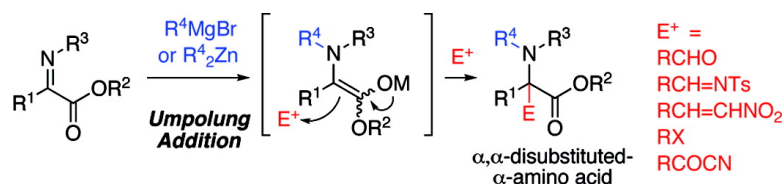Communication

Three Component Coupling of #-Iminoesters via Umpolung Addition of Organometals: Synthesis of #,#-Disubstituted #-Amino Acids

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Three Component Coupling of α-Iminoesters via Umpolung Addition of Organometals: Synthesis of α,α-Disubstituted α-Amino Acids

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α-Amino acids and their derivatives are vital synthetic building blocks in organic synthesis and play an integral role in pharmaceutical research. Therefore, the synthesis of both natural and nonnatural α-amino acids continues to be a subject of intense study.[1] In particular, the formation of α,α-disubstituted α-amino acids is difficult due to the quaternary center even though such compounds have useful properties. For example, when incorporated into peptides, α,α-disubstituted α-amino acids confer increased stability under physiological conditions and stabilize secondary structure motifs.[2] They also have relevance in natural product total synthesis.[3] Herein we report that α-iminoesters engage in an umpolung addition with organometallic reagents providing a three component coupling route toward α,α-disubstituted α-amino acids.

Our laboratory has discovered processes for the asymmetric addition of diorganozinc reagents to aldehydes,[4] α-ketoesters,[5] and α-aldiminoesters.[6] During exploration of the related α-ketiminoesters (eq 1), we observed an unusual reaction pattern. In addition to the expected C-alkylation[7] (3) and reduction[8] (4) products, an N-alkylation product (2) was observed. Depending on the N-substitution and organometallic reagent, it is possible to form any of the three products in eq 1 selectively (Table 1). Electron-withdrawing groups on nitrogen tend to favor reduction (4). With N-aryl substitution, the more reactive organolithiums favor C-alkylation (3) while the Grignard, aluminum, and zinc reagents bias the reaction toward N-alkylation (2).

(1)

a, R = Ts
b, R = POPh₂
c, R = NHCOPh
d, R = 4-MeOC₆H₄

2 (N-Alkylation)   3 (C-Alkylation)   4 (Reduction)
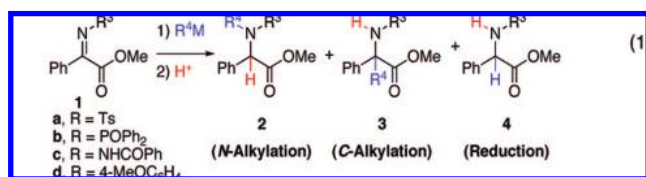
A few reports[9−12] indicate that Grignard reagents in the absence of a Lewis acid yield N-alkylated products only with unhindered ($R^1 = H$) or doubly activated α-iminoesters ($R^1 = CO_2Me$).[13] On the other hand, hindered iminoesters undergo reduction or C-

Table 1. Conditions vs Addition Mode to α-Iminoesters (Eq 1)[a]

entry	1	R⁴M	solvent	2 (%)[b]	3 (%)[b]	4 (%)[b]
1	1a	EtMgCl	THF	0	<15	70
2	1b	Et₂Zn	CH₂Cl₂	0	0	100
3	1c	Et₂Zn	PhCH₃	NR	NR	NR
4	1d	Et₂Zn	PhCH₃	81	7	12
5	1d	n-pentylZnBr	THF	NR	NR	NR
6	1d	EtLi	THF	0	34[c]	0
7	1d	Et₂AlCl	MeCN	>90	<5	<5
8	1d	EtMgCl	THF	79	21	0
9	1d	EtMgBr	THF	>90	<5	<5

[a] Reaction conditions: 0.19 M 1a−d, 1.5−3.0 equiv R⁴M, −78 °C to rt. [b] Conversion by ^{1}H NMR spectroscopy. [c] With 49% 1d.

alkylation. Surprisingly, we found that the hindered α-iminoester 1d ($R^1 = Ph$, $R^3 = PMP$) departs from this trend (Table 1, entries 4, 7−9) and provides entry to 2 via the *tetra*-substituted enolate (5; eq 2).[14] With facile entry to such an enolate, we proposed the synthesis of α,α-disubstituted α-amino acids via a three component coupling process (eq 2).

