AgOTf-catalyzed one-pot reactions of 2-alkynylbenzaldoximes with α,β-unsaturated carbonyl compounds

Qiuping Ding¹, Dan Wang¹, Puying Luo*², Meiling Liu¹, Shouzhi Pu*³ and Liyun Zhou¹

Abstract
AgOTf-catalyzed one-pot reactions of 2-alkynylbenzaldoximes with various α,β-unsaturated carbonyl compounds under mild conditions are described, which provides a facile and efficient pathway for the synthesis of 1-alkylated isoquinoline derivatives. The method tolerates a wide range of substrates and allows for the preparation of the products of interest in moderate to excellent yields.

Introduction
One-pot combinations of multi-catalysis and multi-component cascade reactions [1-6], in which several bond-forming steps take place in a single operation, play an important role in atom-economical organic chemistry. A cascade reaction is the most efficient way for targeting fine chemicals, agrochemicals, pharmaceutical drugs, drug intermediates and ingredients by a one-pot reaction in environmentally and economically friendly synthetic processes. Isoquinoline derivatives, an important class of nitrogen-containing polycyclic heteroarenes, have attracted considerable attention because of their pharmacological activities, including antitumor, antifungal, antimarial, antihypertensive and antihistaminic activity, and their photo- and electrochemical properties [7-15]. Over the past decade, there has been growing interest in the development of new methods for the
construction of isoquinoline. For instance, Yamamoto [16-19],
Larock [20-27], and Wu [28-35] have reported mild and effi-
cient methodologies to synthesize substituted isoquinolines.

Despite the aforementioned versatile and efficient methods for
the direct construction of isoquinolines, the selective functional-
ization of isoquinoline species is still a challenging task.
Recently, there has been some progress in this aspect. Wu and
co-workers described an efficient three-component reaction of a
2-alkynylbenzaldoxime and an α,β-unsaturated carbonyl com-
pound with bromine or iodine monochloride under mild condi-
tions, which generates the 1-alkylated isoquinolines in good to
excellent yields [36]. Wu and co-workers also reported many other highly functionalized isoquinoline derivatives by
cascade reactions in good yields under mild conditions, such as
1-aminoisoquinolines [37] and 1-(isoquinolin-1-yl)ureas
[38,39]. Recently, Deng and co-workers also described a new
Pd-catalyzed C–H oxidation system for the regioselective alkyl-
ation of isoquinoline N-oxide and its derivatives with sulfox-
ides for the synthesis of 1-alkylated isoquinolines [40].

We also reported the synthesis of 1-arylated 1,3-disubstituted
isoquinoline N-oxides in a one-pot reaction characterized by a
Ag-catalyzed intramolecular addition cyclization/Pd-catalyzed
direct arylation of 2-alkynylbenzaldoximes [41]. Inspired by
the key contributions from the groups of Wu [36-39] and Deng
[40], we envisioned that 1-alkylated isoquinolines could be
generated in a one-pot AgOTf-catalyzed cyclization/1,3-dipolar
cycloaddition/rearrangement or fragmentation from 2-alkynyl-
benzaldoximes and α,β-unsaturated carbonyl compounds.

Based on previous results [36-39,41-43], we expect 2-alkynyl-
benzaldoxime 1 to easily convert at room temperature to
isoquinoline N-oxide A by a AgOTf-catalyzed cyclization.
Compound A produced in situ might undergo a 1,3-dipolar
cycloaddition with α,β-unsaturated carbonyl compound 2
leading to 2,10b-dihydro-1H-isoxazolo[3,2-a]isoquinoline
intermediate B [44,45], which may then suffer a rearrangement
or fragmentation resulting in compound 3 (Scheme 1)
[35,36,38,42]. To demonstrate the feasibility of this assumed
route, we started to investigate the possibility of this one-pot
process.

Results and Discussion
Initially, a set of experiments was carried out with 2-alkynyl-
benzaldoxime 1a and methyl methacrylate (2a) as model
substrates in the presence of AgOTf (5 mol %). As expected,
the reaction proceeded smoothly in CH2Cl2 at room tempera-
ture to afford the desired product 3a in 55% yield. We also
tested other solvents, such as 1,4-dioxane, NMP, DMSO, DMA,
toluene and DMF (Scheme 2). The solvent screening demon-
strated that DMF was the best choice for the reaction at 60 °C.
From these results, it was found that this one-pot process was
highly efficient to construct 1-alkylated isoquinolines under
very mild conditions.
With the optimized conditions in hand, the scope of the procedure was investigated for the reaction of 2-(p-tolylethynyl)benzaldehyde oxime (1b) with a series of α,β-unsaturated carbonyl compounds 2a–g (Table 1). In most cases, substrate 1b reacted with α,β-unsaturated carbonyl compounds 2 leading to the corresponding 1-alkylated isoquinolines in

