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Deoxygenative Alkynylation of Amides via C=O Bond Cleavage

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A novel deoxygenative alkynylation of amides promoted by a synergistic action of a divalent rare-earth element and a transition metal has been developed. In this method, α-alkynyl substituted amines are synthesized from unactivated amides and alkynes in a single transformation. Broad substrate scope and excellent selectivity for C=O cleavage has been demonstrated. This approach represents a general method for the construction of versatile α-alkynyl substituted amines from unactivated amide bonds.

α-Alkynyl-substituted amines, also known as propargyl-amines, are biologically active compounds that have been widely used throughout the field of chemistry, including organic synthesis, drug development and complex materials (Figure 1A).[1] Therefore, the development of synthetic methods for the assembly of α-alkynyl-substituted amines has been a topic of significant interest (Figure 1B).[2-8] The initial approach hinged upon the addition of preformed alkynyl reagents to imines, a method that involves condensation of aldehydes with primary amines to form imines followed by nucleophilic addition of alkynyl metals to produce the desired propargylamines.[3-5] However, in view of limitations of these methods and air-sensitivity of preformed alkynyl metals, a series of methods involving reacting imines directly with terminal alkynes have been developed.[6] The direct alkynylation can successfully achieve the synthesis of propargylamines; however, these reactions are less ideal from the economic standpoint, which increases the reaction cost and reduces the practicality of the reaction. A further limitation is that these methods are only applicable to primary amines. Simultaneously, one-pot transforms to synthesize propargylamines by reacting aldehydes, amines, and alkynes together have been developed.[7-8] This approach requires only one step to achieve the synthesis of α-alkynylamines and both primary and secondary amine substrates are applicable. However, this class of reactions is restricted by poor selectivity and generation of multiple byproducts. At present, there are numerous challenges posed by the synthesis of α-alkynyl substituted amines that need to be urgently addressed.

In this context, amides represent ideal substrates for organic synthesis.[9] Amides as carboxylic acid derivatives have major advantages, such as ubiquity, user- and environmentally-friendly profile and extraordinarily high stability.[10] In particular, due to amidic resonance, amide bonds exhibit approximately 40% double bond character (Figure 1C).[11-14] Therefore, amide bonds are very stable and can be readily carried over numerous steps in synthetic campaigns.[15-18] In recent years, amides have been widely used as electrophilic reagents in transition-metal-catalyzed cross-coupling reactions by N–C(O) bond cleavage.[19] In contrast, we hypothesized that propargylamines can be directly obtained from amides by the C=O bond cleavage and selective reaction with terminal alkynes. At present, there are two main methods for synthesizing α-alkynyl substituted amines using amides: (1) activating amides into iminium using reactive anhydrides, and then reacting with alkynyl-metal reagents (Figure 1D);[20-21] (2) using iridium hydrides to catalyze the reduction of amides to silyl ethers, which then react with alkynyl-lithium or alkynyl-magnesium reagents.[22] Recent research has shown that the alkynyl-metal reagents used in the second step can be substituted by terminal alkynes to achieve this reaction under copper-catalyzed conditions (Figure 1E).[23] At present, both approaches require two steps to achieve the synthesis of propargyl-amines and require the use of air-sensitive alkyne-metal reagents.[24] Among the challenges that need to be solved for the direct conversion of amides to propargyl-amines in a selective and predictable fashion are (1) one-step method to convert amides to α-alkynyl substituted amines, (2) the use readily available terminal alkynes, and (3) the development of new mechanistic pathways that enable synergistic combination of C=O bond cleavage with productive C–C bond forming reactions.

The pioneering study of samarium diiodide/samarium-mediated deoxygenative coupling of amides was achieved by Ogawa and Sonoda group, and the initial work in this field focused on achieving SmI_2/Sm-mediated deoxygenative self-dimerization of amides.[25] In 2021, the Wang research group achieved the first SmI_2/Sm-mediated deoxygenative arylation reaction of amides.[26] Subsequently, a series of deoxygenative functionalization of amides induced by SmI_2/Sm were developed.[27-32] In 1997, Ogawa group reported a single example of SmI_2/Sm-mediated deoxygenative alkynylation of amides using HMPA.[33] We attempted the deoxygenative alkynylation of other amides and alkynes under these conditions, but the results showed that other types of amides and alkynes are not applicable to this SmI_2 system.

