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Formation of *o*-Allyl- and Allenyl-Modified Amides via Intermolecular Claisen Rearrangement

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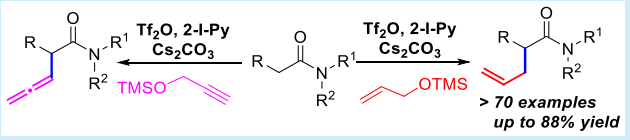
ABSTRACT: We developed a new transition-metal-free intermolecular Claisen rearrangement process to introduce allyl and allenyl groups into the α position of tertiary amides. In this transformation, amides were activated by trifluoromethanesulfonic anhydride to produce the keteniminium ion intermediates that exhibit strong electrophilic activity. This atom-economical process delivers α position-modified amides under mild conditions in moderate to good yields and showcases a broad substrate compatibility.



As the general building blocks of peptides and proteins, amides are very important bioactive skeletons in natural products, medicines, and functional materials (Figure 1).[1,2]

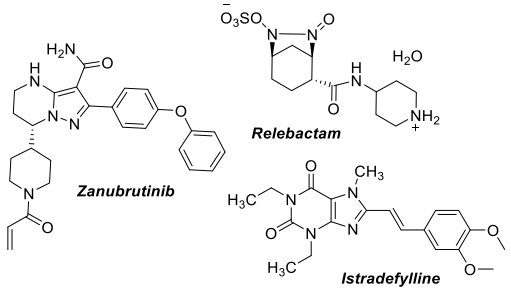


Figure 1. Amide derivatives in drugs.

The activation of amide has become an efficient strategy for realizing the modification of protein macromolecular compounds. Because of this, the activation and modification of amides remain challenging due to the well-understood resonance effects and have been high priorities of organic chemists. A large number of works on amide activation have been published in the past few decades. At first, elegant works that employed palladium and a Ni complex as the transition-metal catalyst to activate the C−N bond of amide were developed by Garg,[3] Hu,[4] Szostak,[5] and others.[6] The single-electron reductant samarium(II) iodide (SmI_2) was also used to generate the ketyl radicals from amides and to proceed to the activation and modification of amide.[5d,7]

Trifluoromethanesulfonic anhydride (Tf_2O) had been initially employed by Ghosez in the 1970s to realize the electrophilic activation of amide without using noble metals.[8] Recently, the groups of Charette,[9] Maulide,[10] and Huang[11] have published numerous related works on amide modification and transformation atop this foundation. On the basis of a long-standing interest, our group has also employed the Tf_2O-activated amide in the crucial process of producing high-bioactivity organic skeletons.[12] Mechanistic research has demonstrated that the keteniminium ion with a high electrophilic reactivity was generated when the amides were activated by Tf_2O and pyridines (Scheme 1).[9c,13]

Since being discovered by Claisen in 1912, sigmatropic rearrangement ranks among the most powerful tools in organic chemist's toolbox.[14] It was also employed in amide modification by Maulide,[13d,15] Ye,[16] and other groups.[17] As the strong electrophilic reagent, keteniminium species could react with diphenyl sulfoxide or *N*-aryl hydroxamic acid to undergo [3,3]-sigmatropic rearrangement and form the α position aryl-substituted amide.[15d] Intramolecular [3,3]-sigmatropic rearrangement also plays a part in the stage, employing allyloxyamides as starting materials to generate lactones.[15a−c] Among them, the allyl and allenyl modifications of the amide *ortho* position by intermolecular rearrangement are considered challenging. Herein, the progress of the hypothesis mentioned above, as well as the mechanistic studies of the reaction, is presented.

