of the *N*-alkylation product (**31**) along with 24% *C*-alkylation (**50**, Scheme 18). By using ethylaluminium dichloride or diethylaluminium chloride the reaction became more regioselective for *N*-alkylation (32 and 66% yield, respectively). Nevertheless, Grignard reagents still seem to be superior *N*-alkylating agents for these substrates.

While Grignard reagents proved to be the reagents of choice in the reactions of iminomalonates, the synthesis of 1,2-diamines *via* iminoesters (Scheme 19) was superior with the alkylaluminium reagents.[34,35] Similar to the discovery of van Koten[30,31] (Scheme 11), the intermediate enolate (**52**), formed upon treatment of α-aldiminoester (**51**) with dialkylaluminium reagents, reacted with another equivalent of substrate **51** by means of imine addition. Here, however, cyclization did not occur. Rather, the amine anion (**53**) was either protonated or trapped with an acyl or trifluoroacetate group producing diamine **54** in 59–95% yield. In all cases, the reaction proceeded with 62–90% diastereoselectivity in favor of the *anti* diamine. The side products of this reaction were

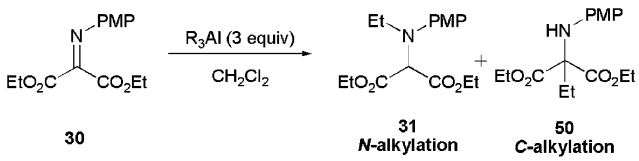


Scheme 15 Chelate effect on diethylzinc additions to α-aldiminoesters.



Solvent	Yield	Yield
THF	40%	23%
Toluene	80%	15%

Scheme 16 Diethylzinc additions to iminomalonates.



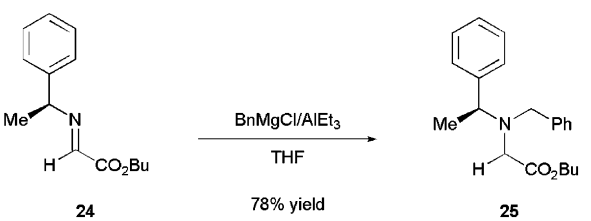
R_3Al	Yield	Yield
Et_3Al	25%	24%
$EtAlCl_2$	32%	0%
Et_2AlCl	66%	0%

Scheme 18 Addition of alkyl aluminium reagents to iminomalonates.

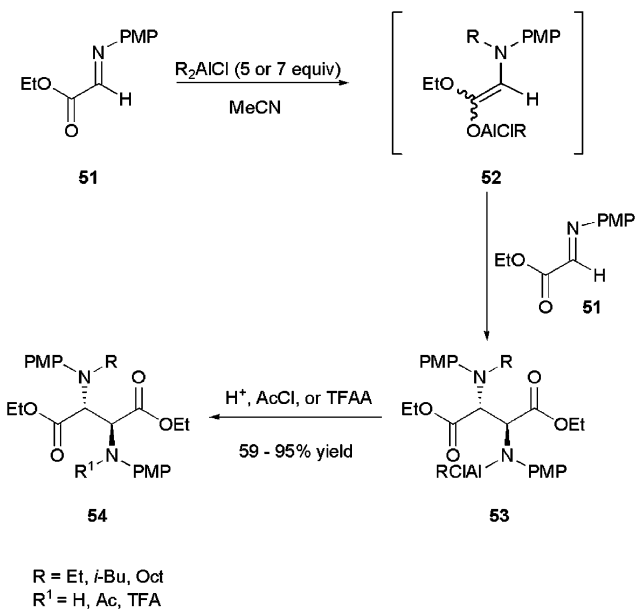
small amounts of *C*- and *N*-alkylated products (~10%). The use of 3 equivalents of diethylaluminium chloride led to a decreased yield of the coupling product (33%) and an increased yield of the *C*- and *N*-alkylated products (58%, 47 : 53, respectively). It was only when a large excess of the aluminium reagent was employed (5 or 7 equivalents) that *C*-alkylation could be suppressed and high yields of coupled product obtained.

Other alkylaluminium reagents were ineffective in the coupling reaction of **51** (Scheme 19). When triethylaluminium was used only the *C*-alkylation product was obtained in 24% yield. The reagent ethylaluminium dichloride provide a 29 : 71 mixture of *C*- and *N*-alkylated products in 66% yield. None of the coupling product was seen in either case.

