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COMMUNICATION

An Efficient [3+2] Annulation for the Asymmetric Synthesis of Densely-Functionalized Pyrrolidinones and γ-Butenolides†

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Disclosed here is a new [3+2] annulation of siloxy alkynes that provides robust access to highly enantioenriched, fully-substituted pyrrolidinones and γ-butenolides, whose direct synthesis remains challenging. This process also represents a rare asymmetric synthesis of enantrioenriched molecules from siloxy alkynes.

Pyrrolidinones (γ-lactams) and γ-butenolides are substructures prevalent in numerous natural products and biologically active molecules possessing diverse properties (Figure 1, e.g., antibacterial, anticancer, antiviral, anti-inflammatory, antifungal).[1,2] They also serve as valuable intermediates in organic synthesis.[1,3-7] For example, pyrrolidinones are known precursors to γ-aminobutyric acid (GABA) analogues, key inhibitory neurotransmitters in the mammalian central nervous system.[3] After ring-opening, the chirality established in these heterocycles could be easily imparted to the functionalized chiral linear molecules, whose asymmetric synthesis might not be so straightforward by direct functionalization of the configurationally more flexible linear framework. Consequently, asymmetric synthesis of pyrrolidinones and γ-butenolides has been a subject of intensive investigations over the past few decades. Although various approaches have been developed, the majority generate only one or two stereogenic centers.[4-6] Indeed, it remains as a formidable challenge to establish three contiguous stereogenic centers in pyrrolidinones. Moreover, direct access to the densely-substituted core of these two heterocycles remains scarce (Figure 1). Here we report a new approach to addressing these challenges by a [3+2] annulation of siloxy alkynes.

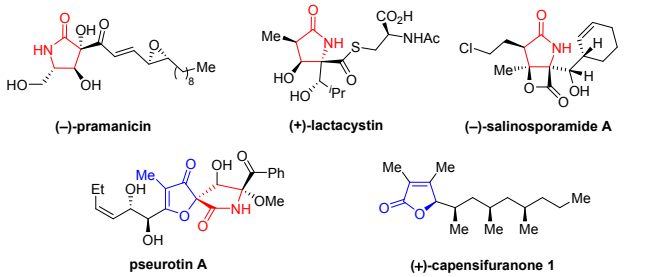
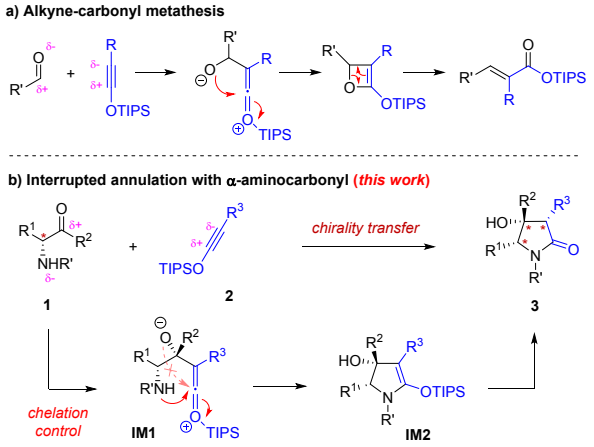


Fig. 1 Useful molecules containing pyrrolidinones and γ-butenolide subunits.

Siloxy alkynes are versatile but less explored species in organic synthesis.[7] The polarized electron-rich C–C triple bond has enabled them to participate in a range of annulation processes.[7,8] However, to the best of our knowledge, the utilization of siloxy alkynes to create new stereogenic centers in enantiospecific manner is essentially unknown. Siloxy alkynes can participate in alkyne-carbonyl metathesis with aldehydes to form α,β-unsaturated esters via stepwise [2+2] cycloaddition followed by electrocyclic opening of the β-lactone intermediate (Scheme 1a).[9] We envisioned that this process might be interrupted by using an α-amino ketone as the reaction partner



Scheme 1 Alkyne-carbonyl metathesis and its interrupted annulation.

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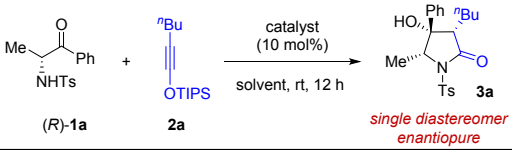
(Scheme 1b). With suitable Lewis acid activation, the initial C–C bond formation results in **IM1**. Instead of nucleophilic attack from the resulting oxygen motif to form the strained four-membered oxetene, the nitrogen nucleophile is better positioned to cyclize with the silyl ketenium to form the five-membered ring **IM2**, which leads to pyrrolidinone **3** after desilylation. Furthermore, the chirality in the α-amino ketone is expected to induce the two new stereogenic centers in the product. In the first step, the diastereoselectivity is expected to be control by chelation. The final diasteroselective protonation step is expected to be thermodynamically controled.

