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Iron-Catalyzed Aminomethyloxygenative Cyclization of Hydroxy-α-diazoesters with *N,O*-aminals

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Summary of main observation and conclusion: A new and efficient cyclization reaction has been developed to synthesize cyclic α,α-disubstituted β-amino esters via iron-catalyzed intramolecular aminomethyloxygenative cyclization of diazo Compounds with *N,O*-aminal under mild reaction conditions. A broad range of hydroxy-α-diazoesters with different substituents and various *N,O*-aminals were compatible with this protocol, affording the corresponding α,α-disubstituted β-amino esters bearing with a five- to eight-membered oxacycle in good yields.

Background and Originality Content

α,α-Disubstituted β-amino acids are key motifs found in numerous natural products and biologically active molecules,[1] and they are also key building blocks in organic synthesis.[2] More specifically, cyclic α,α-disubstituted β-amino acids are interesting compounds due to their unique biological activities and antiviral properties. For example, the chiral dysibetaine and epidysibetaine have been isolated from the aqueous extract of the marine sponge Dysidea herbacea collected from Yap, Micronesia,[3] the proline-derived spiro-β-lactam **III** serves as an efficient β-turn nucleator,[4] CCR5 antagonists display potent anti-HIV activity,[5] whereas Sch58053 exhibits cholesterol absorption inhibiting activity (Figure 1).[6] On the other hand, cyclic α,α-disubstituted β-amino acids can be utilized as synthetic precursors for spiro-β-lactams.[7] However, despite the substantial interest in these amino acids and their applications in drug design, only a few synthetic approaches have been developed, with the majority of them being of limited scope. Therefore, the development of more general and straightforward synthetic methods toward these compounds is in high demand.

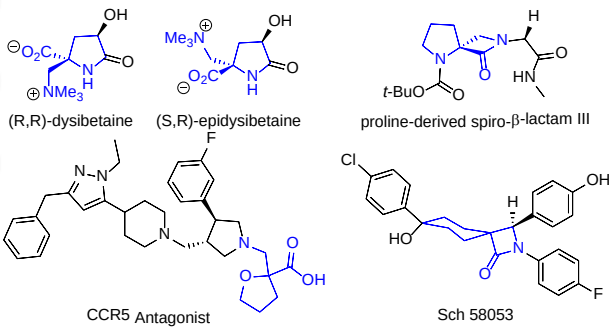
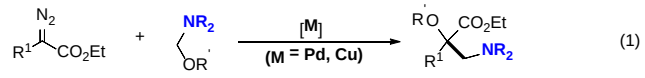


Figure 1. Biologically active molecules containing cyclic *α,α*-disubstituted β-amino acid units

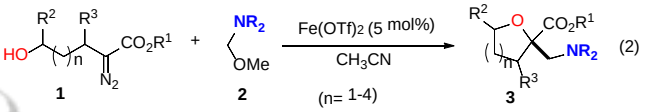
α-Diazocarbonyl compounds are quite valuable precursors in synthetic organic chemistry due to their versatile reactivity and remarkable synthetic values. They have been utilized in a broad range of transformations such as metal-catalyzed X-H (X = N, O, S, Si, et al) bond insertions, cyclopropanation, ylide formation, and 1,2-migration reactions.[8] Among these reactions, strategies for constructing amino acids have drawn increasing attention by using α-diazo esters. For instance, transition-metal-catalyzed insertion of metal carbenes or carbenoids generated in situ from α-diazoesters into N-H bonds has been developed to the preparation of α-amino acid derivatives,[8d-e,g-j] and transition-metal-catalyzed multicomponent reactions involving diazo compounds with alcohols and imines (iminiums) were documented for the construction of α-hydroxy-β-amino esters.[9] In 2015, we developed a synthetic methodology for the efficient construction of a,β-diamino acid esters bearing a quaternary carbon-center by palladium-catalyzed formal insertion of carbenoids into aminals via C-N bond activation.[10] More recently, we and several other groups have demonstrated that *N,O*-aminals are also valuable aminomethylation reagents to react with diazo compounds to deliver the α-hydroxy-β-amino esters (Scheme 1-1).[11] These results inspired us to consider whether the construction of oxacycles- α, α-disubstituted β-amino esters can be achieved by reacting hydroxyl tethered *α*-diazoesters with *N,O*-aminals under suitable conditions. In continuation with our ongoing interest in the aminal chemistry,[10,11a,12] we herein report an iron-catalyzed intramolecular aminomethyloxygenative cyclization reaction between hydroxyl-tethered α-diazoesters and *N,O*-aminals, which provides a new and rapid approach to oxacycle-containing α,α-disubstituted β-amino esters (Scheme 1-2).

