

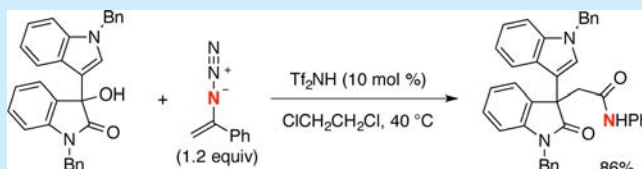
Tf₂NH-Catalyzed Amide Synthesis from Vinyl Azides and Alcohols

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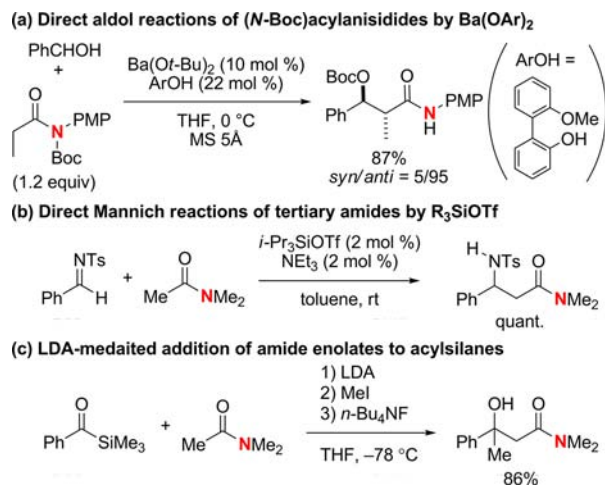
S Supporting Information

ABSTRACT: Triflimide (Tf₂NH) 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 are described.



The amide functionality is ubiquitous in various functional molecules of biological, pharmaceutical/medicinal, and materials importance.¹ Amides also serve 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).

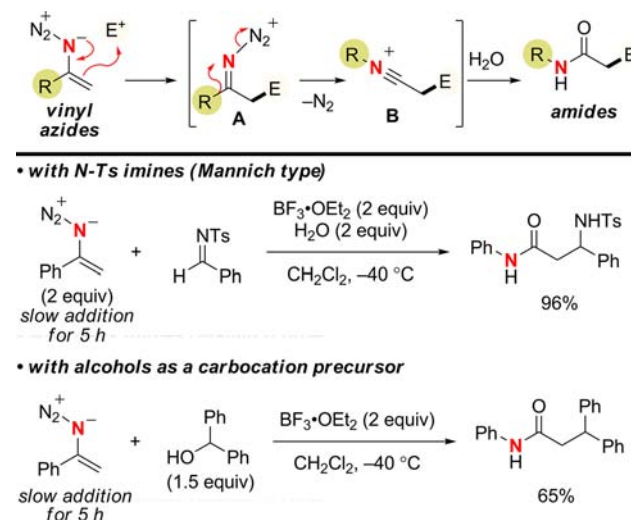
Scheme 1. Reactions of Amide Enolates



Recent advancement in this field involves Kobayashi's direct aldol/Mannich reactions of (*N*-Boc)acylanisidides with barium phenoxide as a catalyst (Scheme 1a)³ as well as direct Mannich reactions of unactivated tertiary amides catalyzed by trialkylsilyl triflate (Scheme 1b).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 1c).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*-*T*s imines, aldehydes, and carbocations derived from alcohols in the presence of BF₃·OEt₂ forms iminodiazonium ions **A** with C–C bond formation (Scheme 2).^{6,7} Subsequent substituent migration generates

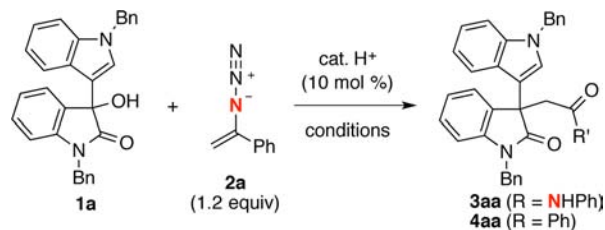
Scheme 2. Amide Synthesis by Nucleophilic Attack of Vinyl Azides



nitrilium ions **B**, which are finally hydrolyzed to give amides. However, the process needs to use excess amounts (2 equiv) of BF₃·OEt₂, that causes another procedure requirement of a 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

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Table 1. Optimization of the Reaction Conditions^a

