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General one-step access to unsymmetric propargylic acetals *via* alcohol functionalization with allenyl ethers†

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We report a straightforward and robust protocol for synthesizing unsymmetric propargylic acetals through single-step alkoxypropargylation of aliphatic alcohols. This method employs allenyl ethers and hypervalent iodine reagents to achieve direct functionalization under mild conditions, producing 26 distinct acetals in 60–94% yields. The reaction's broad substrate compatibility accommodates diverse hydroxyl-containing molecules, offering a versatile and scalable platform for installing alkynyl moieties in complex molecular architectures.

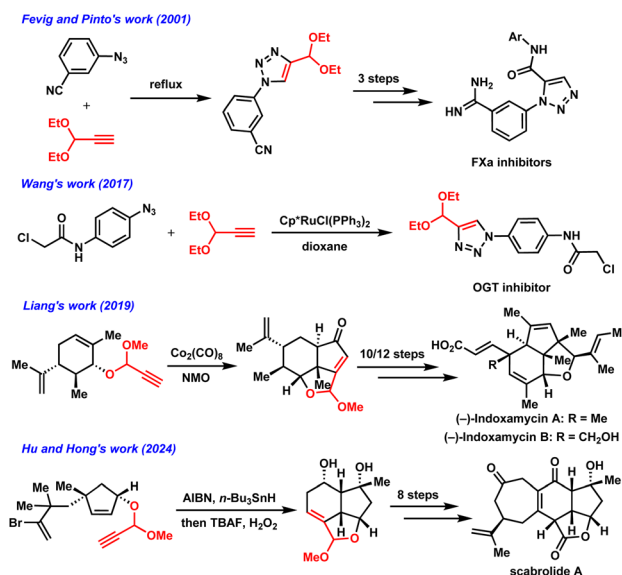
Introduction

Propargylic acetals have emerged as versatile synthetic building blocks, demonstrating remarkable utility across click chemistry and natural product synthesis. For instance, Fevig and Pinto employed 3,3-diethoxypropyne in azide–alkyne click chemistry to construct serine protease factor Xa (FXa) inhibitors (Scheme 1).¹ Wang and coworkers utilized the identical 3,3-diethoxypropyne acetal to access O-GlcNAc transferase (OGT) inhibitors.² In the total synthesis of indoxamycins, Liang designed an unsymmetrical propargylic acetal precursor to enable the pivotal Pauson-Khand cycloaddition step.³ Similarly, Hu and Hong developed a synthetic strategy for assembling scabrolide A's tricyclic core *via* cascade radical cyclization using propargylic acetal-based chemistry.⁴

Several synthetic methods have been developed for propargylic acetal construction (Scheme 2). Forsyth's seminal work pioneered a two-step protocol for unsymmetrical propargylic acetals through bromoacetalization of allenyl ether substrates followed by β -hydride elimination.⁵ This methodology was subsequently adopted in the aforementioned total syntheses. In 2014, Zhou reported a Cu(I)-catalyzed coupling strategy between terminal alkynes and oxadiazolines, achieving unsymmetric propargyl acetals *via* dialkoxycarbene pathway.⁶ Wang's 2019 investigation demonstrated a decarboxylative cross-coupling of 2,2-diethoxyacetic acid with alkynyl bromides for streamlined propargylic acetal assembly.⁷ However, in contrast to Forsyth's direct alcohol functionalization protocol, these contemporary

approaches necessitate elaborate precursors while proving incompatible with terminal alkyne generation.

A related class of compounds, *N,O*-propargylic acetals, was recently accessed by Yu through $\text{PhI}(\text{OAc})_2$ -mediated oxidation of allenamides, generating propargylic iminium ions that undergo 1,2-addition with alcohols.⁸ Building upon our expertise in allenyl ether chemistry,^{9,10} we now report a one-step synthesis of unsymmetric propargylic acetals *via* hypervalent iodine oxidation of allenyl ethers followed by alcohol trapping.¹¹ This method eliminates the need for pre-functionalized intermediates and enables direct alcohol functionalization under mild conditions.

