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Cu^{I}/Rh^{II}-Catalyzed Tandem Convergent Multicomponent Reaction for the Regio- and Stereocontrolled Synthesis of γ-Oxo-β-amino Esters

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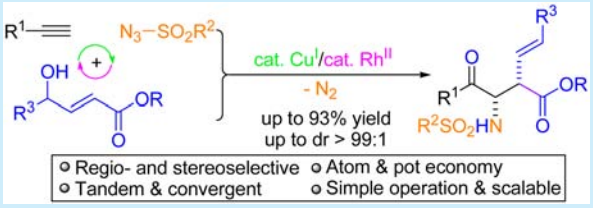
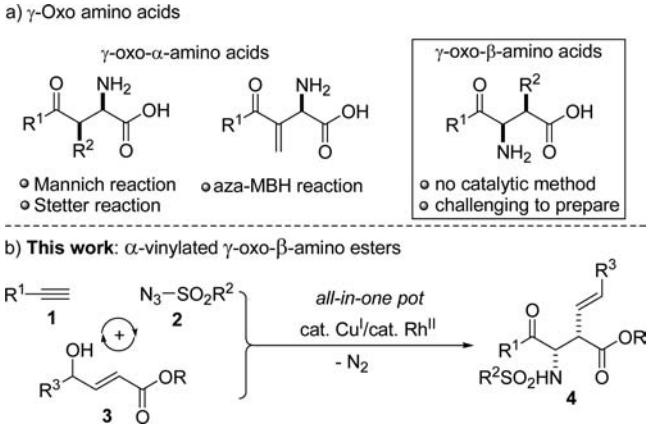
Supporting Information

ABSTRACT: The first example of a highly regio- and stereoselective catalytic method for the three-component one-pot synthesis of highly functionalized α-vinylated γ-oxo-β-amino esters is disclosed. In this catalytic triad, the Cu^{I}-catalyst selectively catalyzes the cycloaddition of the 1-alkyne and sulfonyl azide first resulting in the corresponding 1-sulfonyl-1,2,3-triazole. An α-imino Rh^{II}-carbene is generated from an open-chain α-imino diazo of the triazole, and this species reacts with γ-hydroxy α,β-unsaturated esters to form allylic (Z)-amino vinyl ethers. Rapid deconjugative [3,3]-sigmatropic rearrangement affords the α-vinyl γ-oxo-β-amino esters in high yields with high levels of diastereoselectivity.



Amino acids play a vital role in living systems and provide an important under-utilized inventory of building blocks for protein engineers, medicinal chemists, and materials scientists.[1] Given their significance, the development of succinct catalytic methods for the regio- and stereocontrolled synthesis of non-natural amino acids is a continuing challenge in organic synthesis.[2,3] Due to the multifunctionality of γ-oxo amino acid derivatives enabling further synthetic elaborations, these amino acids have drawn considerable interest. Indeed, many reliable catalytic methodologies including Mannich-type reactions,[4] the Stetter reaction,[5] and aza-Morita–Baylis–Hillman reactions[6] have been developed for the synthesis of γ-oxo-α-amino esters (Scheme 1a). In contrast, the analogous γ-oxo-β-amino esters, although equally useful, are far less accessible. To the best of our knowledge, no catalytic methods for the synthesis of γ-oxo-β-amino esters have been developed to date, and the multistep transformations of aspartic acid or homoserine are the current synthetic methods of choice for this class of compounds.[7] Herein we disclose the first example of a highly regio- and stereoselective catalytic method that enables access to highly functionalized α-vinylated γ-oxo-β-amino esters **4** from readily available 1-alkynes **1**, sulfonyl azides **2**, and γ-hydroxy α,β-unsaturated esters **3** (Scheme 1b). In this catalytic triad, the Cu^{I} and Rh^{II} catalysts assembled the starting molecules in a tandem convergent manner to generate allylic (Z)-amino vinyl ethers, which rapidly undergo deconjugative [3,3]-sigmatropic rearrangement (Claisen rearrangement) to afford γ-oxo-β-amino esters **4** in high yields with high levels of diastereoselectivity.