We initiated the process by employing amide **1a** and allyloxytrimethylsilane **2a** as the model substrates. At the very beginning, there was no anticipated product and even byproducts were produced when the reaction was carried out with Tf_2O and 2-iodopyridine in 1,2-dichloroethane (DCE) at 80 °C for 12 h (Table 1, entry 1). With this primary result, we speculated that before substrate **2a** reacted with the keteniminium ion generated by the Tf_2O-activated amide, it might be rapidly decomposed under the acidic condition. On

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Scheme 1. Previous Works and Our Initial Rearrangement Design

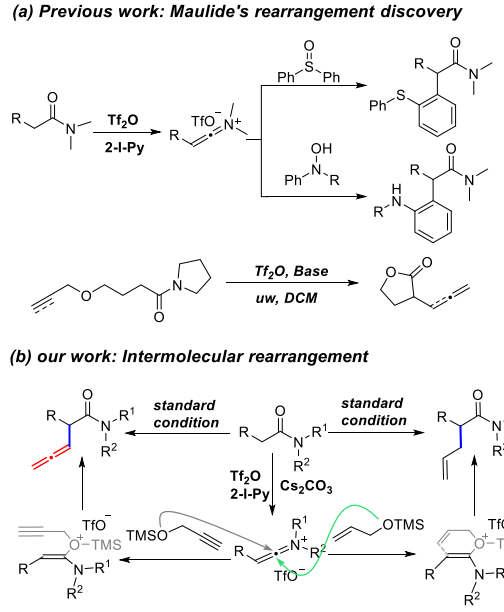
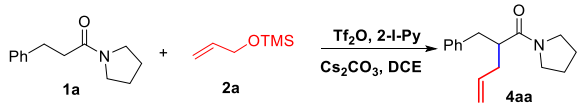


Table 1. Optimization of Reaction Conditions[a]



entry	base	additive	temp (°C)	time (h)	yield[b] (%)
1	2-iodopyridine	none	80	12	0
2	2-iodopyridine	Cs_2CO_3	80	12	50
3	2-iodopyridine	Na_2CO_3	80	12	ND
4	2-iodopyridine	K_2CO_3	80	12	ND
5	2-chloropyridine	Cs_2CO_3	80	12	trace
6	2-fluoropyridine	Cs_2CO_3	80	12	11
7	2-bromopyridine	Cs_2CO_3	80	12	trace
8	2-methylpyridine	Cs_2CO_3	80	12	ND
9	2,4,6-collidine	Cs_2CO_3	80	12	ND
10	2-iodopyridine	Cs_2CO_3	60	12	63
11	2-iodopyridine	Cs_2CO_3	70	12	76
12	2-iodopyridine	Cs_2CO_3	90	12	37

[a]A mixture of an amide (0.2 mmol) and a base (2.2 equiv) in DCE (1 mL) was treated with Tf_2O (1.4 equiv) in 0 °C for 15 min, and then the mixture of **2a** (3.5 equiv) and an additive (3.5 equiv) was added and stirred at rt. After being stirred at rt for 15 min, the reaction mixture was hetaed in an oil bath at the reported temperature for a further 12 h. Abbreviations: Tf_2O, trifluoromethanesulfonic anhydride; DCE, 1,2-dichloroethane; TMS, trimethylsilyl. [b]Isolated yields.

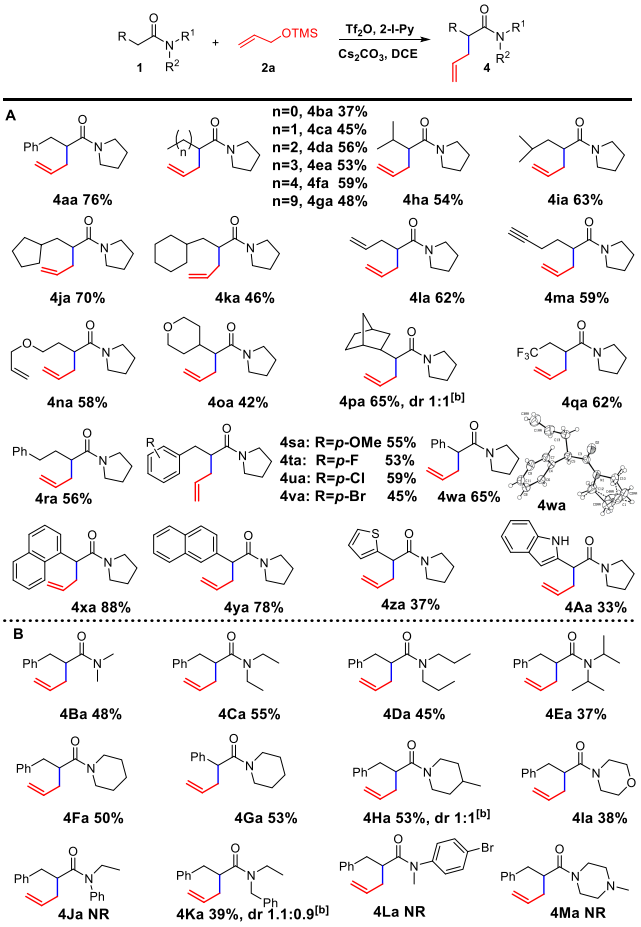
the basis of our hypothesis, different additives were tested (Table S1). To our delight, the desired product was achieved with a low yield when cesium carbonate (Cs_2CO_3) was added as the additional base (entries 2–4).