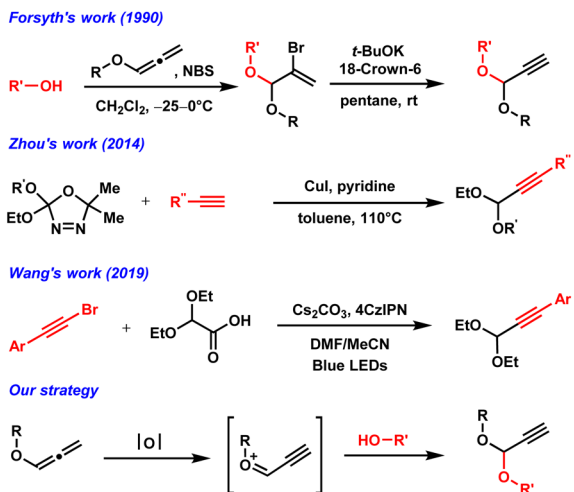


Scheme 1 Applications of propargylic acetals.

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Scheme 2 Synthesis strategy of unsymmetric propargylic acetals.

Results and discussion

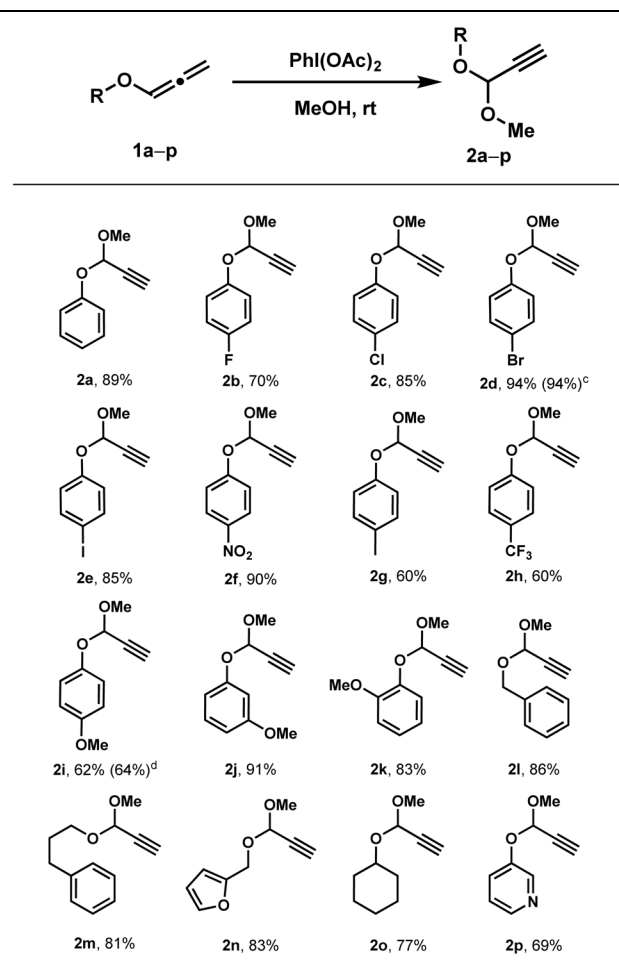
Inspired by Yu's iminium ion strategy,⁸ we hypothesized that allenyl ethers could undergo analogous oxidation to generate propargylic oxonium ions, which might be trapped by alcohols to form acetals (Scheme 2). Initial studies focused on optimizing the oxidation of phenyl allenyl ether (**1a**) in methanol. Screening of oxidants revealed $\text{PhI}(\text{OAc})_2$ as optimal, delivering the methyl acetal **2a** in 89% yield within 5 minutes at room temperature (Table 1).

With optimized conditions (1.2 equiv. $\text{PhI}(\text{OAc})_2$, 0.3 M in MeOH), diverse allenyl ethers were evaluated. As summarized in Table 2, a wide range of aryl allenyl ethers proved effective in this transformation, delivering the corresponding acetals in good yields. Three *para*-substituted phenyl allenyl ethers—bearing $-\text{CF}_3$ (**2h**), $-\text{Me}$ (**2g**), and $-\text{OMe}$ (**2i**) groups—exhibited moderately reduced yields (60%, 60%, and 62%, respectively). In contrast, methoxy-substituted substrates at meta (**2j**, 91%) and ortho (**2k**, 83%) positions maintained high efficiency. The protocol extended successfully to aliphatic and *N*-heterocyclic-