To test the above hypothesis, we employed the readily accessible enantiopure α-aminketone (*R*)-**1a** and alkyne **2a** as the model substrates (Table 1).[10] The Brønsted acid $HNTf_2$ was initially examined as a potential catalyst, as it has proven to be superior in a range of reactions of siloxy alkynes.[7,8,11] Unfortunately, no desired lactam **3a** was observed (entry 1). Next, various Lewis acids were tested. $Sc(OTf)_3$ was catalytic inactive either (entry 2). While the reaction could proceed in the presence of BF_3•OEt_2, the desired product **3a** was only formed in 12% yield (entry 3). In contrast, silver salts with weak counter anion were found to be much more active (entries 4-6). Among them, $AgPF_6$ showed the best performance (entry 6). Next, different solvents were compared, which identified MeCN to be the best choice. Finally, increasing the loading of **2a** combined with a higher concentration could improve the yield to 85% (entry 11). It is worth noting that the densely-substituted product **3a** with three contiguous stereogenic centers was formed as a single diastereomer. More importantly, HPLC analysis confirmed that the product was formed in the enantiopure form.

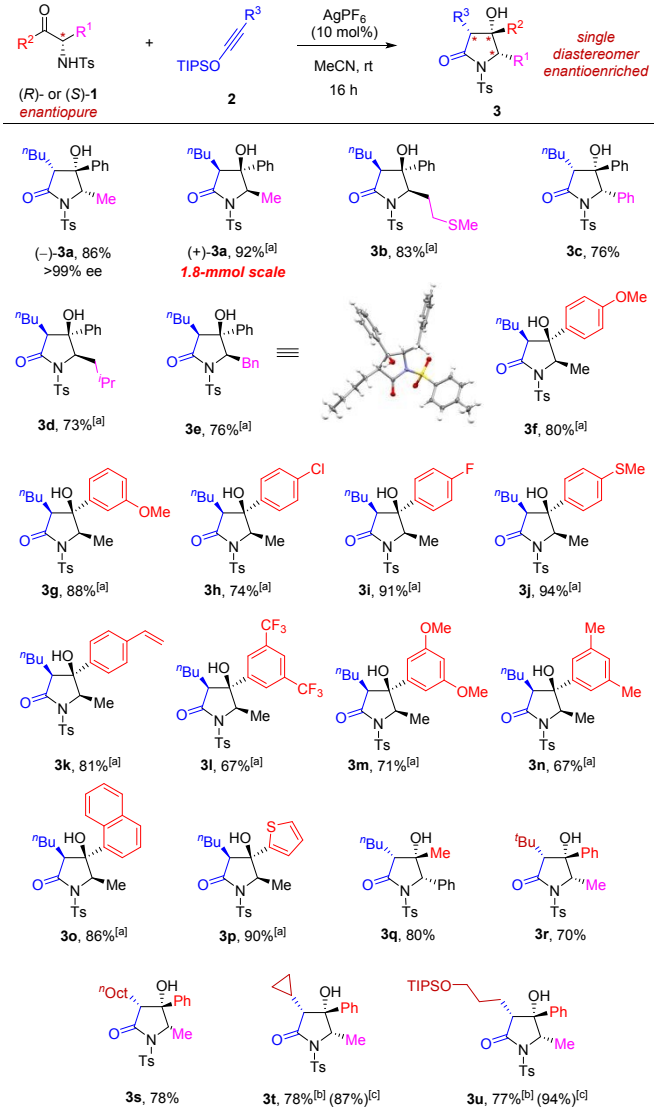
Table 1 Condition optimization[a]



Entry	Catalyst	Solvent	Conv. (%)	Yield (%)
1	$HNTf_2$	DCM	< 5	-
2	$Sc(OTf)_3$	DCM	< 5	-
3[b]	BF_3•OEt_2	DCM	54	12
4	AgOTf	DCM	55	31
5	$AgNTf_2$	DCM	50	36
6	$AgPF_6$	DCM	65	46
7	$AgPF_6$	$CHCl_3$	74	26
8	$AgPF_6$	toluene	77	38
9	$AgPF_6$	MeCN	93	57
10[c]	$AgPF_6$	MeCN	96	75
11[d,e]	$AgPF_6$	MeCN	100	85

[a]Reaction scale: (*R*)-**1a** (0.05 mmol), **2a** (0.1 mmol), solvent (0.5 mL). The conversion, yield, and dr values are based on ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard. [b]Run with 1.5 equiv of BF_3•OEt_2. [c]Run with 1.5 equiv of **2a**. [d]Run with 2.0 equiv of **2a**. [e]Conc. = 0.2 M.