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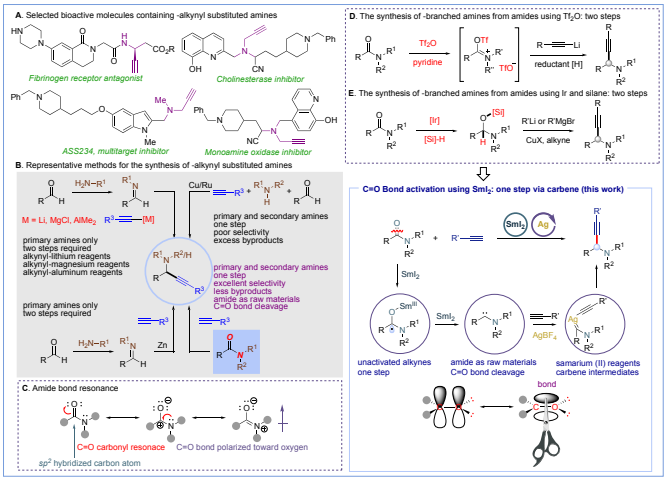


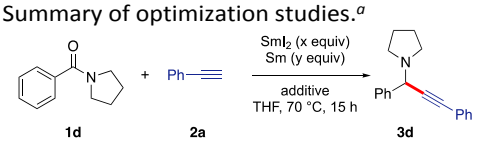
Figure 1. Context of this study and the synthesis of α-alkynyl substituted amines.

Therefore, the development of general SmI_2/Sm-mediated deoxygenative alkynylation method of amides that applicable to different amides and alkyne substrates is highly desirable.

In this manuscript, we report a novel deoxygenative alkynylation of amides promoted by a synergistic action of a divalent rare-earth element and a transition metal. There are several noteworthy features of this transformation: (1) α-alkynyl substituted amines are synthesized directly from unactivated amides and alkynes in a single transformation; (2) the method is characterized by broad substrate scope and excellent selectivity for C=O cleavage; (3) the reaction mechanism involves carbene intermediates;[34] (4) the method enables simultaneous cleavage of a π bond and the formation of a σ bond. This novel approach represents a general method for the construction of versatile α-alkynyl substituted amines from unactivated amide bonds.

The proposed deoxygenative alkynylation of amides was first investigated using SmI_2 as an electron donor in the presence of phenyl(pyrrolidin-1-yl)methanone (**1d**) and phenylacetylene (**2a**) as model substrates (Table 1). We found that this reaction gave trace quantity of the desired product using samarium diiodide and samarium (entry 1). This reaction presumably proceeds by the samarium carbene C–H insertion into the alkyne.[25] Next, we extensively screened different additives to enhance the efficiency of the reaction system. We determined that the addition of rhodium, copper, silver and cobalt salts promoted a significant increase in the reaction yield, presumably though the formation of more reactive carbene intermediates (entries 2-5). Interestingly, the use of palladium, nickel, and iron salts was ineffective (entries 6-8). Additional optimization using copper salts revealed that the yield could be modestly improved by adjusting the reagent stoichiometry (entries 9-12). We also extensively tested the effect of silver salts and found that this catalyst gave the highest reaction yield (entries 13-15). Control experiments revealed that the reaction does not occur in the absence of samarium diiodide (entry 16). Furthermore, only trace product was obtained in the absence of samarium metal (entry 17), this demonstrating that both samarium diiodide and samarium are required to generate the carbene intermediate by electron transfer to the amide C=O bond. Importantly, the collapse of the carbinolamine intermediate N–C(O–) has not been observed under the reaction conditions, indicating high specificity of the reagent system for the selective C=O cleavage.

Table 1. Summary of optimization studies.[a]



1d 2a 3d

entry	2a (equiv)	SmI_2 (equiv)	Sm (equiv)	add (mol%)	yield (%)
1	2.0	2.2	2.0		13
2	2.0	2.2	2.0	$Rh(PPh_3)_3Cl$ (2)	41
3	2.0	2.2	2.0	CuI (10)	37
4	2.0	2.2	2.0	$AgBF_4$ (10)	36
5	2.0	2.2	2.0	CoI_2 (10)	32
6	2.0	2.2	2.0	$Pd(PPh_3)_2Cl_2$ (5)	<5
7	2.0	2.2	2.0	$Ni(PCy_3)_2Cl_2$ (5)	<5
8	2.0	2.2	2.0	$FeCl_3$ (10)	<5
9	3.0	2.2	2.0	CuI (10)	33
10	4.0	2.2	2.0	CuI (10)	45
11	5.0	2.2	2.0	CuI (10)	38
12	4.0	2.2	2.0	CuI (10)	53
13	4.0	2.2	2.0	$AgBF_4$ (20)	69
14	4.0	2.2	2.0	$AgBF_4$ (30)	80
15	4.0	2.2	2.0	$AgBF_4$ (40)	60
16	4.0		2.0	$AgBF_4$ (30)	<5
17	4.0	2.2		$AgBF_4$ (30)	14