(2)
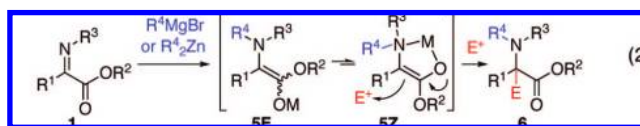
Optimization of the N-alkylation reaction revealed that alkyl magnesium bromides in THF were superior (Table 1, entry 9). Upon protonation of the enolate adduct, products 6da and 6db (from EtMgBr and n-pentylMgBr) could be obtained in 84 and 85% yield, respectively (Chart 1). Furthermore, the enolate could readily be exploited to achieve a one-pot three component coupling reaction using a range of electrophiles (eq 2, Chart 1).

When benzaldehyde was employed as the electrophile high conversion (∼80%) to the three component product as a single diastereomer (6dc, Chart 1) was seen. Additional aldehydes reacted with high diastereoselection with representative Grignard reagents (R^4 = Et, n-pentyl) providing the three component coupling products (6dd−6dh) in very good yield and diastereoselection. The N-tosyl imine also proved to be an effective electrophile furnishing a single diastereomeric product (6di). The *syn* diamine relative stereochemistry was verified from the crystallographic structure and

Chart 1. Three Component Coupling of 1d with Different Electrophiles (Eq 2: R^1 = Ph, R^2 = Me, R^3 = PMP, R⁴MgBr = EtMgBr 7a or n-pentylMgBr 7b)[a]
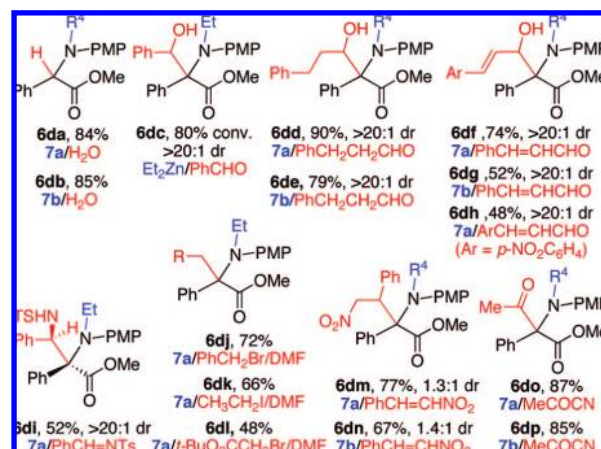
[a] PMP = 4-MeOC₆H₄. Reaction conditions: 0.19 M 1d, 1.2−2.0 equiv of R⁴MgBr, THF, −78 °C to rt, followed by 5 equiv of E⁺.
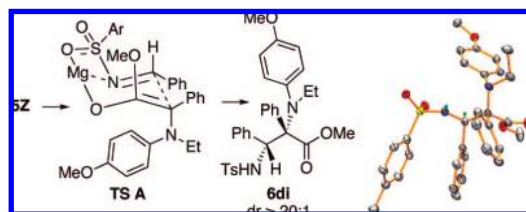
Figure 1. ORTEP of **6di** and putative transition structure.

is in accord with a chair-like transition state commencing from the Z enolate **5Z** (Figure 1).

Initial attempts to use alkyl halide electrophiles provided very low yields of the three component coupling products (<10%). We discovered that DMF as a solvent greatly increased the yield in this instance. For example, reaction with BnBr or EtI afforded 72% and 66% yield (**6dj** and **6dk**, Chart 1). Furthermore, *tert*-butyl bromoacetate provided **6dl** in 48% yield.

