Amide Synthesis Hot Paper

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Amide Synthesis by Nucleophilic Attack of Vinyl Azides**

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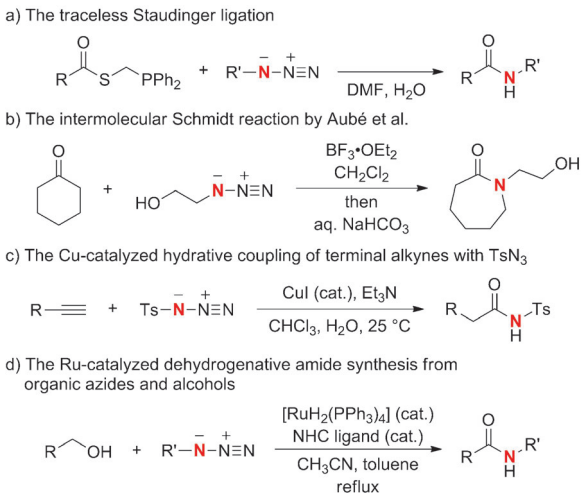
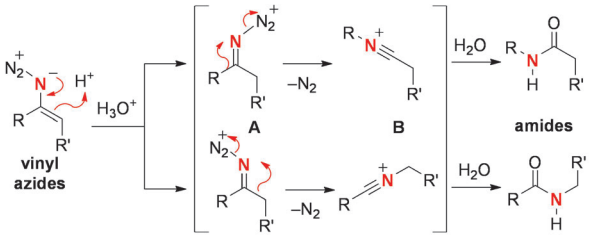
Abstract: *A method for the synthesis of amide-containing molecules was developed using vinyl azides as an enamine-type nucleophile towards carbon electrophiles, such as imines, aldehydes, and carbocations that were generated from alcohols in the presence of $BF_3{\cdot}OEt_2$. After nucleophilic attack of the vinyl azide, a substituent of the resulting iminodiazonium ion intermediate migrates to form a nitrilium ion, which is hydrolyzed to afford the corresponding amide.*

Organic molecules with amide linkages are prevalent not only in peptides and proteins, but also in pharmaceuticals, agrochemicals, and functional materials.[1] Therefore, many chemical approaches have been developed to access amide-containing molecules in atom- and step-economical manners.[2] Among the various nitrogen sources that are utilized for amide synthesis, organic azides have shown a wide spectrum of chemical reactivity with different types of reaction modes (Scheme 1). For example, the traceless Staudinger ligation is a powerful method to construct an amide bond using organic azides and phosphinothioesters and has been successfully applied for the synthesis of biofunctional peptides (Scheme 1 a).[3–5] Aubé and co-workers developed Lewis acid mediated reactions of ketones (mainly cyclic ketones) with 2-azidoethanols or 3-azidopropanols for the synthesis of amides (mainly lactams) by the Schmidt reaction through the in situ formation of hemiketal intermediates (Scheme 1 b).[6–9] Chang et al. developed an amide synthesis that proceeds through the copper-catalyzed hydrative coupling of terminal alkynes and sulfonyl azides in the presence of water through an azide–alkyne [3+2] cycloaddition (Scheme 1 c).[10,11] A dehydrogenative amide synthesis from organic azides and alcohols that is catalyzed by a ruthenium N-heterocyclic carbene (NHC) catalyst system was elegantly designed by Hong and co-workers.[12]



Scheme 1. Amide synthesis with organic azides.

Vinyl azides have served as versatile synthons for the synthesis of various nitrogen-containing molecules, in particular azaheterocycles.[13] Our continuous interest in the potential chemical reactivity of vinyl azides[14] motivated us to use them as enamine-type nucleophiles. The groups of Hassner and Moore reported that protonation of vinyl azides by aqueous acids generates iminodiazonium ion intermediates **A**, which further undergo a Schmidt-type 1,2-migration to form nitrilium ions **B** with elimination of dinitrogen (N_2; Scheme 2).[15] Hydrolysis of the nitrilium ions produces the corresponding secondary amides.[16] As two isomers of iminodiazonium ions (the *E* and *Z* isomers) might be formed, and the substituent that is *anti* to the $N{-}N_2^+$ bond should undergo 1,2-migration,[17] the reactions could potentially afford two constitutional isomers; their ratio might depend on the reaction conditions and the migratory aptitude of the substituents.