Previous work: formal insertion of carbenoids into *N,O*-aminals



(1)

This work: aminomethyloxygenative cyclization with *N,O*-aminals



(2)

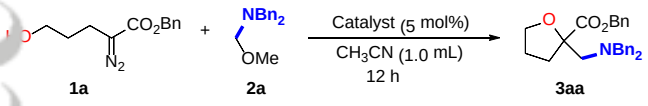
- **alcohol & phenol hydroxyl**
- **mild reaction conditions**
- **inexpensive metal catalyst**
- **five to eight-membered rings**

Scheme 1 Catalytic aminomethyloxygenative cyclization of hydroxy-α-diazoesters with *N,O*-aminals.

Results and Discussion

On the basis of our previous results, we initially commenced our study by investigating the reaction between benzyl 2-diazo-5-hydroxypentanoate (**1a**) and *N*-dibenzyl-1-methoxymethanamine (**2a**) in CH_3CN at 80 °C with 5 mol% of palladium catalyst. However, only moderate yields were obtained (Table 1, entries 1 and 2). To our delight, when $Zn(OTf)_2$ was introduced into the reaction system, the aminomethyloxygenative cyclization product **3aa** was obtained in 67% isolated yield (Table 1, entry 3). Inspired by this result, we then investigated a series of Lewis acids. When $Fe(OTf)_2$ was introduced into the reaction system, the reaction proceeded well to give **3aa** in 72% isolated yield while other Lewis acids didn't give better results (Table 1, entries 4-11). To maximize the efficiency of this reaction, a variety of solvents were screened and found that CH_3CN was the best solvent for the present reaction (Table 1, entries 12-14). We then examined the effect of temperature and found that the reaction could proceed smoothly at room temperature to give the desired product in 76% isolated yield (Table 1, entry 17). As anticipated, control reactions demonstrated that only trace amount of the desired product **3aa** was obtained in the absence of catalyst (Table 1, entry 18).

Table 1 Optimization of Reaction Conditions[a]

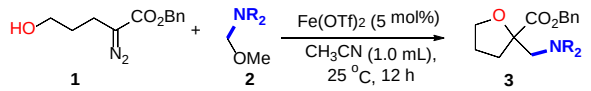


Entry	Catalyst	Solvent	T (°C)	Yield (%)[b]
1	$Pd(XantPhos)(CH_3CN)_2(OTf)_2$	CH_3CN	80	26
2	$Pd(dppe)(CH_3CN)_2(SbF_6)_2$	CH_3CN	80	42
3	$Zn(OTf)_2$	CH_3CN	80	67
4	$Sc(OTf)_3$	CH_3CN	80	70
5	$Yb(OTf)_3$	CH_3CN	80	66
6	$Cu(OTf)_2$	CH_3CN	80	69
7	AgOTf	CH_3CN	80	14
8	$Fe(OTf)_3$	CH_3CN	80	71
9	$Fe(OTf)_2$	CH_3CN	80	72
10	$Fe(acac)_3$	CH_3CN	80	41
11	$FeCl_3$	CH_3CN	80	70
12	$Fe(OTf)_2$	DCM	80	67
13	$Fe(OTf)_2$	PhCN	80	68
14	$Fe(OTf)_2$	DMF	80	60
15	$Fe(OTf)_2$	CH_3CN	60	75
16	$Fe(OTf)_2$	CH_3CN	40	76
17	$Fe(OTf)_2$	CH_3CN	25	76
18	-	CH_3CN	25	<5

[a] Reaction condition: **1a** (0.45 mmol), **2a** (0.3 mmol), catalyst (0.015 mmol), solvent (1.0 mL), 12 h. [b] Isolated yield.

