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Metal-Free, Regio- and Stereoselective Synthesis of Linear (*E*)-Allylic Compounds Using C, N, O, and S Nucleophiles

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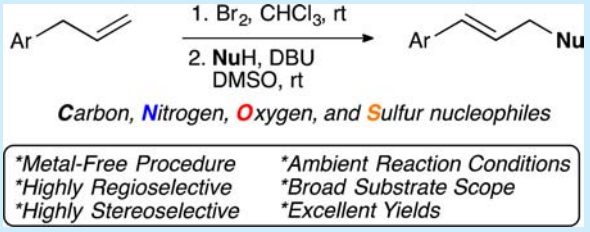
Supporting Information

ABSTRACT: A variety of allylic acetates and derivatives were synthesized by an efficient two-step protocol that employs readily available terminal alkenes as starting materials. This method is highly regio- and stereoselective, affording the linear (*E*)- isomer as the sole adduct. This process tolerates several functional groups including halogen-containing molecules, and it is general for weak oxygen, carbon, nitrogen, and sulfur nucleophiles. Furthermore, adducts were obtained in good to excellent yields.



Allylic acetates and related functional groups are abundant in natural products as well as organic materials. Moreover,

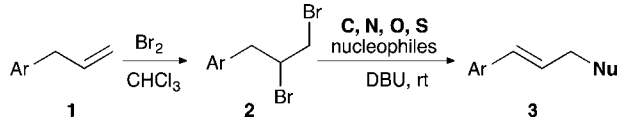
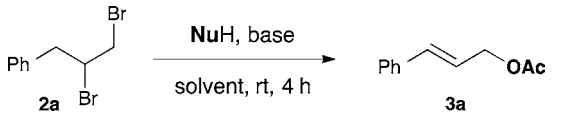


Figure 1. General approach toward linear (*E*) allylic compounds.

they represent versatile building blocks that are used in diverse carbon−carbon and carbon−heteroatom bond-forming reactions.[1] As such, the development of methods for rapid and efficient synthesis of allylic compounds remains an active area of research.[2] For example, advances in the synthesis of allylic acetates from monosubstituted olefins has been achieved via C−H oxidation.[3] These methods rely on palladium catalysts in combination with a stoichiometric oxidant or molecular oxygen under high pressure. Nevertheless, these processes afford highly regio- and stereoselective allylic acetates directly from terminal alkenes. In 2004, White and co-workers documented that the combination of $Pd(OAc)_2$, benzoquinone (BQ), and DMSO or a bis(sulfoxide) ligand promoted the regio- and stereoselective allylic acetoxylation of terminal alkenes.[3b] Kaneda et al. reported a regioselective method for the synthesis of linear allylic acetates using $PdCl_2$ and molecular oxygen as the sole oxidant; in this case, high pressures of O_2 (6 atm) were required.[3e,4] Incorporation of bipyrimidines as ligands were also found to improve the allylic acetoxylation of olefins,[5] as well as the employment of additives such as bases for the Pd-catalyzed oxidation of terminal alkenes.[3a] More recently, Stahl and co-workers have developed an elegant method that enables the use of O_2 (1 atm) as the terminal oxidant.[3d] Although these methods present advantages such as broad substrate scope and readily available starting materials, they often generate mixtures of (*E*/*Z*) and linear/branched allylic acetates. Correspondingly, White and co-workers recently reported the extension of their allylic acetoxylation protocol (oxygen nucleophiles),[6] using

Table 1. Optimization of Reaction Conditions[a]



entry	AcOR (mol %)	base (2 equiv)	solvent	yield[b] (%)
1[c]	$Pd(OAc)_2$ (50)	none	DMSO	24
2[c]	**$Pd(OAc)_2$ (50)**	**K_2CO_3**	**DMSO**	**83**
3	AcOH (110)	none	DMSO	0
4	AcOH (110)	K_2CO_3	DMSO	84
5[d]	AcOH (110)	K_2CO_3	DMA	60
6[d]	AcOH (110)	K_2CO_3	DMF	50
7[d]	AcOH (110)	K_2CO_3	toluene	<5
8[d]	AcOH (110)	K_2CO_3	THF	<5
9	**AcOH (110)**	**Cs_2CO_3**	**DMSO**	**85**
10	**AcOH (110)**	**DBU**	**DMSO**	**85**
11	AcOH (110)	Na_2CO_3	DMSO	71
12	AcOH (110)	DMAP	DMSO	<5
13	AcOH (110)	Et_3N	DMSO	46
14	AcOH (110)	*i*-Pr_2EtN	DMSO	53
15	AcOH (110)	KO*t*Bu	DMSO	32
16	AcOH (110)	KOH	DMSO	57
17	AcOH (0)	DBU	DMSO	0[e]

