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Synthesis of 2-(Isoquinolin-1-yl)prop-2-en-1-ones via Silver(I)-Catalyzed One-Pot Tandem Reaction of *ortho*-Alkynylbenzaldoximes with Propargylic Alcohols

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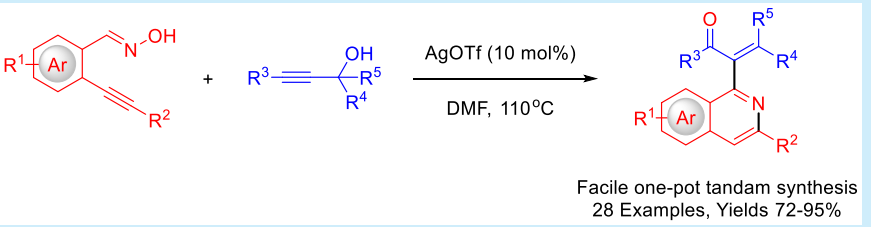
Supporting Information



ABSTRACT: The silver(I)-catalyzed reaction of *ortho*-alkynylbenzaldoximes with propargylic alcohols represents a new strategy for the divergent one-pot synthesis of 2-(isoquinolin-1-yl) prop-2-en-1-ones via tandem 6-*endo*-cyclization, 1,3-dipolar cycloaddition, and intramolecular dehydrative opening of the 2,3-dihydroisoxazole ring. This synthetic protocol tolerates a wide variety of *ortho*-alkynylbenzaldoximes and propargylic alcohols and affords the corresponding products in excellent yields.

π-Acidic metal catalyzed reactions have revolutionized the art and science of organic synthesis due to their ability to elaborate and extend carbon frameworks via a series of C−C and C−heteroatom bonds formations. These reactions have the potential to provide reactive intermediates compatible with a broad range of functionalities in a highly efficient and facile manner under mild reaction conditions.[1] Such intermediates can be harnessed as valuable synthetic building blocks for further transformations through tandem reactions.[2] They can be applied in intermolecular or intramolecular cascade reactions to generate complex molecular frameworks from simple starting materials in a single step. In particular, functionalized alkynes can be employed for generation of active species through π-acidic metal catalyzed activation of the alkyne moieties.[3] Among them, *ortho*-alkynylbenzaldoximes are excellent candidates due to their potential to form reactive isoquinoline-*N*-oxide intermediates in the presence of Lewis acid catalysts[4] or electrophiles[5] that can subsequently undergo a number of reactions.

In this regard, intense interest has been directed toward the reactions of *ortho*-alkynylbenzaldoximes with many different types of unsaturated compounds with excellent reactivity in various 1,3-dipolar cycloaddition reactions.[6] These types of reactions lead to the formation of complex small molecules via novel skeletal rearrangement reactions.[7] The nature of these intramolecular skeletal rearrangement reactions and the possible reaction products depend on the nature of the unsaturated compounds involved. For example, the reaction of *ortho*-alkynylbenzaldoximes (**I**) with carbodiimides (**II**) in the presence of catalytic amounts of silver triflate affords the corresponding 1-(isoquinolin-1-yl)ureas (**III**) through tandem 6-*endo*-cyclization, 1,3-dipolar cycloaddition, and intramolecular rearrangement.[8] Employing arynes in the silver(I)-catalyzed tandem reaction of *ortho*-alkynylbenzaldoximes gives rise to the corresponding 2-oxa-6-azabicyclo[3.2.2]nona-6,8-dienes (**V**).[9] This reaction proceeds via tandem 6-*endo*-cyclization, 1,3-dipolar cycloaddition, and radical intramolecular rearrangement. Through a similar mechanism, silver(I)-catalyzed reactions of *ortho*-alkynylbenzaldoximes with alkylidenecyclopropanes[10] (**VI**) and 1-((cyclopropylidenemethyl)-2-alkynyl)-arenes[11] (**VIII**) furnish the corresponding derivatives of benzo-7-azabicyclo[4.2.2]dec-7-en-4-one (**VII**) and 1-((1,3-dihydroisobenzofuran-1-yl)methyl)isoquinoline (**IX**), respectively (Scheme 1).