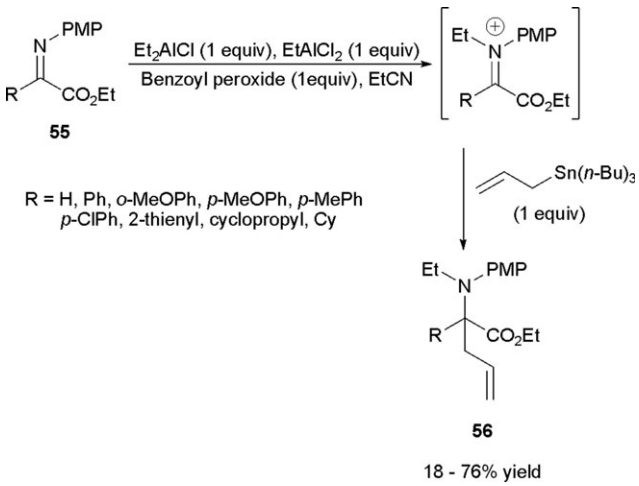
When the protecting group on the nitrogen of **51** was changed to either *para*-tolyl or *para*-chlorophenyl, the ethyl addition and coupling reaction proceeded in moderate yields (62 and 41%, respectively) and still favored formation of the *anti* product. Furthermore, switching to the *para*-methoxybenzylimine failed to provide any of the desired coupling product **54**.



Scheme 17 Addition of benzyl organometals to α-aldiminoesters.



Scheme 19 Synthesis of 1,2-diamines.



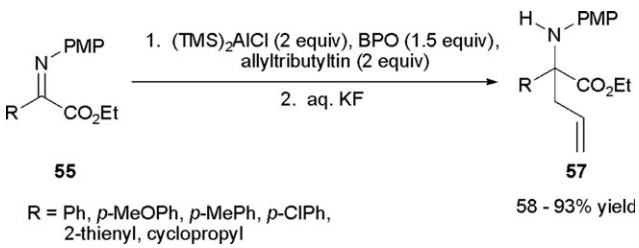
Scheme 20 Tandem *N*-alkylation-*C*-allylation reaction.

The use of oxygen-free acetonitrile did not alter the yield in the reactions with **51**, but improved the diastereoselectivity of the reaction from 66 to 81% *anti*. Use of the corresponding isopropyl or cyclohexyl ester of **51** also improved the diastereoselectivity, but in the case of the cyclohexyl ester the yield was slightly decreased. Similar to van Koten's work,[30,31] cyclization to the β-lactam could be effected by treatment with isopropylmagnesium bromide.

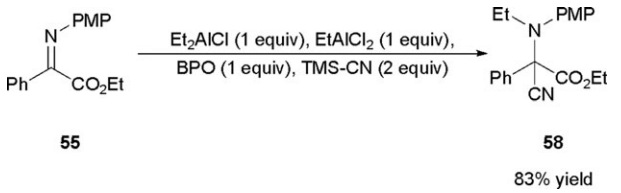
Most recently, Shimizu and Niwa have developed a tandem *N*-alkylation–*C*-allylation reaction using α-ketiminoesters.[36] In this reaction (Scheme 20), an alkylaluminium reagent initially adds to the imine nitrogen of the α-ketiminoester (**55**). The intermediate enolate is then oxidized with benzoyl peroxide (BPO) in one pot to the iminium salt. This iminium species can then undergo allylation with allyltributyltin to produce an α,α-disubstituted amino acid derivative (**56**).

It was found that a combination of Et_2AlCl and $EtAlCl_2$ gave better yields and regioselectivity than the use of either reagent alone. When the keto-group (R) (**55**, Scheme 20) was a substituted phenyl ring or phenyl itself, the yields were between 47–76%. Switching to 2-thienyl or the aliphatic cyclohexyl and cyclopropyl groups resulted in slightly lower yields in the 34–50% range. Finally, the use of the aldiminoester (R = H) gave a very low yield (18%).

In a similar manner, bis(trimethylsilyl)aluminium chloride could be used as a *N*-silylating agent to provide the TMS protected nitrogen analog. The silyl group was then cleaved *via* aqueous potassium fluoride to yield the allylated products (**57**, Scheme 21) in 58–93% yield.



Scheme 21 Tandem *N*-silylation-*C*-allylation reaction.



Scheme 22 Tandem *N*-silylation-*C*-cyanation reaction.

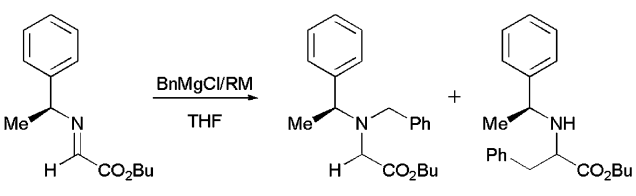
The use of trimethylsilyl cyanide *in lieu* of allyltributyltin yielded the *N*-alkylated-*C*-cyanated product **58** in 83% yield (Scheme 22). This product could also be formed in 73% yield by using diethylaluminium cyanide as both the alkylating and cyanating agent, in the presence of benzoyl peroxide. In order to probe the mechanism, these reactions were undertaken in the presence of the radical scavengers galvinoxyl and 1,4-cyclohexadiene. Since no change in yield was observed, it was concluded that the reaction progresses through an ionic, rather than radical, mechanism as described in Scheme 5.