[a]Reactions were carried out with **2a** (0.2 mmol, 55.6 mg, 1 equiv), base (2 equiv), and AcOH (110 mol %) at 22 °C in 1.0 mL of solvent for 4 h. [b]Isolated yields (average of 2−3 runs) by silica gel flash chromatography. [c]50 mol % of $Pd(OAc)_2$ was employed. [d]The starting material was recovered. [e]For details, see the Supporting Information.

similar reaction conditions, to carbon nucleophile (alkylation)[7] and nitrogen nucleophile (amination)[8] reactions. In these studies, highly stereo- and regioselective syntheses were observed, albeit in moderate yields. Despite progress, all of these methods rely on palladium, an expensive and precious

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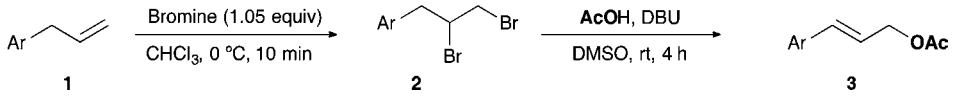
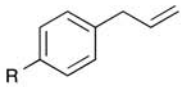
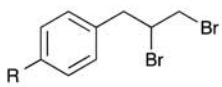
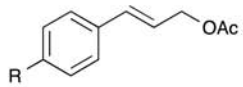
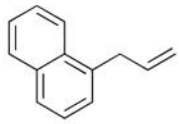
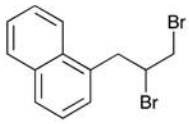
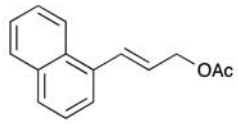
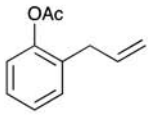
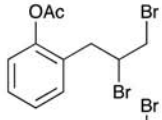
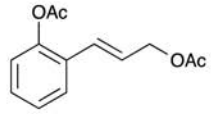
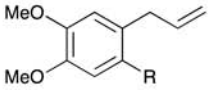
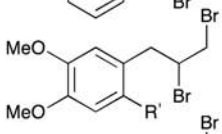
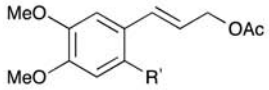
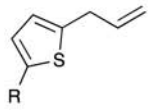
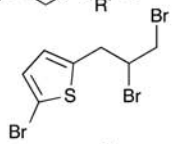
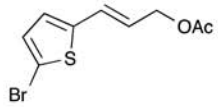
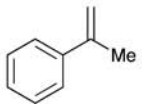
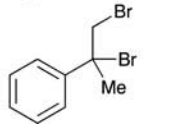
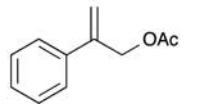
Table 2. Substrate Scope of the Two-Step Protocol



1 2 3

entry	activated alkene no.		dibromide no.[a]		yield (%)[b]	allyl acetate no.[c]		yield (%)[b]
1		**1a** R = H		**2a**	94		**3a**	85
2		**1b** Br		**2b**	95		**3b**	72
3		**1c** Cl		**2c**	96		**3c**	75
4		**1d** F		**2d**	90		**3d**	76
5		**1e** CF_3		**2e**	98		**3e**	94
6		**1f** Ph		**2f**	95		**3f**	96
7		**1g**		**2g**	91		**3g**	88
8		**1h**		**2h**	87		**3h**	58
9[d]		**1i** R = H		**2i** R' = Br	90		**3i** R' = Br	71
10		**1j** Cl		**2j** Cl	86		**3j** Cl	72
11[d]		**1k** R = H		**2k**	88		**3k**	70
12		**1l** Br		**2k**	84		**3k**	70
13[e]		**1m**		**2m**	–		**3m**	43