<table>
<thead>
<tr>
<th>Entry</th>
<th>2</th>
<th>Product 3</th>
<th>Yielda (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>3b</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>3c</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>3d</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>3e</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>3f</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>3g</td>
<td>80 (1/6)</td>
</tr>
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</table>

Table 1: AgOTf-catalyzed one-pot reactions of 2-(p-tolylethynyl)benzaldehyde oxime (1b) with α,β-unsaturated carbonyl compounds 2.
Table 1: AgOTf-catalyzed one-pot reactions of 2-(p-tolylethynyl)benzaldehyde oxime (1b) with α,β-unsaturated carbonyl compounds 2. (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Yield (% yield)</th>
<th>Ratio (syn/anti)</th>
<th>Note</th>
</tr>
</thead>
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<tr>
<td>7</td>
<td>2g</td>
<td>81</td>
<td>1/6</td>
<td>Isolated yield based on 1b.</td>
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<tr>
<td>8</td>
<td>2h</td>
<td>40</td>
<td>-</td>
<td>Ratio of syn/anti, determined by 1H NMR.</td>
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</table>

moderate to excellent yields. For instance, the reaction with 2b under standard conditions gave rise to the desired product 3e in 81% yield (Table 1, entry 2). An excellent yield was observed when butyl acrylate (2e) was utilized in the reaction (98% yield, Table 1, entry 5). When tert-butyl acrylate (2f) was employed, the reaction led to the formation of the desired 1-alkylated product 3g (80% yield, Table 1, entry 6) with a molar ratio of syn- and anti-isomers of ~1/6. It is noteworthy, that in other cases only a single product was observed. But-3-en-2-one (2g) was less reactive than the investigated acrylic acid esters and delivered the desired product only in moderate yield (40%, Table 1, entry 7). On the other hand, when substrate 1b was treated with acrylonitrile (2h) under such conditions, the starting materials were recovered almost completely (Table 1, entry 8).

Next, we examined the effect of substituents at the 2-alkynylbenzaldoxime 1. In most cases, 2-alkynylbenzaldoxime 1 reacted with acrylates 2 leading to the desired products 3 in moderate to good yields. For instance, reaction of 2-((4-methoxyphenyl)ethynyl)benzaldehyde oxime (1c) with methyl methacrylate (2a) under the conditions described above gave the desired product 3j in 75% yield (Table 2, entry 1). A better yield was obtained when substrate 1e was employed in the reaction (83% yield, Table 2, entry 3). The usage of 2-(cyclopropyl-ethynyl)benzaldehyde oxime (1f) in the reaction led to a similar yield (80% yield, Table 2, entry 5). However, low yields were obtained when 2-(hex-1-yn-1-yl)benzaldehyde oxime (1g) reacted with methyl methacrylate (2a). In the case of substrate 1h (R2 = SiMe3) only desilyl product 3p was observed in poor yield due to the instability of the product. When R2 was changed to H (2-ethynylbenzaldehyde oxime (1i), Table 2, entry 8), there was no reaction at all. Good yields were obtained when 2-alkynylbenzaldoximes substituted with other electron-donating groups (such as 1j and 1k) reacted with acrylate 2a (Table 2, entries 9–12). However, substrates with electron-donating groups attached on the aromatic ring of 2-alkynylbenzaldoxime (such as substrate 11, Table 2, entry 13) did not afford a desired product.

Recently, 1-alkenylated isoquinoline 4 was synthesized via a Pd-mediated C–H bond activation approach in a one-pot reaction. The intermediate isoquinoline N-oxide A was produced in situ from 2-alkynylbenzaldoximes and reacted with the α,β-unsaturated carbonyl compound 2e to yield 1-alkenylated isoquinoline 4 (Scheme 3). This observation indicated that the Palladium-catalyzed alkenylation reaction mechanism might be similar to that described by Cui and Wu [46].

Scheme 3: Pd-catalyzed one-pot alkenylation reaction of 2-alkynylbenzaldoxime 1a and butyl acrylate (2e).
Table 2: One-pot reactions of 2-alkynylbenzaldoximes 1 with acrylates 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Alkynylbenzaldoxime 1</th>
<th>2</th>
<th>Product 3</th>
<th>Yield(^a) (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1c</td>
<td>2a</td>
<td>3j</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>1d</td>
<td>2a</td>
<td>3k</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>1e</td>
<td>2a</td>
<td>3l</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>2f</td>
<td>3m</td>
<td>70 (1/4)(^b)</td>
</tr>
<tr>
<td>5</td>
<td>1f</td>
<td>2a</td>
<td>3n</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>1g</td>
<td>2a</td>
<td>3o</td>
<td>35</td>
</tr>
</tbody>
</table>

\(^a\) Yield based on 2-alkynylbenzaldoxime.

