<table>
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<tr>
<th><strong>Title</strong></th>
<th>Tf 2 NH-catalyzed amide synthesis from vinyl azides and alcohols (Main article)</th>
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<tr>
<td><strong>Author(s)</strong></td>
<td>Zhang, Feng-Lian; Zhu, Xu; Chiba, Shunsuke</td>
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ABSTRACT: Triflimide (Tf$_2$NH) specifically catalyzed reactions of alcohols and vinyl azides, enabling efficient construction of amides with C-C bond formation through nucleophilic attack of vinyl azides onto the putative carbocation intermediates derived from alcohols.

The amide functionality is ubiquitous in various functional molecules of biological, pharmaceutical/medicinal, and materials importance.¹ It also serves as a versatile synthon for a variety of molecular transformations, especially for synthesis of nitrogen-containing molecules. Therefore, installation of the amide moiety onto organic frameworks is one of the most valuable processes in synthetic chemistry.² Nucleophilic attack of amide enolates onto suitable carbon electrophiles could be one of the most-step economical ways to introduce an acetamide unit through C-C bond formation (Scheme 1). Recent advancement in this field involves Kobayashi’s direct aldol/Mannich reactions of (N-Boc)acylanisidides with barium phenoxide as a catalyst (Scheme 1-a)³ as well as direct Mannich reactions of un-activated tertiary amides catalyzed by trialkylsilyl triflate (Scheme 1-b).⁴ Scheidt recently reported base-mediated amide enolate addition to acylsilanes, which subsequently induces the Brook rearrangement to form the corresponding carbanions, enabling efficient construction of tertiary β-hydroxy amides with alkyl halides (Scheme 1-c).⁵

As an alternative amide enolate equivalent, we have recently utilized vinyl azides. Nucleophilic attack of vinyl azides onto several carbon electrophiles such as N-Ts imines, aldehydes, and carbocations derived from alcohols in the presence of BF$_3$•OEt$_2$ forms iminodiazonium ions A with C-C bond formation (Scheme 2).⁶,⁷ Subsequent substituent migration generates nitrilium ions B, which are finally hydrolyzed to give amides. However, the process needs to use excess amounts (2 equivalents) of BF$_3$•OEt$_2$, that causes another procedure requirement of slow addition of vinyl azides to the solution to prevent decomposition of vinyl azides.⁸ Therefore, we have strived to develop a catalytic process of the acetamide installation using vinyl azides, that could be implemented under...
milder reaction conditions with easy and simple operation. Herein, we report realization of the catalytic acetamide incorporation with vinyl azides using triflimide (Tf$_2$NH) as the catalyst for the reactions with a series of alcohols as a carboxylation precursor. 

We became interested in construction of 3-indolyloxindole skeletons via the reaction of 3-hydroxy-3-indolyloxindoles with vinyl azides, as these scaffolds are prevalent in biologically active alkaloids. The recent seminal reports by Gong, Guo, Peng, and Ma demonstrated that 3-hydroxy-3-indolyloxindoles could be activated by Brønsted acid catalysts to generate the corresponding carboxylation equivalents, which are trapped by ketone enolate-type carbon nucleophiles. Inspired by these findings, we surmised that direct installation of acetamide unit using vinyl azides is enabled by Brønsted acid catalysts. We commenced our study to screen Brønsted acids in the reactions of 3-hydroxy-3-indolyloxindole 1a and vinyl azide 2a to target amide 3aa (Table 1). The reactions with TsOH•H$_2$O, BINOL-linked phosphoric acid, and (PhSO$_2$)$_2$NH as the catalyst (10 mol %) resulted in the C-C bond formation but afforded ketone 4aa in moderate yields as the major product (runs 1-3), in which almost no formation of desired amide 3aa was observed. The results indicated that these acids are incapable of enabling migration of the phenyl group from the iminodiazonium intermediate. On the other hand, use of CF$_3$SO$_2$H rendered the process very rapid, consuming 1a within 5 min to give 1:1 mixture of amide 3aa and ketone 4aa (run 4). We envisaged that strength of the acidity might be the key to enable selective formation of amide 3aa. Further screening revealed that the reaction with triflimide (Tf$_2$NH) (10 mol %) provided much better selectivity to afford amide 3aa in 75% yield and ketone 4aa in 15% yield (run 5). Slightly higher reaction temperature enhanced the selectivity further (runs 6 and 7), giving amide 3aa as a sole product (86% yield) when the reaction was conducted in 1,2-dichloroethane (DCE) at 40 °C (run 7).