Aware that Lewis acid catalyzed reaction of propargylic alcohols with a broad spectrum of nucleophiles and electrophiles has been extensively employed in the synthesis of various classes of heterocyclic compounds in recent years,[12] we have envisioned that propargylic alcohols may be suitable reaction partners in the reaction with *ortho*-alkynylbenzaldoximes. Herein, we wish to report a silver(I)-catalyzed one-pot tandem reaction of *ortho*-alkynylbenzaldoximes with propargylic alcohols for the step-economic synthesis of corresponding 2-(isoquinolin-1-yl)prop-2-en-1-ones via a reaction cascade involving 6-*endo*-cyclization, [3 + 2] cyclo-

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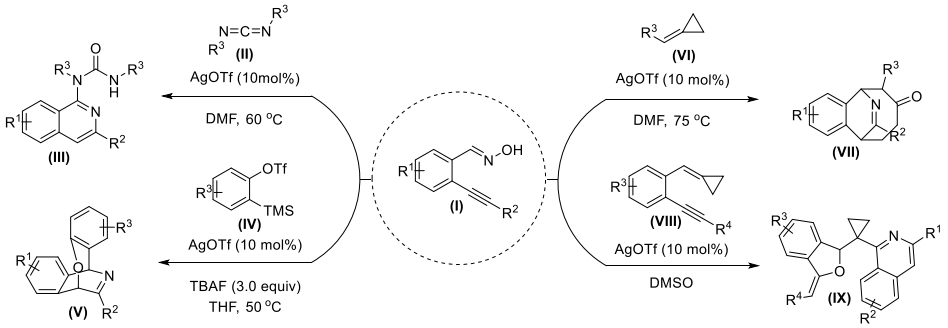
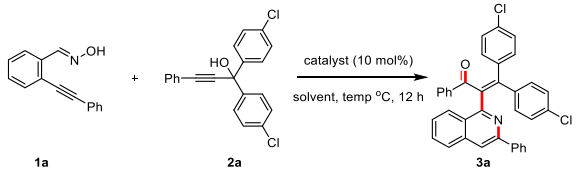
Scheme 1. Tandem Reactions of *ortho*-Alkynylbenzaldoximes with Different Types of Unsaturated Compounds with Excellent Reactivity in Various 1,3-Dipolar Cycloaddition Reactions



addition, and intramolecular dehydrative opening of the 2,3-dihydroisoxazole ring.

Initially, for testing our hypothesis, the reaction of **1a** with **2a** was carried out in the presence of a catalytic amount of AgOTf (10 mol %) in DMF at 110 °C. Product **3a** was obtained as the sole product in 91% isolated yield and exclusive regioselectivity (Table 1, entry 1). By using $AgNO_3$ or $AgBF_4$ as the catalyst, the reaction yield decreased dramatically to 22% and 49%, respectively (Table 1, entries 2–3). When $(Ph_3P)AuCl$ or $Bi(OTf)_3$ were employed, no reaction was observed (Table 1, entries 4–5), whereas $InCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, and $ZnCl_2$ gave 52%, 40%, 15%, and 19% yields, respectively (Table 1, entries 6–9). There was no reaction in the absence of the catalyst. The screening of various solvents revealed that the reaction proceeds efficiently in DMF. Moreover, the effect of the temperature was also investigated. By lowering the temperature from 110 to 100 °C, the yield was decreased to 71% (Table 1, entry 13). When the reaction temperature was increased from 110 to 120 °C, no improvement in yield was observed (Table 1, entry 14).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	yield[b] (%)
1	AgOTf	DMF	110	91
2	$AgNO_3$	DMF	110	22
3	$AgBF_4$	DMF	110	49
4	$(Ph_3P)AuCl$	DMF	110	NR[c]
5	$Bi(OTf)_3$	DMF	110	NR[c]
6	$InCl_3$	DMF	110	52
7	$In(OTf)_3$	DMF	110	40
8	$Sc(OTf)_3$	DMF	110	15
9	$ZnCl_2$	DMF	110	19
10	AgOTf	DMSO	110	85
11	AgOTf	1,4-Dioxane	110	38
12	AgOTf	Toluene	110	22
13	AgOTf	DMF	100	71
14	AgOTf	DMF	120	90

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (10 mol %), solvent (1 mL), temp °C, 12 h. [b]Isolated yields. [c]No reaction observed.