Scheme 2. Protonation of vinyl azides for the formation of amides.

Therefore, we wondered whether we might be able to use carbon electrophiles (E^+) for the reaction with vinyl azides, in which a C–C bond could be formed by nucleophilic attack of a vinyl azide to the electrophile to generate an iminodiazonium ion intermediate **A** (Scheme 3). Subsequent Schmidt-type rearrangement might form nitrilium ion **B**, hydrolysis of which could produce the amide linkage. In this context, we

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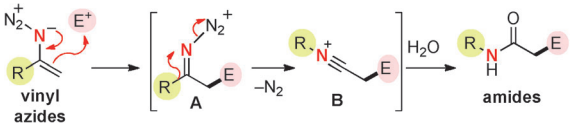
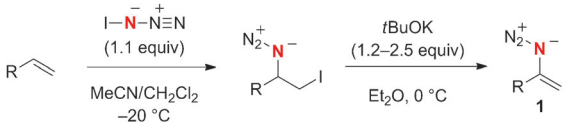


Scheme 3. Reactions of vinyl azides with carbon electrophiles.

would strive to design a reaction system and chose reaction conditions that enable the selective formation of a single amide product with predictable migration selectivity. Herein, we report the $BF_3{\cdot}OEt_2$ mediated reaction of vinyl azides with a series of carbon electrophiles, which enables the efficient synthesis of amide-containing molecules.

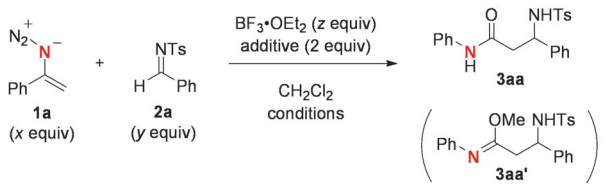
Vinyl azides **1** were readily prepared from the corresponding alkenes by following Hassner's method, which entails the addition of IN_3 followed by elimination of HI in the presence of *t*BuOK (Scheme 4; see the Supporting Information for details).[18]



Scheme 4. Preparation of vinyl azides **1**.

Based on the hypothesis shown in Scheme 3, we commenced our study with vinyl azide **1a** and *N*-tosyl benzaldimine **2a** in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid promoter (Table 1). Treatment of a mixture of vinyl azide **1a** and imine

Table 1: Optimization of the reaction conditions.[a]

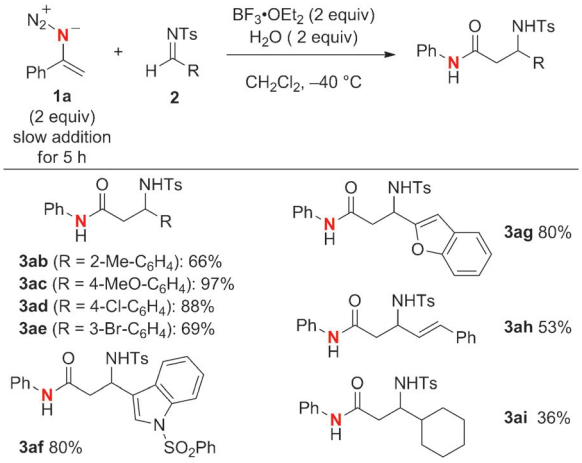


Entry	*x*	*y*	*z*	Additive	*T* [°C]	*t* [h]	Yield[b] [%]
1	1	1.2	3	–	0→RT	0.2	12
2	1	1.2	2	HFIP	0→RT	0.2	22
3	1	1.2	2	HFIP	−40	0.2	49
4	1	1.2	2	HFIP	−40	4[c]	68
5	1	1.2	2	AcOH	−40	5[c]	81
6	1	1.2	2	TFA	−40	5[c]	65
7	1	1.2	2	H_2O	−40	5[c]	71
8	1	1.2	2	MeOH	−40	5[c]	34[d]
9[e]	1.5	1	2	H_2O	−40	5[c]	95
10[e]	1.5	1	2	AcOH	−40	5[c]	95
11[e]	2	1	2	H_2O	−40	5[c]	96