[a]Reactions were carried out with alkene **1** (4 mmol, 530 mg, 1 equiv) and bromine (1.05 equiv) at 0 °C in 15.0 mL of $CHCl_3$ for 10 min. [b]Isolated yields (average of 2−3 runs) by silica gel flash chromatography. [c]Reactions were carried out with dibromide **2** (0.2 mmol, 1 equiv) and AcOH (1.1 equiv) at rt in 1.0 mL of DMSO for 4 h. [d]2 equiv of bromine was used. [e]One-pot procedure; **2m** not isolated.

metal. As such, we sought to develop a complementary mild, metal-free approach toward allylic compounds. Herein, we report an efficient, two-step protocol that commences from readily available terminal olefins and is highly regio- and stereoselective. Moreover, the method is compatible with a wide-range of nucleophiles, including carbon, nitrogen, oxygen, and sulfur nucleophiles (Figure 1).

Our optimization of reaction conditions commenced from an observation made while investigating the $Pd(OAc)_2$-mediated aerobic oxidation[9] of (2,3-dibromopropyl)benzene (**2a**) to (*Z*)-2-bromo-3-phenylacrylaldehyde. We observed that in the presence of 50 mol % of $Pd(OAc)_2$ the formation of the linear (*E*)-allylic acetate (**3a**) resulted, albeit in a modest 24% yield (Table 1, entry 1). Of note, the addition of K_2CO_3 significantly increased the yield of **3a** to 83% (entry 2). We speculated that palladium was unnecessary and that acetic acid could serve as the nucleophilic source. To explore the potential of acetic acid as nucleophile in promoting the substitution reaction, we examined different reaction conditions in the presence of 2.0 equiv of a base and focused on the conversion of **2a** to **3a**. The essential bromination of terminal olefins[10] proceeded in straightforward manner, and dibromide **2a** was obtained in high yield. In DMSO, no reaction was observed in the absence of K_2CO_3 (Table 1, entry 3). However, addition of K_2CO_3 (2 equiv) afforded the allylic acetate in 84% yield (entry 4). Other quantities of K_2CO_3 provided no improvement (not shown). DMSO proved to be the best solvent, delivering the product in excellent yield while maintaining a high level of regio- and stereoselectivity compared to DMA, DMF, toluene, and THF (entries 4−8); other nonpolar or protic solvents were not effective. The bases KOH, KO-*t*-Bu, Et_3N, *i*-Pr_2EtN, and DMAP promoted the reaction, but the yields were low compared to K_2CO_3. High yields were observed when Na_2CO_3, K_2CO_3, and Cs_2CO_3 were employed, with Cs_2CO_3 affording the highest yield (85%, entry 9). DBU also proved to be highly effective and was comparable to the use of Cs_2CO_3 (85%, entry 10). We decided to employ DBU[11] for further investigations.

Having optimized conditions for the conversion of dibromide **2a** to allylic acetate **3a**, we next investigated the scope of the two-step protocol. A variety of terminal olefins (**1a−m**) were initially treated with bromine at 0 °C to room temperature in chloroform.[10,12] As expected, the dibromide adducts **2a−m** were obtained in good to excellent yields (Table 2, left). Importantly, the dibromination process was general and tolerated electron-rich, electron-poor, sterically hindered, and heteroaryl substrates. However, it is important to note that upon addition of 2.0 equiv of bromine, 4-allyl-1,2-dimethoxybenzene (**1i**) and 2-allylthiophene (**1k**) also underwent a selective aromatic bromination reaction to afford the tribrominated adducts **2i** and **2k** in 90% and 88% yield, respectively (Table 2, entries 9 and 11). In addition to monosubstituted olefins, we prepared the disubstituted dibromide **2m** from α-methylstyrene (**1m**) (Table 2, entry 13). However, this adduct was used in the subsequent step without purification.