With the optimal reaction conditions identified, the generality of the iron-catalyzed aminomethyloxygenative of diazo compounds was investigated. The scope of various *N,O*-aminals **2** was explored firstly with benzyl 2-diazo-5-hydroxypentanoate **1a** at 25 °C by using $Fe(OTf)_2$ as the catalyst. As illustrated in Table 2, The reaction of *N,O*-aminals, derived from benzylamines bearing a variety of electron-withdrawing (F) and -donating groups (Me, OMe), proceeded well to deliver the products in the range of 63-74% yields (**3aa**-**3ad**). *N,O*-Aminals derived from CH_3OH and simple aliphatic amines, such as diallylamine, dipropylamine, dibutylamine and dicyclohexylamine could react smoothly with **1a** to give the corresponding products in moderate yields (**3ae**-**3ah**). At the same time, *N,O*-aminals prepared from cyclic amines were also applicable as coupling partners, giving the corresponding products (**3ah** and **3ai**) in good yields.

Table 2 Substrate scope of *N,O*-aminals[a]

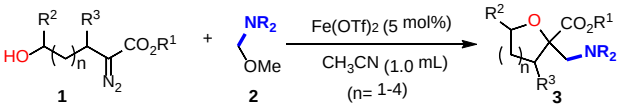


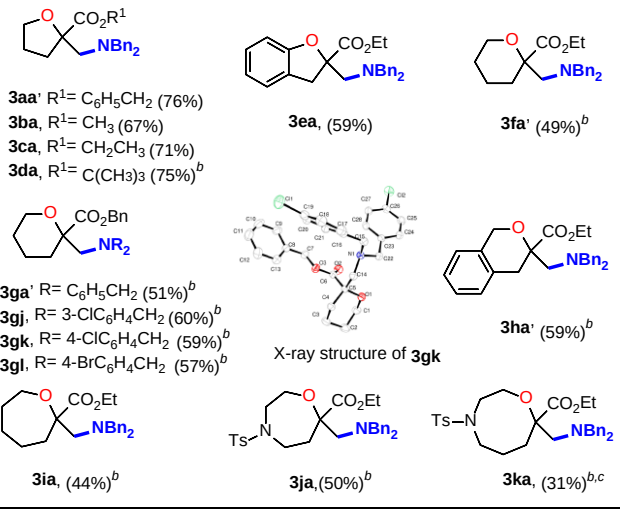
Entry	R	3	Yield (%)
1	$C_6H_5CH_2$	**3aa**	76
2	4-Me$C_6H_4CH_2$	**3ab**	74
3	4-MeO$C_6H_4CH_2$	**3ac**	63
4	2-F$C_6H_4CH_2$	**3ad**	71
5	CH_2CHCH_2	**3ae**	37
6	$CH_2CH_2CH_3$	**3af**	55
7	$CH_2CH_2CH_2CH_3$	**3ag**	48
8	-$CH(CH_2)_5$	**3ah**	50
9	-$CH_2CH_2OCH_2CH_2$-	**3ai**	65

[a] Reaction condition: **1** (0.45 mmol), **2** (0.3 mmol), $Fe(OTf)_2$ (0.015 mmol, 5 mol%), CH_3CN (1.0 mL), 25 °C, 12 h. Isolated yield.