\(^b\) Byproduct.
### Table 2: One-pot reactions of 2-alkynylbenzaldoximes 1 with acrylates 2. (continued)

<table>
<thead>
<tr>
<th>7</th>
<th>1h</th>
<th>2a</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1i</td>
<td>2a</td>
<td>3p</td>
</tr>
<tr>
<td>9</td>
<td>1j</td>
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</tr>
<tr>
<td>13</td>
<td>1l</td>
<td>2a</td>
<td>3u</td>
</tr>
</tbody>
</table>

*a* Isolated yield based on 1b. *b* Ratio of syn/anti, determined by $^1$H NMR.

### Conclusion

In summary, we have demonstrated that one-pot reactions of 2-alkynylbenzaldoximes with α,β-unsaturated carbonyl compounds catalyzed by AgOTf occur smoothly under mild conditions. The present method provides a facile and efficient pathway for the synthesis of 1-alkylated isoquinoline derivatives in moderate to excellent yields with a wide range of substrates. The present one-pot catalyst system was also found to be applicable to the synthesis of 1-alkenylated isoquinoline derivatives.
Experimental General

All reactions were performed in test tubes under a nitrogen atmosphere. Flash column chromatography was performed with silica gel (200–300 mesh). Analytical thin-layer chromatography was performed on glass plates pre-coated with 0.25 mm 230–400 mesh silica gel and impregnated with a fluorescent indicator (254 nm). Spots on thin-layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at 25–35 °C. Commercial reagents and solvents were used as received. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Bruker AV 400 spectrometer at 400 MHz (\(^1\)H) and 100 MHz (\(^{13}\)C) at ambient temperature. Chemical shifts are reported in parts per million (ppm) on the delta scale (\(\delta\)) and referenced to tetramethylsilane (0 ppm). HRMS analyses were performed in ESI mode on a Bruker mass spectrometer.

General procedure for the AgOTf-catalyzed one-pot reactions of 2-alkynylbenzaldoximes 1 with \(\alpha,\beta\)-unsaturated carbonyl compounds 2: A mixture of 2-alkynylbenzaldoximes 1 (0.3 mmol) and AgOTf (0.015 mmol, 5 mol %) in CH\(_2\)Cl\(_2\) (2 mL) was stirred at room temperature for 2 h, until 2-alkynylbenzaldoxime 1 was completely consumed. The solvent was removed under reduced pressure. Then, \(\alpha,\beta\)-unsaturated carbonyl compound 2 (1.5 mmol, 5.0 equiv) and PdCl\(_2\)(PhCN)\(_2\) (0.015 mmol, 5 mol %) in DMF (1 mL) was added to the residue, and allowed to stir at 60 °C overnight under a nitrogen atmosphere. After completion of the reaction as indicated by TLC, the reaction was quenched by water and extracted with ethyl acetate. The organic layers were dried with anhydrous MgSO\(_4\), the solvent was evaporated under reduced pressure. Then, the solvent was removed under reduced pressure. Finally, the residue was purified by column chromatography with EtOAc/petroleum ether (1:5, \(v/v\)) as an eluent to yield the desired products 3. For details, see Supporting Information File 1.

Procedure for the synthesis of 1-alkenylated isoquinoline 4 by a Pd-mediated C–H bond activation approach: A solution of 2-alkynylbenzaldoxime 1a (0.3 mmol) and AgOTf (0.015 mmol, 5 mol %) in CH\(_2\)Cl\(_2\) (2 mL) was stirred at rt for 2 h. Then, the solvent was removed under reduced pressure. Subsequently, a solution of \(\alpha,\beta\)-unsaturated carbonyl compound 2e (1.5 mmol, 5.0 equiv) and PdCl\(_2\)(PhCN)\(_2\) (5 mol %) in NMP (1 mL) was added to the residue, and allowed to stir overnight at 110 °C under a nitrogen atmosphere. After completion of the reaction as indicated by TLC, the reaction was quenched by water and extracted with ethyl acetate. The organic layers were dried with anhydrous MgSO\(_4\), the solvent was evaporated under reduced pressure. The residue was purified by column chromatography with EtOAc/petroleum ether (1:3, \(v/v\)) as an eluent to yield the desired products 4. For details, see Supporting Information File 1.

Supporting Information

Supporting Information File 1

Experimental part.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-231-S1.pdf]

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References