[a] Unless otherwise noted, the reactions were carried out with vinyl azide **1a** (0.3 mmol) in CH_2Cl_2 (0.1 M). [b] Yields of isolated products. [c] A solution of vinyl azide **1a** (in 1.5 mL of CH_2Cl_2) was slowly added using a syringe pump for the indicated time, and the reactions were quenched upon completion of the addition. [d] Yield of isolated imidate **3aa′**. [e] The yield of **3aa** is based on imine **2a** (0.3 mmol). TFA = trifluoroacetic acid.

2a (1.2 equiv) with $BF_3{\cdot}OEt_2$ (3 equiv) in CH_2Cl_2 at 0 °C to room temperature resulted in rapid consumption of **1a** within ten minutes (entry 1); the desired β-amino amide **3aa** could be isolated in 12% yield along with unidentified complex mixtures that included unreacted imine **2a**. When the reaction was carried out in the presence of hexafluoroisopropanol (HFIP, 2 equiv) as an additive at a lower reaction temperature (−40 °C), the yield of **3aa** slightly improved to 49% (entry 3). The poor yields of the target product **3aa** are probably due to decomposition of vinyl azide **1a** by the reaction with $BF_3{\cdot}OEt_2$. We thus examined the slow addition of a solution of vinyl azide **1a** (for 4–5 h with a syringe pump) to a mixture of imine **2a** (1.2 equiv), HFIP (2 equiv), and $BF_3{\cdot}OEt_2$ (2 equiv; entry 4). As expected, the yield of **3aa** was further improved to 68%. Screening of the additive revealed that AcOH and H_2O worked more efficiently, giving **3aa** in 81% and 71% yield, respectively (entries 5–7). These additives probably play a role in trapping the highly reactive nitrilium ion intermediate immediately after its formation. The reaction in the presence of MeOH as an additive afforded imidate **3aa′**, which confirms the formation of the nitrilium ion **B** (entry 8). We found that the addition of 1.5–2 equivalents of vinyl azide **1a** to imine **2a** in the presence of H_2O or AcOH (2 equiv) could further improve the yield of **3aa** (entries 9–11).

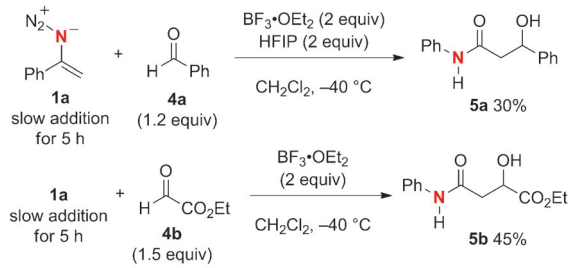
With the established procedure in hand (Table 1, entry 11), the generality of this transformation for the synthesis of β-amino amides was next explored using a variety of *N*-tosyl-substituted aldimines **2b–2i** and vinyl azide **1a** (Scheme 5).[19] Various aromatic aldimines **2b–2g**, including



Scheme 5. Scope of *N*-tosyl aldimines **2**.

those with indolyl or benzofuranyl moieties, could be utilized to give the corresponding β-amino amides **3ab–3ag** in good to excellent yields. The reaction with α,β-unsaturated aldimine **2h** resulted in the 1,2-addition product **3ah** in 53% yield. Likewise, the aliphatic aldimine **2i** was reacted to afford the desired amide **3ai**, albeit in lower yield (36%).