After investigating the generality of *N,O*-aminals, various hydroxyl-tethered *α*-diazoesters **1** were employed in the reaction with *N,N*-dibenzyl-1-methoxymethanamine **2a**. As shown in Table 3, the substrates with 5-hydroxy chains (**1a**-**1e**) afforded the corresponding β-amino esters with five-membered rings in good yields (**3aa**-**3ea**). Substrate **1d** with a *tert*-butyl ester group afforded the desired product in 75% yield by increasing the temperature to 80 °C. It is worth mentioning that *α*-diazoesters attached to a phenolic hydroxyl group was applicable to this reaction (**3ea**). To our delight, the catalyzed reaction was also suitable for the aminomethyloxygenative cyclization of benzyl 2-diazo-6-hydroxyhexanoate, which yielded the corresponding oxacycle-containing α,α-disubstituted β-amino esters with six-membered rings under 80 °C in the presence of 5 mol% of catalyst (**3fa**-**3ha, 3gj**-**3gl**). *N,O*-aminals, derived from benzylamines bearing electron-withdrawing (Cl, Br) group were helpful for increasing the yield of the reaction (**3gj**-**3gl**). Moreover, a benzo group in the chain of the substrate also had a positive effect on the reactivity (**3ha**). The solid state structure of **3gk** was unambiguously determined by single-crystal X-ray crystallographic analysis.[14] Motivated by the successful construction of cyclic α,α-disubstituted β-amino esters with five- and six-membered rings, we sought to extend the present reaction to more challenging cycle with large ring sizes. As expected, when 7-hydroxy-2-diazoesters (**1i** and **1j**) were used as substrates, the desired products with a seven-membered ring were isolated in moderate yields. Importantly, the eight-membered ring product was also successfully produced in 31% yield (**3ka**) by using this method under slightly modified reaction conditions.

Table 3 Substrate scope of α-diazoesters[a]

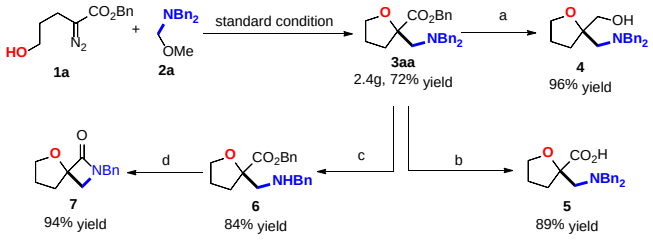




[a] Reaction condition: **1** (0.45 mmol), **2** (0.3 mmol), $Fe(OTf)_2$ (0.015 mmol, 5 mol%), CH_3CN (1.0 mL), 25 °C, 12 h. Isolated yield. [b] 80 °C. [c] $Fe(OTf)_2$ (0.03 mmol, 10 mol%), CH_3CN (5.0 mL), 12 h.

We further evaluated the utility of this reaction by performing a large-scale experiment (Scheme 2). Under the standard reaction conditions, the desired product **3aa** could be obtained in gram scale (2.4 g) with 72% isolated yield. The scalability and robustness of this transformation indicate its potential application in the preparation of fine chemicals. Then we carried out several transformations of cyclization product **3aa** (Scheme 2). Reduction of the ester group with $LiAlH_4$ gave the product **4** in 96% isolated yield.[13] Hydrolysis of the ester with LiOH as the base gave carboxylic acid **5** in good yield. In addition, one benzyl group contained in **3aa** could be selectively removed to give benzyl-2-((benzylamino)methyl)tetrahydrofuran-2-carboxylate **6** in 84% yield in the presence of $ClCO_2CHClCH_3$.[15] Cyclization of product **6** with *i*-PrMgBr gave the spiro-lactam 2-benzyl-5-oxa-2-azaspiro[3.4]octan-1-one **7** in 94% yield.[11a]

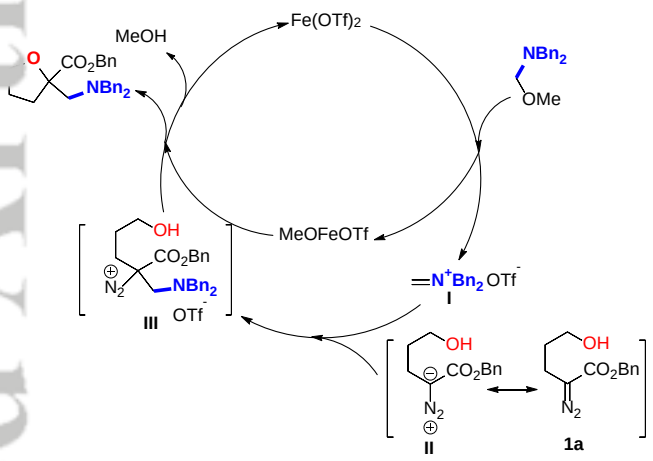
Scheme 2 Reaction scale-up and functional group transformation[a]