Table 1. Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>run</th>
<th>acid catalysts</th>
<th>conditions</th>
<th>time</th>
<th>3aa [%]</th>
<th>4aa [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsOH•H$_2$O</td>
<td>CH$_2$Cl$_2$, rt</td>
<td>0.5 h</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>BINOL-P(O)OH$^a$</td>
<td>CH$_2$Cl$_2$, rt</td>
<td>2 h</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>(PhSO$_2$)$_2$NH</td>
<td>CH$_2$Cl$_2$, rt</td>
<td>14 h</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>CF$_3$SO$_2$H</td>
<td>CH$_2$Cl$_2$, rt</td>
<td>5 min</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>(CF$_3$SO$_2$)$_2$NH</td>
<td>CH$_2$Cl$_2$, rt</td>
<td>20 min</td>
<td>75</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>(CF$_3$SO$_2$)$_2$NH</td>
<td>CH$_2$Cl$_2$, reflux</td>
<td>10 min</td>
<td>80 (78$^c$)</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>(CF$_3$SO$_2$)$_2$NH</td>
<td>DCE, 40 °C</td>
<td>5 min</td>
<td>88 (86$^c$)</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ All the reactions were carried out using 0.3 mmol of 1a in the presence of 10 mol % of acid catalysts in solvent (0.1 M). $^b$ $^1$H NMR yields. $^c$ Isolated yields. $^d$ (±)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate.

With the optimized reaction conditions in hand, we next investigated the substrate scope (Scheme 3). By varying the substituent R$^1$ of vinyl azides 2, a series of aryl groups could be incorporated in the amide formation generally in good yields (for 3ab-3af), while the reactions with methoxyphenyl-substituted vinyl azides 2b and 2c needed 30 mol % of Tf$_2$NH to complete the processes. The reaction with α-alkyl-substituted vinyl azide 2g also required 30 mol % of Tf$_2$NH to give amide product 3ag in 54% yield. In this case, the putative iminodiazonium ion possesses two different secondary alkyl substituents, while only formation of 3ag via migration of the phenethyl group was observed probably because of bulkiness of the 3-indolyloxindole moiety in another secondary alkyl group prevents its migration. The reaction with β-methyl substituted vinyl azide 1h (R$^1$ = Ph, R$^2$ = Me) proceeded in diastereoselective manner, giving 3ah in 78% yield with 3:1 dr ratio. As the substituents R$^1$ and R$^2$ on the nitrogens of 3-hydroxy-3-indolyloxindoles 1, not only benzyl but also phenyl (for 3a), hydrogen (for 3c), and methyl groups (for 3db) could be installed. Amide 3db is the key intermediate in synthesis of folicanthine by Gong, in which the 4-methoxy-
Unless otherwise noted, the reactions were conducted using alcohols 1 (0.20-0.34 mmol) with vinyl azides 2 (1.2 equiv) in the presence of Tf₂NH (10 mol %) in DCE (3 mL) under a N₂ atmosphere. See the Supporting Information for more details.

Isolated yields were recorded above.

Structure of the major isomer was described, which was determined by X-ray crystallographic analysis. See the Supporting Information.

The present catalytic amide synthesis with vinyl azides could be successfully applied for other types of benzylic (for 6a-6c), allylic (for 6d), and propargylic alcohols (for 6e), providing the corresponding amide products 7 of synthetic and medicinal relevance (Scheme 5). For example, 2-(9H-xanthenyl)acetamide 7c functions as an acyl-CoA cholesterol acyltransferase (ACAT) inhibitor for treatment of atherosclerosis. β-Alkynyl-carboxamide 7e is served as a useful synth for construction of pyrrolidone scaffolds.

Scheme 4. Construction of Pyrrolindolinone Structures

$^a$ Unless otherwise noted, the reactions were conducted using amides 3 in THF (3 mL) under a N₂ atmosphere. See the Supporting Information for more details. $^b$ Isolated yields were recorded above. $^c$ Structure of the major isomer was described, which was determined by X-ray crystallographic analysis. See the Supporting Information.

All the reactions were conducted using 0.08-0.1 mmol of amides 3 in THF (3 mL) under a N₂ atmosphere. See the Supporting Information for more details. $^b$ Isolated yields were recorded above. $^c$ Structure of the major isomer was described, which was determined by X-ray crystallographic analysis. See the Supporting Information.

PMP = 4-methoxyphenyl.

Scheme 5. Amide Synthesis from Alcohols 6 with Vinyl Azide 2a.
In summary, we have developed Tf$_2$NH-catalyzed reactions of alcohols with vinyl azides, enabling a straightforward access of synthetically and medicinally useful amide derivatives. Further upgrading of this catalytic method to the asymmetric variant as well as application of Tf$_2$NH to other types of catalytic transformations is now under way in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization of new compounds, and CIF data of 3ah. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

† F.-L. Z. and X. Z. contributed equally to this work.

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### REFERENCES


(12) The reactions in entries 1-4 formed acetophenone and acetaldehyde by the reactions of vinyl azide 2a with the acid catalysts. See Table S1 in the Supporting Information for more details.


(15) Origin of the diastereoselectivity was discussed in the Supporting Information.


(18) Tellitu, I.; Serna, S.; Domínguez, E. Arkivoc 2010, iii, 7.