[a]Conditions: **1d** (1.0 equiv), **2a** (2.0 equiv), SmI_2 (2.2 equiv), Sm (2.0 equiv), additive, THF, 70 ℃, 15 h.

With the optimized conditions in hand, the substrate scope of this deoxygenative alkynylation of amides was next investigated (Scheme 1A). The scope of amides was first explored. To our delight, we found that the reaction is broadly compatible with various classes of acyclic amides, such as *N*,*N*-dimethyl (**3a**), *N*,*N*-dipropyl (**3b**), and *N*,*N*-dibutyl amides (**3c**). Furthermore, cyclic amides, such as *N*-pyrrolidinyl (**3d**), *N*-piperidinyl (**3e**), *N*-azepanyl (**3f**) and *N*-morpholinyl (**3g**), could be well tolerated by this method. Notably, amides bearing electron-neutral (**3h–3k**), electron-rich (**3l**), and electron-deficient (**3m**) substituents could be converted to the desired α-alkynyl substituted amines. In addition, amides with substituents at *meta*-position (**3n–3o**) and 3,4-disubstitution (**3p–3q**) were also well-compatible with this reaction. Furthermore, even challenging sterically-hindered amides (**3r–3t**) could also be employed to deliver the desired amine products. In addition, heterocyclic amides as illustrated by 2- and 3-thienyl substitution could also be well-tolerated by this strategy (**3u–3v**). Next, the substrate scope of alkynes was explored (Scheme 1B). Pleasingly, phenylacetylenes bearing electron-neutral (**3aa–3ac**), electron-donating (**3ad**) and electron-withdrawing (**3ae–3af**) substituents were found to be well-compatible with this approach. Moreover, substrates with sensitive halide groups (**3ae–3ag**) could also be well-tolerated by this method. Furthermore, even sterically-hindered alkynes (**3ah-3aj**), and heterocyclic alkynes (**3ak–3al**) could be successfully employed in this approach.

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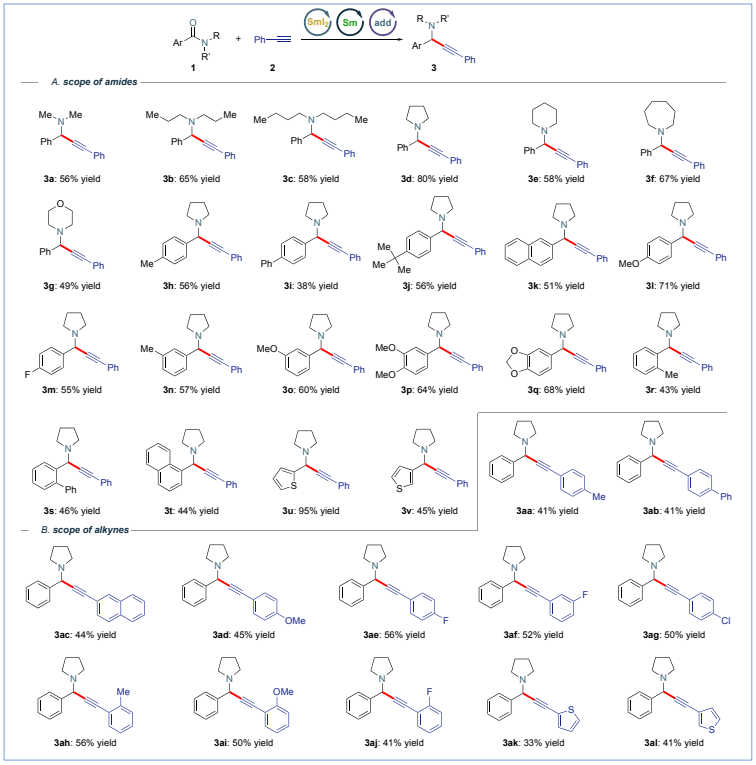
Scheme 1. Substrate Scope of Deoxygenative Alkynylation of Amides via C=O Bond Cleavage.[a]



[a]Conditions: amide (1.0 equiv), alkyne (4.0 equiv), SmI_2 (2.2 equiv), Sm (2.0 equiv), additive = $AgBF_4$ (30 mol%), CuI (40 mol%), $Rh(PPh_3)_3Cl$ (2 mol%) or $NaBF_4$ (10 mol%), THF, 70 °C, 15 h. See SI for details.