Scheme 1. Catalytic Methods for the Synthesis of γ-Oxo Amino Acids



The [3,3]-sigmatropic rearrangement is one of the most powerful reactions for carbon–carbon bond formation.[8] Pioneering work by Wood et al. using Rh^{II} catalysts has shown that Rh^{II}-carbenoid-promoted [3,3]-sigmatropic rearrangements can be an efficient method for the stereocontrolled construction of homoallylic quaternary alcohols starting from diazocarbonyl compounds and allylic alcohols.[9,10] Thanks are due to Murakami and co-workers, who recently extended the [3,3]-sigmatropic rearrangement to include α-imino Rh^{II}-carbenes **A**, generated from open-chain α-imino diazo compounds **5′** from 1-sulfonyl-1,2,3-triazoles **5**, resulting in α-allylated α-*N*-sulfonyl aminoketones.[11] This process takes place via a mechanistic pathway where insertion of the Rh^{II}-carbene into the O–H bond of an allylic alcohol generates an ally (Z)-amino vinyl ether that can undergo [3,3]-sigmatropic rearrangement. To date, however, no functionalized allylic alcohols other than simple alkyl groups have been investigated for Rh(II)-carbenoid promoted [3,3]-sigmatropic rearrangements.

The 1-sulfonyl 1,2,3-triazoles **5** could easily be formed by the Cu^{I}-catalyzed alkyne–azide cycloaddition of 1-alkynes **1** and

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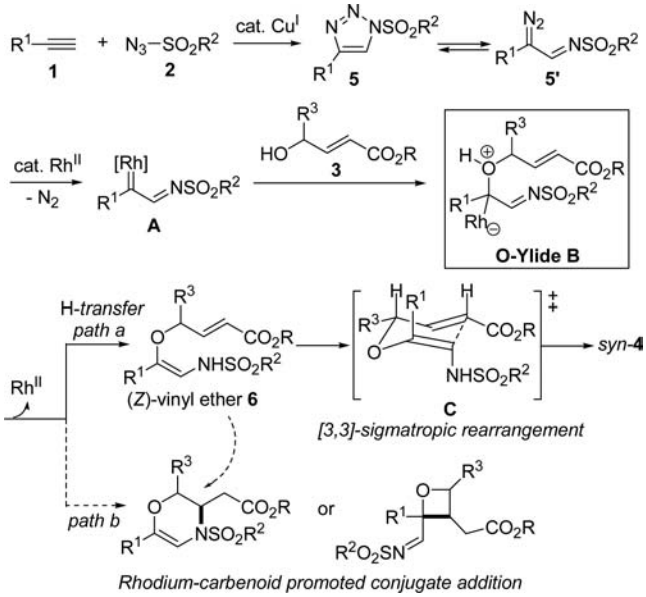
sulfonyl azides **2**[12] and have received a great deal of attention in recent years as a docile precursor for α-imino metallocarbenes.[13] We recently reported that the Rh^{II}-catalyzed reaction of triazoles **5** with β-enaminoesters bearing a nucleophilic enamine and electrophilic α,β-unsaturated esters (Michael acceptor) proceed through the N−H 1,3-insertion/conjugate addition of an α-imino Rh^{II}-carbene (Rh-carbenoid promoted conjugate addition) to afford 3-imidazolines.[14b] With these precedents in mind and in connection with our previous study on the catalytic conversion of readily available γ-hydroxy α,β-unsaturated esters **3** to unnatural γ-amino acid derivatives,[15] we anticipated that reaction of **A** with **3** could generate the rhodium-associated *O*-ylide **B**, which could potentially possess two different reactivity profiles. One possible reaction pathway of **B** would involve a proton transfer resulting in allyl (*Z*)-amino vinyl ether **6**,[16] enabling deconjugative [3,3]-sigmatropic rearrangement via the chairlike transition state **C** to afford highly functionalized α-vinyl γ-oxo-β-amino ester **4** in a stereoselective manner (path a, Scheme 2). On the other hand, if *O*-ylide **B** could follow the Rh^{II}-carbenoid promoted conjugate addition pathway, either oxazines or oxetanes could be produced (path b, Scheme 2).