Conjugate acceptors were also effective electrophiles. For example, *trans*-β-nitrostyrene furnished the three component products in good yields (**6dm** 77% and **6dn** 67%, Chart 1). In contrast to aldehydes or imines (Figure 1), poor diastereoselection (1.3−1.4:1) was observed indicating poor organization of the incoming nitrostyrene and the intermediate enolate compared to that shown in Figure 1.

While acid chlorides gave poor yields, acyl cyanides such as pyruvonitrile were particularly effective, furnishing the product in 85−87% yield (Chart 1, **6do** and **6dp**). As a result, pyruvonitrile was employed with a range of α-iminoesters (Table 2). The identity of the ester group could be readily changed while retaining good yields (68−87%; entries 1−4). Variation of the electronic and steric features of the keto-group was also well tolerated (58−86%, entries 5−8). The role of the α-iminoester N-substitution on chemoselectivity has been well documented (See Table 1, entries 1−4).[13] Nonetheless, replacing the PMP group with a phenyl still provided the three component coupling product with good yield (73%, entry 9).

Cyclic α-amino acid derivatives are also of great synthetic and pharmaceutical interest.[2a,b,15] Therefore, we envisioned an *intramolecular* three component coupling reaction in which the organometal and electrophile are tethered (Scheme 1). Much to our delight, this intramolecular cyclization was found to occur to afford piperidine **9a** and azepane **9b** in a one-pot procedure.[16] This protocol proceeds well with other α-iminoesters as illustrated by formation of **9c**. Also, removal of the PMP group was straightforward with ceric ammonium nitrate (CAN).
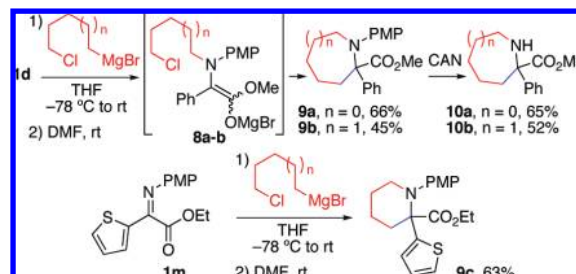

Scheme 1. Intramolecular Three Component Coupling to Form Cyclic α-Amino Acid Derivatives

In conclusion, the rapid construction of α,α-disubstituted α-amino acid derivatives can be achieved in high yields from α-iminoesters. The reaction proceeds through an umpolung addition of an organometallic reagent to the nitrogen. The resultant enolate reacts with a variety of electrophiles to form a quaternary center. Furthermore, high diastereoselection occurred in the three component coupling reactions with aldehydes and imines. This methodology provides straightforward access to a variety of pharmacologically and synthetically useful products. Further details into the scope of the reaction and other aspects of this methodology will be reported in due course.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the internet at http://pubs.acs.org.

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(16) **9a** and **9b** could also be obtained in a stepwise fashion in 50 and 62% overall yields, respectively.

Table 2. Three Component Coupling of Different α-Ketiminoesters **1** with EtMgBr and Pyruvonitrile (Eq 3)[a]

entry	1	R^1	R^2	R^3	prod.	yield (%)
1	**1d**	Ph	Me	PMP	**6do**	87
2	**1e**	Ph	*i*-Pr	PMP	**6eo**	68
3	**1f**	Ph	*t*-Bu	PMP	**6fo**	78
4	**1g**	Ph	Bn	PMP	**6go**	68
5	**1h**	*p*-MeOC₆H₄	Me	PMP	**6ho**	86
6	**1i**	*p*-ClC₆H₄	Me	PMP	**6io**	58
7	**1j**	*o*-MeC₆H₄	Et	PMP	**6jo**	71
8	**1k**	N-Bn-Indole	Me	PMP	**6ko**	72
9	**1l**	Ph	Me	Ph	**6lo**	73

[a] Reaction conditions: 0.10−0.17 M **1**, 1.5−2.0 equiv of EtMgBr, THF, −78 °C to rt, followed by 5 equiv of E⁺.