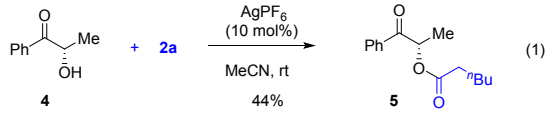
With the above optimized conditions, we examined the reaction scope (Scheme 2). A range of enantiopure α-amino ketones and siloxy alkynes participated smoothly in this [3+2] annulation. Ketones with different electronic properties were all successful substrates. The corresponding diversely substituted pyrrolidinone products were all generated with high efficiency. The structure and stereochemistry of **3e** were confirmed unambiguously by X-ray crystallography. The mild conditions tolerated various functional groups, including ether, thioether, styrene, aryl halide, and silyl-protected alcohol. Heterocycles could also be incorporated into the products. When the reaction was scaled up (1.8 mmol), the product yield remained excellent (92%, **3a**). Notably, in all these examples, the products were generated as a single diastereomer, and the stereochemistry is consistent with chelation control in the intermolecular C–C bond forming step.



Scheme 2. Scope for the synthesis of pyrrolidinones. Reaction scale: **1** (0.3 mmol), **2** (0.6 mmol). Isolated yield. [a](*S*)-**1** was used. [b]Run at 50 °C for 48 h. [c]Yield in parentheses is based on recovered starting material.

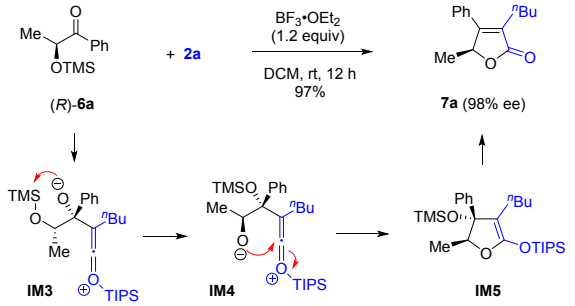
The success in the synthesis of γ-lactams prompted us to further explore its extension to the synthesis of γ-butyrolactones from the corresponding α-hydroxy ketones.

Unfortunately, under the standard conditions, the reaction between **4** and **2a** resulted in no desired lactone formation. Instead, ester **5** was formed, likely via initial silver activation of the electron-rich alkyne followed by nucleophilic addition by the hydroxy group and then desilylation.



4 **5**

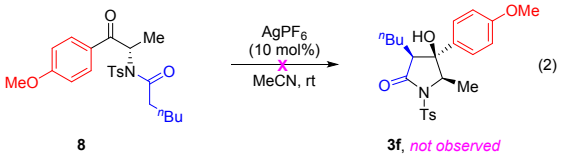
To minimize the interference of the free hydroxy group but still retain its ability to participate in cyclization, we hypothesized that suitable protection of the hydroxy with a labile TMS group might solve the problem. Thus, substrate **6a** was evaluated for this process (Scheme 3). While silver salts proved to be incapable of catalyzing the desired lactone formation, considerable efforts were devoted to further optimization. Finally, we were delighted to find that BF_3•OEt_2 could promote the formation of γ-butenolide **7a** in 97% yield. No obvious erosion in enantiopurity was observed in this process (98% ee confirmed by HPLC). We also evaluated other less labile silyl groups (e.g., TBS), but they were inferior. We believe that the key role of the TMS group is to avoid the path in eq. 1 in the first step, thereby permitting the desired C–C bond formation to form **IM3**. Next, a silyl shift likely forms **IM4**, which cyclizes to form **IM5**. Further desilylation and elimination led to the observed product **7a**.



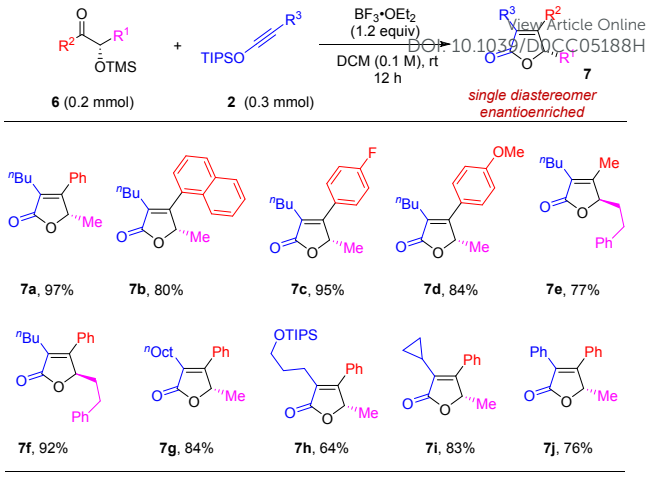
Scheme 3 Synthesis of γ-butenolides.