Scheme 2. Possible Reaction Pathways of Rh-Associated *O*-Ylide



To study the intrinsic aspects of *O*-ylide **B**, we first conducted a reaction between the presynthesized 1-sulfonyl-1,2,3-triazole **5a** (R^1 = Ph), prepared from **1a** (R^1 = Ph) and **2a** (R^2 = tolyl), and γ-hydroxy (*E*)-α,β-unsaturated ester **3a** (R^3 = Ph, R′ = Et) in the presence of catalytic amounts of the Rh^{II} catalyst. The reaction of **5a** and **3a** using 1.0 mol % $Rh_2(OAc)_2$ in toluene at 60 °C afforded **4aa** in only 27% yield, but with very promising diastereoselectivity of dr = 91:9 (entry 1, Table S1). After screening various Rh^{II} catalysts (for details see Supporting Information), 1.0 mol % $Rh_2(^tBuCO_2)_4$ was found to be optimal affording an α-vinyl oxo-β-amino ester **4aa** in 93% isolated yield with excellent *syn* diastereoselectivity (dr = 91:9). In addition, the use of molecular sieves could prevent formation of the water-addition product, α-*N*-tosylamino acetophenone.[17] The structure of *syn*-**4aa** was unambiguously determined by X-ray crystallography (Figure 1).[18] There was

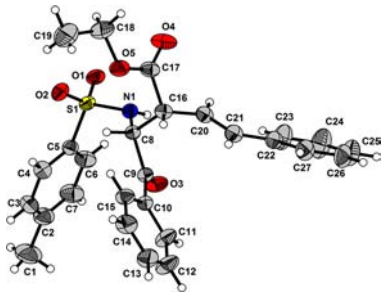
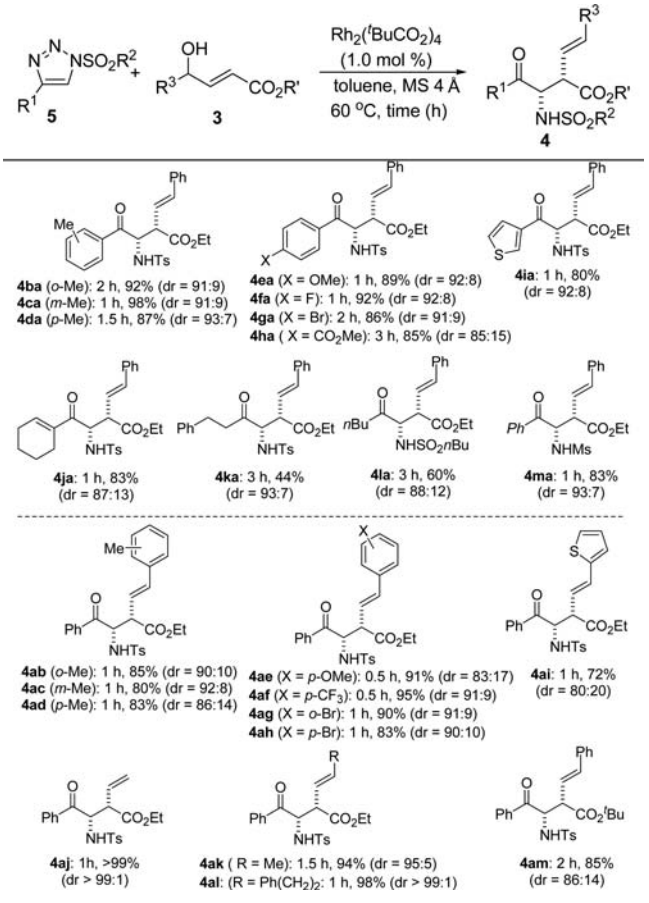


Figure 1. X-ray structure of **4aa**.

no sign of the formation of oxazine, and although the vinyl ether **6** was not detected, the formation of α-vinylated γ-oxo-β-amino esters **4aa** clearly indicates that the *O*-ylide **B** follows a proton transfer/[3,3]-sigmatropic rearrangement cascade pathway (path a in Scheme 2).

With optimal conditions in hand, we investigated the generality of this protocol (Scheme 3). A broad range of 4-phenyl substituted triazoles **5b**−**5e** bearing electron-donating methyl and methoxy substituents on the phenyl ring reacted with **3a** to form the corresponding **4ba**−**4ea** with excellent yields and diastereoselectivities. The 4-phenyl triazoles bearing electron-withdrawing substituents such as a fluoride (**5f**),

Scheme 3. Synthesis of α-Vinylated γ-Oxo-β-amino Esters[a]



[a]Reaction conditions: **5** (0.2 mmol), **3** (0.22 mmol), and Rh(II) (1.0 mol %) in toluene (1.6 mL) at 60 °C. Time for complete conversion of **5** by TLC, isolated yield, and dr were determined by ^{1}H NMR analysis of the crude reaction mixture.