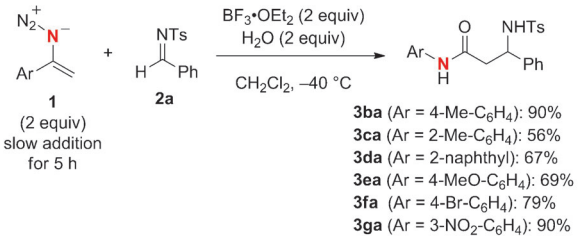
We next examined the use of aldehydes **4** as electrophiles instead of *N*-tosyl aldimine **2** for the synthesis of β-hydroxy amides **5**, which turned out to be rather challenging



Scheme 6. Reactions with aldehydes **4a** and **4b**.

(Scheme 6). The reactions of vinyl azide **1a** with benzaldehyde (**4a**) and ethyl glyoxal (**4b**) gave the corresponding β-hydroxy amides **5a** and **5b** in only 30% and 45% yield, respectively, under the reaction conditions stated above, although the reaction conditions were re-examined to improve the yields (see the Supporting Information).

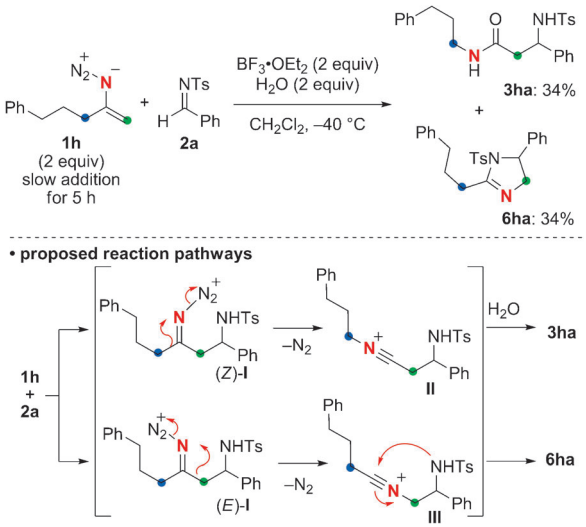
We then turned our attention towards the scope of vinyl azides **1** in the reaction with *N*-tosyl benzaldimine **2a** (Scheme 7–9). When varying the aryl group on the α-aryl vinyl azide **1** (Scheme 7), we found that both electron-rich and -deficient aryl groups were tolerated by the present method and delivered the corresponding products in good yields, whereas the reaction with a sterically hindered 2-methylphenyl group resulted in a lower yield (56%) of amide product **3ca**.



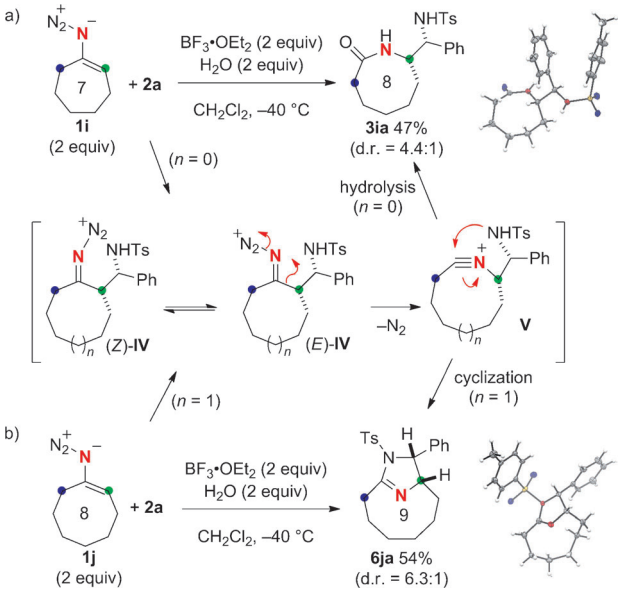
Scheme 7. Scope of α-aryl vinyl azides **1**.

The reaction of α-alkyl-substituted vinyl azide **1h** with imine **2a** provided a 1:1 mixture of amide **3ha** and dihydroimidazole **6ha** in a combined yield of 68% (Scheme 8). This result indicated that the addition of vinyl azide **1h** to imine **2a** would generate a 1:1 mixture of the iminodiazonium ions (*Z*)-**I** and (*E*)-**I**, which bear two different secondary alkyl substituents (marked in blue and green). For (*Z*)-**I**, migration of the substituent leads to nitrilium ion **II**, hydrolysis of which then delivers amide **3ha**. On the other hand, nitrilium ion **III**, which is derived from (*E*)-**I**, undergoes cyclization to afford dihydroimidazole **6ha**.