In order to explore the practicality of this method, a series of experiments were performed (Scheme 2A–2B). Firstly, silylated acetylenes were tested (**2n**), and the experimental results showed that the versatile Si handle is well-tolerated in this reaction. Furthermore, the reaction was directly applied to amide pharmaceuticals (Scheme 2B). The value of this methodology stems from the fact that the amide bond is the most common functional group in drug discovery and development of new therapeutics.[9] Thus, the direct deoxygenative alkynylation of CX-546 (antipsychotic) (**3ao**), trimetozine (sedative) (**3ap**), and cinnarizine (antihistamine) (**3aq**) can be readily achieved without modification of the reaction conditions. While the yields of the alkynylation of these functionalized drugs are modest, the results clearly demonstrate the potential of this methodology to convert amides to valuable α-alkynyl substituted amines.

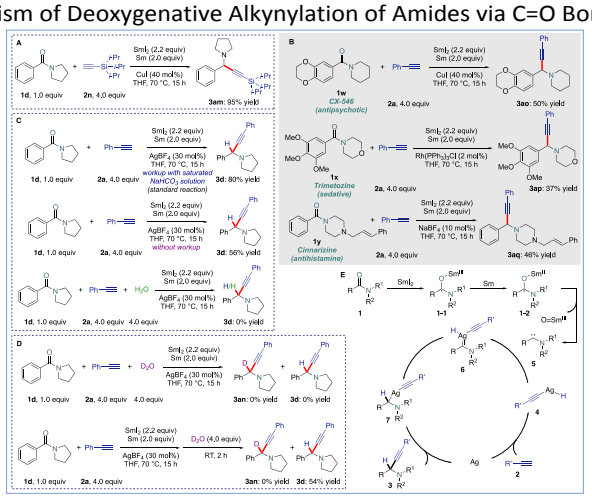
Preliminary studies were conducted to gain insight into the reaction selectivity (Scheme 2C-2D). As shown, an 80% yield could be received under standard conditions. Notably, 56% yield was achieved under the conditions without workup, indicating that the key proton attached to the tertiary carbon in the desired product is derived from terminal alkynes rather than post-reaction work-up. Importantly, the reaction cannot occur if a small amount of water or D_2O is added to the system before the reaction, which further confirms that (1) the proton attached to the tertiary carbon of the product does not originate from the trace water of starting materials or solvent; (2) water is not compatible with the reaction. When the reaction was quenched by D_2O, we obtained 54% yield of the desired product with no deuterium incorporation, demonstrating that the proton attached to the tertiary carbon does not originate from the aqueous solution during workup.

A tentative mechanism is shown on Scheme 2D. First, reductive activation of the amide C=O group by samarium diiodide generates amino-ketyl radical **1–1**, which is then further reduced to carbinolamine intermediate **1–2** by samarium. Subsequent elimination generates $O=Sm^{III}$ and samarium carbene intermediate **5**. Simultaneously, silver reacts with terminal alkyne **2** to form alkynyl-silver **4**, which then reacts with samarium carbene to form silver-carbene **6**. The proton migratory to generate intermediate **7**. Finally, the desired α-alkynylamine product was received via reductive elimination.

Conclusions

In conclusion, we have reported a novel deoxygenative reductive alkynylation of amides to directly generate α-alkynyl substituted amines. This reaction is promoted by a combination of a divalent rare-earth element and a transition metal. In this approach, the desired α-alkynyl substituted amines are prepared in a single step using unactivated amides and terminal alkynes. Broad substrate scope and high selectivity for the C=O cleavage has been demonstrated. We expect that this method for synthesizing valuable α-alkynyl amines will find wide application in engaging inert amide bonds by simultaneous activation by two distinct metals in both academic and industrial arenas.

Scheme 2. Applications and Mechanism of Deoxygenative Alkynylation of Amides via C=O Bond Cleavage.



Data Availability Statement

The data underlying this study are available in the published article and its Electronic Supplementary Information (ESI).

Conflicts of Interest Statement

There are no conflicts to declare.

Acknowledgements

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