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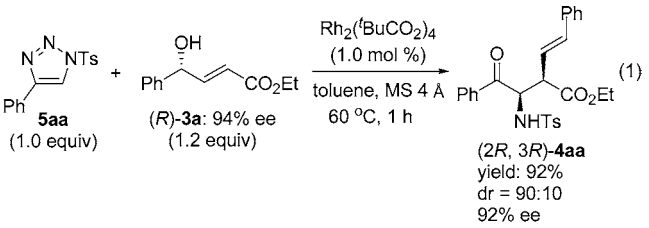
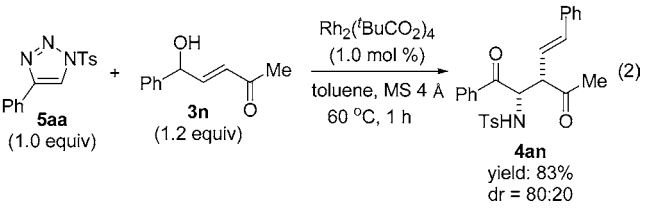
bromide (**5g**), or an ester (**5h**) were also suitable for the reaction and provided the corresponding amino esters **4fa**–**4ha** with no apparent change in yield or diastereoselectivity. Heteroaromatic 3-thiophenyl substituted triazole **5i** also worked well affording the corresponding γ-oxo-β-amino ester **4ia** in good yield with dr = 98:2. Remarkably, this method was compatible with cyclohexenyl triazole **5j** giving **4ja** in good yield (83%) and good diastereoselectivity (dr = 87:13). The alkyl triazoles **5k** and **5l** also furnished the γ-alkylated amino esters **4ka** and **4la** with high diastereoselectivity, albeit in diminished yields. The *N*-methanesulfonyl triazole **5m** also reacted with **3a** to afford the corresponding oxo-amino ester **4ma** in high yield with excellent diastereoselectivity. The generality of the present protocol toward γ-hydroxy esters **3** was also investigated using triazole **5a**. Thus, hydroxyl esters **3** having electron-donating and -withdrawing substituted phenyl (**3b**–**3h**) and thiophenyl (**3i**) groups were successfully utilized to afford the corresponding **4ab**–**4ai** in high yields with good to excellent diastereoselectivities. Notably, almost a single diastereomer of α-vinyl γ-oxo-β-amino ester **4aj** can be obtained from the reaction with the γ-unsubstituted hydroxyl ester **3j** in quantitative yield. From the reactions with alkyl substituted **3k** and **3l**, it was also found that the reaction efficiency was almost retained, resulting in the corresponding γ-oxo-β-amino esters **4ak** and **4al** with excellent diastereoselectivity. The reaction with **3m** bearing a *tert*-butyl ester also reacted efficiently to give **4am** in high yield with reasonable diastereoselectivity. Although the reason is not clear at the present time, the reaction of (*Z*)-**3a** did not proceed at all. When optically active (*R*)-**3a** (94% ee) was used, an excellent level of chirality transfer was observed resulting in a chiral (2*R*,3*R*)-**4aa** with 92% ee (eq 1). Moreover, the present

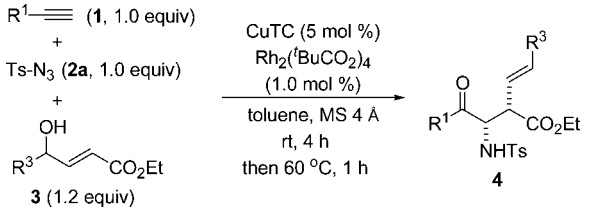




protocol could also be applied to γ-hydroxy enone **3n** allowing the regioselective installation of amine and vinyl functionalities onto the 1,4-diketone backbone, resulting in **4an** in 83% yield with dr = 80:20 (eq 2).

To improve the sustainability of this protocol, we next investigated the tandem one-pot convergent multicomponent reaction of terminal alkynes **1**, tosyl azide **2a**, and γ-hydroxy-α,β-unsaturated esters **3** in the presence of 5.0 mol % CuTC (TC = thiophencarboxylate) and 1.0 mol % $Rh_2(^tBuCO_2)_4$ (Table 1). The mixture of all reactants and catalysts was stirred at room temperature for 4 h and then further stirred at 60 °C for 1 h to afford the corresponding α-vinylated γ-oxo-β-amino esters **4** in yields ranging from 63% to 93% with almost the

Table 1. All-in-One-Pot Synthesis of α-Vinylated γ-Oxo-β-amino Esters[a]