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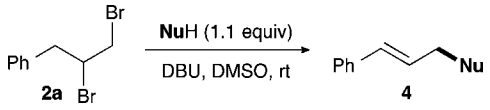
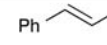
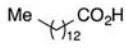
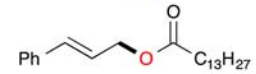
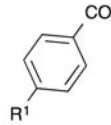
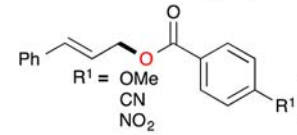
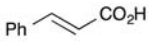
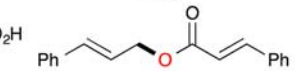
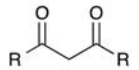
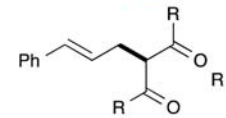
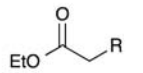
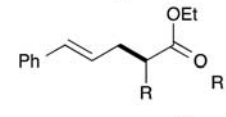
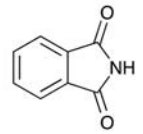
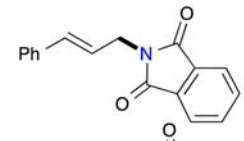
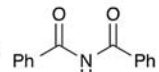
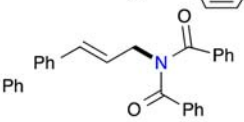
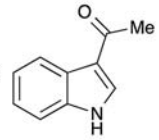
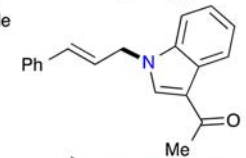
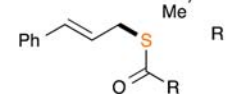
Table 3. Scope of Nucleophiles[a]

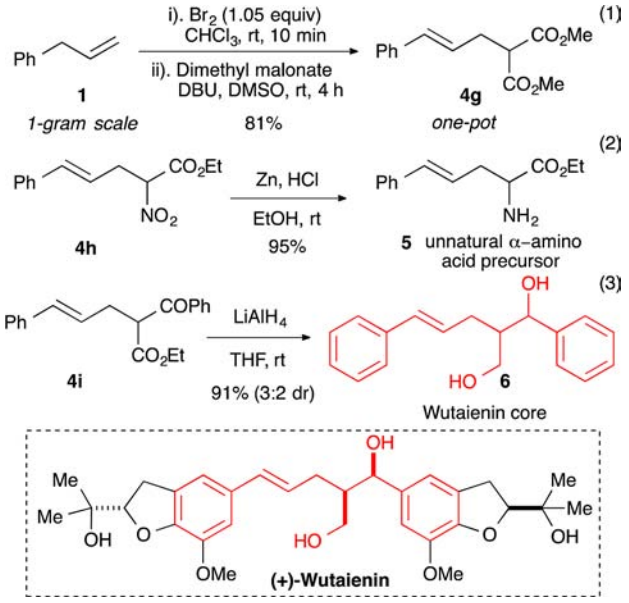


entry	NuH	product no.	yield (%)[b]
1	AcOH		**3** 85
2			**4a** 76
3		 R[1] = OMe	**4b** 73
4		CN	**4c** 68
5		NO_2	**4d** 79
6			**4e** 55
7		 R = OMe	**4f** 93
8		OEt	**4g** 82
9		 R = NO_2	**4h** 34
10		COPh	**4i** 58
11[c]			**4j** 48
12[c]			**4k** 51
13[c]			**4l** 36
14		 R = Me	**4m** 62
15		Ph	**4n** 71

[a]Reactions were carried out with **2a** (0.2 mmol, 55.6 mg, 1 equiv), DBU (2 equiv), and NuH (1.1 equiv) at 22 °C in 1.0 mL of DMSO for 4 h. [b]Isolated yields (average of 2−3 runs) by silica gel flash chromatography. [c]Excess of **2a** did not increase the yield.

With the dibrominated adducts in hand, we investigated the scope of this two-step protocol by examining the reactivity of the previous freshly prepared dibromides **2a**−**m** in the presence of AcOH and DBU at room temperature (Table 2, right). Most reactions were quenched after 4 h for comparison purposes, although starting material still remained. In all cases, the reaction proceeded smoothly in the presence of DBU and the weak nucleophile (AcOH) to afford the corresponding allyl acetates adducts, in good to high yields, at room temperature. For *para*-substituted benzene dibromides, the system is very efficient (entry 1). The reaction of *para*-halogenated benzene dibromides delivered the products in 72% yield (Br), 75% yield (Cl), and 76% yield (F) (entries 2−4). The adduct of electron-poor *p*-(trifluoromethyl)benzene dibromide is obtained in 94% yield and *p*-Ph in 96% (entries 5 and 6). The naphthalene derivative afforded an 88% yield. The *ortho*-substituted