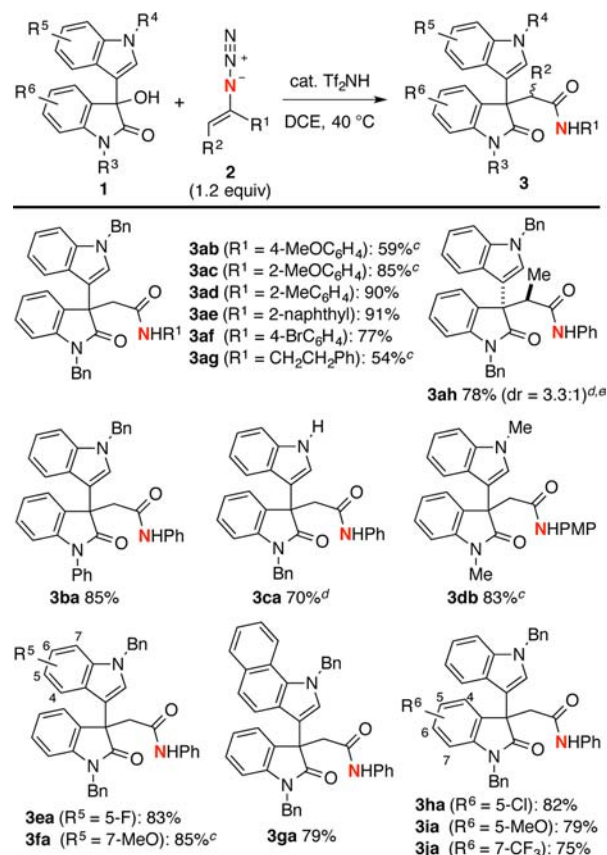
run	acid catalysts	conditions	time	3aa [%] ^b	4aa [%] ^b
1	TsOH·H ₂ O	CH ₂ Cl ₂ , rt	0.5 h	0	51
2	BINOL-P(O)OH ^d	CH ₂ Cl ₂ , rt	2 h	0	43
3	(PhSO ₂) ₂ NH	CH ₂ Cl ₂ , rt	14 h	4	28
4	CF ₃ SO ₃ H	CH ₂ Cl ₂ , rt	5 min	44	41
5	(CF ₃ SO ₂) ₂ NH	CH ₂ Cl ₂ , rt	20 min	75	15
6	(CF ₃ SO ₂) ₂ NH	CH ₂ Cl ₂ , reflux	10 min	80 (78) ^c	trace
7	(CF ₃ SO ₂) ₂ NH	DCE, 40 °C	5 min	88 (86) ^c	0

^aAll 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). ^b¹H NMR yields. ^cIsolated yields. ^d(±)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate.

realization of the catalytic acetamide incorporation with vinyl azides using triflimide (Tf₂NH) as the catalyst for the reactions with a series of alcohols as a carbocation precursor.⁹

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.¹⁰ 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 carbocation equivalents, which are trapped by ketone enolate-type carbon nucleophiles.¹¹ Inspired by these findings, we surmised if the direct installation of the 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·H₂O, BINOL-linked phosphoric acid, and (PhSO₂)₂NH 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.¹² 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 CF₃SO₃H rendered the process very rapid, consuming **1a** within 5 min to give a 1:1 mixture of amide **3aa** and ketone **4aa** (run 4). We envisaged that strength of the acidity¹³ might be the key to enable selective formation of amide **3aa**. Further screening revealed that the reaction with triflimide (Tf₂NH)¹⁴ (10 mol %) provided much better selectivity to afford amide **3aa** in 75% yield and ketone **4aa** in 15% yield (run 5). A 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).

With the optimized reaction conditions in hand, we next investigated the substrate scope (Scheme 3). By varying the substituent R¹ 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 Tf₂NH to complete the processes. The reaction with α -alkyl-substituted vinyl azide **2g** also required 30 mol % of Tf₂NH to

Scheme 3. Substrate Scope^{a,b}

^aUnless 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. ^bIsolated yields were recorded above. ^cTf₂NH was used at 30 mol %. ^dTf₂NH was used at 20 mol %. ^eStructure of the major isomer was described, which was determined by X-ray crystallographic analysis. See the Supporting Information.

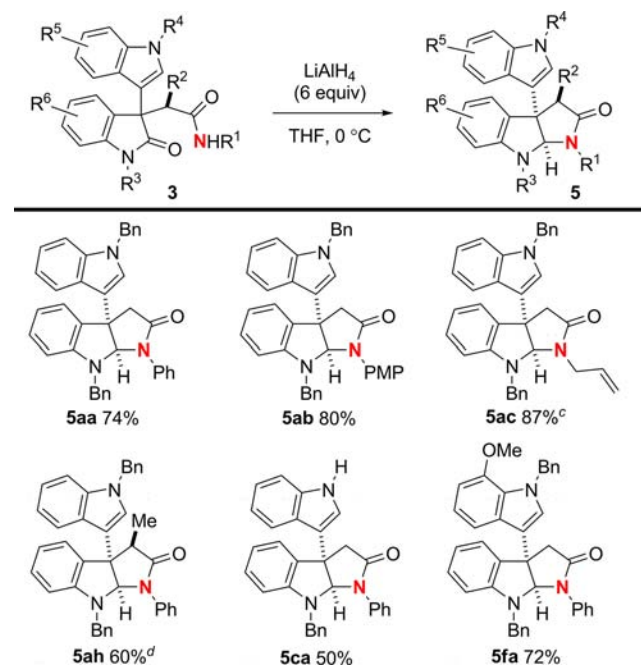
give amide product **3ag** in 54% yield. In this case, the putative iminodiazonium ion possesses two different secondary alkyl