With the preliminary result in hand, we started to investigate the reaction conditions. Various bases and solvents were examined, and different temperatures and times also were screened (entries 5–12, details in the Supporting Information). After different conditions had been optimized, the best result was afforded: 1.4 equiv of Tf_2O and 2.2 equiv of 2-iodopyridine as activating reagents, 4.0 equiv of Cs_2CO_3 as additional base, and DCE as the solvent, stirring in oil bath at 70 °C for 12 h.

After determining the optimal conditions, we examined the scope of amides and the functional group tolerance. A number of alkyl and branched alkyl amides reacted with **2a** and generated the desired products (**4aa**–**4ka**) in moderate to good yields. Amides substituted with alkenyl, alkynyl, and tetrahydro-2*H*-pyranyl could neatly undergo this transformation (**4la**, **4ma**, and **4oa**) and amide **1p** could also give the corresponding product in good yield (**4pa**). It was worth noting that the amide bearing an allyloxy group (**4na**) previously reported for intramolecular rearrangement was also tolerated in this reaction.[15a] To our delight, the trifluoromethyl-substituted amide also performed well in this reaction (**4qa**). Then, we examined the amides substituted with different aryl groups, and the substrates bearing MeO, F, Cl, or Br at the *para* position could be compatible in this reaction (**4ra**–**4wa**). The structure of **4wa** was confirmed by X-ray crystallographic analysis. The α-naphthyl and β-naphthyl type amides coupled with the partner in excellent yields (**4xa**, 88%; **4ya**, 78%). The heterocyclic thiophene and indole were also compatible with this conversion, but the yields were not satisfying (**4za** and **4Aa**).

Then we screened the tertiary amides with different substituents on the N atom (Table 2B). Amides with chain

Table 2. Scope of α-Allyl Amides[a]



[a]All of the reactions were carried out on a 0.2 mmol scale under the standard condition. Isolated yields are given. [b]Determined by ^1H NMR.

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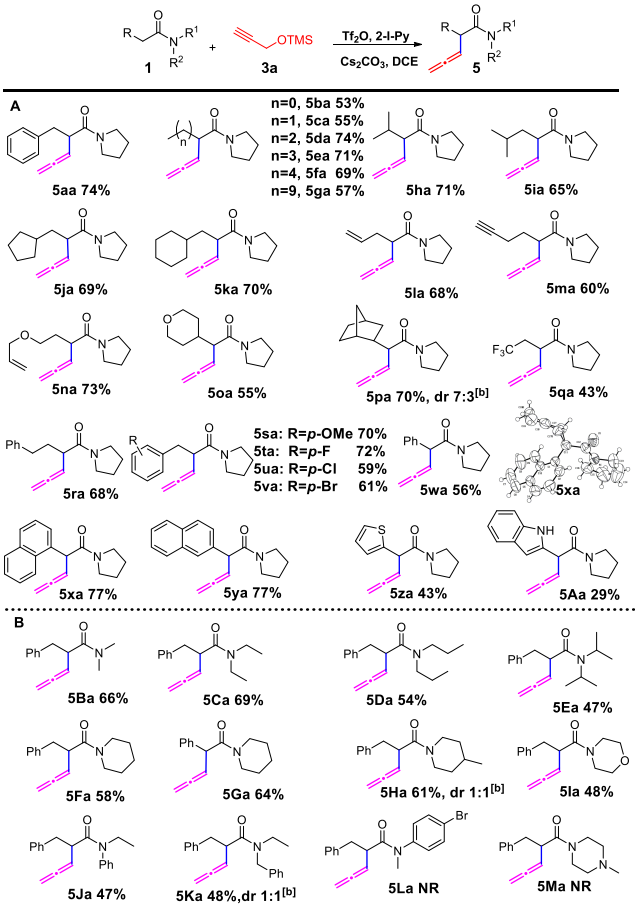
and branched alkyl groups on the N atom could proceed through this reaction smoothly (**4Ba**−**4Ea**), and the cyclic substituted amino groups also performed well in this transformation (**4Fa**−**4Ha**). On the contrary, the results of the investigation of heteroatom-containing cyclic substituted amino amides were not satisfactory (**4Ia** and **4Ka**). Some amides substituted with an aryl group on the N atom also did not perform in this reaction (**4Ja** and **4Ma**).