With the optimized reaction conditions in hand (10 mmol % AgOTf in DMF at 110 °C), we then explored the substrate scope of this tandem reaction using various *ortho*-alkynylbenzaldoximes and propargylic alcohols. The results are summarized in Scheme 2. The reaction showed high generality and functional group tolerance and afforded a variety of 2-(isoquinolin-1-yl)prop-2-en-1-ones in excellent yields. As illustrated in Scheme 2, a wide range of symmetrical propargylic alcohols with either an electron-poor or electron-rich aryl substituent lead to the desired product in good to high yields. Furthermore, propargylic alcohols derived from cyclic ketones behaved well (**3d**, **3l**, **3m**, **3r**, **3s**, **3x**, **3y**). It is notable that propargylic alcohols having an alkyl group in the R^3 position instead of a phenyl group were well tolerated and provided the tandem products in good to high yields (**3h**, **3n**, **3t**, **3z**), However, unsubstituted propargylic alcohols at the terminal position and the α position of the alcohol or propargylic alcohols having two alkyl groups at the α position of the alcohol did not lead to the desired product. Both aromatic and aliphatic groups at the alkynyl part of *ortho*-alkynylbenzaldoximes are tolerated under the reaction conditions. On the other hand electron-withdrawing groups (Cl and NO_2) and electron-donating group (OMe) on the *ortho*-alkynylbenzaldoximes behaved well in this catalytic system.

Using unsymmetrical-substituted propargylic alcohol led to the expected products in high yield (**3za, 3zb**) albeit as a mixture of diastereomers.

All compounds were characterized by IR, ^1H NMR, ^{13}C NMR, and HRMS spectral analysis. Furthermore, the molecular structures of the products were confirmed by the single crystal X-ray diffraction analysis of compounds **3l** and **3m** (Figure 1).

A plausible mechanism is proposed in Scheme 3. In the first step, through silver(I)-catalyzed 6-*endo* cyclization of *ortho*-alkynylbenzaldoximes[8,9]**1**, isoquinoline-*N*-oxides **A** are formed. They undergo a facile 1,3-dipolar cycloaddition reaction with propargylic alcohols **2** leading to cycloadduct intermediates **B**. Finally, a ring-opening/dehydration sequence render the desired 2-(Isoquinolin-1-yl) prop-2-en-1-ones **3**. To gain more insight into the reaction mechanism, the intermediate **A** was prepared independently and was subsequently reacted with propargylic alcohol **2a** under catalyst-free conditions. However, no 1,3-diploar cycloaddition proceeded, which suggests that silver triflate also catalyzes the 1,3-dipolar cycloaddition step.

In conclusion, we have established a facile route to prepare 2-(isoquinolin-1-yl) prop-2-en-1-ones through a silver(I)-