Table 1 Oxidant screening

Entry ^a	Oxidant	Yield ^b (%)
1	CAN	No reaction
2	$\text{Cu}(\text{CF}_3\text{SO}_3)_2$	No reaction
3	$\text{Fe}(\text{CF}_3\text{SO}_3)_3$	No reaction
4	DDQ	Decompose
5	$\text{Pb}(\text{OAc})_4$	75
6	$\text{PhI}(\text{OAc})_2$	89

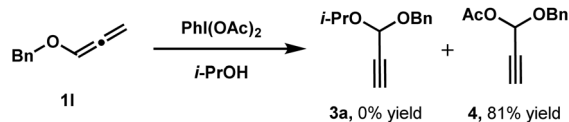
^a All reactions were carried out with 1.50 mmol **1a**, 5.0 mL MeOH, 1.80 mmol oxidant. ^b Isolated yields.

Table 2 Substrates scope of allenyl ethers^{a,b}

^a The reactions were carried out with **1a–o** (100 mg, 1.0 equiv.), $\text{PhI}(\text{OAc})_2$ (1.2 equiv.), in MeOH (0.3 M) at room temperature for 5–30 min. ^b Isolated yields. ^c Yield of a 4.0 g scale reaction. ^d Yield of a 3.2 g scale reaction.

containing allenyl ethers (**2l–2p**), providing acetals in 69–86% yields. To validate scalability, gram-scale reactions of both **2d** and **2i** proceeded efficiently (94% and 64% yield, respectively), confirming the protocol's robustness.

Given our research goal of developing a general alcohol functionalization method, we proceeded to introduce various alcohols into the reaction system. Initial attempts employed isopropanol as both solvent and nucleophile in the reaction of benzyl allenyl ether with $\text{PhI}(\text{OAc})_2$. However, this system exclusively produced the *O*-acetoxy acetal **4** rather than the anticipated *O*-isopropyl product **3a** (Scheme 3). Structural



Scheme 3 Synthetic Attempts toward propargyl isopropyl acetal.



Table 3 Optimization of Reaction Condition^{a,b}

Entry ^a	Oxidant (1.2 equiv.)	Additive	T (°C)	Solvent (0.3 M)	Yield ^b (%)
1	PhI(OCOCF ₃) ₂	—	25 °C	i-PrOH	68
2	PhI(OCOCF ₃) ₂	—	50 °C	THF	No reaction
3	PhI(OCOCF ₃) ₂	—	50 °C	EtOAc	41
4	PhI(OCOCF ₃) ₂	—	25 °C	EtOAc	No reaction
5	PhI(OCOCF ₃) ₂	—	25 °C	CH ₂ Cl ₂	84
6 ^c	PhI(OCOCF ₃) ₂	DIPEA	25 °C	CH ₂ Cl ₂	13
7 ^c	PhI(OCOCF ₃) ₂	Pyridine	25 °C	CH ₂ Cl ₂	32
8 ^c	PhI(OCOCF ₃) ₂	NaHCO ₃	25 °C	CH ₂ Cl ₂	36

^a All reactions were carried out with 1.50 mmol **11**, 5.0 mL solvent, 1.80 mmol oxidant, 2.25 mmol i-PrOH. ^b Isolated yields. ^c All additive were 2.0 equivalent.

analysis of **4** revealed interception of the *in situ* generated oxonium ion by the oxidant's acetate counterion during the 1,2-addition step. This outcome was attributed to the steric bulk and low nucleophilicity of isopropanol, which proved insufficient to compete with the acetate anion.

This observation prompted investigation of oxidants bearing less nucleophilic counterions. Furthermore, to accommodate solid and complex alcohol substrates incompatible with solvent roles, we sought to develop non-solvent-dependent conditions.

Table 4 Substrates scope of alcohols^{a,b}

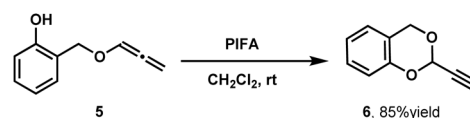
Reaction	Yield (%)
	3a-i
	84%
	72% (75%) ^c
	70%
	60%
	63%
	85% (84%) ^d
	67%
	78%
	67%

^a The reactions were carried out with **11** (100 mg, 0.68 mmol, 1.0 equiv.), PIFA (353 mg, 0.82 mmol, 1.2 equiv.), and the corresponding alcohol (1.03 mmol, 1.5 equiv.) in CH₂Cl₂ (2.28 mL, 0.3 M) at room temperature for 5–30 minutes. ^b Isolated yields. ^c Yield of a 3.0 g scale reaction. ^d Yield of a 2.5 g scale reaction.