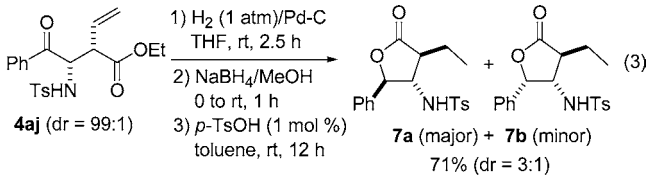


entry	R^1	R^3	**4** (%, dr)[b]
1	Ph	Ph	**4aa** (92%, 91:9)
2[c]	*o*-Me-Ph	Ph	**4ba** (64%, 91:9)
3	*m*-Me-Ph	Ph	**4ca** (73%, 91:9)
4[d]	*p*-Me-Ph	Ph	**4da** (87%, 93:7)
5	*p*-MeO-Ph	Ph	**4ea** (84%, 92:8)
6	*p*-F-Ph	Ph	**4fa** (72%, 92:8)
7	3-thiophenyl	Ph	**4ia** (63%, 92:8)
8	*c*-hexen-1-yl	Ph	**4ja** (63%, 87:13)
9	Ph	*o*-Me-Ph	**4ab** (77%, 90:10)
10	Ph	*m*-Me-Ph	**4ac** (73%, 90:10)
11	Ph	*p*-Me-Ph	**4ad** (70%, 84:16)
12[d]	Ph	H	**4aj** (93%, >99:1) (gram scale)

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), **3** (0.22 mmol), and CuTC (5 mol %) and Rh(II) (1.0 mol %) in toluene (1.6 mL) 4 h at room temperature, then 1 h at 60 °C. [b]Isolated yield, and dr was determined by ^{1}H NMR analysis of crude reaction mixture. [c]Reaction was carried out for 2 h. [d]Reaction was carried out in a 7.0 mmol scale of **1a** for 4 h at room temperature, then 3 h at 60 °C.

same diastereoselectivities obtained in the reactions starting from the isolated triazoles shown in Table 1. It is also noteworthy that the tandem process could easily be scalable allowing multigram synthesis of **4aj** in 93% (2.61 g) yield with dr >99:1 (entry 12, Table 1).

Finally, the synthetic utility of the α-vinyl γ-oxo-β-amino ester was exemplified by the further transformation of **4aj** (dr = >99:1) to polysubstituted γ-lactone **7** (eq 3), which is an



important class of compounds in many natural and bioactive compounds.[19] A sequential hydrogenation of olefin, followed by carbonyl reduction and acid-catalyzed lactonizaton, afforded a mixture of diastereomeric γ-lactone **7** in an overall yield of 71% over three steps with dr = 3:1. The X-ray analysis of minor diastereomer **7b** indicated *trans,cis*-stereochemistry,[18] which suggested the chelate-controlled carbonyl reduction pathway was dominant (Figure 2).

In summary, we have developed a tandem and convergent Cu^I/Rh^{II}-catalyzed multicomponent reaction for the synthesis of highly functionalized α-vinyl γ-oxo-β-amino esters starting from readily available 1-alkyenes, sulfonyl azides, and γ-hydroxy-α,β-unsaturated esters. In this catalytic triad, the Cu^I-catalyst selectively catalyzed the cycloaddition of the 1-alkyne and sulfonyl azide to provide the corresponding 1-sulfonyl-1,2,3-triazole, from which in turn generated the α-imino Rh^{II}-carbene through the action of the Rh^{II} catalyst. Final reaction

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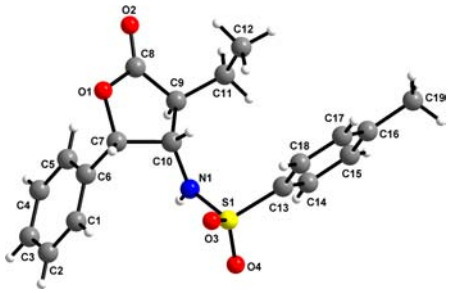

Figure 2. X-ray structure of **7b**.

with γ-hydroxy α,β-unsaturated esters gave access to allylic (*Z*)-amino vinyl ether, which then rapidly undergoes deconjugative [3.3]-sigmatropic rearrangement to afford the α-vinyl γ-oxo-β-amino esters in high yields with high levels of diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for **4** and **7**, and CIFs for **4aa** and **7b**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01587.

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Notes

The authors declare no competing financial interest.

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