The results presented above demonstrate the usefulness of this reaction. We started to ponder the possibility of extending this transformation to introduce allenyl groups at the α position of tertiary amide. To validate this assumption, we employed **1a** and trimethyl(prop-2-yn-1-yloxy)silane (**3a**) as reaction partners to install allenyl groups at the *othro* position of amides under the standard conditions following the reaction recipes presented in Table 2; corresponding product **5aa** was formed in good yield (**5aa**, 74%). Encouraged by this result, we used a number of amides to react with **3a**. As shown in Table 3, alkyl-, branched alkyl-, and cycloalkyl-substituted tertiary

Table 3. Scope of α-Allenyl Amides[a]



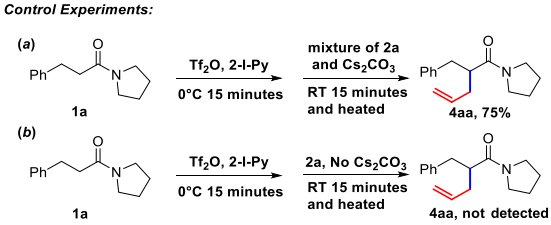
[a]All of the reactions were carried out on a 0.2 mmol scale under the standard condition following the reaction recipes presented in Table 2. Isolated yields are given. [b]Determined by ^{1}H NMR.

amides coupled with **3a** and the corresponding compounds were generated in good yields (**5aa**−**5ka**). Amides bearing alkenyl, alkynyl, allyloxy, tetrahydro-2*H*-pyranyl, CF_3, and 2-bicyclo[2.2.1]heptan-2-yl groups were also employed to yield the desired products (**5la**−**5qa**). After this, aryl chain-substituted tertiary amides bearing MeO and halogen substituents on the aromatic rings were used for coupling with **3a** to generate the desired allenyl group-bearing amides. The α-naphthyl and β-naphthyl type amides and heterocyclic aromatic ring-substituted amides could also be smoothly tolerated in this transformation. The structure of **5xa** was confirmed by X-ray crystallographic analysis.

Different substituents on N atom were also examined (Table 3B, **5Ca**−**5Ma**). To our surprise, amide **1J** performed well with **3a** and yielded **5Ja** in good yield (47%), which gave almost a trace when it coupled with **2a**. Substrates **1L** and **1M** did not react as anticipated. Some unreacted substrates are shown in the Supporting Information.

After examining the capability of this reaction, we conducted some experiments to clarify more details of this reaction. As depicted in Scheme 2, the reaction was carried out under the

Scheme 2. Control Experiments



optimized conditions, and the desired product could be afforded in the reported yields. However, when the reaction proceeded with a nucleophile without Cs_2CO_3, no desired product was observed and substrate **1a** was detected by TLC. These results powerfully confirmed that Cs_2CO_3 plays a significant role in the generation of intermediate **B2** and performs smoothly in the next rearrangement.