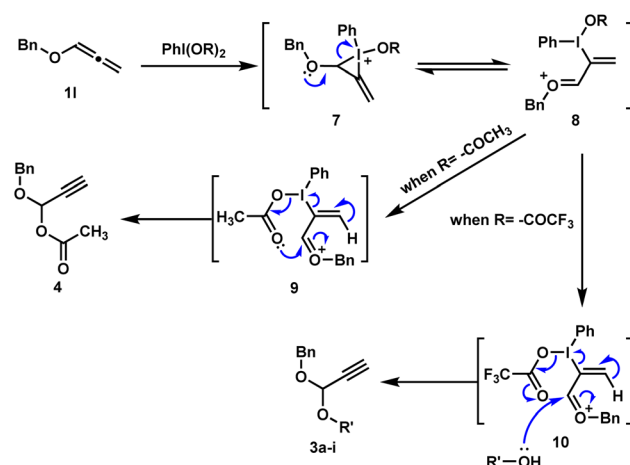
Replacement of PhI(OAc)₂ with PhI(OCOCF₃)₂ in isopropanol successfully afforded **3a** in 68% yield, validating the counterion strategy. Subsequent solvent optimization identified no conversion in THF, partial success in ethyl acetate at elevated temperatures, and optimal performance in CH₂Cl₂ (84% yield at rt) (Table 3).

As shown in Table 4, The refined protocol (PhI(OCOCF₃)₂, CH₂Cl₂, rt) demonstrated broad applicability with alcohols bearing diverse functional groups, including bromo (**3d**, 60%), trifluoromethyl (**3e**, 63%), cyclobutyl (**3f**, 85%), and alkyne (**3h**, 78%) moieties. Notably, solid alcohols such as *L*-menthol (**3i**, 67%)—which cannot serve as reaction solvents due to their physical state at room temperature—were successfully functionalized under these homogeneous conditions. The protocol's scalability was further demonstrated through gram-scale reactions, which maintained efficiency (75% yield for **3b**, 84% for **3f**). Phenolic substrates universally failed under standard conditions, presumably due to hypervalent iodine-mediated dearomatization pathways. A singular exception was observed with 2-hydroxybenzyl allenyl ether, where intramolecular cyclization afforded cyclic acetal **6** (85% yield, Scheme 4).

A plausible reaction mechanism, consistent with prior reports,⁸ is outlined in Scheme 5. Initial oxidation of the electron-rich alkene generates iodonium intermediate **7**, which undergoes oxygen-assisted ring-opening to oxonium ion **8**. When PhI(OAc)₂ is employed, the acetate counterion competes with sterically hindered or weakly nucleophilic alcohols in the subsequent 1,2-addition step. This pathway, proceeding intermolecularly or intramolecularly, culminates in β-H elimination to yield *O*-acetoxy acetal **4**. In contrast, PhI(OCOCF₃)₂—bearing



Scheme 4 Intramolecular cyclization of 2-hydroxybenzyl allenyl ether.



Scheme 5 Possible reaction mechanism.



a less nucleophilic trifluoroacetate counterion—shifts the equilibrium to favor alcohol addition. Subsequent β -H elimination from this intermediate delivers the desired propargylic acetal.

Conclusions

We have developed a novel method for the preparation of unsymmetric propargylic acetals through direct functionalization of alcohols. This approach involves a hypervalent iodine-mediated oxidation of allenyl ethers followed by 1,2-addition of alcohols under mild conditions, proceeding efficiently at room temperature and reaching completion within half an hour. The reaction demonstrates remarkable compatibility with sterically bulky alcohols and solid substrates, consistently delivering corresponding acetals in synthetically useful yields. As a scalable strategy for converting hydroxyl groups into alkynyl functionalities, this methodology offers broad utility in complex molecule synthesis and chemical biology applications.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as potential conflicts of interest.

Acknowledgements

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