Next we examined the scope using the optimized protocol (Scheme 4). Various enantioenriched α-siloxy ketones, including those with electron-withdrawing and electron-donating substituents, were subjected to the annulation with siloxy alkynes. The corresponding enantioenriched densely-substituted γ-butenolides were all obtained with high efficiency.

The result in eq. 1 prompted us to examine whether amide **8** could serve as a viable intermediate toward the cyclization product **3f** by intramolecular aldol-type cyclization (eq. 2). In fact, treating **8** with $AgPF_6$ in MeCN did not form lactam **3f**, which ruled out this possibility.

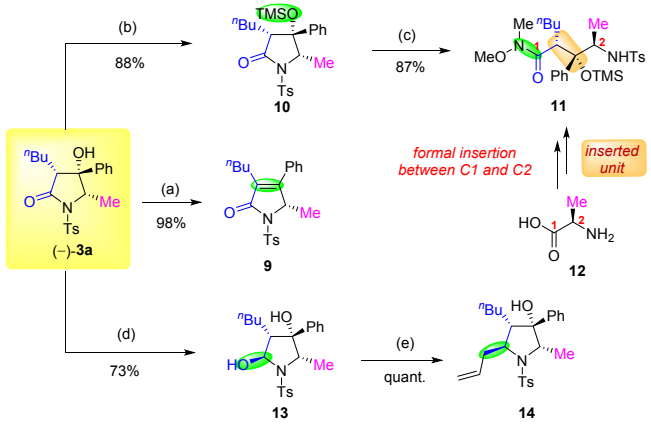


8 **3f**, *not observed*



Scheme 4 Scope for the synthesis of γ-butenolides.

The enantioenriched pyrrolidinone products are useful synthetic precursors to other chiral molecules (Scheme 5). The free hydroxyl group in **3a** could be easily eliminated under basic conditions to form α,β-unsaturated lactam **9**. Alternatively, it could also be protected to form silyl ether **10**, which then underwent ring-opening to form Weinreb amide **11**. It is worth noting that **11** can be regarded as an important precursor to the densely-functionalized γ-amino acids, a family of valuable molecules in medicinal chemistry.[3] In retrospect, comparing with the starting material L-alanine **12**, the formation of **11** is a formal insertion of a two-carbon unit with defined stereochemistry between carbonyl and the α-carbon in **12** without touching the chirality of the amino group. Partial reduction with DIBAL at –78 °C resulted in formation of hemiaminal **13**, which could serve as an attractive intermediate toward pyrrolidines substituted at all positions upon reacting with different nucleophiles. For example, in the presence of BF_3•OEt_2, allylation could proceed quantitatively to form **14**, which has four consecutively stereogenic centers. It is worth mentioning that pyrrolidine is another important unit widely present in natural alkaloids.[12] Notably, in all these transformations, the products were all formed as a single diastereomer.



Scheme 5 Product transformations. (a) MeONa, MeOH; (b) TMSOTf, 2,6-lutidine,

DCM; (c) MeO(Me)NH•HCl, ^{i}PrMgCl, THF; (d) DIBAL, DCM, –78 °C; (e) allyltrimethylsilane, BF_3•OEt_2, MeCN.

In conclusion, we have developed a new [3+2] annulation for the robust asymmetric synthesis of chiral pyrrolidinones, which complements their conventional synthetic strategies, particularly in view of the establishment of three consecutive stereogenic centers. This process also represents a rare demonstration of using siloxy alkynes to access enantioenriched molecules. With suitable design, the use of α-aminoketones successfully interrupted the bond-forming sequence in the alkyne-carbonyl metathesis to furnish a more favored five-membered ring structure. With the superior catalyst $AgPF_6$, the chirality in the α-aminoketones induced the two newly established stereogenic centers in the pyrrolidinones with excellent stereospecificity. This protocol was also successfully extended to the efficient synthesis of chiral γ-butenolides with slight modification of the α-hydroxy ketones as well as the Lewis acid activator. The heterocyclic products are not only valuable themselves in medicinal chemistry but also useful synthetic precursors to other important chiral molecules, such as GABA and pyrrolidine derivatives.

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Conflicts of interest

There are no conflicts to declare.

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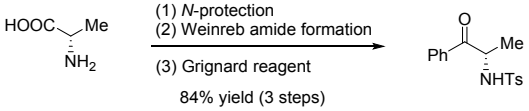
10 The chiral α-aminoketone could be easily synthesized via three simple steps from L-alanine:



84% yield (3 steps)

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