Copper reagents

The reaction of aldiminoester **24**[23] with a benzyl organometal derived from CuI or $CuI/BF_3{\cdot}Et_2O$ resulted in the *N*-alkylated product (**25**) in 22 and 50% yield, respectively (Scheme 23). However, it has been shown that the regioselectivity can be modified to afford reaction at the imine or ester carbon when an allyl cuprate is used instead of a benzyl cuprate.[13,21] In the case of the tetrazolylimines (**32** and **33**, Scheme 10) alkyl cuprates were found to be completely unreactive.[27,28]

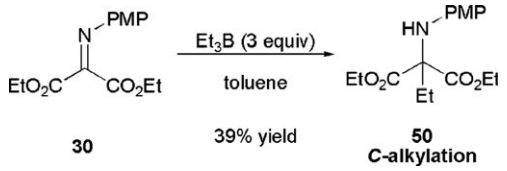
Boron and titanium reagents

Boron and titanium reagents display similar reactivity patterns to the cuprates. In the case of the $Ti(O\text{-}i\text{-}Pr)_3$ and $B(OMe)_2$ benzyl-derived organometals, aldiminoester **24** was *N*-alkylated in 55% and 42% yield, respectively (Scheme 23).[23] Akin to the cuprates, switching to an allylic boron or titanium reagent leads to addition at the imine and/or ester carbon.[21,22] A trialkyl boron reagent, BEt_3, reacts with iminomalonate **30** to yield 39% of the *C*-alkylated product (**50**, Scheme 24).[25,26]

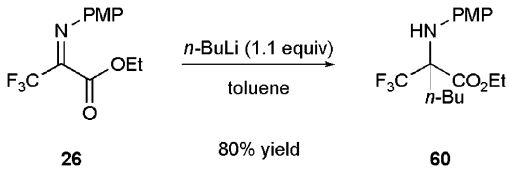


RM	Yield	Yield
$ZnBr_2$	0%	50%
CuI	22%	0%
$CuI/BF_3{\cdot}Et_2O$	50%	0%
$Ti(OiPr)_3Cl$	55%	0%
$B(OMe)_3$	42%	0%

Scheme 23 Addition of benzyl organometals to α-aldiminoesters.



Scheme 24 Alkylboron addition to iminomalonates.



Scheme 25 Addition of alkyllithiums to α-ketiminoesters.

Lithium reagents

In general, lithium reagents react regioselectively at either the imine or ester carbon. In no cases has an alkyl lithium been shown to promote *N*-alkylation. The reaction of *n*-BuLi, PhLi, or MeLi with **26** (Scheme 25) resulted in regioselective addition to the imine carbon (**60**).[24] Similar perfluorinated α-ketiminoesters have also been shown to undergo reaction at the imine carbon with alkyl lithium reagents.[32] With various aldiminoesters, the alkyl lithiums tended to react at the ester carbon along with a very small amount of reaction at the imine carbon.[12,13] In the case of the tetrazolylimines (**32** and **33**, Scheme 10) no reactivity was seen with any alkyl lithium reagents.[27,28]

Cadmium reagents

A very interesting observation was found with organocadmium reagents. When an organocadmium reagent was prepared *in situ* from a magnesium species, aldiminoester **22** (Scheme 6) underwent *N*-alkylation with yields comparable to reaction with Grignard reagents. However, when the same organocadmium reagents were prepared by other methods, addition to the imine carbon was observed in 55–70% yield.[12] Another example has been seen in which organocadmium reagents alkylate at the imine carbon.[13] It is likely that residual magnesium from the *in situ* preparation of the organocadmium reagents can chelate to the iminoester and affect the reactivity pattern.

Conclusions

The nucleophilic *N*-alkylation of α-iminoesters leads to enolate intermediates that are valuable for the construction of substituted amino acid derivatives, as well as other intriguing organic compounds. This unusual chemistry arises from an umpolung reaction mode in which the ordinary electrophilicity of an imine is reversed to allow nucleophilic attack on the nitrogen. Recent efforts have provided insight into the types of organometals that are applicable to this chemistry. In general, alkyl aluminium, dialkylzinc, and Grignard reagents provide regioselective *N*-alkylation of α-iminoesters. There has also been much exploration of iminoester substrate scope, including the effect of different nitrogen protecting groups, ester functionalities, and substituents on the imine carbon, as well as the reaction parameters. The unusual nature of this reaction and its utility as an entry into α-amino acid products ensure its continued study in the future.

Acknowledgements

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