[a] Reaction condition: a. $LiAlH_4$ (1.0 eq.), THF, 0 °C, 1 h; b. LiOH (5.0 eq.), MeOH/H_2O/THF (5:1:1), rt, 12 h; c. (i) $ClCO_2CHClCH_3$ (6.0 eq.), DCE, 80 °C, 12 h, (ii) MeOH, 80 °C, 6 h; d. *i*-PrMgBr (2.0 eq.), rt, 12 h.

In accordance with precedent studies[16] and our experimental results, a plausible mechanism for the formation of **3aa** is proposed (Scheme 3). In the first stage, the iminium **I** could be generated from *N,O*-aminal **2a** under the assistant of $Fe(OTf)_2$. Upon trapping with the nucleophile dizao **II**, the procarbonium ion intermediate **III** could be generated from iminium **I**. Subsequently, the intermediate **III** may undergo intramolecular oxygenative cyclization to produce the desired oxacycle-containing α,α-disubstituted β-amino esters.

Scheme 3. Plausible reaction pathway



Conclusions

In summary, we have developed a new and efficient protocol for the synthesis of oxacycle-containing α,α-disubstituted β-amino esters via iron-catalyzed aminomethyloxygenative of diazo compounds with *N,O*-aminals under mild reaction conditions. The reaction proceeded well to furnish the desired products with good functional-group compatibility, which provided a rapid and reliable approach to unnatural oxacycle-containing β-amino esters with five to eight-membered rings. Further studies to apply this strategy are in progress in our laboratory.

Experimental

The $Fe(OTf)_2$ (5.3 mg, 0.025 mmol) was added to a 25 mL flame-dried Young-type tube in the glove box. Then *N*,*N*-dibenzyl-1-methoxymethanaminel **2a** (0.5 mmol), CH_3CN (1.0 mL), benzyl 2-diazo-5-hydroxypentanoate **1a** (114.0 mg, 1.0 mmol) were added under argon atmosphere. The mixture was stirred at 25 °C for 12 hours. The solvent was removed under reduced pressure after the reaction finished. The reaction mixture was purified by flash column chromatography on silica gel and eluted with EtOAc/hexane (1/30 – 1/10) to afford the desired product **3aa**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2019xxxxx.

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Entry for the Table of Contents

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Title Iron-Catalyzed Aminomethyloxygenative Cyclization of Hydroxy-α-diazoesters with *N,O*-aminals

Yuchen Zou,[a] Tianze Zhang,[a] Siyuan Wang,[a] and Hanmin Huang*[a,b]

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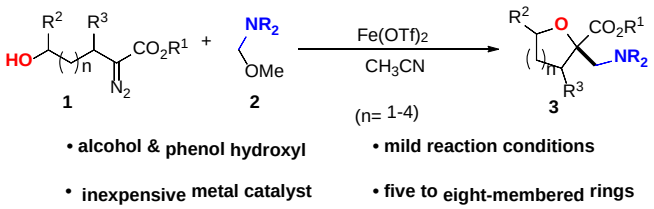

- **alcohol & phenol hydroxyl**
- **inexpensive metal catalyst**
- **mild reaction conditions**
- **five to eight-membered rings**

A new and efficient cyclization reaction has been developed to synthesize cyclic α,α-disubstituted β-amino esters via iron-catalyzed intramolecular aminomethyloxygenative cyclization of diazo Compounds with N,O-aminal under mild reaction conditions. A broad range of hydroxy-α-diazoesters with different substituents and various N,O-aminals were compatible with this protocol, affording the corresponding α,α-disubstituted β-amino esters bearing with a five- to eight-membered oxacycle in good yields.