Scheme 1. Synthetic Utility of Allylic Adducts



derivative afforded a lower yield (58%), likely due to steric effects and deacetylation of phenol (entry 8). Additionally, this AcOH/DBU mixture afforded excellent yields for aromatic and heteroaromatic halogenated molecules (entries 9−12). Of note, functional groups such as bromobenzene derivatives, which could prove problematic with palladium-catalyzed processes,[13] are well tolerated. A notable example from Table 2 includes the reaction of (1,2-dibromopropan-2-yl)benzene (**2m**), which gave 43% yield. The lower yield obtained in this case is the result of incomplete reaction due to the nature of the starting material (lack of benzylic protons); extended reaction times will likely provide increased yields. Overall, we believe that the data in Table 2 provide strong certification for the general scope inherent in our approach.

Encouraged by these results and because (*E*)-allylic acetates and their corresponding derivatives are valuable synthetic intermediates, we next explored the generality and synthetic utility of the DBU-mediated regio- and stereoselective transformation toward different nucleophiles (Table 3). We were pleased to discover that our approach is viable for use with nucleophiles other than AcOH. For example, good results were obtained with a variety of other oxygen-containing nucleophiles, such as aliphatic- and aromatic-derived acids. Tetradecanoic acid gave the adduct **4a** in 76% yield (entry 2). Electron-rich and electron-poor benzoic acids were also good substrates for this transformation with yields up to 79% (Table 3, entries 3−5). In addition, *trans*-cinnamic acid afforded the allylic ester in 55% yield after 4 h. Carbon-based nucleophiles such as dimethyl malonate and diethyl malonate were also tolerated and afforded the desired products in 93% and 82% yield, respectively (entries 7 and 8). However, other carbon nucleophiles exhibited diminished reactivity, presumably due to their pK_a, and were less efficient (entries 9 and 10). To our gratification, nitrogen nucleophiles such as phthalamide and 3-acetylindole afforded the allylic amination adduct in 48% yield and 51% yield, respectively (entries 11 and 12) and 3-acetylindole in 36% yield (entry 13). Likewise, sulfur-based nucleophiles such as thiobenzoic acid with 71% yield and thioacetic acid with 62% yield were also compatible (entries 14 and 15).

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In order to elucidate the mechanistic details of this system, a comprehensive set of experiments was performed.[14] Based on the data acquired, we propose that an E2 elimination, facilitated by DBU, followed by nucleophilic displacement in an S_N2 fashion is occurring. Also, it is likely that the E2 elimination is the rate-determining step. In this regard, we prepared and treated (*E*)-(3-bromoprop-1-en-1-yl)benzene under the standard reaction conditions, which afforded allylic acetate (**3a**) in quantitative yield after 15 min, supporting the high reaction rate for S_N2 reaction. Additional details for the high regio- and stereoselectivity observed are described in the Supporting Information.[14]

To demonstrate the synthetic utility and practicality of this method, the reaction was performed on gram scale using a one-pot procedure. Importantly, this streamlined procedure does not compromise the efficiency of the transformation, as the product was isolated in 81% yield (Scheme 1, eq 1) Although a number of synthetic transformations could be envisioned for the allylic adducts, we focused on a couple of functional group manipulation that highlight the utility of using DBU mediated allylation reactions. The allylic adducts derived from carbon nucleophiles are useful for elaboration of new molecular entities. To highlight this, we prepared the unnatural α-amino acid precursor **5** from allylbenzene (**1**) in three simple steps (eq 2). Likewise, we prepared the core of wutaienin[15] by reduction of **4i**, which could be prepared in two steps, in 91% yield with 3:2 dr (Scheme 1, eq 3).

In conclusion, we have documented a new entry to linear (*E*) allylic compounds obtained directly from terminal alkenes. The method complements existing approaches based on palladium allylic C−H activation. Furthermore, evaluation of the reaction considerations indicates that the reaction conditions using DBU and NuH in DMSO are optimal for carbon, oxygen, nitrogen, and sulfur nucleophiles. Across the board, this reaction protocol results in linear (*E*) allylic products. Thus, this methodology not only broadens the application of traditional Tsuji−Trost adducts, but also provides direct disconnections for rapidly building organic frameworks, an important consideration in many synthetic studies.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00862.

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Notes

The authors declare no competing financial interest.

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