In addition to the control experiments, we also conducted a ^{13}C NMR experiment to monitor the reaction process. As shown in Figure 2, at different times, we tracked signal **a**, which

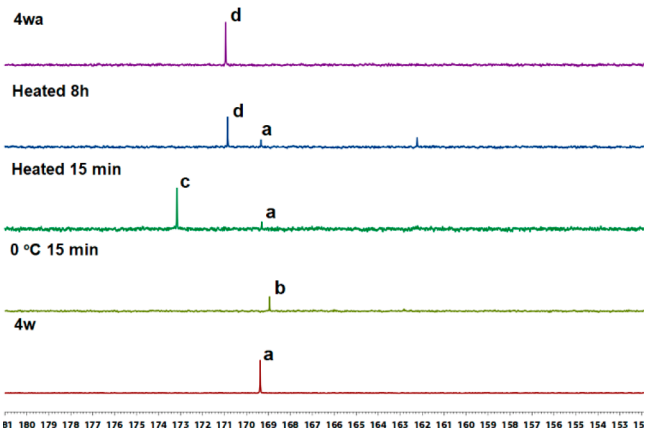


Figure 2. ^{13}C NMR studies of the reaction mechanism.

was indicated to be the carbonyl carbon of amide **4x** (Scheme 3). After the Tf_2O was added and the mixture was stirred at 0 °C for 15 min, signal **b** appeared and it was indicated as the *b*-carbon of intermediate **A**. After the mixture of the nucleophile had been added to this reaction mixture at 0 °C, the system was warmed to ambient temperature for a further 15 min. Signal **c** was observed and was supposed to be the *c*-carbon of intermediate **B1**; signal **a** was also detected at the same time.

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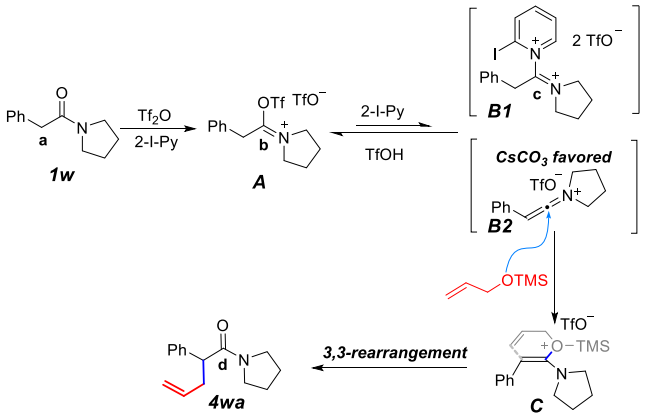
Scheme 3. Proposed Mechanism



These results told us that when the mixture was added, some of the intermediates were converted back into starting materials. After the mixture had been heated at 70 °C for 8 h, we monitored the reaction and found signal **d**, the carbonyl carbon of product **4xa** (more details in the Supporting Information).

Inspired by the control experiments mentioned above and the literature,[13d] we proposed a plausible mechanism (Scheme 3). The amide is first activated by Tf_2O to generate intermediate **A**, and **A** can be easily converted to **B1** or **B2** under the 2-iodopyridine and Cs_2CO_3 conditions. It is worth noting that Cs_2CO_3 is supposed to regulate the acidic environment, and it also favors intermediate **A** being converted into the pivotal intermediate, keteniminium ion **B2**. Then **2a** reacts with keteniminium ion **B2** and produces intermediate **C**. Finally, intermediate **C** performs a traceless [3,3]-sigmatropic rearrangement and gives the target molecule.

In summary, we developed an efficient process for installing allyl and allenyl groups at the α position of amides. The keteniminium ion was suggested as a crucial intermediate in the transformation, and an intermolecular [3,3]-sigmatropic rearrangement was performed. A large number of substrates were tolerated in this work. The mechanistic studies demonstrated the Cs_2CO_3 is an important additional base for the promotion of the generation of the keteniminium ion. More detailed mechanisms and further applications are being examined in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04300.

Experimental procedures, compound characterization, and NMR spectra (PDF)

Accession Codes

CCDC 2049406−2049407 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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