substituents, while only formation of **3ag** via migration of the phenethyl group was observed probably because the bulkiness of the 3-indolyloxyindole moiety in another secondary alkyl group prevents its migration. The reaction with β -methyl substituted vinyl azide **1h** ($R^1 = \text{Ph}$, $R^2 = \text{Me}$) proceeded in diastereoselective manner, giving **3ah** in 78% yield with 3.3:1 dr.¹⁵ As the substituents R^3 and R^4 on the nitrogens of 3-hydroxy-3-indolyloxindoles **1**, not only benzyl but also phenyl (for **3ba**), hydrogen (for **3ca**), and methyl groups (for **3db**) could be installed. Amide **3db** is the key intermediate in synthesis of folicanthine by Gong,^{11e} in which the 4-methoxyphenylamide moiety was constructed via a stepwise sequence including: (1) synthesis of the corresponding ketone by BINOL-linked phosphoric acid-catalyzed reaction of 3-hydroxy-3-indolyloxindole **1d** with enamide; (2) conversion of the resulting ketone into oxime; (3) the Beckmann rearrangement. The present strategy using vinyl azide **2b** provides an operationally straightforward installation of acetamide unit onto **1d**. A variety of substituents could be installed as R^5 and R^6 on the framework of 3-hydroxy-3-indolyloxindoles **1** (for **3ea–3ja**).

Conversion of amides **3** into pyrroloindolinones **5** was demonstrated by careful treatment of **3** with LiAlH_4 in THF (Scheme 4).¹⁶ For synthesis of **5ac** having an allyl group on the nitrogen, exchange from 2-methoxyphenyl to allyl amide was first conducted (see the Supporting Information), and then followed by the reductive ring-closure.

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

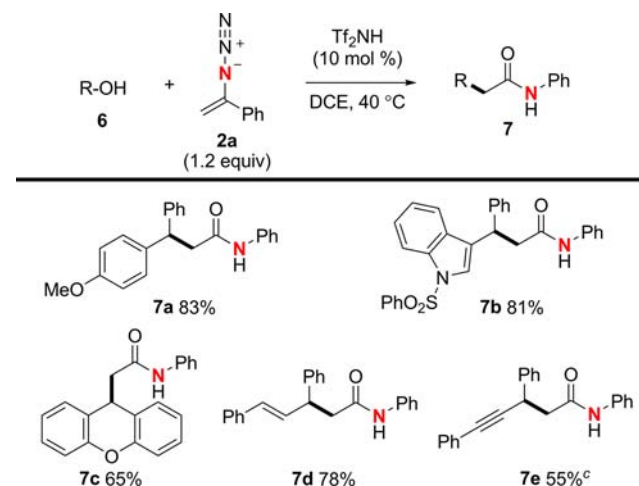
Scheme 4. Construction of Pyrroloindolinone Structures^{a,b}



^aAll the reactions were conducted using 0.08–0.1 mmol of amides **3** in THF (3 mL) under a N_2 atmosphere. See the Supporting Information for more details. ^bIsolated yields were recorded above. ^c**5ac** was synthesized from **3ac** via amide exchange from 2-methoxyphenyl to allyl via stepwise sequence followed by LiAlH_4 reduction. See the Supporting Information. ^dThe reaction was conducted at 30 °C. PMP = 4-methoxyphenyl.

corresponding amide products **7** of synthetic and medicinal relevance (Scheme 5). For example, 2-(9*H*-xanthenyl)-

Scheme 5. Amide Synthesis from Alcohols **6** with Vinyl Azide **2a**^{a,b}



^aAll the reactions were conducted using alcohols **6** (0.30–0.32 mmol) with vinyl azide **2a** (1.2 equiv) and Tf_2NH (10 mol %) in DCE (3 mL) under a N_2 atmosphere. See the Supporting Information for more details. ^bIsolated yields were recorded above. ^cAlcohol **6e** was recovered in 20% yield.

acetamide **7c** functions as an acyl-CoA cholesterol acyltransferase (ACAT) inhibitor for treatment of atherosclerosis.¹⁷ β -Alkynylcarboxamide **7e** is severed as a useful synthon for construction of pyrrolidone scaffolds.¹⁸

In summary, we have developed Tf_2NH -catalyzed reactions of alcohols with vinyl azides, enabling a straightforward access of synthetically and medically useful amide derivatives. Further upgrading of this catalytic method to the asymmetric variant as well as application of Tf_2NH to other types of catalytic transformations is now underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of new compounds, and CIF data of **3ah**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01458.

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Notes

The authors declare no competing financial interest.

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