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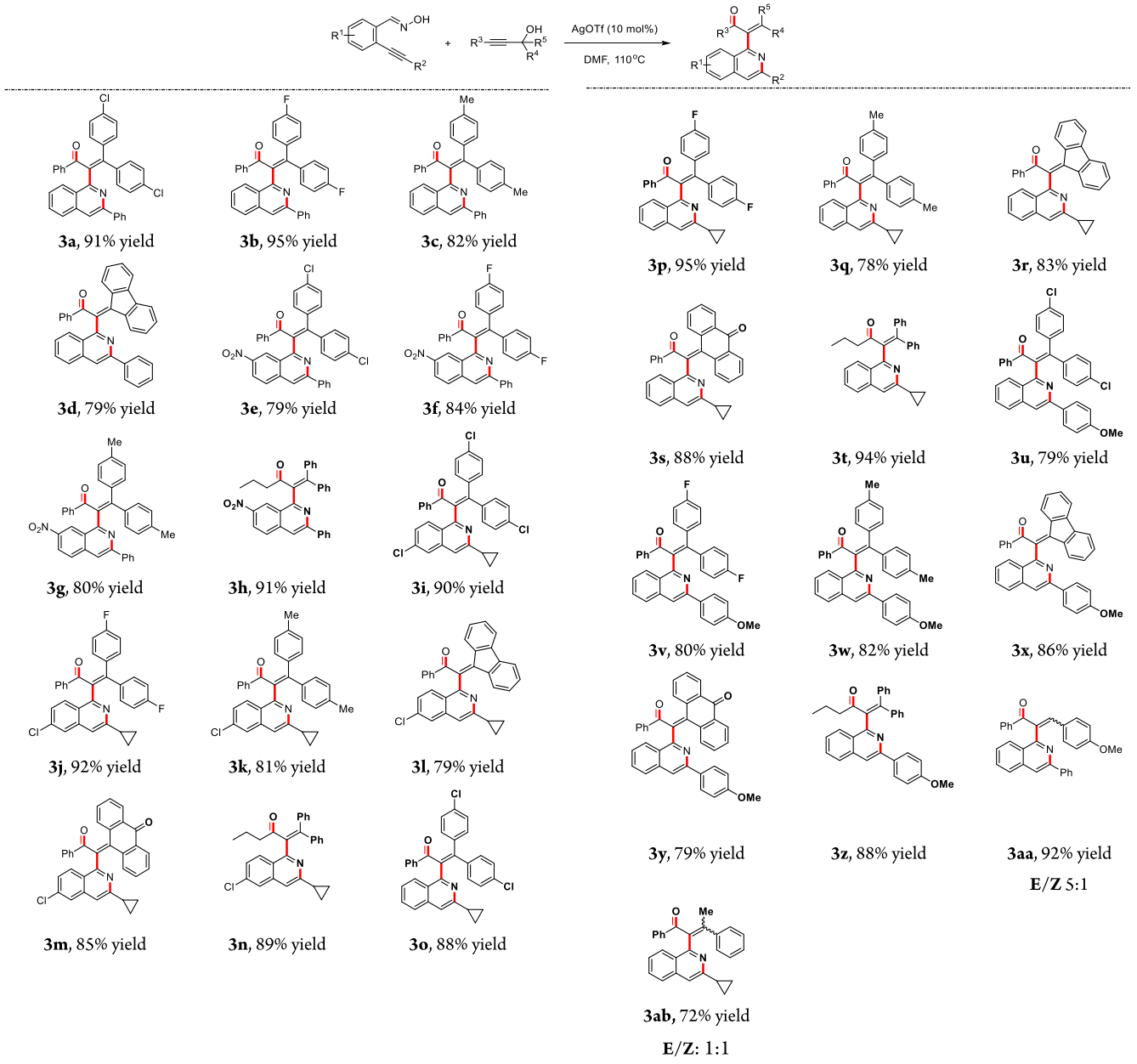
Scheme 2. Substrates Scope for the Silver(I)-Catalyzed One-Pot Tandem Reaction of *ortho*-Alkynylbenzaldoximes with Propargylic Alcohols



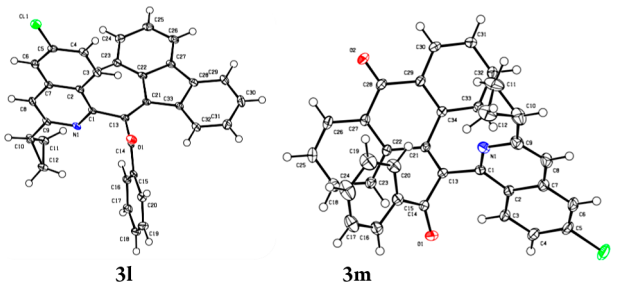
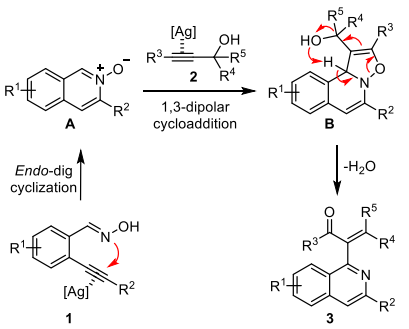


Figure 1. ORTEP view of compounds **3l** and **3m**.

Scheme 3. Proposed Mechanism for the Silver(I)-Catalyzed One-Pot Tandem Reaction of *ortho*-Alkynylbenzaldoximes with Propargylic Alcohols



catalyzed one-pot tandem reaction of *ortho*-alkynylbenzaldoximes with propargylic alcohols. The reaction features a broad substrate scope and good functional group tolerance,

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allowing for efficient access to a wide variety of 2-(isoquinolin-1-yl) prop-2-en-1-ones in excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02952.

Experimental procedures and characterizations (PDF)

Accession Codes

CCDC 1899726 and 1899744 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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