Interestingly, the reaction of 1-azido-cycloheptene (**1i**) with imine **2a** under the standard reaction conditions gave the ring-expanded eight-membered lactam **3ia** in 47% yield (d.r. = 4.4:1, major isomer shown; Scheme 9a). On the other hand, when 1-azido-cyclooctene (**1j**) was reacted with **2a**, the corresponding lactam was not observed, while bicyclic



Scheme 8. Reaction with α-alkyl-substituted vinyl azide **1h**.

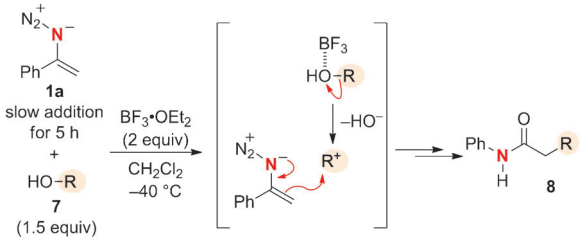


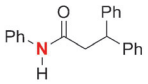
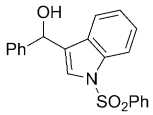
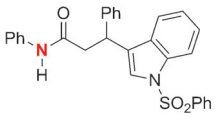
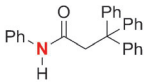
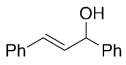
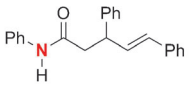
Scheme 9. Reactions of cyclic vinyl azides **1i** and **1j**.

dihydroimidazole **6ja** was obtained in 52% yield (d.r. = 6.3:1, major isomer shown; Scheme 9b). The stereochemistry of the major isomers of **3ia** and **6ja** was determined as *syn* by X-ray crystallography (see the Supporting Information for a preliminary discussion on the diastereoselectivity). These results suggest that the putative iminodiazonium ion intermediate (*E*)-**IV** exclusively undergoes 1,2-migration of the tertiary carbon atom (marked in green) to form nitrilium ion **V**; this process is followed either by hydrolysis to yield lactam **3ia** or by intramolecular cyclization to afford **6ja**. All of these observations implicate that the *E*- and *Z*-configured iminodiazonium ion intermediates may be in equilibrium under the present reaction conditions,[20] which enables the selective rearrangement of the substituent with the higher migratory aptitude (i.e., aryl > alkyl, tertiary alkyl > secondary alkyl).

Taking advantage of the present amide synthesis by nucleophilic attack of vinyl azides **1**, which proceeds under acidic conditions, we finally explored the functionalization of carbocations that are derived from alcohols (Table 2).[21] As expected, the reactions of vinyl azide **1a** with diarylmethanols

Table 2: Reactions with alcohols **7**.



Alcohol	7	Amide	8	Yield [%]
	**7a**		**8a**	65
	**7b**		**8b**	83
	**7c**		**8c**	60
	**7d**		**8d**	53

7a and **7b** (1.5 equiv) in the presence of $BF_3{\cdot}OEt_2$ (2 equiv) resulted in the formation of amides **8a** and **8b** in 65% and 83% yield, respectively. In these processes, BF_3 mediated dissociation of the hydroxide ion from the alcohol first generates the corresponding carbocation, which is subsequently trapped by nucleophilic attack of vinyl azide **1a**. Similarly, triphenylmethanol (**7c**) and 2,3-diphenyl-2-propen-1-ol (**7d**) could be employed as sources for the trityl and π-allyl cations, respectively, giving the corresponding amides **8c** and **8d** in good to moderate yields. These reactions do not require the addition of H_2O.

We anticipate that the present method, which employs vinyl azides as enamine-type nucleophiles, may be readily adopted for the synthesis of biologically and medicinally important amide-containing molecules. Further investigations to develop catalytic asymmetric variants of this method with chiral Lewis acids are currently underway.

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